Mark V. Sauer
Editor

Principles of Oocyte and Embryo Donation

Second Edition

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Foreword to the 2nd Edition

This second edition of *Principles of Oocyte and Embryo Donation*, published 15 years in the wake of the first, is timely and welcome. The volume chronicles more recent stages of a scientific saga that began over 25 years ago when in 1984 the first oocyte and embryo donation births were reported [1, 2]. Though the fundamental science was sound, the first births came only after researchers overcame technological limits of the time and excruciating public and private skepticism. Thus, the first edition in 1997 chronicled the initial investigational and early clinical phases of oocyte and embryo donation. Today, after hundreds of thousands of healthy newborns, the paradigm is mainstream. This new volume describes a very different scientific landscape, where oocyte and embryo donation has been enhanced by novel and sophisticated laboratory embryology, cryobiology, molecular genetics, and more efficient clinical protocols. Success rates have increased. Public acceptance is improved. More diverse applications have been exploited. Today, fresh and cryopreserved oocyte and embryo donations comprise well over 10 % of the IVF cycles and births recorded in the United States by the Center for Disease Control statistics.

As editor, Dr. Mark Sauer assembled an outstanding panel of expertise for this multiauthored work. That expertise begins with Dr. Sauer himself, certainly among the most experienced and highly published figures on the field of oocyte and embryo donation. His participation in the field began with our UCLA team during the earliest days. His personal contributions include initial work on methods to synchronize and enhance the receptivity of the endometrium. His work extended shortly thereafter to establish principles of donor management, adapting the use of transvaginal oocyte retrievals for oocyte donation performed by in vitro fertilization. He pioneered and memorialized the principles and outcomes of oocyte donation to menopausal women of advanced maternal age, and he has played a fundamental role in the setting of good practice standards that have been adopted by widely recognized expert panels and government agencies.

The heart of this book is the expert contributions. The flow of topics is logical in that it begins as practical and ends in useful but futuristic, legal, social, and theological esoterica. The authors are uniformly selected for their expertise in this area, and the contributions are well edited. The topics begin with the practical management issues. Thus, Part I begins with preliminary considerations for patients and clinicians and includes the history of the technique by Dr. Sauer describing practical aspects of experience he lived through

himself. It moves into the various indications for donor oocytes, the screening and evaluation of donors and recipients, pregnancy rates, and genetic aspects of donor selection. Part II addresses the practical management issues and reviews aspects of donor and recipient synchronization, the use of blastocysts vs. cleavage stage embryos, techniques to minimize multiple gestations, outcomes of supernumerary embryos, and ends with complex psychological treatment of parties involved in third-party reproduction, as well as the medical legal issues. Part III deals with office management and includes discussion of the donor nurse coordinator, the finances of oocyte donation, and insurance issues. Part IV, the new frontiers section, deals with oocyte and embryo banking, gestational carriers, assisted reproduction in same-sex couples, and immunological consequences of oocyte and embryo donation pregnancies. Part V deals with regulatory issues, the FDA policies governing reproductive tissues, informed consent, and statutory regulation of third-party reproduction. Each contribution is clearly expert written and well edited.

Readers interested in or working with oocyte and embryo donation will genuinely appreciate the care taken in the organization, expertise, authority, and diversity of content ranging from total basic to technological and social sciences. The work is a scholarly memorial to the continuing evolution of oocyte and embryo donation and to the hundreds of thousands of children born to otherwise impossibly infertile women as a result of it.

It is a joy to see this story unfolding in a book like *Principles of Oocyte and Embryo Donation*. This book contains volumes of useful information that will be highly appreciated by the many readers who will consult it.

Thank you, Dr. Sauer.

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Bustillo M, Buster JE, Cohen SW, et al. Nonsurgical ovum transfer as a treatment in infertile women. JAMA. 1984;251:1171–3.

Foreword to the 1st Edition

This textbook deals with one of the most important aspects of assisted conception today. Oocyte and embryo donation encompasses many of the clinical, scientific, and ethical problems in the field. Oocyte donation, the main theme in the book, demands an empathy with patients in the difficult situation of primary or secondary menopause or who have a severe genetic disease that precludes using their own oocytes. Each couple searches for their own solution to an intractable problem. Perhaps a sister or a friend will donate an oocyte willingly and selflessly, or there may be no other recourse but to hope for help from a stranger who may or may not be paid for her oocytes. The donor must be prepared to forgo any right to a resulting child. Donation requires counseling and advice to the couple and to the donor. Two cycles must be balanced, in donor and recipient, to ensure synchrony between embryo growth and a receptive endometrium in the mother, and to ensure that all clinical and scientific practices accord with state law. Fertilization and embryo growth are watched closely by donors and recipients, within a framework of a busy in vitro fertilization (IVF) clinic where hopes and fears are high, and disappointment is, sadly, more often the outcome than pregnancy. Success is wonderful, especially for patients who have been trying to establish their pregnancy for many years and now find themselves well past menopause. In today's world of science and medicine, their cause is not lost, for they too have the chance of pregnancy.

All of this is the stuff of high emotions and expectations, ethics and law, allied to first-class embryology and gynecology. A book devoted to this topic, and organized and edited by one of the world's leading exponents in this field, would be expected to be comprehensive, realistic, and sympathetic to the patients searching for help. Mark Sauer has led this field from the front to establish an authority second to none, and a glance at the contents is enough to confirm that this book lives up to the highest of expectations.

The in-depth coverage of these chapters is provided through the fascinating, detailed, and responsible contributions of many distinguished commentators. No stone is left unturned in describing the search for happiness through oocyte donation and the ethical, social, and legal challenges it has brought in its wake. All this knowledge displayed so carefully, and compassionately, makes me recall our earliest days in human IVF, when Steptoe and I debated all the ethical issues that could possibly arise- cloning, sexing, surrogacy, spare parts surgery, and oocyte donation- and also decided that the benefits overwhelmingly outweighed the risks. Today, many voices are heard on ethics

and law, and many countries have legislated strict or liberal laws in attempts to regulate every possible aspect of this field. My own opinion is that the ethics of care should be paramount and raised above many of the other issues. We have witnessed the application of too much written legislation in my country, concerned with the destruction of many cryopreserved embryos and the withholding of a dead husband's semen from his widow. We must accept a fundamental truth- that virtually all of our patients are searching for happiness, and usually within a framework of love for a child and a partner. This book addresses these issues dispassionately and provides much room for thought. It will stand tall among the books published on the care and practice of assisted conception, and especially among those on oocyte donation.

Robert G. Edwards, Ph.D.

Preface to the 2nd Edition

The versatility of oocyte and embryo donation has proven to be extremely valuable to both patients and doctors engaged in reproductive medicine. Originally thought to be applicable only to a rather small subset of infertile women, who were mostly young with premature ovarian failure, today busy practices commonly recommend the procedure to serve the reproductive needs of an aging population who in the past were considered to be hopeless cases. In the United States only a handful of centers offered egg and embryo donation throughout the 1980s, but contemporary estimates suggest that nearly all of the 400 or more IVF programs provide these services. Oocyte and embryo donation has established itself as a mainstay procedure within assisted reproductive care, and the breadth, depth, and complexity of practice are deserving of focused attention.

I recognized in the mid-1990s a need to address the many facets of oocyte and embryo donation within a single dedicated textbook, and thus the 1st edition of *Principles of Oocyte and Embryo Donation* was written. Much has changed within our field since it was published 15 years ago. The need for an updated and more expansive text was apparent to me, especially as the practice continued to grow in popularity and expand throughout the world. This 2nd edition resembles the 1st edition in title only, as the content is essentially all new, contributed by different authors with up-to-date information and perspectives from around the world. Each author was specifically chosen because of their prominence and active involvement with oocyte and embryo donation. Their individual perspectives weave a nice consortium of opinion, not necessarily always in agreement, but all equally valid and representative of the diversity of practice that occurs within our field.

This book provides an overview of the major issues affecting men and women engaged in the practice of oocyte and embryo donation. A primary emphasis has been placed on defining the standards of practice that have evolved over the past 30 years, clearly stating the outcomes expected from adhering to these established protocols. Details of both the basic science and the clinical medicine are presented together and always in the important context of the social sensitivities surrounding gamete donation that have been a part of the discussion from its inception.

Attention is also focused on the nonreproductive aspects inherent to this unique method of assisted reproduction that involves opinions from lawyers, ethicists, mental health-care professionals, and theologians. This book is meant to be informative to physicians and the lay public alike, discussing the

major topics involved in oocyte and embryo donation including both medical and nonmedical ones. It is meant to serve as a complete and comprehensive reference and guide.

Any book on oocyte and embryo donation should be provocative and generate some discussion and debate. My commentary after each chapter is meant to remind the reader of the fact that there is a history behind every topic that often is rooted in sensation. I have watched oocyte and embryo donation evolve over nearly 30 years, as both an academician and a practitioner; some of the changes I have embraced, others I have fought or rejected. But I can honestly say that I have found all the controversy to be fascinating. I have come to believe that we do not always have to agree, but we should be fair and balanced in our analysis.

It is my hope that the 2nd edition will be welcomed by both medical professionals and the lay public. Despite over three decades of focused attention on the topic, I found an incredible amount of new and interesting information in this book and much that I did not know. Oocyte and embryo donation requires a working knowledge of the medicine, the law, and the ethics that underlies its foundation. The amount of information coming out today is just too much for any reader to keep fully abreast of the subject matter. This book attempts to coral it for at least a little while. However, I doubt that we can go another 15 years before updating it again.

I truly hope that the reader enjoys this book. It is my belief that it will serve as a basis and rationale for delivering quality care to women needing oocyte and embryo donation and a trusted reference to students of our field of medicine who wish to understand more about this fascinating and complex therapy.

Mark V. Sauer, M.D.

Acknowledgments

This 2nd edition, as true of the 1st, would quite simply not exist were it not for the dedicated efforts of my contributors. Their hard work is very much appreciated. They are colleagues and friends. It is not easy to write a book chapter. Much discovery and research goes into a review, and the need for a fair and balanced presentation requires a lot of thought and a great deal of time. Authors receive a "free" book for all their efforts. Clearly it is their vocational calling that motivates them to write, not monetary gain. Again, I cannot thank them enough for all their efforts in making this a fine medical textbook. In addition, the dedicated and concerted efforts of the staff at Springer, particularly my editor Michael Griffin, made my own job of editing this book much easier.

On a more personal note, this book is dedicated to my grandfathers, Harry Sauer and William Sanchez, and my father, Victor Sauer, who taught me how to be a responsible man; to my children Julie, Christopher, Jeffery and Emily who strengthen me with their love and encourage me to have hope for the future; and to my wife Lynda who for more than 30 years has faithfully stood beside me, oftentimes when others did not. I am forever indebted to them all.

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Part I

Preliminary Considerations for Patients and Clinicians

History of Oocyte and Embryo Donation

1

Mark V. Sauer

Key Points

- Egg and embryo donation has proven to be a highly effective treatment modality for many types of infertility producing thousands of children for women who in most cases were not candidates for conventional infertility care.
- Lessons related to the importance of embryo quality, embryo development, embryo implantation, and endometrial receptivity have been learned by studying pregnancy events in recipients of embryos created through egg donation.
- Egg and embryo donation may be the most scrutinized and criticized form of assisted reproduction and warrants careful supervision and adherence to guidelines and laws pertinent to its safe practice.
- Egg and embryo donation has proven to be the most effective treatment of age-related infertility and may be safely employed to address the fertility needs of healthy perimenopausal and menopausal women.

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Both oocyte and embryo donation will soon be celebrating thirtieth anniversaries as viable treatments for human infertility. This also means, of course, that the original children conceived as a result of these novel experiments are approaching middle age! It seems hard to believe that so much time has passed for those of us lucky enough to be a part of the early development of these methods, but soon, we will be entering the twilight of our own professional years. Humbly speaking on behalf of those who were truly the "pioneers" of this noteworthy medical achievement, I think it is important to point out that many aspects of modern assisted reproductive care were either directly or indirectly attributable to developments within the field of egg and embryo donation. To that end, I wish to reflect back on some of these noteworthy achievements and highlight the events that, in my opinion, were integral to the evolution of today's modern practice.

The Early Years

There is general agreement that the sentinel events leading to the first births from egg and embryo donation occurred in 1983. What is often confused is the fact that independent teams of investigators, using two different methods, on separate continents an ocean apart, were achieving success at nearly the same time. One technique, spearheaded by Drs. Carl Wood and Alan Tounson in Melbourne, Australia, utilized conventional methods of in vitro fertilization (IVF), which in those

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days meant that the donor underwent invasive surgery [1]. They synchronized the menstrual cycles of a 25-year-old woman with premature ovarian failure, using a combination of oral estradiol and vaginal progesterone, to an infertile 29-year-old "donor" stimulated with human menopausal gonadotropin (hMG), providing four eggs for herself and one for the recipient. The donor's eggs were retrieved by laparoscopy, performed under general anesthesia, and days later, a single early cleavage stage embryo was placed transcervically into the recipient. The recipient successfully conceived; the donor did not.

The same year, Gary Hodgen, Ph.D., in nonhuman primates, successfully replicated this approach. Dr. Hodgen and researchers at the National Institutes of Health (NIH) demonstrated that hormonally prepared rhesus and cynomolgus monkeys experienced surprisingly high pregnancy rates if cleavage stage embryos were transferred from donors to the recipients' fallopian tubes [2]. In many ways, this experiment was the harbinger of the human trials that would later focus international attention on the method.

Meanwhile, across the Pacific in Torrance, California, a team of clinical researchers headed by John E. Buster, M.D., was applying a completely different technique patterned after an approach known to be successful in animal husbandry. *Uterine lavage* was first introduced as a means for recovering preimplantation embryos in animals and had gained popularity over several decades of use as a safe way to enhance the efficiency of reproducing prize livestock and exotic animals [3]. Unlike the encumbering surgical and laboratory requirements of human IVF, uterine lavage utilized the donor as both the egg provider and the incubator and required only knowledge of in vivo embryo transport, along with an irrigating tool (Figs. 1.1 and 1.2) and collecting device (Fig. 1.3) for retrieving the embryo from the donor's uterus.

Although this method was rather well worked out in cattle, it certainly was not in humans, and it took years of clinical research work, and much courage on the part of the investigative team, to apply it as such. The experiments conducted at Harbor-UCLA Medical Center synchronized naturally cycling women, one infertile and the other the ovum donor, and uterine lavage on the donor was carried out over

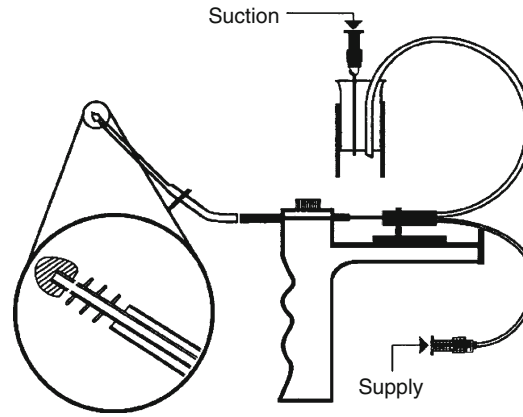

Fig. 1.1 Schematic drawing of the uterine lavage tool and irrigating catheter used to harvest in vivo fertilized ova from donors (Courtesy of John E. Buster, M.D.)

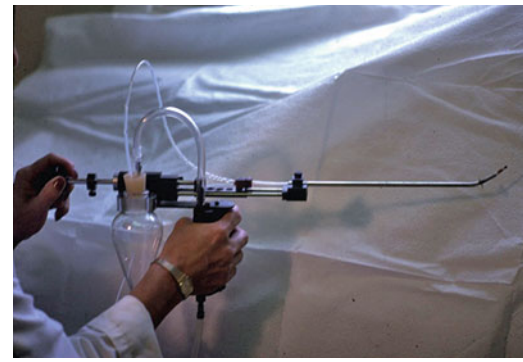

Fig. 1.2 Photograph of lavage tool used at Harbor-UCLA Medical Center (Courtesy of Mark V. Sauer, M.D.)

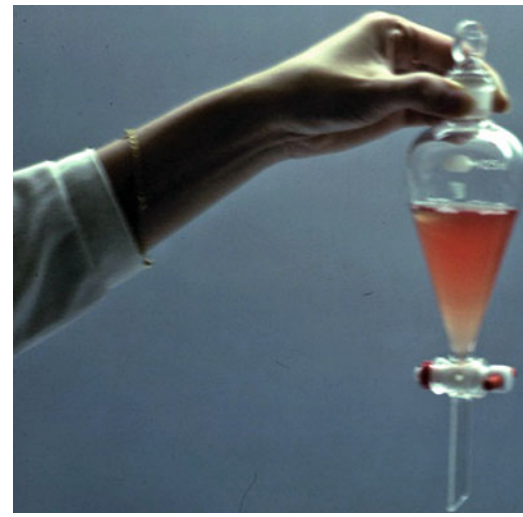

Fig. 1.3 Collecting flask filled with uterine lavage flushing post-endometrial irrigation from an ovum donor (Courtesy of Mark V. Sauer, M.D.)


New York Stocks

Los Angeles Times

Late Final

Friday, February 3, 1984

Historic Embryo Transfer

Woman Bears Donor's Baby

LATE NEWS

Stocks Suffer Sharp Drop

Golden Knight Chutist Killed

Shuttle Roars Into Orbit Flawlessly

The world's first baby born to an infertile woman from a donated embryo sucks his pacifier.

'Beautiful' Boy Born in Long Beach

Jobless Rate Drops to 8%; L.A.'s Level Climbs to 8.4%

105 Vehicles Pile Up West

Fig. 1.4 Front page of *Los Angeles Times*, Friday, February 3, 1984, announcing birth of world's first embryo donation baby

several days post-ovulation and insemination (beginning as early as 96 h following the LH peak) since it was not clear exactly when the embryos would arrive in the uterus [4]. Over the course of numerous cycles, donors and recipients were matched and synchronized in hope of successfully recovering a viable embryo and establishing a pregnancy. What was learned from the effort was the importance of normal embryo cleavage and development to successful implantation and pregnancy; essentially, if an expanded blastocyst was not recovered, a pregnancy did not occur [5]. Furthermore, the inefficiency of natural cycle human reproduction was painfully evident and paralleled the long struggles experienced by Steptoe and Edwards in establishing the first IVF pregnancy until resorting to ovarian hyperstimulation.

Although viable pregnancies occurred during the same year using both techniques, the birth of the world's first "egg donor" recipient occurred in Long Beach, CA, in January 1984 from an embryo harvested from an in vivo fertilized egg through uterine lavage (Fig. 1.4) [6]. The UCLA researchers actually kept the announcement from the public until they were reassured that the baby was fine and safely at home almost 3 weeks later! (Fig. 1.5) The news was an international sensation and triggered fierce debates on the ethics of enlisting the services of healthy young women to help infertile patients have children that continue to this very day.

In addition to the medical novelty that uterine lavage represented, there were several other notable features that should not be lost in the historical retelling of this breakthrough. The researchers at Harbor-UCLA were the first to openly pay women for participation in egg/embryo donation. Others have incorrectly claimed the idea occurred years later, but it was no small feat getting approval by the UCLA Human Subjects Committee and the IRB that provided the oversight of this project. An opinion from the UCLA School of Law was solicited that also agreed on the strategy of fairly compensating women for their participation as human subjects, similar in many ways to men who were providing sperm donor services at the medical center. Payment was approximately $250 per cycle, in line with a $50 per day compensation provided for the five required office visits. Second, from the initial announcement going forward, discussion about the medical ethics of egg and embryo donation was inherent to every conversation

Fig. 1.5 Photograph of John E. Buster, M.D.; Maria Bustillo, M.D.; and Sydlee Cohen, RN, with world's first embryo donation baby in Long Beach, California (Courtesy of Maria Bustillo, M.D.)

that occurred about it. Perhaps the headline announcing the first birth in the *LA Times* best reflected the public skepticism as it proclaimed "Woman Bears Donor's Baby." Although hundreds of thousands of babies have now been born from egg donation throughout the world, the method remains controversial in its application and is still banned or highly restricted in many places. Finally, it was soon apparent that uterine lavage was only as efficient as the underlying human reproductive biology, and therefore the majority of ovulatory cycles of fertile women failed to produce a viable embryo that could be successfully recovered and transferred. Thus, the low efficiency of the technique challenged its practicality for routine clinical use.

Defining and Refining the Technique

The next few years focused principally on attempts to make the process of embryo donation more efficient. Uterine lavage in animals had been similarly problematic until ovarian hyperstimulation of the ovum donor was introduced. Unfortunately, attempts to improve ovum recovery in humans undergoing lavage by hyperstimulating the ovaries failed to produce a pregnancy and actually resulted in retained pregnancies in several of the egg donors, despite rigorous safety precautions to prevent pregnancy that included prescribing the donor progesterone receptor antagonist (RU-486, now known as mifepristone) and performing a post-lavage uterine curettage [7, 8]. Given this major setback and the coincident onset of the HIV epidemic coming to light in the mid-1980s, all further attempts at improving the technique were discontinued, and the method was abandoned.

Transition to Egg Donation

The introduction of nonsurgical ultrasound-directed transvaginal needle aspiration of oocytes provided the impetus to refocus efforts on developing egg donation. Donors who had been asked to participate in the original work at Harbor-UCLA using uterine lavage were now recruited to undergo ovarian hyperstimulation and egg retrieval at the University of Southern California (USC). This program founded in 1987 by the team of Drs. Mark V. Sauer, Richard J. Paulson, and Rogerio A. Lobo was the first to actively solicit, screen, and compensate women to perform egg donation using IVF technology in the USA [9]. Payment for services at that time was $500 per cycle of participation, twice the amount

paid to donors previously undergoing uterine lavage. However, egg donation was much more complicated than ovum donation, requiring more office visits, injectable medications, and ultimately anesthesia to retrieve the eggs transvaginally. Although conscious sedation was required in order to render the short procedure painless, the IVF technique had distinct advantages over lavage including neither having to directly inseminate the donor nor having to worry about retrieving the fertilized ovum from her body. Another major benefit was that in practically all cases, there would be embryos to transfer to waiting recipients. The initial series produced a high pregnancy rate and appeared applicable to a number of differing infertility diagnoses. This included recipients with premature ovarian failure, patients with gonadal dysgenesis, patients who had failed multiple attempts at IVF, and women with inaccessible ovaries. From that point on, all attention was focused on refining the IVF technique and expanding its applicability.

Synchronization Schemes and Endometrial Preps

The earliest attempts at preparing the endometrium to receive a donated embryo focused on recreating the natural patterns of sex steroid (e.g., estrogen and progesterone) expression as reflected by studies of ovarian hormone levels in the blood. This was problematic for numerous reasons. First, the prescribed medications available for use were not approved in pregnancy. Warning labels cautioned of serious side effects, including anomalies that had been noted in the offspring of women and laboratory animals taking similar hormone preparations [10]. Secondly, the pharmacologic effects of administered drugs were quite different from measured physiologic steroid levels. For instance, to achieve normal values of serum estradiol, either estradiol valerate or micronized estradiol was orally administered in stepwise increased dosages until mid-cycle. Although "follicular" levels of estradiol were typically demonstrated, the by-products and metabolites (e.g., estriol, estrone, estrone glucuronide, estrone sulfate) of the drug were also circulating bound to sex hormone binding globulin and unbound at supraphysiologic levels for extended periods of time [11]. These hormones were never measured clinically, yet undoubtedly, these "weaker" estrogens also exerted physiologic effects upon target tissues.

Progesterone was also problematic. When provided as an intramuscular injection, typically given twice daily, exaggerated blood levels were noted; yet, tissue levels of steroid were found to be much lower, and variable endometrial expression of response was observed when studying histology, steroid receptors, or prolactin expression compared to vaginally administered products [12]. However, early attempts at vaginal application using progesterone dissolved in suppositories of polyethylene glycol or cocoa butter were difficult to use and erratic in their delivery. Silastic cylindrical delivery systems were also tested, but the large surface area required for physiologic levels in the serum again made their use impractical [13]. Therefore, until the early 1990s, at which time vaginal micronized progesterone was introduced, progesterone was typically administered as twice daily intramuscular injections, despite its numerous drawbacks (Fig. 1.6).

Throughout the mid- to late 1980s, many studies were performed on the endometrium of functionally agonadal women preparing for embryo donation. Most report the attainment of "normal" endometrial histology when biopsies were performed during the mid-luteal (period of time implantation occurs) or late luteal phase (best for dating). However, a more critical analysis of the endometrial histology described atypical features normally not seen in natural cycles. Within a single sample, it was common to observe disordered patterns of both glandular and stromal development. In one field, the stroma might appear "advanced" while in other areas "delayed." Glandular crowding was common, as well as delayed maturation in various areas adjacent to normal expression. Lack of synchrony between the glands and stroma was very common, with one or the other compartment being either slightly advanced or, in other cases, slightly delayed making conventional "dating" problematic [15] (Fig. 1.7).

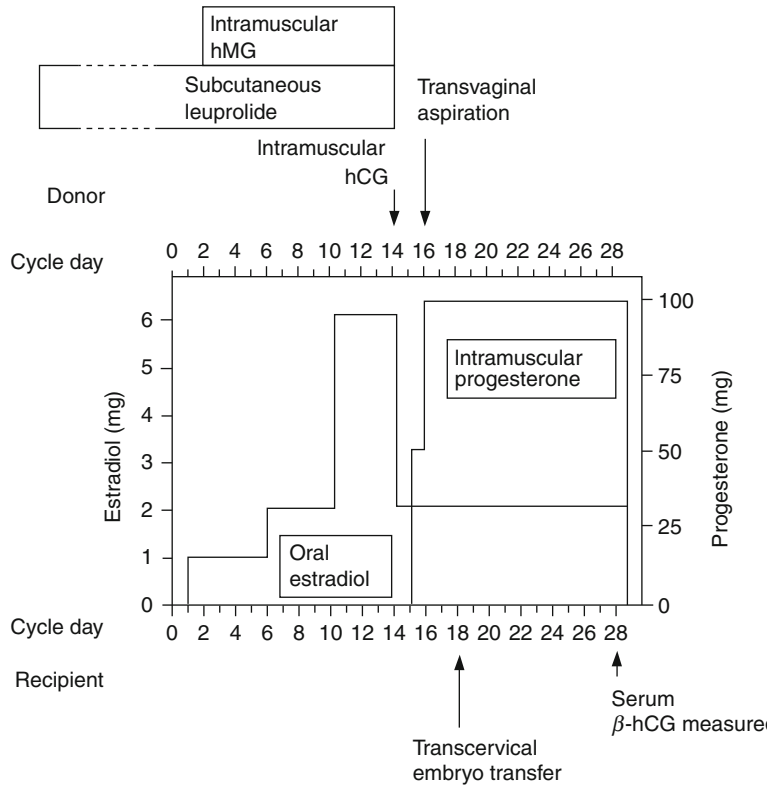

Fig. 1.6 Prescribed course of medications used by egg donors and embryo recipients 1990 (From Sauer et al. [14]. Copyright (c) (1990) Massachusetts Medical Society. Reprinted with permission)

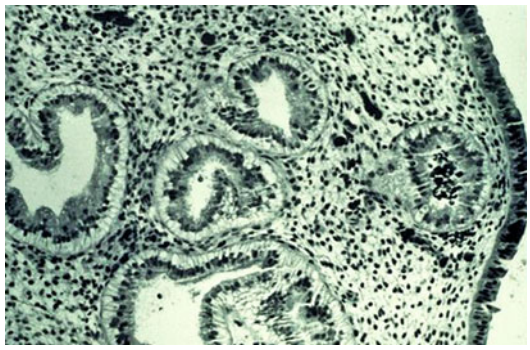

Fig. 1.7 Endometrial biopsy taken from menopausal woman during the mid-secretory phase of an artificial cycle (Courtesy of Mark V. Sauer, M.D.)

While at USC, during those years, we routinely performed "mock cycles" on all potential recipients, with endometrial sampling taking place either on day 21 or day 28 of the prescribed hormone regimen. I came to rely upon the well-trained eyes of Dr. Dean Moyer, a noted histopathologist who regularly reviewed biopsies with me in his basement office of Los Angeles County-USC Women's hospital. We became accustomed to these unusual patterns of endometrial expression and decided when using the pharmacologic replacement scheme prescribed that such variations were "normal" for what was being attempted, the creation of an endometrium that allowed embryo implantation in otherwise functionally agonadal women. I mention this only because when endometrial samples are given to a hospital pathologist for interpretation, who typically is not accustomed to reading such biopsies, it is common to receive reports that may alarm both the patient and the physician, including "atypical hyperplastic endometrium," "bizarre disordered endometrium," and "unable to date due to unusual features" endometrium.

By 1990, prescribing simplified hormone replacement schemes became more in vogue than trying to recreate serum levels: this following the introduction of fixed dose regimens [16]. Fixed dosing was easy to remember, provided a more flexible regimen for synchronizing the donor to

the recipient, and, most importantly, was associated with the same high rates of pregnancy in the recipient. The type of estrogen prescribed also varied, with pregnancies reported using a number of different compounds and routes of delivery. Births occurred from transdermal, transvaginal, intramuscular, oral, and transrectally administered estrogens. Even Premarin was used successfully, although I would not recommend it myself. Perhaps more interesting are births that followed the discontinuance of all hormone replacement therapy post-transfer (erroneously stopped by misunderstanding patients) which begged the question as to whether or not medications were necessary at all once implantation had taken place [17].

Suffice it to say, that most prescribed preparations were adequate and led to high pregnancy rates in recipients. Today, the debate continues as to whether or not one regimen is superior to another; however, most studies find that non-injectable routes are just as good as those requiring painful daily intramuscular shots, which are associated with injection site complications (e.g., abscess, skin discoloration, fat necrosis, chronic pain at injection site) [18].

We prefer using a fixed dose oral estradiol combined with a daily vaginally administered micronized progesterone due to the ease of use, low cost, and simple to remember format (Fig. 1.8). This has been my standard regimen for nearly 20 years and has served several thousand patients well. The most common complaint is the localized buildup

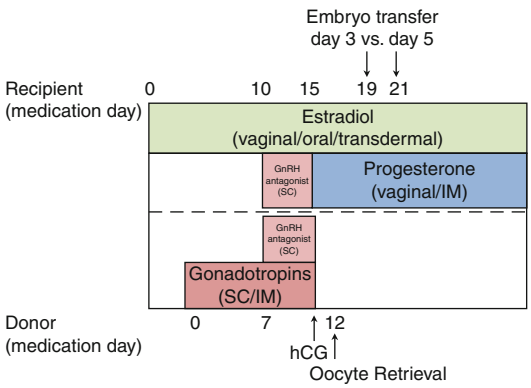

Fig. 1.8 Current prescribed hormonal regimen used at Columbia University for synchronizing egg donors and recipients (Courtesy of Mark V. Sauer, M.D.)

of the vaginal progesterone when using either capsules or gels due to the inability of the vagina to fully absorb the vehicle in which the micronized spheres of progesterone are housed and suspended. Patients frequently mistake the white clumps of packing (usually starch or galactose) for the progesterone itself and are reluctant to douche or flush the product from the vagina for fear of "losing" their steroid. Others may mistake the "discharge" as vaginitis, and I have even seen physicians erroneously treat patients for Candida on multiple occasions. Pregnant patients will use these products throughout the first trimester, so it is important to forewarn women of this inevitability to prevent unnecessary alarm, or worse, medical intervention. Simple digital flushing of the vagina while bathing every few days prior to an application prevents any buildup of product.

The use of these simple regimens to recreate the endometrium has been extended to the rank and file of patients undergoing conventional in vitro fertilization and is now routinely used to synchronize the endometrium of women receiving cryopreserved embryos. Early studies comparing "natural" cycles to cycles in which the endometrium was prepared by hormone replacement therapy (HRT) noted similar, if not superior, rates of pregnancy success in women receiving HRT [19]. However, the ease of scheduling and certainty of performing the ET procedure (i.e., avoiding cancellations secondary to early inadvertent LH surges or anovulation in the patient) made pharmacologic preparation the preferred method. Today, practically all transfers of cryopreserved embryos are preformed using these regimens perfected by researchers' intent on improving the success rate of recipients of donor eggs.

Window of Implantation and Endometrial Receptivity

Daniel Navot, M.D., published an important paper in 1988 detailing the "window of implantation" which defined the temporal relationship of uterine receptivity to embryo implantation [20]. His findings were in line with the previous observations from our work at Harbor-UCLA that noted only blastocysts arriving

at the uterus between 96 and 120 h post-ovulation were likely to implant when transferred to a synchronized recipient. In Navot's paper, cleavage stage embryos replaced either too soon or too late within the recipient's uterus were not associated with pregnancy. This window was defined by the number of days of prescribed progesterone exposure and was not dependent upon the days of estradiol priming, if at least 1–2 weeks of estrogen had been delivered. The scheme outlined in this paper continues to form the basis for timing the ET used today and is also applicable to women who now undergo HRT for replacement of their cryopreserved embryos from autologous cycles of IVF.

Another observation that came to light around this time was the curious finding that not only do recipients become pregnant at high rates of success, but it also appeared that their implantation rate per embryo transferred was actually higher than what was reported in younger women undergoing conventional IVF [21]. Likewise, it was noted that hormonally prepared women receiving eggs were more likely to achieve pregnancy than their counterparts providing "extra" eggs to them while going through IVF for themselves [22]. The decrease in uterine receptivity noted in IVF patients was felt to be secondary to the supraphysiologic levels of hormone produced by ovarian hyperstimulation and their detrimental effects on the endometrium [23]. Over time, other observations have been reported which may explain the endometrial differences such as changes in growth factor and integrin expression, histological abnormalities, and pinopod disruption, just to name a few [24–26]. In the conglomerate, these physiologic aberrancies may be the reason why hormonally prepared endometria of the *artificial* cycle demonstrate superior pregnancy rates compared to endometria under the influence of ovarian hyperstimulation since it mimics more closely the *natural* cycle.

Breakthrough in Applicability: Menopausal Mothers

In my opinion, the event that most radically altered the course of egg donation in the USA and throughout the world was the achievement of successful pregnancies in a small group of menopausal women in their 40s in 1990 [14]. Up until that time, egg and embryo donation had occurred in younger recipients, mostly with ovarian failure, but healthy enough in all other ways to reproduce. We had published our methods and results with these women and attracted many patients with similar reproductive issues who were older. They too had been evaluated, undergone mock cycles of endometrial preparation, and, although of advanced reproductive age, seemed healthy enough to attempt pregnancy. After gaining approval from our IRB to offer egg donation to this older cohort, we embarked on a small preliminary clinical trial involving just seven women; six conceived and five later delivered. We published this finding in the *New England Journal of Medicine*. The news was an international sensation, and as the saying goes, "the rest is history."

Overnight, we were deluged with requests to perform this technique on older and older patients, and the now apt question of "how old is too old" was increasingly being asked [27]. We followed this trial with yet another including women up to age 50 published in the *Journal of the American Medical Association* (JAMA) in 1992 and then another series of women over the age of 50, all with natural menopause, in the journal *Lancet* in 1993 [28, 29]. These three papers, all designed as observational studies, were unique in that each demonstrated the real possibility for safely establishing pregnancy in older women.

The impact of these papers can best be assessed by merely looking at the number and ages of women attempting egg donation since the early 1990s (Fig. 1.9). Numbers quickly grew as the method was published, easily replicated, and most importantly served the needs of a large, previously underserved population of perimenopausal and menopausal women who wished to have children [30]. It is fair to say that this effect spilled over into the general population of IVF patients as well since increasing numbers of older patients also attempted IVF with their own eggs during this timeframe, a national trend that continues to this day.

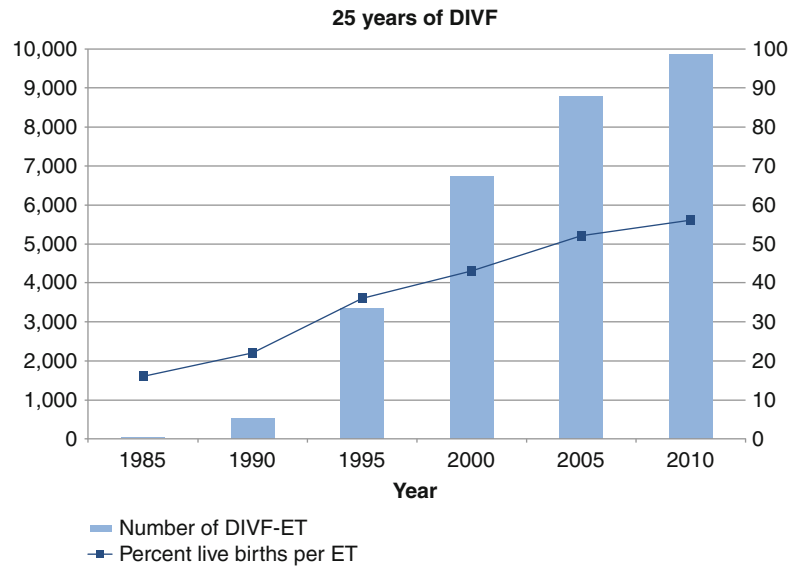

Fig. 1.9 Increasing number of fresh embryo transfers performed in the USA in which donor eggs were used over a 25-year period (http://www.cdc.gov/art/)

Hodgen and Stem Cells

I would like to add a few more words about Gary Hodgen, Ph.D., and his important contributions to egg and embryo donation [31]. I had the distinct pleasure of meeting Dr. Hodgen during my fellowship in 1985 while at Harbor-UCLA when he came to visit John E. Buster, M.D. He was there to review our work with uterine lavage and advise us on ways to make it more efficient. As I mentioned before [2], Dr. Hodgen was first to demonstrate that embryos could be successfully transferred in the castrate and hormonally replaced nonhuman primate using a method that basically predated all that we do today. Furthermore, he grew up on a farm in Indiana and was well acquainted with the process of uterine lavage for breeding dairy cows and offered much support to us in our early clinical trials with uterine lavage.

Dr. Hodgen was a bold innovator responsible for many breakthroughs in reproductive medicine. Another of his avant-garde experiments pertinent to egg donation was the deliberate production of human blastocysts using donor sperm and donor eggs to produce human embryonic stem cells [32]. This project would raise eyebrows today, but he began this work in 1997 and published his results in 2001! The embryos appeared on the cover of *Fertility Sterility* and generated a great deal of debate and controversy. It also refocused attention on the use of donor gametes for research initiatives. Ahead of his time, undoubtedly, but I am confident that if he were alive today, he would be supportive of our efforts to responsibly enlist the support of egg donors for research initiatives involving somatic cell nuclear transfer, as recently published in *Nature* in 2011 [33].

Price Wars

As mentioned earlier, participants in egg and embryo donation at centers in the USA were compensated for their time and efforts from the very beginning. From 1984 through 1987, the program at Harbor-UCLA provided women $250 per cycle according to guidelines reviewed and approved by the IRB and Human Subjects Committee. When I moved to USC in 1987, I arbitrarily raised that amount to $500, largely to reflect the greater involvement required of donors now undergoing ovarian hyperstimulation and egg harvesting under conscious sedation. The donor pool was relatively small then, less than a dozen women during those years, and we elected to raise payments to $1,000

in 1990 in order to better attract new candidates to serve the increasing demand for donors needed for women of advanced reproductive age. This amount was again raised to $1,500 in 1992 as intense competition for donor services began to occur in the LA area and once again raised to $2,500 in 1995 for the same reason.

Each of these increases brought on new debate as to whether or not women were being induced or overly enticed to participate in a potentially dangerous procedure. However, there were very few complications and given the overall safety record of the method, the importance of the medical intervention for women who without these eggs would be hopelessly infertile, and the increasing complexity of the donors' involvement (which necessitated they use daily injections for nearly 2 weeks and undergo a transvaginal needle aspiration under anesthesia), the amount of compensation did not seem excessive to me and was viewed by most medical ethicists as reasonable under the circumstances.

The spotlight was turned on egg donor payment in 1997 when a sudden escalation in New York jumped reimbursements from $2,500 to $5,000 [34]. Differing opinions as to whether or not such amounts were "reasonable" or "excessive" spilled over into both the popular press and the medical literature. Soon afterward, the Ethics Committee of the American Society for Reproductive Medicine attempted to address the growing price wars by issuing a statement of opinion regarding the upper limits that should be considered when compensating donors [35].

These problems were further compounded as a growing number of agencies, and "donor brokers" entered the medical marketplace. Since the early 1990s, this type of business has grown in number and popularity. Although ASRM has asked agencies to register with its organization in order to ensure accountability, they remain largely unregulated and continue to advertise aggressively for clients, both donors and recipients, in newspapers, on subway platforms, in movie theaters, on commuter trains, and on the Internet. Not uncommonly, ads solicit distinct pedigrees and other trait-based profiles with promises of up to $100,000 for women meeting specified requirements. However, to my knowledge, few, if any women, have ever actually been compensated anything close to that amount of money, and what these solicitations more likely represent are "teaser ads" which entice women to call the agency and then enlist them into their program, usually at a much lower rate of compensation.

Critics who are quick to call for "regulation" of the payments should be aware of the recent class action lawsuit filed against both ASRM and a West Coast fertility group who refused to pay a young donor in excess of the $10 K limit recommended by the ASRM Ethics Committee [36]. The basis of the litigation relates to restriction of fair trade and argues that women employed as donors should be paid any sum, regardless of how high the amount, commensurate with their value in the open marketplace. So in essence, the old argument of undue enticements to undertake a medical procedure has been thrown out the window in favor of what the law allows any commercial vendor to demand. As of right now, "the jury remains out" on this issue.

Extension to Surrogacy

Surrogacy was available prior to egg and embryo donation, but it was largely limited to couples in which the woman was physically unable to carry a baby secondary to either a serious underlying medical condition or was without a uterus. In such cases, in the early days, surrogates were inseminated with whole ejaculates intravaginally placed and later by washed intrauterine insemination techniques. A federal registry, as required today, did not track cases, so it is hard to ascertain the true popularity of the method. However, this method fell out of favor during the decade of the 1980s due to several factors, including legal vulnerability of couples losing custody of their child to the surrogate and fear of transmitting HIV or hepatitis to the surrogate. Using donor eggs, instead of a surrogate's autologous gametes, was touted as a way to hasten pregnancy, increasing the odds of success per cycle of treatment while also diminishing the surrogate's biologic tie to the offspring and legal claims. This approach additionally lessened the need for the

surrogate to undergo ovulation induction and in vitro fertilization. Although costs were greatly escalated when combining the two methods (traditional surrogacy and egg donation), the popularity of this approach is evident in reviewing the number of cases performed in the USA through the decade of the 1990s and beyond. More than 1,000 cases occur annually, and most utilize either donated eggs or embryos.

Lessons learned from egg donation were once again employed to enhance success of gestational carrier surrogacy. Stimulation regimens for the donor are the same as those typically used in traditional egg donation; surrogates acting as recipients are synchronized to donors, or to their frozen embryos, in order for the transfer to occur during the window of receptivity. This method not only allows women with medical or reproductive disability the opportunity to have a child, but it has also allowed men to begin families without the need of a female partner. Delivery of children conceived for openly gay men has fostered much controversy but is an increasingly popular and sought after service.

The FDA and Oversight

Egg donation has enjoyed its fair share of celebrity, but it has also always been under intense public scrutiny. From the outset, critics voiced concern over the ethics, safety, and long-term effects on society that might result from extending third-party reproduction to infertile women and couples. The AIDS epidemic and the known deadly risk of transmitting infectious disease provided additional impetus to insure public safety and professional compliance.

Prior to 1990, oversight of egg and embryo donation fell mainly to the local IRB. Most clinical activities during this era existed within university research programs, where oversight and quality assurance programs were in place and regularly monitored. However, after the publication of menopausal pregnancies in the early 1990s, increasing numbers of private centers began offering the method (Fig. 1.10) as well, and concerns were voiced at many levels as to whom, if anyone, was going to police or regulate this growing industry.

The ASRM, at the time named the American Fertility Society (AFS), issued its first committee report in 1993 detailing basic guidelines for the safe practice of egg donation [37]. Although providing directives for the screening of donors and recipients, it did not have authority to insure compliance. Since this initial publication, revisions have been made multiple times, and additional publications including those from the Ethics Committee of ASRM have helped to further define professional duties and obligations.

The *New York State Life and the Law Task Force: Assisted Reproductive Technologies:*

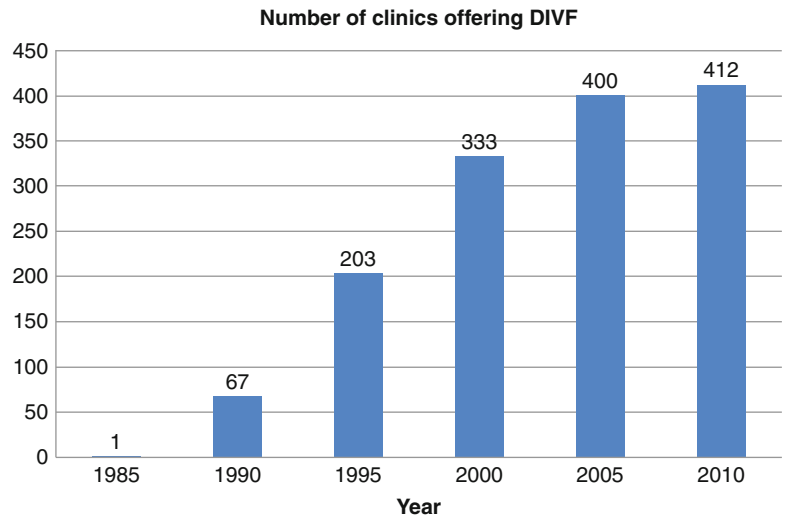

Fig. 1.10 Increasing number of US programs performing egg donation services over the last 25 years (http://www.cdc.gov/art/)

Analysis and Recommendation for Public Policy, published in 1998, was a noble attempt to formalize approaches and set professional boundaries for the practice of assisted reproduction, including egg and embryo donation [38]. Exhaustive in its breadth and depth of detail, among the many specific standards proposed were recommendations for the proper consenting, screening, and care of egg donors. Although intended to serve as a template for law, it died a legislative death, and these recommendations remained as such, just recommendations. However, the work exemplifies the seriousness with which the public views assisted reproductive techniques, including egg and embryo donation, and the regulation of such practices.

Real regulation came to our field in 2008 with the mandated oversight of gamete donation by the FDA [39]. Focused on protecting participants from infectious diseases that might be transmitted through gamete donation, specific testing and reporting is now mandatory and under federal jurisdiction. Regular audits occur and noncompliance is punishable and includes loss of privileges to practice egg donation and even fines and imprisonment. Whether viewed as an important safety measure or an unnecessary encumbrance, everyone in the field practicing egg donation in the USA has been affected by the changes brought on by the FDA.

I think it is likely that further regulations, either at the local, state, or federal level, will occur. In the USA, we have seen attempts to block assisted reproduction at the municipal (City of Naperville, IL), state (AZ, IN, VA), and federal levels (proposed bans) that threaten the practice of egg donation, as well as the overall provision of assisted reproductive services to the general public. We have been fortunate not to have suffered from an outright ban on gamete donation, as occurred in Italy in 2004, but American physicians need to appreciate the public sensitivities to the practice of reproductive medicine and specifically to reported abuses [40, 41].

Our published professional practice and ethical guidelines are formulated by a consortium that includes doctors, lawyers, bioethics, social workers, and psychologists, just to name a few, all coming together to collectively offer recommendations for safe and ethical practice. If these published standards are ignored, we ultimately cannot blame the general public for legislating control of our field of medicine.

Egg Banking

Perhaps one of the most important and exciting breakthroughs to occur in egg donation has only recently been reported. The clinical practice of oocyte donation has always been hampered by the need to secure the services of an appropriate egg donor, who then must be matched and synchronized to a phenotypically similar recipient, and maintained in clinical harmony until egg harvest and embryo transfer is accomplished. Clearly, this process is not an easy task, and over the years, many attempts have gone awry, creating grief among all parties involved. However, largely due to methodologic limitations in the ability to reliably cryopreserve unfertilized oocytes, the approach at synchronization of the donor and recipient has been the preferred one.

Driven by the need to circumvent laws in Europe that preclude fertilizing supernumerary eggs obtained during standard IVF, renewed interest in perfecting the technique of slow freezing and vitrifying eggs led to great improvements with enhanced clinical outcomes. Principally employing vitrification, the ability to achieve success rates that rival those reported in fresh cycles has renewed interest in egg banking [42, 43]. Large clinical series reports using banked oocytes for egg donation in Spain and the USA detail outstanding rates of success while greatly simplifying the process [44, 45].

Although still hampered by the "experimental" label assigned to egg freezing by the ASRM, I believe it is just a matter of time until oocyte freezing and banking becomes standard practice in the USA and elsewhere. There are many advantages to be gained including the ability to retrieve donors based solely upon their availability, maximizing the egg harvest by potentially splitting the number of retrieved oocytes among various recipients, maintaining a cohort of eggs for future use by couples

with success desiring siblings, and potentially reducing overhead and cost. Time will tell, but I do anticipate that more and more programs will establish egg banks, similar in many ways to sperm banks, and this process may ultimately replace the methods used for the last 30 years.

Summary

Research and clinical efforts to advance the field of egg and embryo donation have resulted in impressive gains in the delivery of care to patients with infertility. Assisted reproduction in general has also profited from much of the knowledge gained including a better understanding of embryo development, implantation, and uterine receptivity and how each factors into successful pregnancy outcome.

Refinement of techniques has improved pregnancy rates with each passing decade, and today, recipients can reasonably expect a baby in more than 50 % of cases performed, nearly double that anticipated 20 years ago. Increased clinical activity has brought on greater need for oversight and regulation, including agencies at the state and federal level. Recent improvements in egg freezing will likely further improve availability of services and reduce the cost, making the technique even more attractive and accessible to patients.

Editor's Commentary

A few post hoc comments related to the history that I just described. I don't know about you, but personally, I get very tired of people calling themselves "pioneers." I have often been labeled such for my role in egg and embryo donation, and quite frankly, it makes me quite uneasy. I do believe that I was a good student, and as good students do, I asked a lot of questions. These questions led to projects, and these projects led to my career in academic medicine. I reserve the label of "pioneer" for very few. To me, they were the founding fathers, Robert Edwards and Patrick Steptoe and Alan Trounson and John Buster.

Clearly, it is important to recognize and to celebrate the contributions of many clinicians and researchers who provided the basic framework and the mentoring guidance needed to launch the method of egg and embryo donation. It ultimately was the role of their students to sustain it. I feel very fortunate to have been a part of that research effort, and many of my papers undoubtedly served as a catalyst for making egg donation a mainstream therapy. But, clinical research does not exist in a vacuum and collaborative efforts built upon previous published, and unpublished work by many investigators leaves a long trail. For instance, I know firsthand that the work at *Harbor-UCLA Medical Center* involved countless hours of planning, discussion, and ultimately clinical execution involving many people over many years including Drs. John Marshall, John Buster, Maria Bustillo, Ian Thorneycroft, Steve Boyer, Jim Simon, Ingrid Rodi, and myself. Similarly, when I left UCLA and moved to the University of Southern California, the friendship and professional partnership formed between myself, Drs. Rick Paulson, and Roger Lobo proved equally nurturing and led to many great new ideas and projects. Who among all of these people, and I obviously didn't name them all, should stand alone as pioneers? I truly believe that everyone deserves their share of credit, and I trust that everyone involved will look back on their professional life with a great deal of satisfaction and pride for having performed his or her part in making this method so successful.

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Indications for Egg and Embryo Donation

2

Molina B. Dayal

Key Points

- Egg and embryo donations are viable treatments to address infertility in women with ovarian failure, reproductive aging, or other poor prognostic indicators to have children.
- Patients with Turner syndrome have an increased risk of sudden death during pregnancy secondary to aortic aneurysm rupture.
- Supernumerary cryopreserved embryos may be donated by individuals in order to establish pregnancy in women or couples interested in receiving them. In some cases, this approach may represent an attractive and affordable option when finances are limited.
- Pregnancy rates in women receiving donated cryopreserved embryos are generally lower than those from freshly retrieved donor eggs probably a result of multiple factors including selection bias of the frozen cohort, the effect of cryopreservation on the embryo, and the older-aged egg donors who were generally infertile women going through the process of IVF for themselves.

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Egg donation was first introduced as a treatment for infertility in 1983, with its popularity steadily increasing over the past three decades [1]. In the USA, egg donation accounted for approximately 10 % of all assisted reproductive therapies in 2009 compared to 8 % in 2000 [2, 3]. In 2009, nearly 15,000 transfers (both fresh and frozen combined) were performed using donated eggs [2].

Because uterine receptivity appears to be unchanged as a woman ages [4, 5], pregnancy occurs in greater than 50 % of embryo transfers using donated eggs in the setting of a hormonally prepared uterine lining [6]. This pregnancy rate is remarkable since most recipients are often older and typically would not be capable of conceiving with their own eggs (Fig. 2.1). According to the 2009 Centers for Disease Control (CDC) data, the majority of recipients are older than 40 years of age [2]. Because egg donors are women at the "peak" of their fertility potential, aged 21–32 years old, the percentage of live births from anonymous donated eggs is >50 % regardless of the age of the recipient [2].

Embryo donation (ED), or embryo adoption, has become an increasingly attractive method to achieve pregnancy for infertile couples that have either failed to conceive or have chosen not to pursue IVF using their own gametes. The first birth from a donated embryo occurred in 1984, with its popularity continuing to increase over the last three decades [7]. Because embryo donation does not require the recipient woman to undergo oocyte retrieval, the procedure is medically less complex and typically less expensive than IVF or oocyte donation [8, 9].

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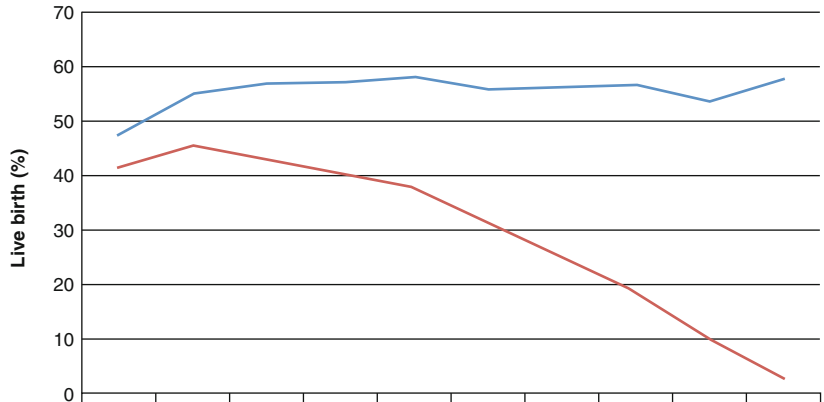

	26 years old	28 years old	30 years old	32 years old	34 years old	36 years old	38 years old	40 years old	42 years old	42 years old
Donor eggs	47.4	54.8	56.9	57	58	55.7	56.1	56.6	53.6	57.6
Own eggs	41.4	45.6	42.6	40.3	37.7	31.5	25.3	18.7	10	2.9

Fig. 2.1 Percentage of transfers resulting in live birth

Because many ART cycles produce more embryos than can be transferred safely at one time, extra embryos may be cryopreserved for later transfer. For those couples who become pregnant and do not desire another pregnancy, or who have other reasons for not wishing to use their supernumerary embryos, the option of discarding these embryos or donating them to other individuals or to research exists.

According to a study performed by SART in 2003, there were nearly 400,000 embryos stored in cryopreservation facilities across the country at that time [10]. Although this is a high number, the majority of these embryos (88.2 %) were being held by clinics for patients hoping to have children in the future. It was estimated that 4 % of cryopreserved embryos were available for donation, less than half of which were to be donated to other infertile couples with the goal of producing a successful pregnancy. Typically, genetic parents donate these additional embryos to a fertility clinic or "embryo bank" where they are stored until a suitable recipient is found for them. Usually the process of matching the embryo(s) with the prospective parents is conducted by the agency itself, at which time the clinic transfers ownership of the embryos to the prospective parents.

In the USA, women seeking to be recipients of donor eggs or embryos undergo communicable disease screening required by the US Food and Drug Administration (FDA), as well as reproductive tests to medically determine the normalcy of the uterine cavity and endometrial synchronization before the actual embryo transfer occurs. The amount of screening the donated egg or embryo has already undergone is largely dependent on the genetic parents' own IVF clinic testing parameters and medical history.

This chapter reviews the medical indications for egg and embryo donation with special considerations discussed with regard to embryo donation.

Indications for Egg and Embryo Donation

Egg and embryo donation provides a treatment strategy for infertile women with ovarian failure, reproductive aging, or other poor prognostic indicators to have children. According to the 2009 Society for Advanced Reproductive Technology (SART) database, nearly half (44 %) of women utilizing oocyte donation were assigned a diagnosis of diminished ovarian reserve [2]. Other

reasons for use of egg donation include tubal factor (1 %), ovulatory dysfunction (2 %), uterine factor (1 %), and male factor (3 %); multiple factors accounted for >30 % of egg donation cases. In addition, either of these treatment modalities can be used in women or men who are affected by or are carriers of a significant genetic illness or who have a family history of a condition for which the carrier status cannot be determined. Women with poor oocyte and/or embryo quality can also benefit from both approaches as can couples with multiple previous failed ART attempts.

Cancer survivors often experience hypergonadotropic hypogonadism as a result of gonad toxic chemotherapy and/or radiation. In these cases, patients often enter an early menopause and/or have severely diminished ovarian reserve, either of which provides a guarded prognosis to those undergoing ovarian stimulation.

Older recipients, especially those more than 48 years of age, should undergo a thorough medical evaluation prior to undertaking an embryo transfer. Specific morbidities to exclude relate to the cardiovascular system, and it is recommended that these patients be evaluated prior to conception by a perinatalogist as well, perhaps, as a cardiologist [11]. Currently, according to the ASRM, women 54 years or older at the time of delivery should reconsider being a recipient as the incidence of a catastrophic event during pregnancy (i.e., myocardial infarction, stroke, renal failure, or death) approximates 10 % [12].

Women with premature ovarian failure should be evaluated for autoimmune disorders as well as genetic screens for Turner Syndrome and Fragile X [13]. Patients with Turner syndrome have an increased risk of sudden death during pregnancy secondary to aortic aneurysm rupture. Even if an echocardiogram or cardiac MRI evaluation of the aorta is normal, Turner syndrome patients need to be closely monitored throughout pregnancy as case reports suggest an increased risk of aortic root dissection and rupture even following normal antenatal testing. If a structural abnormality is imaged and discovered during antenatal testing, patients should be dissuaded from attempting pregnancy.

Embryo Donation: Special Considerations

A 2009 study concluded that embryo donation is approximately twice as cost-effective as oocyte donation in terms of cost per live birth [8]. According to the authors, if a couple embarks on a strategy of up to three cycles with donated embryos until one live delivery is achieved, they can expect a cost per live delivery less than half of the expense incurred by a couple who begins with a fresh embryo made from a donated oocyte followed by two frozen cycles ($22,000 per live delivery for embryo donation compared to $41,000 for oocyte donation). Thus, using a donated embryo might be an attractive option for couples with limited finances [8].

Factors other than finances often influence reproductive choices. Autologous IVF is not possible for some couples because the female partner may not be able to produce viable oocytes. Furthermore, a couple whose male partner produces no viable sperm cannot do either autologous IVF or egg donation unless donor sperm is used. An advantage of embryo donation for some couples is that they may prefer to have a child genetically unrelated to either of them rather than to just one parent. Yet, other couples may believe that human life begins at conception and may envision using a donated embryo as a means of "saving" that life, whereas egg donation may be viewed as the creation of a life outside the marriage bond. Regardless of the reason for choosing egg or embryo donation, the pregnancy rate from a donated embryo is not as high as that with oocyte donation given that embryos were cryopreserved and generated from infertile couples in which the age of the infertile donating female usually exceeds the typical age of an egg donor.

Conclusions

Over the years, egg and embryo donation has evolved alongside conventional fertility care and provides a means for establishing a family in recipients with a guarded prognosis for pregnancy success using their autologous eggs. Egg donation is one of the most successful of treatment modalities available for these high-risk

individuals, and it is associated with similar pregnancy rates to those observed in younger women undertaking conventional assisted reproduction. For this reason, egg donation remains the treatment of choice for older women and younger patients with ovarian failure.

Embryo donation provides another, less costly, means of establishing a family. However, success rates using this approach tend to be less than rates associated with donated eggs, as donated embryos are usually derived from older couples with a history of infertility. Perinatal outcomes in children born from either approach have been favorable and reassuring; however, obstetrical risks and complications in older recipients are significantly increased. Practice guidelines for the safe and ethical use of donated eggs and embryos have been published by both ASRM and ESHRE and should be adhered to in order to optimize outcomes of recipients while minimizing the risks to donors.

Editor's Commentary

Much has changed since egg and embryo donation was first introduced in 1983. Originally the method was reserved for women with premature menopause or women with surgically inaccessible ovaries (remember in those years IVF was a surgical procedure!) Today, donor gametes and embryos are used to treat just about any condition known to cause infertility, and contemporaneous use most often relates to addressing infertility in women who simply have outlived their aging ovaries. I have even successfully treated younger patients with unexplained infertility who for perplexing reasons cannot conceive despite heroic efforts at ART and who then finally turn to egg or embryo donation before either giving up or adopting.

The method has performed well over three decades of application and has certainly survived the test of time. It is probably fair to say that anyone with a reasonably normal uterus, and who enjoys health satisfactory enough to survive a 9-month pregnancy, is a candidate for treatment. Unfortunately, a common limiting factor to ultimately attaining pregnancy success may actually be financial, not biological, for women that are interested in pursuing treatment.

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Success and Anticipated Pregnancy Outcomes for Oocyte and Embryo Donation

3

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Key Points

- Women of advanced reproductive age have decreased fertility potential and have their greatest chance of achieving a successful pregnancy through oocyte donation.
- There are mixed findings as to whether or not age impacts upon uterine receptivity and pregnancy rates in recipients of donor eggs, although it appears that if age plays a role, it is a relatively minor one.
- Embryo quality in egg donation cycles affects pregnancy outcome, and as the quality of embryo grade diminishes, so does implantation and live birth rates.
- Donor egg IVF is associated with a higher percentage of multiple gestations than standard IVF, with nearly 10 % of births being triplets in several series reports.

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Almost three decades ago, oocyte and embryo donation became an option for women who had experienced unsuccessful fertility treatments or were not candidates for other assisted reproductive technologies. Women with surgical or natural menopause, diminished ovarian reserve, premature ovarian failure, recurrent pregnancy loss, poor ovarian response to stimulation, or carriers of an inheritable disorder were provided with a new option for fertility [1]. Women that were previously considered sterile were now able to have successful pregnancy and childbirth.

What originated in the cattle breeding industry years prior was introduced to human patients in 1983 [2]. Originally, the technique relied on embryo transfer after uterine lavage of the donor. The naturally cycling donor underwent intrauterine insemination from the partner of the recipient. After fertilization, the uterus was irrigated with the intent to capture embryos that had not implanted. The embryos would then be replaced into the recipient's uterus [2]. Buster et al. reported the first successful live birth using the uterine lavage technique [3]. The initial attempts were completed on recipients that still had normal menstrual cycles, therefore not requiring additional hormones.

Trounson et al. reported the first human pregnancy achieved from oocyte donation as currently performed. Rather than undergoing uterine lavage, the donor underwent oocyte retrieval followed by in vitro fertilization with the recipient partner's sperm [4]. The resulting embryo was then transferred to the recipient. Although the

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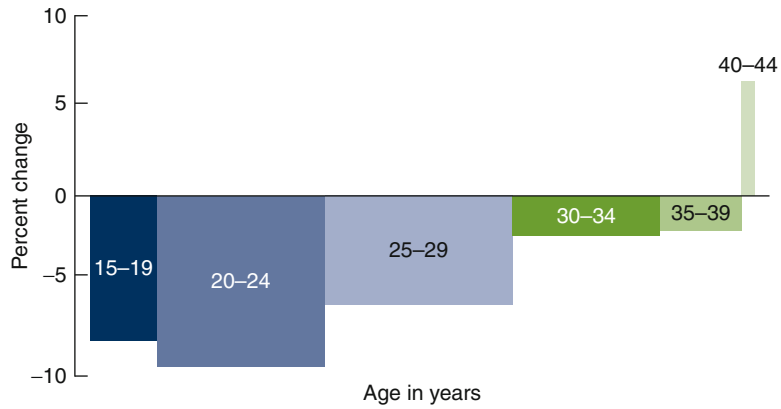

Fig. 3.1 Percent change in birth rates by selected age of mother: United States, 2007–2009. Notes: The area of each column represents the group's contribution to the overall change. Column width is proportional to the number of births in 2007 in each group. Data for 2009 are preliminary (Source: CDC/NCHS, National Vital Statistics System)

transfer was successful, the pregnancy resulted in a spontaneous abortion [4].

As more results were reported, the use of uterine lavage fell out of favor [2]. Specific concerns for the donor began to arise, including the transmission of sexually transmitted infections and accidental pregnancy. In addition to the risks for the donor, a successful clinical pregnancy rate of less than 5 % per cycle also contributed to the demise of uterine lavage in 1987 [2].

With more experience, physicians became interested in using oocyte and embryo donation in women with diminished reproductive potential. Physicians began to use supplemental hormones to produce a receptive uterine lining for implantation as well as maintain an early pregnancy [2]. In the early 1990s, multiple studies emerged indicating that oocyte donation could be successful in older female patients. Researchers presented clinical pregnancy rates of 18–37 %, significantly greater than would be expected in a woman in her 40s or 50s [2].

Recent studies show even higher clinical pregnancy and live birth rates in recipients of donor oocytes. Precise synchronization of the donor and recipient cycles and improved techniques in oocyte retrieval and in vitro fertilization led to significant advancements in egg donation. The National Vital Statistics Reports from 2009 confirm the increased success and use of oocyte donation in older patients. In 2009, pregnancy rates decreased in every age group (teens, 20–24, 25–29, 30–34, and 35–39 years of age) except in women 40–44 years of age. That category of women reached the highest rate of pregnancy since 1967. Women 45–49 years of age maintained a stable pregnancy rate of 0.7 per 1,000 [5]. Of the older patients that are conceiving at an advanced maternal age, a large majority are nulliparous (Fig. 3.1).

The Society for Assisted Reproductive Technology (SART) reported 9,485 embryo transfers were completed using oocyte donation in 2009. Those embryo transfers resulted in a live birth rate of 55.1 %. Since 2003, the live birth rate from donation has been greater than 50 % [6]. This remarkably high live birth rate makes the use of oocyte donation the most successful assisted reproductive technology available today [7].

In the early twenty-first century, interest increased in embryo donation as well. Political recognition and national publicity encouraged couples that had completed their family building to make decisions about the disposition of their frozen embryos [8]. Couples were encouraged to discard them, donate them to research, or donate them to other infertile couples [8]. Given that embryo donation is not utilized as frequently as oocyte donation, most data on success rates is based on case series. Keenan et al. evaluated data from ten case series reports; they found a clinical pregnancy rate of 44.7 % and a live birth rate of 35.5 % [8]. Although success rates do not appear to be as high as with oocyte donation, there may be specific advantages to embryo donation over oocyte donation, such as decreased cost [8].

In order to maintain such a high level of success for pregnancies secondary to gamete donation,

more recent research has been devoted to determine which factors will improve outcomes. There is a well-known decline in fecundity as women age. This is seen in spontaneous pregnancies as well as with assisted reproductive technologies. A large retrospective study by Schwartz et al. evaluated pregnancy outcomes in women requiring artificial insemination for male factor. Although published almost three decades ago, the results still hold true; women of advanced maternal age have decreased fertility potential and have their greatest chance of a successful pregnancy through oocyte donation [9]. Given the knowledge that women of advanced reproductive age have poor pregnancy outcomes when using autologous gametes, it is not surprising that the age of the donor is the greatest factor impacting successful oocyte donation.

Fewer research articles have been done exclusively on the age of the donor and the likelihood of a successful pregnancy outcome. However, data from autologous in vitro fertilization cycles have consistently shown a decrease in fertility potential starting in the fourth decade. This well-known decline is responsible for the guidelines placed at many donor programs, recommending that ovum donors be under age 35 [2].

Young donors tend to be extremely sensitive to gonadotropin stimulation. There is a natural tendency for the physician and the recipient to expect a large number of oocytes at retrieval, with the expectation that it will increase the chance of success [10]. A study in 2005 by Letterie et al. refuted that belief. They found no differences in fertilization rates or clinical pregnancy rates regardless of the number of oocytes retrieved (4–42) [11]. The only advantage to obtaining a higher number of oocytes at retrieval was the opportunity for cryopreservation of remaining embryos [11].

Within the donor population, there appears to be a subset that is particularly successful. Martin et al. evaluated the reproductive potential of oocytes in "best prognosis donors" (those with at least two retrievals that resulted in live births) to standard donors. The two groups had similar numbers of oocytes retrieved and embryos transferred [10]. The best prognosis donors were noted to have a statistically higher embryo-to-baby and oocyte-to-baby rate. They also noted that the best prognosis donors had a higher live birth rate per oocyte if fewer oocytes were retrieved [10].

With the outcome of the cycle relying heavily on the donor, interest arose regarding what factors unique to the recipient may contribute to the outcome. One of the earliest concerns was that women of advanced reproductive age would not be able to maintain a pregnancy because of aging of the uterus. Early research in rodents suggested that decreased fertility potential was a consequence of the uterus [2]. However, in the early 1990s, when oocyte donation was initiated in women of advanced reproductive age, this same decline in fertility outcome was not seen. Instead, it was noted that older women had pregnancy success rates that paralleled the age of the donor [1]. A 2001 retrospective analysis of a large university-based donor oocyte program confirmed these earlier findings. They obtained donor oocytes from volunteer anonymous donors (18–34 years) and directed donors (19–40 years) and compared clinical pregnancy rate and live birth rate based on recipient age. They failed to show any significant difference in clinical pregnancy rate or live birth rate in recipients ranging from less than 35 years old to those greater than 45 years old. Clinical pregnancy rates ranged from 57 to 63 % and live birth rates ranged from 45 to 53 % in all categories [12].

More recent publications have questioned these findings. Check et al. reported a slight decline in live birth rate per transfer at the age of 50 [13]. They noted a significant decline from 64.3 % down to 34.6 %. This poor outcome was attributed to the recipient, likely secondary to poor uterine receptivity. They postulated that the possible reason for this decline related to either decreased uterine blood flow or increased frequency of uterine leiomyomas with increasing age [13]. An additional study compared 3,089 donor oocyte cycles noting a significantly lower pregnancy rate and higher spontaneous abortion rate in women greater than 45 years of age [14, 15]. The mixed findings on the impact of age and uterine receptivity indicate that recipient age may play a role, although probably a much smaller one than other factors.

Table 3.1 Factors affecting oocyte donation success

Greatest impact	Minimal to no impact
Age of donor	Number of oocytes retrieved
"Best prognosis" donors	"Age" of uterus
"High-quality" embryo	
Endometrial thickness >9 mm	

Hormonal supplementation with estrogen and progesterone is required in non-cycling recipients. Even ovulatory recipients are frequently supplemented with hormones after a period of downregulation in order to synchronize them with the donor. Prior to the retrieval, recipients are typically monitored to confirm adequate endometrial thickness and pattern to support a pregnancy. Clinical pregnancy rates and live birth rates trend toward greater success when the thickness is greater than 9 mm [12]. Although pregnancies were even documented at a thickness of less than 6 mm, there was a lower success rate [12]. The transvaginal ultrasound assessment of the uterine pattern being a triple line, intermediate, or solid in appearance showed no significant difference in pregnancy and live birth rate [12].

The overall quality of the oocyte and eventually the embryo can provide the physician insight into the likelihood of success. A high-quality embryo, those with at least five cells and minimal blastomere fragmentation on day 3, led to the highest clinical pregnancy (63 %), live birth (54 %), and implantation (36 %) rates [12]. As the quality of embryo grade suffered, so did the live birth (8 %) and implantation (10 %) rates [12] (Table 3.1).

Recipients prepared to proceed with donor oocytes must be aware of possible pregnancy complications unique to this assisted reproductive technology. It is well known that pregnant women of advanced maternal age are at an increased risk for adverse outcomes. Women greater than 35 years of age have higher rates of gestational diabetes, gestational hypertension, preeclampsia, placental abnormalities, preterm delivery, and cesarean section [16]. It is clear that women requiring oocyte donation would also be at risk of these complications, mostly given the high proportion of women at advanced maternal age. Current research is attempting to determine if the nature of oocyte donation alone, irrespective of age, places a pregnant recipient at even greater risk of complications.

Early studies reported significant increases in pregnancy complications in recipients. Although lacking appropriate sample sizes and control populations, investigators recognized significant risks that could be attributed to oocyte donation. One of the most consistent findings in the literature is the high rate of multiple gestations [17]. Natural conception of twins occurs in close to 1 % of pregnancies; with assisted reproductive technology, the chance of multiple gestations jumps to close to 30 %. In donor in vitro fertilization cycles, Henne et al. reported an even higher rate of 42 %, with 8.7 % being triplets [17]. The presence of multiple gestations can be a significant contributor to pregnancy risk, making it difficult to determine if the donor oocytes are the primary contributor to pregnancy complications. That being said, more recent studies have attempted to reduce confounders, such as multiple gestations, age-related concerns, and in vitro fertilization-related risks, to identify the risks related solely to oocyte donation.

In 2005, Wiggins et al. quoted a significantly elevated risk of gestational hypertension in nulliparous pregnancies achieved with oocyte donation. Although the findings were significant, the control group was 37.7 years of age, 2.2 years younger than the recipient group, allowing for a significant confounding variable [18]. A study that compared age-matched in vitro fertilization groups (mean age 39.8 vs. 40.2), those using autologous cycles to those requiring oocyte donation, found similar results for gestational hypertension [19]. The risk of gestational hypertension was 7 % in autologous cycles, which is consistent with the risk in spontaneous pregnancy, versus 24.7 % in donor oocyte cycles [19].

Although the majority of patients requiring donor oocyte are of advanced reproductive age, there is a small subset of younger recipients. Keegan et al. evaluated gestational hypertension in recipients that were younger than 35 years old compared to age-matched conventional in vitro fertilization controls [20]. The recipients

(mean age 31.7 years) had a reported rate of gestational hypertension of 42 %, compared to 12 % in the control population [20]. The increased risk of gestational hypertension in recipients younger than 35 years of age specifically identifies donor oocytes as a risk factor, without including the confounding variable of advanced maternal age.

Within the spectrum of hypertensive diseases of pregnancy, preeclampsia has also been identified as a risk factor for recipients. Klatsky et al. identified an increased risk of preeclampsia in oocyte recipients, 4.9 % versus 16.9 % [19]. In the general population, preeclampsia occurs in roughly 5 % of pregnancies, which is consistent with the control group [16]. Although the specific etiology of preeclampsia is unknown, there are many factors that have been associated with it. Abnormalities within the vasculature of the placenta leading to hypoperfusion, as well as poor placentation, have been linked to preeclampsia. Immunologic interactions between maternal, paternal, and fetal tissues have also been implicated in the pathogenesis of preeclampsia. Nulliparous, young women with minimal exposure to the male partners' semen have a higher incidence of the disease [19]. The presumed causes of preeclampsia are likely to be similar in patients using donated gametes. Donated oocytes and embryos theoretically would initiate the same immunologic response in the recipient [19].

The trend toward multiple gestations may be responsible for the increased risk of preterm delivery and cesarean section as well. Klatsky et al. noted an increased risk of preterm delivery in oocyte donation cycles, 34 % versus 19 % in autologous in vitro fertilization cycles [19]. Similar findings were noted by Henne et al. When controlling for multiple gestations and maternal age, they identified an odds ratio of 2.69 for preterm labor [17]. Oocyte recipients tended to deliver 2.42 weeks before the control population, and with removal of multiple gestations from the data, the recipients still delivered 1.28 weeks earlier [17].

Although reason for cesarean section has not been documented in data from prior studies, there does appear to be higher risk of cesarean section in recipients [17, 20, 21]. Henne et al. calculated an odds ratio of 4.56 to deliver by cesarean section if a patient used donor oocytes [17]. When they controlled for maternal age, early gestational age, and multiple gestations, they still saw a significantly elevated risk for cesarean section at 61 % [17]. The risk of cesarean section reported in the literature ranges from 30 % to as high as 78 % for recipients of donor oocytes [22].

Contrary to the above findings, Krieg et al. in 2008 did not confirm the elevated risks for recipients during pregnancy. Donor oocyte recipients were compared to age-matched controls undergoing conventional in vitro fertilization. The retrospective study controlled for confounders, such as twin pregnancies, and identified no increased risk of preterm labor, premature rupture of membranes, gestational diabetes, or preeclampsia [21]. The only patients that were noted to have an elevated risk of preeclampsia were those recipients with multiple gestations [21]. Additionally, multiple studies have documented no increased fetal risks. Infants born from donor oocytes did not suffer from an increased risk of intrauterine growth restriction or intrauterine fetal demise [17, 21].

A unique subset of oocyte recipients are perimenopausal and postmenopausal women. A retrospective review by Simchen et al. looked at pregnancy outcomes of women 45–49 years of age versus women greater than 50 [23]. Although the number of women included in the study that were greater than 50 years old was small, there were still significant findings for older recipients. There was a significantly elevated risk of hospitalization during the pregnancy. The most alarming findings looked specifically at the fetal outcomes. They noted a significantly earlier gestational age at delivery as well as significantly lower birth weight in babies born to mothers greater than 50 years of age [23]. A slightly older study by Paulson et al. in 2002 also addressed pregnancy in the sixth decade [24]. In the 77 women observed that were greater than 50 years old (ages 50–63), there was a 54.5 % live birth rate [24]. Those pregnancies were also challenged with multiple pregnancy complications. The cesarean section rate was 78 % for all live births and 68 % for singletons [24]. The older pregnancies were also complicated by an overall preeclampsia rate of

35 %, but it went as high as 60 % in women greater than 55years old [24]. Gestational diabetes was also much more common in the older patients, 20 % [24]. The risk of diabetes did approach 40 % in women that were greater than 55 years old [24]. This trend toward increasing rates of gestational diabetes with increasing age is consistent with earlier research that indicated a rate of 3.7 % in women younger than 20 years old, 7.5 % in women 20–30 years old, and 13.8 % in women older than 30 years old [25].

Many infertility centers worldwide place an age limit on women pursuing oocyte donation; however, there are always exceptions to the rule. To date, the oldest documented mother from oocyte donation gave birth in India at the age of 70. Although she successfully gave birth in 2008, it is reported that she is now very ill [26]. Similar stories are popping up in the media on a regular basis. Although these pregnancies are frequently "newsworthy," the serious complications that can arise in these older recipients are not taken as seriously.

To circumvent these potential complications, multiple programs adopt an aggressive screening program for potential recipients. Women must undergo a physical examination, extensive blood work, glucose screening, electrocardiography, and exercise stress testing [17, 24, 27]. It is advised they have a consultation with a maternal fetal medicine specialist to discuss their increased risks. This is in addition to the psychological and social evaluations required prior to proceeding with gamete donation [27] (Table 3.2).

Table 3.2 Suggested medical screening of oocyte recipients

All recipients	All women over 39 years old
Medical history and physical examination	Electrocardiogram
Complete blood count	Chest x-ray
Serum electrolytes, liver and kidney tests	Mammogram
Thyroid-stimulating hormone	Glucose tolerance test
Rubella	Cholesterol and lipid profile
Hepatitis	
Venereal disease research laboratory	
Human immunodeficiency virus 1/2	
Human T-lymphotropic virus 1/2	
Urinalysis and culture	
Gonorrhea and chlamydia cultures	
Pap smear	
Transvaginal ultrasound	
Uterine cavity evaluation	

From: Sauer and Kavic [27]

The concern over pregnancy complications goes beyond the antepartum and intrapartum period. Psychiatrists and family counselors evaluate donor gamete recipients' ability to cope with the stress and psychological demands of parenting as well as the decision to disclose the method of conception to the offspring. In 2007, a study by Steiner et al. looked specifically at parenting capacity in women older than 50 years of age. They did not find any significant difference in physical or mental ability to parent, nor did they report increased levels of stress in the older donor recipients [28]. There is also evidence that recipients tend to have normal psychiatric profiles and report low levels of distress, emotional lability, anxiety, and depression compared to women who participate in other assisted reproductive technologies [29]. Multiple studies have also evaluated the decision as to whether or not to disclose the donor conception to offspring. In what appears to be a shift in thinking about disclosure, many more gamete donation families are informing their children about their conception. In the early twenty-first century, it was noted that only 5–11 % of offspring were made aware of their genetic origins [30]. More recent data indicates that there is a trend toward earlier disclosure to the offspring. As many as 29–59 % of families plan to tell [31].

The development of oocyte and embryo donation has dramatically changed the way we counsel and treat infertile patients. Women suffering from infertility secondary to menopause, diminished ovarian reserve, or recurrent in vitro fertilization failure now have a viable option to help them fulfill their procreative goals. Although controversy still exists regarding high-risk pregnancy outcomes for recipients of donor oocytes,

the cumulative pregnancy rate of more than 90 % per participating recipient can be quite encouraging to the hopelessly infertile patient [27]. As more and more women delay childbearing, oocyte donation undoubtedly will ultimately be turned to in order to allow many of them to fulfill their desire to have a successful pregnancy.

Editor's Commentary

Pregnancy success rates in recipients of donor eggs have been astonishingly good since the method was first introduced as a treatment for infertility. Progressive improvements in the methodology of ART have translated to greater pregnancy success in DIVF as well, with birth rates that rivaled or surpassed those noted in young women undergoing conventional IVF. Decade after decade, births per embryo transfer continued to increase, 25 % in the 1980s, 30–40 % in the 1990s, and greater than 50 % since 2000. Most impressive was the fact that success was being obtained in women who would have essentially no chance of pregnancy if relying upon their own eggs to conceive, with or without IVF, and who are often at very advanced maternal age.

Lynn Westphal, M.D., notes that although success rates are high and outcomes are generally favorable, the number of multiple gestations following oocyte donation remains unacceptably high. This is clearly an iatrogenic complication that could be dramatically reduced by a policy of transferring fewer embryos. With the evolution of laboratory science, which now allows for reliable extended culture of embryos to the blastocyst stage of development, and cryogenics that permit the safe freezing of supernumerary embryos, it is prudent to strongly consider the transfer of a single well-selected embryo in order to address this problem directly. Although many patients seem to desire twins, the goal of all practitioners must remain focused on the delivery of a healthy baby at term, one at a time.

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Selecting and Screening Donors

4

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Key Points

- Screening of egg donors is an intricate and multifaceted process that includes obtaining informed consent; securing a detailed medical, genetic, psychosocial, and reproductive history; performing a thorough physical examination; and testing for specific infectious diseases.
- Screening criteria proposed by ASRM recommends that all donors should be in excellent health and without history of hereditary or communicable diseases.
- The FDA requires a full historical assessment of potential infectious disease risk factors as well as the performance of specific tests utilizing nucleic acid testing (NAT) for HIV and hepatitis C within 30 days of egg harvest.
- Anti-Müllerian hormone (AMH) represents an accurate serum marker for ovarian responsiveness to ovarian stimulation and is a useful adjunctive measure in predicting both poor response and hyperresponse in oocyte donors.

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Oocyte donation was originally established in 1983 as a treatment option for younger women with premature ovarian failure and for women with severe pelvic disease whose ovaries, as a result, were surgically inaccessible [1, 2]. The indications for donor oocyte in vitro fertilization (IVF) have now expanded to include not only women with hypergonadotropic hypogonadism but also those with advanced reproductive age, diminished ovarian reserve, significant genetic disease risk, poor oocyte or embryo quality, or multiple failures in prior attempts to conceive using conventional assisted reproductive technology (ART). Oocyte donation has also been recently used as an important source of material to promote the study of stem cell research [3].

In these first cases of donation, gametes were obtained primarily from women already undergoing

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Table 4.1 Summary of institutional guidelines for laboratory testing of oocyte donors

	FDA [8]	ASRM [7]	NYSDH[a]
ABO and Rh type		X	X
HIV-1 and HIV-2	X	X	X
Hepatitis B core antibody	X	X	
Hepatitis B surface antigen	X	X	X
Hepatitis C antibody	X	X	X
Human T-lymphotropic virus (type 1)			X
Syphilis	X	X	X
Chlamydia	X	X	X
Gonorrhea	X	X	X
West Nile virus		X	

FDA US Food and Drug Administration, *ASRM* American Society for Reproductive Medicine, *NYSDH* New York State Department of Health

[a]Reproductive Tissue Banks. Part 52 of Title 10 (health) of the official compilation of codes, rules and regulations of the state of New York 2007; Subpart 52–8:64–74

IVF who had excess oocytes at the time of retrieval [1]. Today, most egg donors are not currently pursing infertility treatment themselves but are willing to donate their gametes for altruistic or commercial reasons. Since its initiation, oocyte donation services have spread throughout the USA and to many areas of the world. In the USA, 9,000–10,000 donor oocyte cycles occur annually [4]. Though donor oocyte IVF is available throughout the USA, globally the practice of oocyte donation varies due to legal restrictions in many countries (Chap. 30).

The compensation and recruitment practices for oocyte donors vary worldwide and largely depend upon current legal or cultural practices in that locale. For instance, countries, such as the UK and Canada, have strict restrictions on donor compensation, while others, such as Italy and Germany, prohibit compensation [5]. Donor compensation guidelines do not exist in the USA, and regional differences in compensation do occur [6, 7]. In the USA, donors are recruited mainly through the Internet, television, radio, and newspaper advertisements. Donors are "matched" to recipient couples often based on educational credentials, extracurricular activities, phenotypic traits, and ethnic origins. Though providing recipients with the choice of egg donors who exhibit these traits and qualities is important, the selection and screening process is much more comprehensive in order to ensure the safety and health of the donor, recipient, and the offspring.

Screening Oocyte Donors

Screening women interested in becoming oocyte donors is an intricate and multifaceted process that includes obtaining informed consent, taking a thorough medical history, performing a complete medical examination, testing for infectious diseases, providing a genetic screen, and evaluating the donor psychologically. Ideally, programs want to secure the services of women who are in good health without any past history of risky behavior or familial diseases. The screening process has evolved since the introduction of oocyte donation with recommendations and evidence provided by the American Society for Reproductive Medicine (ASRM), the US Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), and state health departments (Table 4.1) [8, 9]. The FDA finalized the donor eligibility and the good tissue practice rules to ensure public safety through proper screening for risk factors and testing of donors for pertinent transmissible diseases [9].

Before putting potential oocyte donors through the screening process, it should be determined whether they meet the initial requirements for donor selection. In general, donors should be healthy without a history of hereditary disease. Donors are recommended to be between ages 21 and 34 years of age according to the 2008 ASRM screening guidelines [8]. Using donors less than 21 years of age should be determined on an individual basis

after a thorough psychological evaluation by a qualified mental health professional [8]. The use of donors over age 34 requires a discussion of the risk of aneuploidy and lower pregnancy rates associated with older women [10–12]. Those individuals with employment ties to or financial interests in a donor oocyte program or recruiting agency should not be used as oocyte donors due to the obvious conflict of interest.

Informed Consent

Prior to participating in oocyte donation, the potential legal, medical, and psychosocial issues involved in the process should be discussed with the donor while obtaining informed consent. Legal issues include but are not limited to understanding rights to maintain and protect anonymity, discovering outcomes of donation, and whether or not future contact with any resulting children is desired [13]. For example, future anonymity could theoretically be reversed in court situations where the importance of the offspring knowing his/her genetic background is deemed to outweigh the donor's desire for privacy [13]. Arguments in favor of revealing the donor's identity stem from the fact that children born through donated oocytes were not a part of the original decision-making process. Though not yet regularly employed by centers nationally, informed consent should also contain information about the disposition of cryopreserved embryos resulting from oocyte donation, i.e., use for future pregnancies or donation for research [3, 13, 14]. However, these cryopreserved embryos cannot be reclaimed by donors in the future [13]. In summary, the potential donor should consider all legal matters both known and possible during the informed consent process (further discussed under Obligations and Rights).

Detailed medical risks involved with the process of oocyte donation should also be discussed while consenting. Donors need to be aware of the acute risks and adverse effects of ovarian stimulation and oocyte retrieval, including but not limited to ovarian hyperstimulation syndrome (OHSS), intraperitoneal hemorrhage, and pelvic infection (Chap. 19) [15]. There may also be risks associated with the use of anesthesia provided during the oocyte retrieval including allergic reaction to anesthetic drugs and respiratory compromise secondary to aspiration. However, among the young healthy population of donors, this risk is very small [16]. In fact, previous studies have suggested that donors are at lower risk for OHSS and other adverse events than patients undergoing autologous IVF [17]. Programs may wish to provide donors with adequate *supplemental* insurance coverage for medical complications arising from oocyte donation, and the terms of such coverage should be disclosed to the donor (further discussed in Chap. 20).

The potential increased risk of ovarian cancer should also be introduced during the discussion of the possible medical risks from oocyte donation. There have been concerns that controlled ovarian stimulation (COS) might increase the long-term risk of ovarian cancer in women using fertility drugs. Recently published data have not confirmed a cause and effect relationship between the drugs used for COS and ovarian cancer [18]. However, undoubtedly most donors have either heard about the association of fertility drugs and cancer or read that it exists in the popular media or Internet, and therefore, questions regarding the long-term safety of participation should be anticipated.

Unintended pregnancy in donors discontinuing oral contraceptives in order to participate also occurs. Potential donors should be counseled on this possibility and offered options for prevention [8]. Along with the discussion of pregnancy risk during informed consent, it is important to stress the importance of patient compliance with follow-up, use of contraception, and/or abstinence in order to lessen the risk of unplanned pregnancy.

Egg donors should be advised about the emotional and psychosocial consequences of participation. They should understand the potential impact that providing eggs to an infertile woman may have upon their own offspring or future offspring, including whether or not to ever disclose to their own children or spouse the fact that they formerly participated. Although highly unlikely, there are notable concerns that offspring could

potentially marry and procreate with an unrecognized half-sibling [16]. In addition, the donor's present or future spouse or partner may have an interest in the outcome of prior oocyte donation, and disclosure may have a negative effect on their relationship [13].

Defining Obligations, Rights, and Duties

Obligations, rights, and duties of donors should be thoroughly explained prior to participation. For instance, donors may ask about the right to specify the type of recipients that receive their donation, the right to learn about the outcome of their donations, the right to contact any future offspring, and, as discussed previously, their right to anonymity. Each of these obligations must be agreed upon prior to initiating a cycle of treatment.

Entering the oocyte donation process, some donors believe that they may direct their egg donation to include only specific demographics of recipients. Such triage might be based on the age of the recipients, or perhaps their marital status, sexual orientation, health, race, religion, or education. The request of donors to specify to whom their gametes may be given is typically refused by donor programs, except in the obvious cases of designated friends or family members openly participating with known recipients. The choice to not allow anonymous donors to direct the use of their gametes is currently supported by the Ethics Committee of the ASRM [13]. Potential donors should understand that their preferences to donate only to certain types of recipients will likely not be considered in gamete donation. Furthermore, the future use of embryos created by the donated eggs lies with the recipient and cannot be easily predicted or later controlled.

Programs should give consideration to the fact that donors may express an interest in learning the outcome of their donation. Whether or not outcomes will be disclosed should be defined prior to participation. According to current guidelines, programs are not ethically bound to reveal whether or not a pregnancy occurred because the donation is made without regard to the outcome which is consistent with current blood and non-gamete tissue donation practices [13]. Disclosing information about cycle success or failure may at times cause unanticipated emotional distress to donors possibly secondary to the news of offspring or, in cases of failure, cause concern about the donor's own fertility [13]. Some argue that outcomes *should* be disclosed because donors deserve to know whether their gametes resulted in a successful pregnancy. The knowledge of outcomes could be helpful in the event of planned or unplanned contact from the offspring, give donors the opportunity to tell their children about genetic half-siblings, and put psychological closure on their participation in oocyte donation [13]. Some programs allow donors the option of learning whether a child was born, yet there exist few research studies to support disclosure or nondisclosure of pregnancy to determine which approach is preferable.

We believe that donors should be asked and documented as to whether they are willing to have contact with any offspring. Initially, some participants may be content with simply providing their gametes. However, in the future, some donors may have an interest in knowing their offspring. On the other hand, donors have the right of not having potential obligations to offspring imposed on them without their consent [13]. These are strong considerations, and asking them to anticipate their future inclination is complex given that their feelings may and are likely to change considerably during their lifetime.

There may be competing interests between donors, recipients, and subsequent offspring. Disclosing to offspring the donor's genetic history does not necessarily require knowing the actual identity of the donor or meeting her. However, with increasing interest in the issues surrounding future contact between donors and their offspring, there should be some acknowledgement of the potential for new situations and responsibilities to arise concerning participants as regulations and laws change in the future. It has also been suggested that donors and recipient couples may wish to consider executing legal documents that attempt to define or limit the rights and duties of each with regard to any future offspring [13].

The need for compliance with treatment should be stressed to oocyte donors. This will assist in maximizing cycle outcomes and minimizing the potential medical risks. Informed consent requires donors to be forthcoming about their personal medical history and behaviors so that any genetic and/or health issues that affect the well-being of offspring are known in advance [13]. It is the responsibility of the donor to update the donor program with any changes to her health or risk factor status [8]. However, it is less clear about the donor's obligations after donation to keep the program informed of any changes in her health status. Programs may encourage donors to provide updates as they encounter medical conditions that may be pertinent to the offspring's health. Standard operating procedures (SOP) should be in place with regard to medical updates, and programs should clearly convey this to their participating donors and the recipients of donor eggs.

Donors should be assured that their confidentiality will be protected as federal and local state laws permit. The medical records containing the information about their participation will be protected and sustained according to local statutes [8]. The FDA requires that the records of donor screening and testing be maintained for at least 10 years; ASRM actually recommends maintaining a permanent record of each donor's selection process, screening, testing, and follow-up evaluations [8]. These records, including those with clinical outcomes, should be maintained for any potential information sharing in the future with offspring based on future statutes or permission of the donor.

Table 4.2 FDA/ASRM donor history screening guidelines [7]

Medical history
History of hereditary disease
History of hemophilia or other coagulation disorders who have received human-derived clotting factor concentrates
Exposure within the last 12 months to blood known or suspected to be infected with HIV, hepatitis B, and/or hepatitis C virus
Treatment for syphilis, gonorrhea, or chlamydia within last 12 months
Risk for or family history of transmissible spongiform encephalopathy
Recent West Nile viral infection
Acute SARS infection or risk factors for SARS infection
History of xenotransplant or close contact with xenotransplant patient
History of human organ or tissue transplant or human extracts
Recent smallpox vaccination
Social history
Injected drug use for nonmedical reasons in last 5 years
Engagement in casual sexual relations frequently with different partners
Participation in sex in exchange for money or drugs in the last 5 years
History of incarceration in jail for more than 72 h in the last 12 months
Living with another person with viral hepatitis within last 12 months
Acupuncture, body piercing, or tattooing procedures within the last 12 months in which sterile procedures were not or suspected to be not used
Sexual intercourse in the last 12 months with persons with any of the above medical or social history

Past Medical History

When evaluating a potential oocyte donor, a comprehensive review of their past medical history is requisite. According to the recommended screening criteria of the ASRM, the donor should be healthy and give no history to suggest hereditary or communicable disease [8]. The goals of screening are to ensure that the donor is not at risk for suffering an untoward event during the stimulation/retrieval process and to also ensure that the donor is not at risk of transmitting a possible blood-borne pathogen. The ASRM Practice Committee recommendations for screening oocyte donors are not law and are strictly guidelines from the professional organization based on regulation from the FDA. ASRM, in congruence with the FDA, has recommended that donor programs not accept donors, who in the past 5 years, have injected drugs for nonmedical reasons, have received human-derived clotting factor concentrates, or have had sex in exchange for money or drugs (Table 4.2) [8]. Donors, who in the preceding 12 months, have had sex or close contact with any person having HIV

infection including a positive or reactive test to HIV virus, hepatitis B infection, or clinically active (symptomatic) hepatitis C infection; have been incarcerated in a lockup, jail, or prison for more than 72 consecutive hours; had or have been treated for syphilis, gonorrhea, or chlamydia; or have undergone body piercing and/or tattooing procedures in which sterile procedures were not used or it is unclear whether sterile procedures were used, should also be excluded (Table 4.2) [8].

The FDA requires the further assessment of potential risk factors based upon the donor's travel history, given that many individuals may be harboring indolent communicable infections. The criteria clearly recommend rejecting women who spent 3 months or more cumulatively in the UK from the beginning of 1980 through the end of 1996; those who are current or former US military members, civilian military employees, or dependents of a military member or civilian employee who resided at US military bases in Northern Europe (Germany, Belgium, and the Netherlands) for 6 months or more cumulatively from 1980 through 1990, or elsewhere in Europe (Greece, Turkey, Spain, Portugal, and Italy) for 6 months or more cumulatively from 1980 through 1996; those who spent 5 years or more cumulatively in Europe from 1980 until present; those who received any transfusion of blood or blood components in the UK or France between 1980 and the present; those whom sexual partners who were born or lived in certain countries in Africa (Cameroon, Central African Republic, Chad, Congo, Equatorial Guinea, Gabon, Niger, or Nigeria) after 1977; and those who have received a blood transfusion or any medical treatment that involved blood in the countries listed above after 1977 [9].

Interestingly, the FDA makes special note about the importance of including a comprehensive review of symptoms to ensure that no donors are included who are at risk for West Nile virus. Given that the disease can have profound neurologic sequelae, those who are at risk or have symptomatology consistent with an infection are recommended to defer donation for at least 120 days after onset of symptoms or diagnosis, whichever is later [9]. Along the same lines of communicable neurologic disease, the FDA bans women from donating who have been diagnosed with variant Creutzfeldt-Jakob disease (vCJD) or any other form of CJD, diagnosed with dementia or any other degenerative or demyelinating disease of the central nervous system or other neurologic disease of unknown etiology, received a non-synthetic dura mater transplant, human pituitary-derived growth hormone, or have one or more blood relatives diagnosed with CJD. Even those women who have a history of CJD in a blood relative should not be included unless the diagnosis of CJD was subsequently found to be in error, the CJD was iatrogenic, or laboratory testing (gene sequencing) demonstrates that the donor does not have a mutation associated with familial CJD [9].

Lastly, given the potential for infection and transmission of pathogens to patients receiving organ transplants, those women who have received xenotransplants (live cells, tissues, or organs from a nonhuman animal source or human body fluids, cells, tissues, or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or organs), have been in close contact with a xenotransplant recipient, or have received human organ or tissue transplants or treatment with human extracts are not eligible as well [9].

Though not listed in the published guidelines, physicians may also consider other aspects the donor's medical history that could preclude or limit participation in egg donation. Knowledge of current medical conditions, such as polycystic ovarian syndrome, may assist clinicians in selecting appropriate treatment protocols in order to reduce the risk for ovarian hyperstimulation syndrome. Donors with a history of obesity, endometriosis, or pelvic surgery will alert clinicians to possible diminished ovarian reserve or difficulty with ovarian access during retrieval. Finally, clinicians may consider assessing the donor's family history for other inheritable traits and diseases, such as color blindness, diabetes, or premature ovarian failure.

Physical Exam

The screening of oocyte donors must include a thorough and focused physical exam. When performing the physical exam, the ASRM has outlined

Table 4.3 ASRM recommended components of the oocyte donor's physical exam [7]

Physical evidence for risk of sexually transmitted disease such as genital ulcerative lesions, herpes simplex, chancroid, and urethral discharge
Physical evidence for risk of or evidence of syphilis
Physical evidence of anal intercourse including perianal condylomata
Physical evidence of nonmedical percutaneous drug use such as needle tracks; the examination should include examination of tattoos, which might be covering needle tracks
Physical evidence of recent tattooing, ear piercing, or body piercing
Disseminated lymphadenopathy
Unexplained oral thrush
Blue or purple spots consistent with Kaposi sarcoma
Unexplained jaundice, hepatomegaly, or icterus
Large scab consistent with recent history of smallpox immunization
Eczema vaccinatum, generalized vesicular rash, severely necrotic lesion (consistent with vaccinia necrosum), or corneal scarring (consistent with vaccinial keratitis)

the requisite components (Table 4.3) focused on assessing the donor's general health and potential for harboring an infection that may be transmitted to a recipient. As discussed previously, the donor should also be evaluated for pelvic findings that might complicate the treatment (i.e., polycystic appearing ovaries, endometriosis, and pelvic disease) with a transvaginal ultrasound.

Laboratory Testing

Infectious Disease

A thorough medical history, as discussed previously, is important in determining individuals at high risk for infection. The testing for infection among potential donors has been regulated by the FDA and American Association of Tissue Banks (Table 4.4). Testing should be performed within 30 days prior to oocyte collection, and abnormal results need to be verified prior to disclosure to the donor [8]. During disclosure, centers should have options for counseling and medical referral if needed. Any positive screening tests will exclude potential donors from anonymous donation except for a history of treated Neisseria gonorrhoeae and Chlamydia trachomatis infections [8]. Oocyte donation should be deferred for 12 months after a negative test of cure for donors who have a history of these specific infections [8]. However, due to the increased risk of infertility in these women, in general, participation should be discouraged.

In the event that a concern for donor infection arises during a treatment cycle, recipients should be offered the option of embryo cryopreservation and quarantine for 180 days until the donor is tested and confirmed negative for infection [8]. In such rare events, the program should also properly counsel recipients about their frozen embryo transfer (FET) pregnancy rates and the chance of seroconversion of the donor after cryopreservation of embryos in order for the recipients to make appropriate decisions regarding pursuit of FET.

Non-anonymous donors undergo the same testing as anonymous donors. However, known donors who test positive are not automatically excluded from oocyte donation according to the current FDA guidelines as long as the physician is aware of the results [9]. Though the FDA does not require disclosure of positive test results, ASRM recommends informing and properly counseling recipient couples prior to use of oocytes [8].

There are no formal recommendations for testing of the male partners of recipients, but a few tests may be considered. These include semen analysis, blood type, Rh factor, infectious disease blood work, and genetic screening depending on the male partner's ethnic background [8].

HIV

Centers should test for the HIV-1 and HIV-2 antibodies with enzyme immunoassay (EIA) techniques

Table 4.4 FDA-approved infectious disease laboratory tests [8]

	Source	Test
HIV	Serum	EIA HIV-1 and HIV-2 antibodies NAT test for HIV-1
Hepatitis B	Serum	Hepatitis B surface antigen EIA hepatitis B core antibodies (IgG and IgM)
Hepatitis C	Serum	EIA hepatitis C antibody NAT for HCV
Syphilis	Serum	Nontreponemal (initial): RPR, VDRL, automated reagin test Treponemal (confirmatory): FTA, TP-PA, TPI, or EIA for specific antibodies to *T. pallidum*
Neisseria gonorrhoeae	Cervix, vagina, and urine	Culture NAT
Chlamydia Trachomatis	Cervix, vagina, urethral meatus, and urine	Culture NAT

EIA enzyme immunoassay, *NAT* nucleic acid testing, *TP-PA T. pallidum* particle agglutination, *TPI T. pallidum* immobilization test

and utilize the nucleic acid testing (NAT) for viral particles. The FDA requires the use of nucleic acid tests because of the ability to detect infection at a significantly earlier stage than traditionally used antibody or antigen testing [9, 19]. There are tests currently available that are also sensitive for the detection of HIV group O antibodies. Centers that do not have access to the FDA-licensed test for the group O antibodies should evaluate donors for risks associated with HIV group O infection [9]. Participants that may be at risk include those who were born, lived in, or received blood transfusion or any medical treatment in Cameroon, Central African Republic, Chad, Congo, Equatorial Guinea, Gabon, Niger, or Nigeria after 1977 [8].

Hepatitis

Serologic testing for hepatitis B infection utilizes EIA for the detection of antigens and antibodies, specifically the hepatitis B surface antigen and hepatitis B core antibodies (IgG and IgM) [8, 20]. These tests will reveal any infected donors and further distinguish between acute or chronic hepatitis. Though the majority of adults infected with the virus experience recovery, 1–5 % of immunocompetent adults are at risk for chronic hepatitis and thus cirrhosis and hepatocellular carcinoma [21]. Viral infection acquired during childhood or the perinatal period has a risk of persistent infection ranging from 20 to 90 % [21]. Women infected with hepatitis B infection should be excluded from egg donation and given appropriate recommendations for follow-up with a primary care physician or infectious disease specialist. Many donors may have received hepatitis B vaccination in childhood or adolescence. In these instances, past immunization may be confirmed by testing the serum for hepatitis B surface antibody [20].

Like hepatitis B, chronic hepatitis C infection has the similar sequelae of cirrhosis and hepatocellular carcinoma, and up to three quarters of infected persons are unaware of their infection status [22]. Testing for hepatitis C among donors requires serologic EIA testing for the hepatitis C antibody and NAT for viral particles [8].

Syphilis

Serologic testing for syphilis is recommended by the FDA for screening and diagnosis because the bacterial source, *Treponema pallidum*, cannot be cultured [8, 23]. Serologic testing of donors initially involves the nontreponemal assays, such as rapid plasma regain (RPR) and venereal disease research laboratory (VDRL) [8]. These assays detect antibodies for phospholipids which are present not only on *T. pallidum* but also occur in autoimmune or inflammatory conditions [24]. Positive nontreponemal assays should be confirmed

with FDA-approved treponemal-based assays, such as fluorescent treponemal antibody (FTA), *T. pallidum* particle agglutination (TP-PA), or EIA for specific antibodies to *T. pallidum* [8]. Unlike nontreponemal assays, treponemal-based assays remain positive for years after treatment and infection [25]. Donors may be eligible for oocyte donation if the treponemal-based assays are negative.

Neisseria Gonorrhoeae and Chlamydia Trachomatis

Testing for these two sexually transmitted infections involves cervical cultures or nucleic acid amplification tests [8]. Samples may be taken from urine or a swab from the cervix, urethral meatus, or vagina [8]. As discussed previously, egg donors with a history of these infections should generally be discouraged from donation.

Blood Type

Testing potential donors for blood type and Rh factor is not considered mandatory by the FDA or ASRM. It may be recommended to ensure compatibility with the maternal genotype. The potential for Rh incompatibility and the obstetric implications (e.g., hemolytic disease of the fetus, hydrops fetalis, and intrauterine fetal demise) should be divulged to recipients.

Genetics

The minimum genetic screening for oocyte donors involves ruling out any history of Mendelian disorders, such as autosomal dominant disorders, X-linked disorders, and autosomal recessive inheritance. If donors are from certain ethnic backgrounds that are high risk for genetic disorders, they should be tested for their carrier status. For example, patients of African or Mediterranean descent should have cell blood counts and hemoglobin electrophoresis to assess any risk for sickle cell anemia or beta-thalassemia among future offspring [26]. Those individuals with Southeast Asia ancestry are at high risk for alpha-thalassemia and should be screened with DNA-based testing as they may have normal hemoglobin electrophoreses [27, 28]. Donors of Askenazi jewish descent should be screened for Tay-Sachs disease, Gaucher disease, Fragile X syndrome, Fanconi anemia, Canavan disease, Niemann-Pick type A, Bloom syndrome, maple syrup disease, glycogen storage syndromes, familial dysautonomia, and mucolipidosis type IV [17, 29].

We believe that all ethnicities should be screened for cystic fibrosis and spinal muscular atrophy (SMA) due to its relatively high carrier rate prevalence. The carrier frequency of cystic fibrosis among the Caucasian, Hispanic, and African American populations is 1 in 25, 1 in 46, and 1 in 65, respectively [30]. The carrier risk of SMA is 1 in 47 among the Caucasian population and 1 in 67 among the Ashkenazi Jewish population [31]. Among the Asian, African American, and Hispanic populations, the carrier risk is 1 in 59, 1 in 72, and 1 in 68, respectively [31].

Donors heterozygous for autosomal recessive disorders need not always be excluded, but screening requires testing of the carrier status of the recipient's partner. It is also important to ascertain a history of major malformations of multifactorial or polygenic etiology that are associated with any serious functional or cosmetic handicap (e.g., cardiac and uterine malformations). Donors are excluded if they have any known karyotypic abnormality or any significant familial disease with a major genetic component among first-degree relatives (e.g., BRCA-positive breast cancer) [8].

Routine karyotyping and testing for Tay-Sachs or Fragile X is not currently recommended by ASRM for donor genetic screening but may also be considered. A recent retrospective study compared the ASRM screening guidelines with enhanced universal screening, which included Tay-Sachs, Fragile X, and karyotype analysis [32]. Over a 12-year period, investigators found an additional 25 candidate exclusions with enhanced universal screening of 1,300 potential donors, making up 19 % of all genetic exclusions [32]. Although karyotyping is not customarily recommended in the USA, it is part of donor screening in some European countries. An IVF center in Valencia, Spain, which regularly analyzes the karyotypes potential donors, found that 1.4 % of

karyotypes were abnormal over a 10-year period [33]. At this time, enhanced genetic screening does not fall under current ASRM guidelines; however, Counsyl Medical Genomics offers a comprehensive panel of more than 100 recessive single gene disorders that would broadly expand surveillance (Table 4.5) [34]. However, until there is more research into the cost-effectiveness of testing and how best to advise patients of the many results, it cannot be routinely recommended.

Ovarian Reserve

Restricting the age of potential donors is important in maintaining a successful program, and retrieving a good number of oocytes is central to successful pregnancy outcomes. Selecting an optimal donor and predicting ovarian response based solely upon age are limited by individual variation in response to ovarian stimulation. In conjunction with age, ovarian reserve testing among prospective donors is useful in assessing the donor's ovarian reserve status, predicting ovarian response and assessing risk for OHSS.

Anti-Müllerian hormone (AMH) represents an accurate marker of ovarian response to gonadotropin stimulation in IVF cycles. Several studies have suggested that AMH accurately predicts poor ovarian response [35, 36]. Our center found significant correlations between AMH and the number of oocytes retrieved and estradiol levels among oocyte donors (Table 4.6) [37]. AMH may be useful in predicting IVF cycle outcomes and helpful in individualizing dosing protocols [37]; however, further studies are needed.

Investigators have also suggested that antral-follicle count (AFC) could be used similarly to predict oocyte donor response to controlled ovarian hyperstimulation [38]. Follicle-stimulating hormone (FSH) in conjunction with estradiol has been used for assessment of ovarian reserve; however, they have not been found to reliably predict ovarian reserve in young patients [39]. Premature diminished ovarian reserve would be important to ascertain early in the donor screening process not only for the effect on oocyte yield but also for the knowledge of the donor.

The use of CGG triple nucleotide repeats on the Fragile X (*FMR1)* gene has also been suggested as an addition to future ovarian reserve testing among oocyte donors given its association with premature ovarian failure [40]. One pilot study suggested that FMR1 gene testing in conjunction with age-specific AMH may be a useful adjunct measure [41].

Cervical Dysplasia

Prospective donors should undergo screening for cervical dysplasia in accordance to current recommendations by the American Society for Colposcopy and Cervical Pathology (ASSCP). At presentation to our center, donors should have record of a normal PAP smear within the past 3 years. Abnormal cytology or pathology should be referred for appropriate treatment according to current guidelines prior to participating.

Toxicology

Information regarding current and past drug and/or alcohol abuse can be obtained during the donor evaluation of past medical and psychosocial history; therefore, many programs do not routinely perform urine drug screening of donors. Over a 4-year period of universal drug screening, one center found positive urine toxicology in 7 % of their donor population who initially denied current drug use [42]. Though toxicology testing is not routinely performed, centers may wish to consider testing potential donors with a worrisome past medical or psychosocial history. We routinely test all of our donors, and from 2004 to 2010, we found 3 % of women screened to have positive urine toxicology [43]. Our center uses the Quest Diagnostics ten drug urine toxicology panel (Table 4.7).

Psychological Screening

ASRM currently recommends psychological and social assessment of oocyte donors by a qualified mental health professional [8]. Typically, these

Table 4.5 Counsyl genetic panel of recessive single gene disorders

ABCC8-related hyperinsulinism	Cohen syndrome	Hereditary fructose intolerance	Muscle-eye-brain disease	Smith-Lemli-Opitz syndrome
Achromatopsia	Congenital disorder of glycosylation type Ia	Hereditary thymine-uraciluria	NEB-related nemaline myopathy	Spinal muscular atrophy
Alkaptonuria	Congenital disorder of glycosylation type Ib	Herlitz junctional epidermolysis bullosa, LAMA3-related	Niemann-Pick disease type c	Steroid-resistant nephrotic syndrome
Alpha-1 antitrypsin deficiency	Congenital Finnish nephrosis	Herlitz junctional epidermolysis bullosa, LAMB3-related	Niemann-Pick disease, SMPD1-associated	Sulfate transporter-related osteochondrodysplasia
Alpha-mannosidosis	Costeff optic atrophy syndrome	Herlitz junctional epidermolysis bullosa, LAMC2-related	Nijmegen breakage syndrome	Tay-Sachs disease
Andermann syndrome	Cystic fibrosis	Hexosaminidase A deficiency	Northern epilepsy	TPP1-related neuronal ceroid lipofuscinosis
ARSACS	Cystinosis	HFE-associated hereditary hemochromatosis	Pendred syndrome	Tyrosinemia type I
Aspartylglycosaminuria	D-bifunctional protein deficiency	Homocystinuria caused by cystathionine beta-synthase deficiency	PEX1-related Zellweger syndrome spectrum	Usher syndrome type 1F
Ataxia with vitamin E deficiency	Factor V Leiden thrombophilia	Hurler syndrome	Phenylalanine hydroxylase deficiency	Usher syndrome type 3
Ataxia-telangiectasia	Factor XI deficiency	Hypophosphatasia, autosomal recessive	Pompe disease	Very long-chain acyl-coA dehydrogenase deficiency
Autosomal recessive polycystic kidney disease	Familial dysautonomia	Inclusion body myopathy 2	PPT1-related neuronal ceroid lipofuscinosis	Wilson disease
Bardet-Biedl syndrome, BBS1-related	Familial Mediterranean fever	Isovaleric acidemia	Primary carnitine deficiency	X-linked juvenile retinoschisis
Bardet-Biedl syndrome, BBS10-related	Fanconi anemia type C	Joubert syndrome 2	Primary hyperoxaluria type 1	
Beta-thalassemia	Fragile X syndrome	Krabbe disease	Primary hyperoxaluria type 2	
Biotinidase deficiency	Galactosemia	Limb-girdle muscular dystrophy type 2d	PROP1-related combined pituitary hormone deficiency	
Bloom syndrome	Gaucher disease	Limb-girdle muscular dystrophy type 2e	Prothrombin thrombophilia	
Canavan disease	GJB2-related DFNB 1 nonsyndromic hearing loss and deafness	Lipoamide dehydrogenase deficiency	Pseudocholinesterase deficiency	

(continued)

Table 4.5 (continued)

ABCC8-related hyperinsulinism	Cohen syndrome	Hereditary fructose intolerance	Muscle-eye-brain disease	Smith-Lemli-Opitz syndrome
Carnitine palmitoyltransferase IA deficiency	Glucose-6-phosphate dehydrogenase deficiency	Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency	Pycnodysostosis	
Carnitine palmitoyltransferase II deficiency	Glutaric acidemia type 1	Maple syrup urine disease type 1B	Rhizomelic chondrodysplasia punctata type 1	
Cartilage-hair hypoplasia	Glycogen storage disease type Ia	Medium-chain acyl-CoA dehydrogenase deficiency	Salla disease	
Choroideremia	Glycogen storage disease type Ib	Megalencephalic leukoencephal-opathy with subcortical cysts	Segawa syndrome	
Citrullinemia type 1	Glycogen storage disease type III	Metachromatic Leukodystrophy	Short-chain acyl-CoA Dehydrogenase deficiency	
CLN3-related neuronal ceroid lipofuscinosis	Glycogen storage disease type V	MTHFR deficiency	Sickle cell disease	
CLN5-related neuronal ceroid lipofuscinosis	GRACILE syndrome	Mucolipidosis IV	Sjogren-Larsson syndrome	

https://www.counsyl.com/diseases/

Table 4.6 Association of AMH to donor and outcome parameters [34]

	Donor age	Donor BMI	Peak estradiol	Total oocytes	Total gonadotropin dose
r (Pearson)	−0.042	−0.158	0.235	0.232	−0.35
P-value	NS	NS	0.024	0.024	0.05

BMI body mass index, *NS* not statistically significant

Table 4.7 Quest diagnostics urine toxicology screen

Amphetamines
Benzodiazepines
THC (marijuana)
Cocaine
Methadone
Methaqualone (Quaaludes)
Opiates
Phencyclidine (PCP/angel dust)
Barbiturates
Propoxyphene (Darvon)

EMIT enzyme multiplied immunoassay technique

are psychologists, psychiatrists, or social workers familiar with issues pertaining to gamete donation. The medical health professional collects a thorough psychosocial history that includes family history, educational background, assessment of emotional stability, motivation to donate, current life stressors and coping skills, difficult or traumatic reproductive history, interpersonal relationships, sexual history, travel history, history of major psychiatric and personality disorders, substance abuse in donor or first-degree relatives, legal history, and history abuse or neglect [8]. Presence of significant psychopathology, positive family history of heritable psychiatric disorders, substance abuse, two or more first-degree relatives with substance abuse, current use of psychoactive medications, history of sexual or physical abuse without professional treatment, excessive stress, marital instability, impaired cognitive functioning, mental incompetence, and high-risk sexual practices may warrant exclusion of the prospective donor [8]. Ineligible donors should be explained the reasons for their exclusion with appropriate referral as needed [8].

In the case of a known donor, complete psychosocial evaluation and counseling is strongly recommended for both the donor and the recipients in order to fully assess the potential impact of donation, pregnancy, and even treatment failure on their future relationship. Evaluation needs to rule out any undue financial or emotional coercion or enticement [8]. Programs should confirm that the donor maintains autonomy in her decision to participate and understands the potential effects on her relationships with the recipients and other family members if she withdraws or continues to participate [44].

The details of the psychological evaluation are not specifically defined and vary between centers. As a result the Mental Health Professional Group created guidelines for psychological testing of prospective oocyte donors. The Minnesota Multiphasic Personality Inventory (MMPI) has been traditionally used to evaluate oocyte donors in order to differentiate healthy individuals from those predisposed to psychiatric disorders [45]. The second edition of this test, MMPI-2, has been shown to distinguish between those individuals who answer truthfully and those who try to underplay any psychopathologic behavior. Prior studies have found differences in MMPI-2 scores between donors who completed a donation cycle and those who were psychologically excluded, but were not able to reliably differentiate those accepted who would subsequently be noncompliant [46, 47]. ASRM guidelines do not currently require psychological testing with MMPI-2, but centers often use this evaluation in addition to their current psychological screening methods to assess potential oocyte donors.

Summary

Screening and selection of egg donors is a comprehensive process in order to help protect the safety and health of donors, recipients, and future offspring. For potential donors, it is a stepwise

sequence of events beginning with the review possible risks associated with treatment. Once an egg donor consents, after understanding the risks and their rights, duties, and obligations, the process of donor screening and selection belongs to the egg donor program under the guidance and recommendations of the FDA, ASRM, and local state health departments. Obtaining a thorough medical history, performing a complete physical exam, infectious disease testing, genetic screening, and psychosocial evaluation require a dedicated, organized, and thorough multidisciplinary team of reproductive endocrinologists, nurses, mental health professionals, and social workers. As further research develops regarding the screening and selection process, there will likely be further changes of the guidelines discussed in this chapter, and it will be prudent to have a multidisciplinary team to help make adjustments to these changes an ongoing and efficient process. For now, following the current recommendations and guidelines will assist programs in the appropriate selection of oocyte donors and maximize the chances for a successful pregnancy in recipients.

Editor's Commentary

The participation of young healthy women as egg donors has engendered more controversy and public scrutiny than perhaps any other aspect of egg donation. It has been attacked from the beginning by critics of the method as a dangerous, exploitive, unprofessional, and sexist practice, and yet it endures. To combat such ferocious criticism, it is imperative that practitioners of egg donation pay careful attention to every aspect of donor recruitment and participation. Responsible practice fosters good outcomes and continued success. There will always be a great amount of pressure to either supply donors or accept donors that may be less than ideal (e.g., PCOS, hypothalamic amenorrhea), but doctors need and must be able to say no when faced with choices that pose undue risk to all participating.

For the first decade of practice, the model for screening donors was essentially lifted from the manner in which men were screened prior to donating sperm. However, sperm and egg donation shares little in common with respect to time involvement and risk of participation, and therefore the need for more specific and detailed professional guidelines and safety measures was necessary to protect the women donating eggs, the women receiving them, and most importantly the child that results from their collaborative efforts. Dr. Thornton reviews the important basic requirements for establishing an egg donor program. Many of these professional activities are now being provided by "agencies," which are typically not run by physicians, who then supply patients or programs with "matches." Regardless of whether an agency supplies the donor or a program chooses to screen potential donors themselves, the outlined steps provided in this chapter are crucial to follow in order to ensure safety and health. Ultimately, the responsibility falls to the doctors providing the hands-on care and in every case full knowledge of the donor's pedigree, health history, and reason for participating must be known.

During the developmental years of the method, egg and embryo donors were married middle-class mothers in their early 30s. Today, we are working with the youngest women in the history of the technique, typically in their midtwenties, single, and without children. Injury to any one of them is catastrophic and ironically may in fact leave them infertile. We also can assume that some of these women will later experience infertility themselves and naturally will assume that their work as an egg donor contributed to their problem. Disclosure of all potential risks, including later regret, is difficult to do without frightening potential donors away. However, I believe it is better to inform each of them of the known complications and lose a few candidates rather than to perform

a procedure that later leads to lifelong regret. It has always been my hope that every egg donor will look back on the experience with pride and satisfaction for having provided a truly unique gift of life.

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5 Selecting and Screening Recipients: Diminished Ovarian Reserve and Premature Ovarian Failure

Hakan Cakmak and Mitchell P. Rosen

Key Points

- Focus on female educational and vocational pursuits has resulted in a clear rise in the mean age at which women deliver their first child as well as creating an increase in age-related infertility.
- Interest in noninvasive markers of ovarian aging that predict both ovarian reserve and the likelihood for successful pregnancy has led to increased use of serum AMH and FSH determinations as well as antral follicle count measurements.
- Premature ovarian insufficiency occurs in approximately 1 in 100 women under the age of 40, and in most cases, the etiology is unknown.
- In women with Turner syndrome, the risk for aortic dissection or rupture during pregnancy is higher than 2 %, and the risk of death during pregnancy is increased as much as 100-fold.

As a result of chronologic aging, both oocyte quantity and quality, and therefore reproductive potential, are known to decline in women [1]. Studies involving historical populations have shown a clear drop in fecundity after the age of 30 years, leading to fertility loss at a mean age of 41 years, with a wide range between 23 and 51 years [2–4]. Increasing female educational levels and participation in the workforce resulted in a clear rise in the mean age at which women deliver their first child in the USA [5]. Between 1990 and 2002, the birth rate for women 35–45 increased 53 % [5]. In other words, more than ever before women in their 30s and early 40s are attempting pregnancy for the first time. This general tendency to postpone childbearing also creates a growing number of infertile women who depend upon assisted reproductive techniques (ART) to achieve a pregnancy, solely on the basis of ovarian aging and decreased ovarian reserve. However, ART is able to compensate for the decreased natural fertility only to a limited extent, leaving many couples childless after prolonged and demanding infertility therapies. For these couples, egg donation often represents an excellent alternative treatment plan

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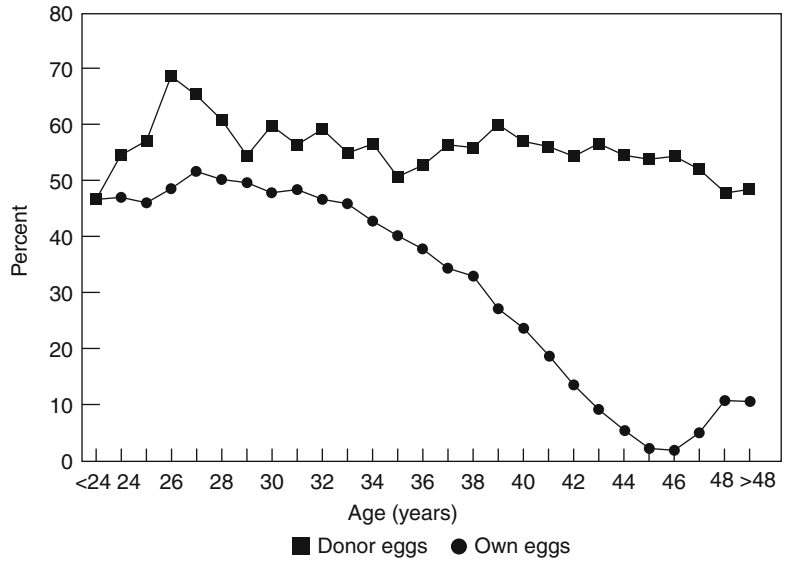

Fig. 5.1 Change in percentages of transfers that resulted in live births for ART cycles using fresh embryos from own eggs and ART cycles using donor eggs by age (Data from Centers for Disease Control and Prevention [7])

and, in many cases, their only hope for having a biologic child.

Oocyte and embryo donation has become a valuable and effective medical alternative for the treatment of infertility in women of all ages with decreased ovarian reserve. Most of these women have regular normal ovulatory menstrual cycles but demonstrate early hormonal signs of the "perimenopause." Therefore, spontaneous pregnancy is still theoretically possible but has become practically unattainable. Ironically, both the implantation and pregnancy rates in women with decreased ovarian reserve using donor oocytes are significantly higher than the most favorable rates attained by patients undergoing standard therapy with their own gametes in any of the ART (Fig. 5.1) [6, 7].

In the clinical setting, it would be useful to correctly identify women who are most unlikely to get pregnant using their own oocytes. An accurate assessment of poor fertility potential may lead to avoiding ineffective and expensive treatments in women destined to have an increased chance of cancellation, treatment costs, and psychological stress and who might be best served by offering oocyte donation early on during their treatment plan.

Over the past decade, considerable interest was focused on determining the value of noninvasive (indirect) markers of ovarian age that may predict both ovarian reserve and the likelihood for successful pregnancy. In this chapter, we summarize the current knowledge of these surrogate biomarkers for clinical decision making with respect to which patients would be best served by oocyte/embryo donation, and we review the medical and reproductive screening of oocyte recipients that should be done prior to attempting pregnancy.

Reproductive Aging and Decreased Ovarian Reserve

The value of knowing a patient's age in predicting performances in IVF is well established. Pregnancy rates in IVF cycles decline with advancing maternal age and more abruptly fall in women in their early 40s [8]. In 2009, live birth rates per attempted cycle of IVF were 12 % at age 41–42 and <5 % in patients more than 42 years [8]. The age-related decrease in fertility is thought to be due primarily to oocyte senescence rather than to poor endometrial receptivity, as suggested by the observation of high pregnancy success rates in oocyte donation programs [9]. Older women produce less oocytes and have lower embryo implantation rates, thus reflecting both the smaller size and the impaired quality of their autologous follicle pool [10]. However, the normal

process of reproductive aging varies considerably among women. Therefore, some women remain fertile well into the fifth decade of life, whereas others face the loss of natural fertility despite being in their mid-thirties. Besides chronologic age, other factors including genetic abnormalities, chronic medical illnesses, exposure to gonadotoxic agents, previous pelvic surgeries, and smoking may adversely affect overall reproductive potential [11–13].

As opposed to chronologic aging, *ovarian aging* is defined by a gradual decrease in the quantity of oocytes residing within the ovaries (*ovarian reserve*). Each woman is believed to receive an endowment of oocytes during fetal development. Germ cells rapidly proliferate by mitosis to reach a maximum of approximately six to seven million oogonia to form the primordial follicle pool by 16–20 weeks of pregnancy [14]. At any particular chronological age, the vast majority (>99 %) of oocytes in the ovary are present as primordial follicles and are considered to be the "*resting" pool.* Subsequently, an inevitable decline in oocytes begins via apoptosis; the number of primordial follicles falls to 1–2 million at birth and to about 300,000–500,000 by the onset of puberty [15]. During the reproductive years of life, the decline in the number of primordial follicles remains steady at about 1,000 follicles per month. Therefore, only about 400–500 oocytes actually ovulate. At the time of menopause, the number of remaining follicles drops below 1,000 [16].

It has been proposed that the intervals defining reproductive senescence (decline in fertility, end of reproduction, and menopause) are fixed, with the variable event being the actual age of menopause [1]. This implies that oocyte quantity and quality decline together and are consistent with the "production line" theory suggesting "the last oocytes out were the last oocytes in" and are intrinsically less healthy [17]. It is clear that with chronological aging, both oocyte quantity (ultimately leading to menopause) and quality (pregnancy potential) decline. It is less clear, however, whether the three parameters of chronological age, oocyte number, and oocyte "health" decline in parallel. However, it appears increasingly evident that women with low ovarian reserve are more likely to experience infertility regardless of their age [18]. It is likely that the diminishing number of oocytes has a more significant impact on fertility potential with increasing reproductive age.

The loss of oocyte quality is believed to be largely due to an increase in meiotic nondisjunction, resulting in an increasing rate of aneuploidy in the early embryos of older women [19, 20]. Underlying mechanisms for this phenomenon may involve accumulated damage of oocytes in the course of a woman's life or age-related changes in the quality of the granulosa cells surrounding the oocyte [21]. It has also been proposed that aneuploidy can independently be attributed to the falling oocyte number resulting from poorer-quality oocytes remaining in the ovary after euploid oocytes have been selected for ovulation [22].

Mitochondrial dysfunction has also been implicated in decreased oocyte quality and aneuploidy [23]. Both the function and morphology of mitochondria are found to be impaired in oocytes from older mice [24]. Increase in the rate of DNA mutations in oocyte mitochondria, decrease in mitochondrial metabolic activity, inefficiency in mitochondrial ATP production, and changes in mitochondrial calcium homeostasis were correlated with increasing maternal age [25–28]. Insufficient energy supply due to mitochondrial dysfunction with advanced age may cause spindle aberrations and loss of chromosome cohesion, integrity, and stability and may result in genomic instability and aneuploidy [29, 30]. These data are in agreement with those from human oocytes, showing that decreases in activity of mitochondria derived from oocytes of older women are associated with lower embryonic development and low pregnancy rates compared with oocytes obtained from younger women [27]. Overall, there is sufficient evidence to conclude that mitochondrial pathophysiology contributes to decreased female fertility in women of advanced reproductive age. However, the causative factors leading to aging-related changes in mitochondrial structure and function for the most part remain unknown.

Despite the changes in the numbers and the quality of oocytes, the process of ovarian aging remains largely clinically unrecognized unless

Table 5.1 Etiologies for primary ovarian insufficiency

Turner syndrome (45 XO or mosaic)
Fragile X gene (FMR-1) premutation
Trisomy X (47 XXX or mosaic)
Galactosemia (galactose-1-phosphate uridyltransferase deficiency)
Autoimmune polyglandular syndrome types 1 and 2
Follicle-stimulating hormone receptor mutations
Luteinizing hormone receptor mutation
17α-hydroxylase deficiency
Aromatase deficiency
Bloom's syndrome
Ataxia telangiectasia
Fanconi's anemia
Mumps oophoritis
Oophorectomy
Chemoradiation
Idiopathic

attempting to conceive. The first subtle sign of advancement in reproductive aging is a shortening of the length of the menstrual cycle by 2–3 days [31]. Due to the maintenance of regular cyclic menstruation until an age where natural fecundity has been reduced to nearly zero, women are largely unaware of loss of their fertility potential.

Premature ovarian failure (POF), or primary ovarian insufficiency (POI), is an accelerated ovarian aging process clinically defined as the cessation of ovarian function in the setting of hypergonadotropic hypogonadism (with elevated FSH and low estrogen level) before or at the age of 40 years [32]. This condition is characterized by the presence of primary or secondary amenorrhea, infertility, and/or symptoms of estrogen deficiency and is confirmed by two blood tests at least 1 month apart to measure FSH [32]. POF incidence in patients with a 46, XX karyotype is estimated to be around 1:1,000 women under 30 years old, 1:250 in patients in their mid-thirties, and 1:100 at 40 years old [33]. Etiologies for POF are heterogeneous and, for the most part, poorly understood (Table 5.1) [34]. Mechanisms for POF may include reduced genetic endowment of and/or an exaggerated loss of a previously normal complement of ovarian primordial follicles or impaired folliculogenesis [32]. POF in the setting of Turner syndrome (45,X) is a classic example of ovarian insufficiency resulting from a combination of a decreased number of primordial follicles and, subsequently, an accelerated rate of follicular atresia [35]. Infertility is a significant issue for women with POF, and although many women will continue to ovulate following the diagnosis of POF, this cannot be predicted with any degree of reliability. Thus, the chance of spontaneous conception in these patients is less than 5 %, and about 90 % were nulliparous at the time of diagnosis [36]. A number of therapeutic regimens have been evaluated with the aim of restoring fertility; however, prescribing clomiphene, gonadotropins, GnRH agonists, or immunosuppressants does not significantly improve the chance of conception [36]. The only reliable fertility treatment is IVF using donated oocytes or embryos.

For women who wish to become pregnant through ART, it is important to offer counseling about the optimal balance between benefits and risk especially if attempting IVF with autologous eggs. Since these outcomes are highly dependent on ovarian reserve, along with chronological age, much effort has been put into identifying models that are able to predict individual success [37–40]. The IVF prediction models were developed on the basis of both prospectively or retrospectively collected data of selected patient populations. Therefore, it might not predict well in other populations. For most of these models, the ability to predict pregnancy has been evaluated by receiver operating characteristic (ROC) curves. The largest (data from 26,389 women treated with IVF) and most studied model was developed by Templeton et al. in 1996 [40]. In this study, factors such as age, previous pregnancies, duration, and cause of infertility were evaluated, and a model to predict live birth after treatment with IVF was developed [40]. However, male causes and ICSI were not included in this analysis. Templeton's model can distinguish women with a high and low success rate in IVF. However, it systematically underestimates pregnancy chances, and it is not able to give more information about prognosis for the vast majority of patients [38, 41]. Moreover, that model was developed 16 years ago and since IVF has progressed substantially. The more recent models for predicting IVF outcomes are either missing

external validation or clinical impact analysis. The other issue relates to its lack of generalized applicability, since the original model was created for a very specific subgroup of infertile women. Overall, none of the available models can be used consistently and effectively in current IVF practice, and development of new models or improvement of the existing models is therefore necessary.

Since age alone and clinical models have limited predictive value, it would be helpful with respect to both patient counseling and clinical management to have another independent prognostic factor that can predict the true reproductive potential of each woman. Although difficult to assess, ovarian reserve markers have been developed that not only are considered a surrogate marker for the number of oocytes in the resting pool but also directly reflect the ovarian response to ovarian stimulation.

Markers for Ovarian Reserve

A number of ovarian reserve tests have been investigated to predict ovarian response to stimulation with exogenous gonadotropins. Most, and often all, of these tests are used to assess whether or not a patient is a candidate for conventional treatment with ART. When clinical and laboratory tests return uniformly abnormal, then oocyte donation is usually offered since traditional therapies are known to fail. The most commonly studied tests include age, ultrasound measurements of antral follicle count and ovarian volume, serum levels of anti-Mullerian hormone (AMH), basal day 2–3 FSH and inhibin B, and the provocative clomiphene citrate challenge test.

Antral Follicle Count (AFC)

AFC is considered to be one of the most reliable noninvasive methods for determining ovarian reserve. Although resting follicles are too small to be accurately identified using conventional imaging, antral follicles measuring 2–10 mm in diameter can readily be visualized using transvaginal sonography. The number of antral follicles appears to correlate with the number of primordial follicles in the ovary as shown by histological analysis [42]. As women age, the decrease in antral follicle cohort (annual losses of 0.5–1.3 antral follicles/year) parallels the decline in primordial follicle numbers [43, 44]. Although AFC is largely unaffected by the phase of the menstrual cycle, it is recommended that the AFC be performed in the early follicular phase of the menstrual cycle (day 2–3) to minimize the effect of intra-cycle fluctuation and reduce the likelihood of incorrectly including coexisting ovarian cysts or the corpus luteum in the AFC [45].

Although a few studies have suggested that ovarian suppression using short-term GnRH agonist therapy or combined oral contraceptives and ovarian stimulation do not influence AFC, we have found that these agents can cause a significant decline in AFC [46–49]. Moreover, we have shown that AFC is more likely a reflection of the growing pool of oocytes rather than the resting pool [50]. This is evident by the extreme case of women administered with chemotherapy. These patients can have a temporary decrease in AFC to possibly zero, with the subsequent recovery in AFC as menses return. It is possible that AFC is more biologically variable than once thought.

It has also been suggested that AFC may vary considerably from cycle to cycle [51]. However, the inter-cycle variability of AFC is clearly less pronounced than that of other markers of ovarian reserve, such as basal day 2–3 serum FSH levels [52]. This variability does not seem to exert major effects upon the prediction of outcome in terms of ovarian responsive to medications or pregnancy after IVF [53]. The number of oocytes retrieved per cycle remains consistent, despite differences in pretreatment AFCs suggesting that the inter-cycle variability of AFC may be due to inaccurate detection rather than biological variation [52]. However, it is possible that short-term conditions such as psychological stress may influence AFC [54]. Overall, the inter-cycle variability of AFC is generally considered to be of minimal clinical relevance in the prediction of response in IVF [51].

Decreased AFC in women who are infertile and in those with subfertility up to age 40 years

demonstrates an independent association between AFC and reproductive potential [18]. In addition, the prognostic value of the AFC in IVF treatment is well established [55–57]. AFC correlates directly with number of follicles, number of mature oocytes retrieved, number of embryos, and peak estradiol levels [58]. Furthermore, AFC inversely correlates with amount and length of gonadotropins used [58]. An AFC of four or fewer was associated with a significant increase in cycle cancellation (41.0 % vs. 6.4 %) and decrease in pregnancy success (23.5 % vs. 57.6 %) in patients without cancelled cycles [58]. In another study, patients with eight or more AFC had significantly higher pregnancy rates after IVF [59]. Although the AFC has a predictive value for ovarian response to hyperstimulation, similar to other markers of ovarian responsiveness, the independent predictive value of the AFC for ART outcome, in terms of pregnancy, is limited especially at younger ages [58, 60, 61]. Young patients with low AFC (likely due to better quality of oocytes) are still able to achieve pregnancy at a high rate, and AFC does not predict oocyte or embryo developmental competence or the pregnancy potential of an IVF cycle [62]. Therefore, AFC should not be used as a cutoff to exclude patients from IVF treatment in young women, and a trial of ovarian stimulation should be considered even with very low AFC. However, since the pregnancy rate is only about 6 % per cycle in women >42 years with AFC <5 [61], oocyte donation can and should be offered as a more successful alternative.

Overall, the AFC is currently considered to be the best single predictor of ovarian response to stimulation in ART, and it can be used in clinical practice for pretreatment counseling purposes and determining the ovarian stimulation protocol [63, 64].

The assessment of ovarian volume has also been investigated in an attempt to predict ovarian reserve and fertility potential. Studies have shown that ovarian volume is inversely correlated with age and that a statistically significant decrease in ovarian volume is observed in women older than 30 years [65, 66]. However, the practicality of using ovarian volume to predict ovarian responsiveness is limited because clinically meaningful changes become manifest only at the extremes of reproductive life [67].

Anti-Mullerian Hormone (AMH)

AMH is a homo-dimeric disulfide-linked glycoprotein of the TGF-β superfamily [68]. AMH is most recognized for its role in male sexual differentiation because it induces regression of the Mullerian ducts. In females, although AMH is absent in early fetal development, it is detected in the granulosa cells by 36 weeks' gestation [69]. From birth until menopause, AMH is exclusively produced by the follicles within the ovary [70]. Serum levels of AMH are barely detectable at birth, reach their highest levels after puberty, decrease progressively thereafter with age, and become undetectable at menopause [71]. AMH is secreted by granulosa cells of primary, secondary, pre-antral, and early antral follicles up to 6 mm in diameter, and its secretion ceases as follicles grow into dominance [72]. Early antral follicles are likely the primary source of serum AMH because they have higher numbers of granulosa cells compared with other follicles and have a better blood supply. The number of early antral follicles is directly related to the total size of the primordial follicle pool [73]. With the decrease in the number of antral follicles that occurs with age, AMH serum levels also diminish [71]. Therefore, AMH has been suggested as an ideal marker for assessing ovarian reserve [74].

Initial studies demonstrated minimal variation of AMH levels throughout the menstrual cycle, and AMH levels were thought to be unaffected by conditions that alter endogenous gonadotropin production such as GnRH agonist pituitary downregulation or oral contraceptives [75, 76]. However, a significant decrease in AMH levels was demonstrated during the early luteal phase coinciding with a sudden decrease in FSH, suggesting that AMH may fluctuate with changes in endogenous FSH concentration or the number of FSH-dependent follicles [77]. Other studies also supported this finding and showed that a permanent or sustained interruption of FSH release as in GnRH agonist pituitary downregulation and

idiopathic hypogonadotropic hypogonadism may lead to a decrease in AMH levels and therefore an underestimation of true ovarian reserve [50, 78]. In addition, AMH can fluctuate with systemic chemotherapy suggesting that similar to AFC, this serum marker is more likely a measure of the growing pool of follicles rather than the primordial pool [79, 80]. Given the fact that the bulk of AMH detected in the circulation is secreted from gonadotropin-dependent growing follicles, AMH similar to AFC has limitations as a surrogate marker for the resting pool.

Multiple studies demonstrate a strong and positive correlation between basal AMH serum levels and the number of retrieved oocytes in women undergoing ovarian stimulation [81–83]. In contrast, the lack of a consistent correlation between serum AMH and embryo quality has been clearly demonstrated [84]. The utility of AMH in the prediction of poor response to FSH was investigated and reported sensitivity and specificity ranged between 44–97 % and 41–100 %, respectively [81, 85–87]. AMH is accepted to be a better marker in predicting ovarian response to ovarian stimulation compared to day 3 serum FSH and inhibin B [88]. Multiple studies have found a significant correlation between AMH and antral follicular count and concluded that AFC and AMH perform with similar power in the prediction of the ovarian response [55, 81, 87, 89–91].

The vast majority of the studies investigating the performance of serum AMH in the prediction of pregnancy occurrence following IVF reported that AMH measurement is not useful in estimating success [88]. Only two small prospective studies reported a significant cutoff for AMH with respect to predicting pregnancy [89, 92]. Eldar-Geva et al. ($n=56$) reported a cutoff value for either follicular or luteal AMH of 2.52 ng/mL with a positive predictive value of 67 % and a negative predictive value of 61 % for achieving an ongoing pregnancy [92]. However, the mid-luteal AMH value of 2.7 ng/mL that was measured in another study ($n=33$) had better positive and negative predictive values (84.6 and 93.8 %, respectively) for clinical pregnancy [89]. In a larger retrospective study ($n=109$), the cumulative pregnancy rate from both fresh and frozen/thawed embryos was investigated. As a consequence of the relationship between serum AMH and the quantitative ovarian response, women with low AMH levels yielded fewer oocytes and generated fewer embryos, culminating in a 50 % reduction of the cumulative pregnancy rate compared with the high AMH group [87]. There is only one prospective study ($n=340$) correlating serum AMH levels to the live birth rate following IVF [82]. In that study, improved live birth rates were demonstrated with increasing basal AMH values. This trend was valid only for women with basal AMH levels <7.8 pmol/L as above this value there was no discrimination for the live births [82]. Moreover, basal AMH did not predict pregnancy but simply enabled patients to be identified as being at a low or high probability of pregnancy after IVF [82].

Interpreting a low AMH level is difficult since the accuracy of testing for poor response appears to be better than for the prediction of pregnancy and is not fully reliable since a false-positive rate of 10–20 % is expected. False-positive results may have negative consequences on a couple's life since this result might incorrectly prohibit women from attempting IVF. Furthermore, it has been widely demonstrated that many poor responders achieve pregnancy and live birth despite abnormal AMH results [93].

Different cutoff values of AMH were used in various studies. In reports using AMH cutoff value of 0.7–0.75 ng/mL for the identification of poor responders, only 75 % of poor responders were correctly classified, and more importantly, the live birth rate for women with basal AMH <0.7 ng/mL was 15 % which may be considered highly acceptable for patients anticipated to be poor responders [82, 94]. In contrast, using lower AMH cutoff values such as 0.1–0.35 ng/mL would only select women with very poor prognosis [87, 95].

In conclusion, given the importance of minimizing the false-positive test results, AMH measurements for predicting response to controlled ovarian stimulation and pregnancy are best used with very low cutoff values. Moreover, since poor response may not always imply a poor prognosis, especially in younger women, a trial of ovarian

stimulation often should be considered. In contrast, oocyte donation can be offered in older patients (>45 years) regardless of AMH levels, since IVF success is negligible regardless of ovarian responsiveness.

Follicle-Stimulating Hormone

The measurement of serum FSH levels 2 or 3 days after the onset of full menstrual flow has been used as a marker of ovarian reserve since the late 1980s, based on its association with reproductive outcome. Advancing female age is associated with a slow and steady compensatory elevation in FSH [96]. Persistent elevated basal FSH levels are consistent with diminished ovarian reserve; however, some women experience transient elevated basal FSH levels unrelated to their pool of primordial follicles [97]. Furthermore, the pulsatile release of FSH in the circulation and its short half-life adds to potential errors and a false sense of reassurance. Variation in monthly baseline FSH levels may also occur due to a persistence of corpus luteum or functional ovarian cyst [98]. Age has been identified as a better predictor of pregnancy than baseline FSH levels in women undergoing IVF [99]. A systematic review evaluating basal FSH levels in regularly cycling women found that the accuracy of FSH in predicting poor response and pregnancy is adequate only at very high threshold levels (FSH >15–20 IU/L), but because of the very low numbers of abnormal tests, it has little clinical value [100]. Moreover, younger women with elevated basal FSH levels can still have a favorable IVF outcome reflected by a reasonable ongoing pregnancy rate despite poorer IVF performances [101]. The possible explanation for this phenomenon might be that younger patients with elevated basal FSH (≥10 mIU/mL) have a decreased remaining follicle pool, but the quality of their remaining follicles is not diminished. In contrast, women aged 40 years or more with an elevated FSH (≥10 mIU/mL) has been associated with dismal IVF performances (i.e., the ongoing pregnancy rate as low as 4.5 %) [102]. The reasons for such poor results are related to an aging population of oocytes of poor quality and a gradual depletion of the follicle pool. Therefore, this group of patients should be carefully counseled on their low chances of conception with their own gametes, and oocyte donation may be offered as a more reasonable alternative. Overall, considering this along with a false-positive rate of approximately 5 %, the FSH test is not suitable as a diagnostic test to exclude patients from IVF, but should be used only as a screening test for counseling purposes and further diagnostic steps [103].

Inhibin B

Inhibin B is a dimeric polypeptide secreted predominantly during the follicular phase of the menstrual cycle by the developing cohort of antral follicles [104]. Inhibin B is believed to provide a direct assessment of ovarian reserve because it is primarily produced by the FSH-sensitive cohort of antral follicles [104]. However, inhibin B levels do not show a gradual decline with increasing age and are often viewed as a rather late marker of reduced follicle numbers [105]. With the use of basal inhibin B in regularly cycling women, the accuracy in the prediction of poor ovarian response to controlled ovarian stimulation and non-pregnancy is only modest at a very low threshold level (<45 pg/mL) [100]. Inhibin B is probably a better indicator of ovarian activity than of ovarian reserve, due to its direct link with growing follicles, and is much more influenced by fluctuations in ovarian function often seen during late ovarian aging and throughout the menstrual cycle. Therefore, at best, inhibin B may be used as a screening test for counseling purposes for further evaluation rather than directing toward oocyte donation.

Clomiphene Citrate Challenge Test (CCCT)

The CCCT is a provocative test for the measurement of FSH and is still used in some centers for the assessment of ovarian reserve. After measuring day 3 serum FSH, the patient is given 100 mg of clomiphene citrate on days 5–9 of the cycle,

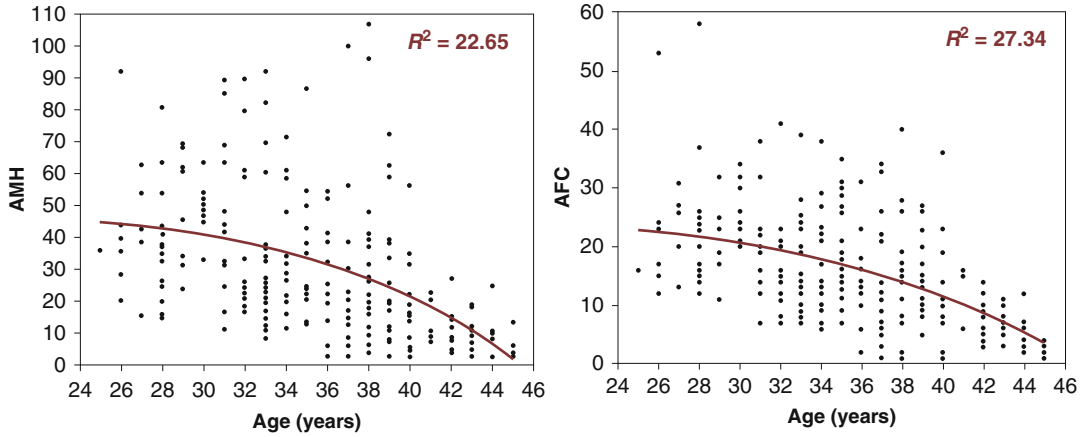

Fig. 5.2 Change in AFC and AMH levels with age [44]

and FSH is measured again on day 10. The test is abnormal if FSH values of either day 3 or 10 are elevated. Normal results are not useful in predicting fertility, but an abnormal result may suggest decreased ovarian reserve and lower rates of both spontaneous pregnancy and pregnancy after infertility treatment [106]. CCCT does not provide any additional advantage over a basal FSH, AMH, or AFC measurement for estimating ovarian response or pregnancy success and thus is not routinely recommended in the initial evaluation of infertile couples [106].

How to Use Ovarian Reserve Markers in Clinical Practice

The age-related fertility decline has been shown to play an important role in the increase in infertility among couples who are trying to conceive. Because of the variation of female fertility within a certain age category, testing the ovarian reserve is suggested.

The purpose of any ovarian reserve test is the identification of women with decreased ovarian reserve for their age. This means that chronological age always is the first step in ovarian reserve assessment. In young women, ovarian reserve tests may help to classify poor responders, and in older women, they may help to identify those cases that still may have acceptable chances of becoming pregnant with their own eggs through IVF as the response to stimulation is anticipated to be normal or even high [107].

The ideal ovarian reserve test permits identification of women who have a chance of pregnancy after IVF, as well as those patients with close to zero chance as a consequence of an extremely reduced ovarian reserve [100]. Ovarian reserve tests known to date have only very modest predictive properties. Although mostly cheap and not very demanding, their accuracy, especially in the prediction of the occurrence of pregnancy, is very limited. Moreover, the use of pregnancy as an outcome parameter for the assessment of ovarian reserve status may not be sufficient if only one treatment cycle is taken into account.

Ovarian reserve tests have been shown to correlate with the pattern of attrition that has been observed with primordial follicle loss observed histologically. Prior studies suggested that there was a dramatic fall in the number of oocytes after 37–38 years [16]. More recently, it has been shown histologically and with ovarian reserve testing that there is an absence of accelerated decline with age (Fig. 5.2) [43, 44]. This is particularly important as these markers alone should not be used to determine aggressive treatment because of fear of rapid loss of follicles.

Accuracy of testing for determining poor ovarian response to stimulation is clearly better than

Table 5.2 Pregnancy rates in patients with or without DOR after IVF and embryo transfer (ET) [61]

	<35	35–37	38–40	41–42	>42
Decreased ovarian reserve (*n*)	25	47	85	68	35
Normal ovarian reserve (*n*)	675	377	343	125	36
	Average number of eggs retrieved				
Decreased ovarian reserve	3.9	3.9	3.8	3.8	3.5
Normal ovarian reserve	17.1	15.3	14.8	16.4	16.8
	Ongoing pregnancy rate				
Decreased ovarian reserve (%)	52.0	31.9	21.2	19.1	5.7
Normal ovarian reserve (%)	53.5	43.2	42.9	32.0	30.1

The decline in oocyte quantity across the age spectrum is not associated with a parallel reduction in quality. Chronological age, independent of quantity, determines egg quality and pregnancy rate

for determining pregnancy. Obviously, the chance of pregnancy after IVF depends on many factors other than ovarian reserve alone and that the occurrence of pregnancy was usually evaluated in only one IVF cycle after ovarian reserve testing, and this may not accurately represent a patient's true reproductive potential. Poor ovarian response has been associated with a reduced chance of pregnancy in the actual treatment cycle as well as in subsequent cycles and as such may well be indicative of ovarian reserve status [93, 108]. Therefore, accurate prediction of poor response could have clinical value if the pregnancy prospects are so unfavorable that a predicted poor responder would be denied treatment especially in older patients. However, poor response to ovarian stimulation may not always imply a poor prognosis in younger women probably because of their higher quality oocytes (Table 5.2) [61]. Therefore, a trial of ovarian stimulation should be at least considered in younger patients.

Psychological and Medical Screening of Recipient Couples

The practice of oocyte donation is not regulated in the USA, although most programs follow the recommended guidelines on gamete donation issued by the American Society for Reproductive Medicine [109]. The evaluation of the potential recipient couples involves the fundamental principles of suitable selection by (a) appropriate medical indication for oocyte donation; (b) the ascertainment of the woman's ability to safely tolerate pregnancy, labor, and delivery both from a physical and psychological standpoint; and, more importantly, (c) the ascertainment of the anticipated psychosocial well-being of the child.

Making the decision to choose to use an oocyte donor entails a significant psychological adjustment. The typical experience for infertile women seeking oocyte donation involves a series of losses – loss of fertility, loss of feelings of normalcy, and loss of the genetic link to the child. Therefore, the screening of couples undergoing oocyte donation involves exploring the parties' understanding of the medical and psychosocial aspects of oocyte donation. Motivation for participation and pertinent psychosocial issues such as disclosure to family, friends, and children should be explored with the recipient couple as the part of the psychological screening process prior to embarking on oocyte donation. Depending on the medical indication for oocyte donation and whether the donor is known, many issues related to the inability to utilize the recipient's own gametes for reproduction need to be evaluated during psychological counseling. This counseling and support will allow the couple to enter into oocyte donation well informed and aware of future issues that may arise unique to families with children resulting from donor gametes.

Routine medical and reproductive histories should be obtained, and a complete general physical examination and workup should be performed according to the standards that are applied to women anticipating pregnancy. These should confirm the general well-being of the women and should be tailored to the age of the women. As

Table 5.3 Recommended medical screening to oocyte donation recipient women

Complete medical history and physical exam
Complete blood count
Rubella and varicella titers
Blood type, Rh factor, and antibody screen
TSH
VDRL or RPR
HIV-1/2
Hepatitis B and C screening
Cervical cultures for gonorrhea and chlamydia
Pap smear
Hysterosonography
Serum chemistry profile (including electrolytes, kidney and liver functions)[a]
Diabetes screening (HbA1c and/or fasting glucose)[a]
Lipid profile[a]
EKG[a]
Mammogram[a]

[a]Recommended for women older than 40 years of age

women age, there is an increase in the incidence of cardiovascular disease, diabetes, hypertension, and breast cancer. These medical conditions can be exacerbated by and further complicated by pregnancy. It may be worthwhile for older women to consult with a maternal fetal medicine specialist since there is higher risk of complications simply due to advanced maternal age. Although there are no federal requirements, standard preconception testing should be performed to oocyte recipients as recommended by ASRM (Table 5.3) [109]. These tests include complete blood count, blood type, Rh factor, antibody screen, rubella and varicella titers, and screening for infectious diseases (including HIV, syphilis, hepatitis B and C, and genital cultures for chlamydia and gonorrhea). Mammogram, kidney functions, electrolytes, and diabetes screening should be obtained for women older than 40 years of age. Recipients should have a normal uterine cavity expected to respond exogenous hormone stimulation to allow embryo implantation. Intrauterine anatomy can be ascertained by sonohysterogram.

Women with Turner syndrome expressing interest in oocyte donation should be carefully screened for cardiovascular malformations, since the increased cardiovascular demands of pregnancy also may pose unique and serious risks for women with Turner syndrome who often have cardiovascular malformations (25–50 % prevalence) [110]. In women with Turner syndrome, the risk for aortic dissection or rupture during pregnancy is higher than 2 %, and the risk of death during pregnancy is increased as much as 100-fold [111]. The initial screening should include chest x-ray and echocardiography, and any significant abnormality should be best regarded as a contraindication to oocyte donation [112]. Even those having a normal evaluation should be thoroughly counseled regarding the high risk of cardiac complications during pregnancy because aortic dissection may still occur [112].

There is concern about the major age discrepancy of elder mothers and their children and possible psychosocial impact that advanced maternal age may have on the children. Another worry is that because older mothers are closer to the end of their life expectancy, there is increased risk the children might either lose or have to deal with age-related mental or physical disabilities in their parents. In 1990, the UK enacted a law determining that the recipients of egg donation should not be over the age of 45 based on the view that it is in the best interest of the children to be parented into adulthood [113]. No such law exists in the USA, and the programs often rely on guidelines issued by ASRM. These guidelines do not suggest age restrictions for treatment [109]. A statement from the Ethics Committee of the ASRM asserted that pregnancy in postmenopausal women "should be discouraged" and that programs should determine on a case-by-case basis whether the woman's health, medical risks, and provision for child rearing justify proceeding with treatment [114].

Oocyte Donation as the Successful Last Step

Ovarian reserve tests provide a snapshot of the pool of primordial follicles and are useful tools for predicting the response to ovarian stimulation. However, their accuracy (besides extreme values in older patients) in the prediction of pregnancy after IVF is very limited. These tests can be considered

as "screening tests" whose abnormal result would necessitate confirmation by another test. This other test may, for instance, be a first IVF attempt where ovarian response is the additional test. Once the poor response is obtained with maximal ovarian stimulation after an abnormal ovarian reserve test, the diagnosis of decreased ovarian reserve can be given and oocyte donation can be suggested.

Oocyte donation is an exciting technology allowing an increasing number of women the experience of pregnancy and birth. Live birth rates of greater than 50 % can be achieved through oocyte donation in women with decreased ovarian reserve regardless of the age of the recipient, as pregnancy rates are almost solely dependent on the age of the oocyte donor (Fig. 5.1) [7]. However, some patients may find oocyte donation unacceptable due to the loss of a genetic relationship between the mother and potential child. Moreover, access to this therapy has been limited by its high cost and insufficient numbers of women who are willing and qualified to serve as oocyte donors. The potential drawbacks to delayed childbearing include increased obstetrical risks and potential psychosocial consequences. Consideration of all of these factors should be taken into account when offering treatment to older women or potentially patients with POF, and patients should be counseled accordingly.

Editor's Commentary

In my opinion, nothing is more heartbreaking, and relatively commonplace in the practice of reproductive medicine, than having to tell a young woman that her ovaries have failed. Although the incidence of premature ovarian insufficiency (POI) in the general population is relatively low, within the population of infertile women that we see every day in our offices, it occurs rather frequently. This is partly because primary care providers, who most often refer these patients to us, have a dwindling amount of time to spend in their office discussing the complexity of such a diagnosis with the patient, and therefore, this chore increasingly falls to us. Thus, it is incumbent upon reproductive endocrinologists to understand how to manage the medical needs of these patients and also to address the psychological trauma that accompanies this discovery.

As Cakmak and Rosen detail in this chapter, ovarian failure is usually an insidious and clinically silent event that often catches both the patient and the physician off guard. From the time of menarche, most reproductive health education is directed at ensuring young women have a timely "period," more to reassure them that they are not pregnant than anything else. Therefore, a linkage is imprinted early on in most women's minds that as long as their periods are on schedule, their reproduction must be fully intact. Reproductive medical specialists know that this is not true, but many if not most people do not understand this, nor do they appreciate the profound changes in reproductive potential that women normally experience while still in their 30s. Sadly, the tenets of a successful young life, that being pursuit of education and then vocation, often turns out to be their reproductive undoing.

Women with POI remain a constant cadre of patients within an infertility practice. However, today they represent a minority of patients partaking in oocyte donation, their numbers eclipsed by women of advanced reproductive age whose only pathology is longevity. Although the treatment is the same as their older counterparts, women with POI have very different clinical and emotional needs, and clinicians should appreciate these differences. This is particularly true of women with Turner syndrome who are known to have underlying cardiovascular abnormalities that may prove life-threatening during pregnancy.

Egg donation has always been a welcome alternative to women with ovarian failure at a young age. The first patients accessing

care were all less than 35 years old. Prior to 1983, all of these patients were told that their only hope for pregnancy rested with the sporadic occasional spontaneous ovulation that allowed approximately 2–3 % of them to conceive and deliver a child. Egg and embryo donation radically altered these chances and provided *real* hope for couples previously with *little or no* hope.

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Selecting and Screening Recipients: Advanced Reproductive Age

6

Briana Rudick and Richard J. Paulson

Key Points

- Women in Western society are delaying childbearing in order to pursue vocational and educational goals placing them at risk for age-related infertility.
- Among women 40 years and older, births have more than doubled in the USA since 1990, and this increase is directly attributable to the greater number of women of advanced reproductive age undergoing assisted reproduction and oocyte donation.
- Older recipients of donated eggs are demographically different from younger recipients in that they are more often parous, often divorced and remarried, and commonly pursuing successful professional careers.
- Even in the absence of maternal comorbidities, increasing maternal age is an independent risk factor for increased maternal and neonatal morbidity and mortality.

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An increasing number of women in modern Western society are choosing to delay childbearing in order to pursue vocational and educational goals. As a consequence, the number of first births to women of advanced maternal age (35 years old and greater) and advanced reproductive age (40 years old and greater) has been increasing. This broad trend toward older motherhood is occurring in all major US race and ethnic groups. In the USA today, one in seven babies is born to women 35 years of age or older. The number of babies born to mothers older than 35 years old was 603,113 in 2008 compared with 367,828 in 1990. This represents a 64 % increase in this older age group, while the total number of US births grew only 2 % during this same time period [1].

These widespread trends are due to an increasing number of women choosing to pursue their career, thus deferring marriage and family. The widespread use and many forms of effective birth control permits reproduction to be planned, even scheduled. The average age of individuals entering marriage is rising, divorce is more prevalent, and second marriages are also more common. The increases in birth rates in the older maternal

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age groups are likely in part due to the success of fertility treatments. The widespread application of in vitro fertilization (IVF) has changed the public perception of fertility. Contemporary couples are increasingly confident that they will achieve fertility when they are ready to start a family socially and financially.

However, conventional IVF utilizing a woman's own eggs is associated with a marked decline in live birth rates per embryo transfer in women over the age of 40. Fortunately, the use of donor oocytes effectively circumvents this manifestation of the "biological clock." Multiple studies have confirmed that oocyte donation leads to a high rate of embryo implantation, regardless of the age of the recipient. It is now established that oocyte donation produces pregnancy rates in older women that are essentially equal to those of younger women [2], in that the success of ART is dependent on the age of the egg donor and not the recipient [3].

It can be argued that it is largely due to oocyte donation that the birth rate among older women has risen to the extent that it has. The number, proportion, and rate of births have grown most among mothers 40 years and older. Despite low absolute numbers of births in older age groups, these women are seeing the highest increase in birth rates: 47 % increase in women ages 35–39 and 80 % increase in women ages 40–44 years [1]. Among women 40 years and older, births have more than doubled from 1990 to 2008, with the number of babies increasing from 50,245 to 113,576 [1]. This increase in births is directly attributable to the greater number of women of advanced reproductive age undergoing assisted reproduction and oocyte donation [4]. Since an increasing number of women of advanced reproductive age are seeking the success afforded with egg donation, it becomes critical to identify how these patients are different from younger recipients of egg donation and how to appropriately screen them both psychologically and medically.

Demographic Differences in Older Recipients of Donor Eggs

Studies performed in younger and older recipients of egg donation confirm that there are demographic differences between these two groups [5]. Recipients in their 40s and 50s were found to have frequently been pregnant in the past, were often divorced and remarried, and were commonly pursuing professional careers. Many of these patients had attempted and failed conventional fertility care prior to undergoing oocyte donation. A large percentage of these older patients had also undergone cosmetic surgery, most commonly breast implantation or "facelifts" in an attempt to maintain a youthful appearance. As a consequence, it has been suggested that their desire to have a baby is motivated by an obsession with youth, with pregnancy providing a very visible sign of fertility, health, and youthfulness. However, as part of pre-cycle screening, the motivations of patients were also assessed. In the majority of cases, the stated desire of the older patient did not differ from views expressed by younger patients, the sole goal being "to have a baby and begin a family."

In comparing recipients in their 50s versus those in their 40s, women who chose to conceive in their 50s tended to be better educated and were commonly employed, but did not use more child care services than their younger counterparts. They were generally married to men significantly younger than themselves and typically married at a later age, versus women in their 30s, who tended to be married to older men. They did not appear to have significant differences in physical or mental functioning and did not suffer from greater degrees of parental stress than their younger counterparts [6].

Medical Concerns in the Older Demographic

As oocyte donation to older women has become more commonplace, society has become increasingly accepting of this practice. However, the consequences of bypassing one's biologic clock to obtain pregnancy in either the post-reproductive years (women in their 40s) or in postmenopausal women (women in their 50s) have brought up many ethical questions. At the forefront of these concerns is the medical maternal-fetal risk of pregnancy at an advanced reproductive age. As women get older, their chances of developing a chronic medical condition such as hypertension

or diabetes increase. These age-related conditions, in turn, increase the risk of illness during a subsequent pregnancy. Older maternal age is also associated with an increase in the number of disorders of the reproductive tract, particularly uterine leiomyomata, which contributes to risks of miscarriage, malpresentation, and preterm delivery. Additionally, egg donation is associated with a higher likelihood of multiple gestations, which further adds to pregnancy risk. An increased incidence of multiple gestations is associated with all forms of ART treatment in this age group, not just egg donation. However, multiple gestations occur in up to 40 % of reported pregnancies from egg donation [4]. However, even in the absence of maternal medical comorbidities and in singleton gestations, increasing maternal age is an independent risk factor for increased maternal and neonatal morbidity. Thus, screening older women for medical conditions that could exacerbate an age-related risk becomes paramount in selecting appropriate candidates for egg donation.

Most recipients of egg donation are women of advanced maternal and reproductive age and therefore represent high-risk pregnancies to obstetricians. Studies that assess obstetric outcomes after oocyte donation report high rates of pregnancy-related obstetric and medical complications, which exist on a continuum with increasing maternal age. Hypertensive disorders of pregnancy ranging from pregnancy-induced hypertension to severe preeclampsia continue to be the leading causes of both maternal and neonatal morbidity and mortality. While the prevalence of hypertensive disorders of pregnancy is roughly 10 % in the non-IVF obstetric complication, this prevalence increases to at least 30 % in most studies of oocyte donation recipients [7–12]. Pregnancy-induced hypertension, especially in its more severe forms, is associated with fetal growth restriction and an increased risk of preterm delivery.

The rate of gestational diabetes also increases parallel to maternal age, with rates increasing from 7.5 % of women 20–30 years old, to 13.8 % of women over 30 years old, to 25 % of egg donation pregnancies [7, 12]. And finally, the rates of cesarean section are reportedly over 70 % in recipients of egg donation [7, 11, 13, 14]. Indications for cesarean delivery in this group often include advanced maternal age, hypertensive disorders of pregnancy, gestational diabetes, previous uterine scar, and multiple pregnancies. Occasionally, an egg donation pregnancy is deemed a high-risk condition in and of itself by the attending physician and represents the sole indication for obstetric intervention [15].

Although the risk of pregnancy complications following oocyte donation in older recipients does appear to exist on a continuum with maternal age, in an appropriately screened patient, the risk is not prohibitive, particularly compared to younger obstetric populations with chronic medical conditions [6, 7, 16–18]. So far, reported outcomes have been favorable, which reflects well on the strict medical prescreening that goes into selecting older patients eligible for treatment.

Medical Screening in Women of Advanced Maternal Age

Given the increased maternal-fetal risk associated with pregnancies in recipients of advanced maternal age, proper medical screening of potential candidates is mandatory, since potentially serious health conditions may be discovered that could further increase obstetric risk. The incidence of chronic diseases such as hypertension, diabetes, and obesity is known to increase with age. A complete medical history should be taken along with a comprehensive physical exam. Upon reviewing the medical history, further evaluations may be necessary depending upon the suspicion for other medical conditions that could adversely affect or be affected by pregnancy. A full list of the recommended medical screening and laboratory tests is presented in Table 6.1 and should be tailored to the age of the woman. Any discovered abnormalities should be individually addressed with the recipient and her primary care physician. Consents prior to proceeding with egg donation should be modified to include the obstetric risks associated with any discovered medical comorbidities, and if substantial comorbidities exist, preconception consultation with a maternal-fetal medicine specialist is indicated.

An assessment of cardiovascular and pulmonary reserve seems particularly important in menopausal recipients. This includes a baseline EKG and treadmill exercise stress test. Although

Table 6.1 Pre-cycle screening of oocyte recipients

Medical evaluation – all oocyte recipients	*Male partner*
Medical history and physical exam	Semen analysis
Complete blood count with platelet count	Blood type and Rh
Blood type and Rh, antibody screen	Hepatitis screen
Serum electrolytes, liver and kidney function tests	Hepatitis B surface antigen
Sensitive TSH	Hepatitis C antibody
Prenatal lab testing	RPR
Rubella titers	HIV
Varicella titers	HTLV 1&2
Hepatitis screen	Appropriate genetic tests
Hepatitis B surface antigen	
Hepatitis C antibody	
RPR	
Human immunodeficiency virus (HIV)	
Pap smear	
Cervical cultures for gonorrhea and chlamydia	
Reproductive testing – all oocyte recipients	
Transvaginal ultrasound	
Endometrial stripe measurement	
Hydrosonogram (saline-injection sonogram)	
Hysterosalpingogram	
Endometrial biopsy on cycle day 21 of mock cycle	
Psychological screening	
Psychosocial counseling	
Additional testing for recipients 40 years old and older	
EKG	
Mammogram	
Glucose tolerance test	
Cholesterol and lipid profile	
Additional testing for recipients 50 years old and older	
Treadmill stress test	
Chest X-ray	
Colonoscopy	
Pre-conceptual counseling (high-risk OB specialist)	

no systematic studies support its routine use, we have recommended exercise treadmill stress tests for all women over the age of 50. If any significant abnormality is found on electrocardiogram or chest X-ray, further testing may need to be performed in consultation with a primary care physician or cardiologist. Patients with significant cardiovascular morbidities or vascular disease are not candidates for egg donation.

Evaluation of the pelvic organs is part of routine screening for all recipients, not just recipients of advanced reproductive age. Uterine cavity assessment is necessary to rule out pathology that may interfere with embryo implantation and/or pregnancy. This workup includes a transvaginal ultrasound of the pelvis and a saline infusion sonohysterogram (SIS). Leiomyomata are more common in older women, but do not pose a problem if they are asymptomatic and small and do not distort the endometrial cavity. Endometrial polyps are also common findings in premenopausal women; although some controversy surrounds their routine universal removal, we recommend that all endometrial polyps be removed prior to embryo transfer. The fallopian tubes should be evaluated to rule out the presence of hydrosalpinges via hysterosalpingogram; not all hydrosalpinges are evident on transvaginal ultrasound. Since hydrosalpinges adversely affect the outcome of oocyte donation (as well as IVF) [19], salpingectomy should be offered to these patients prior to their recipient cycle [20]. Endometriosis is not a major concern, as its presence does not appear to affect pregnancy rates with oocyte donation [21]. Pretreatment is only indicated if symptomatic relief is necessary. Additionally, patients may be reassured that pregnancy commonly ameliorates these symptoms due to the progesterone dominant milieu.

To evaluate the functional adequacy of the endometrium, a mock cycle using sequential estrogen and progestin therapy is often performed, with a timed endometrial biopsy to obtain histological confirmation of a progestational response. In amenorrheic recipients, it is occasionally necessary to prime the endometrium with 1–2 months of sequential estrogen and progestin therapy prior to obtaining a satisfactory response to progesterone.

This appears to be especially true for women who use continuous estrogen plus progestin hormone replacement therapy and may be another reason for utilizing the mock cycle.

The male factor is initially evaluated with a medical history of the male partner and a complete semen analysis, which includes a morphological assessment of the sperm. Any abnormalities should be followed up with appropriate investigation. Oligoasthenospermia or azoospermia should be evaluated by a physical exam and directed laboratory testing, including a karyotype, evaluation of the Y chromosome (for possible microdeletions), and/or testing for cystic fibrosis. Relevant aspects of the history include medications which may affect spermatogenesis, exposure to environmental toxins or heat, and any potential genetic disease that may be carried by the male partner. Increasingly, oocyte donors undergo genetic testing for recessive diseases, and this testing should include any autosomal recessive trait known to be carried by the recipient male partner.

Psychological Screening

Psychological screening and psychosocial counseling should explore the couple's decision to use donor eggs, as well as address issues inherent to older parenting. Patients who have reached this point in treatment have already experienced a fair amount of emotional pain, frustration, and fear. They may have anxiety related to infertility and the process of treatment, as well as the decision to pursue donor egg, and finally to the realization that they will be parents at an older age. Couples of all ages choosing oocyte donation typically participate in a screening process in which a psychologist or licensed mental health-care professional examines the couples' understanding of both the medical and psychosocial aspects of oocyte donation. It is important that the couple understand the complexity of the process from both a medical and psychological standpoint and that they have a realistic expectation of potential successes, failures, and complications. As part of this psychosocial interview, the couple should discuss their motivation for participating in oocyte donation and how they plan on disclosing this information to family, friends, and eventually their child(ren), should the treatment be successful. Oftentimes, the decision to proceed with oocyte donation is made after many failed IVF attempts with a woman's own eggs; thus, the inability to utilize one's own oocytes should be addressed in counseling, since this loss of genetic lineage may result in a loss of self-esteem, anxiety, and depression.

Other issues to explore with recipients include their intended relationship, if any, with the egg donor. Oocyte donors may choose to remain anonymous to the oocyte recipient, they may wish to have a relationship with the recipient, or they may choose to remain anonymous with a willingness to meet the child in the future. It is possible that the recipient may wish to meet the donor while the donor chooses to remain anonymous. These issues must be addressed before participating in oocyte donation so that both parties are fully aware of each other's desires, and there is no infringement upon patient privacy. The goal of this screening is to keep all parties as informed as possible prior to entering oocyte donation, so that these issues do not arise mid-cycle, at a time when anxiety is already high. The psychological counseling involving issues inherent to the egg donation decision, and process are addressed further in Chap. 14.

Psychological and Parenting Concerns of Women of Advanced Maternal Age

There are specific psychological and parenting concerns that should be addressed in older women. For instance, women of advanced maternal age who have spontaneously conceived report less dissatisfaction with children, less parenting stress, and more effective family functioning [22]. However, the results of these studies cannot necessarily be extrapolated to women who conceived using infertility treatment, since the emotional and financial stress of fertility treatment is not

present. Egg donation is associated with physical, mental, emotional, and financial stress; thus, there are concerns regarding the impact of this stress on parental ability and attitudes toward offspring. There is also concern about the major age discrepancy of older mothers and their children and the possible psychosocial impact that advanced maternal age may have on the resulting children. The American Society for Reproductive Medicine Ethics Committee states that "because parenting is both an emotionally stressful and physically demanding experience, older women and their partners may be unable to meet the needs of a growing child and maintain a long parental relationship" [23].

Particularly in postmenopausal women, it becomes difficult to tease out the effects of egg donation versus older motherhood on stress, coping, parental attitudes, and adjustment. Golombok et al. demonstrated that mothers conceiving via gamete donation have more positive parent–child relationships and greater emotional involvement with the child at 9–12 months of age [24]. Another study showed no differences in the quality of parent–child relationships or in the child's socioemotional development between IVF and oocyte donation mothers with children 12 years of age [25]. Thus, despite the high level of stress attributable to the egg donation process itself, there appears to be no harmful effect on parental or child stress and adjustment.

Looking solely at egg donation in women of advanced maternal (and reproductive) age, age itself does not appear to be a separate risk factor for reduced parental capacity. In a study by Steiner et al., women who conceived and delivered in their 50s (via oocyte donation) were compared to women in their 40s. They were administered validated questionnaires addressing parental stress and physical and mental functioning. They found that mothers of advanced maternal age did not have reduced parenting capacity due to physical or mental ability or parenting stress [6]. In fact, the trend in this study was toward better mental functioning and less parental stress in the women over age 50. Although ASRM recognizes the medical and societal concerns in allowing women of advanced age to pursue egg donation, they also state that, "in special circumstances, after careful medical and psychosocial evaluation, oocyte donation should not be excluded on the basis of age alone." In addition, this committee reported that, "any age limits on reproduction should be applied equally to males and females" [26]. Additionally, some argue that in many societies, grandparents traditionally assume the bulk of responsibility for raising their grandchildren. It seems doubtful that the wisdom and experience that accompanies age would be a detriment to parenting. There are concerns regarding the likelihood that the child will be orphaned at an early age, but this would be the same concern in a younger breast cancer survivor who desires a child. It is important to keep in mind that age is but one factor in the prediction of longevity; healthy women at age 50 have a life expectancy that is sufficient to raise the child to adulthood.

Summary

Oocyte donation makes pregnancy possible in virtually any woman with an intact uterus. This includes women beyond the age of natural menopause, a time in life at which pregnancy without treatment would generally not occur. Therefore, it is incumbent on the clinician to appropriately counsel potential recipients of the increased obstetrical risks associated with pregnancy at this advanced reproductive age. Screening tests are designed to rule out underlying diseases and abnormalities of the reproductive tract. Psychosocial counseling is designed to increase the patients' awareness of issues particular to gamete donation and to the ramifications of reproduction beyond the natural age of pregnancy. However, screening tests can merely help estimate the risk of subsequent complications; they cannot prevent complications, nor can they guarantee that complications will not occur. Therefore, in addition to screening and counseling, recipients of advanced reproductive age should also be made aware of the option of gestational surrogacy, which, in many cases, may be associated with a better obstetrical outcome. Nevertheless, with modern obstetrical methods, risks of pregnancy at an advanced reproductive

age are not prohibitive, and there does appear to be sufficient data to suggest that access to oocyte donation should not be restricted on the basis of age alone.

Editor's Commentary

I remember well the first 50-year-old woman who consulted me regarding her fertility. She began the conversation with, "You probably will think that I am crazy but I am a grandmother, remarried to a younger man and I want to have his baby. Can you help me?" Now even today this question may take some aback, but I assure you in 1990 this request was rather daunting. Perhaps because I was only 35 years old at the time and a 50-year-old appeared more like a mother than a sibling, but I was starting to have some second thoughts about how far to take the application of egg donation and age. However, it also struck me how reasonable her request was and that if an older man wished to have a second family with his younger wife we would not hesitate to act. Needless to say, I modified the protocol to include women up to the age of 55 years and went on to successfully treat her, as well as many others.

My partner at the University of Southern California Dr. Rick Paulson has spent most of his career assisting women of advanced reproductive age and often beyond natural menopause, to fulfill their dream of having a baby. This chapter gives testimony to the fact that older patients are different than their younger counterparts. In many respects, they are more complicated, socially, medically, and reproductively. Despite the patient's enthusiasm, practitioners need to have a firm understanding of the medical risks to the health of the woman posed by pregnancy, and gestational problems such as hypertension and diabetes may come as a shock to the patient who never experienced either illness in the non-pregnant state. However, dealing with most of these issues is really a matter of careful screening and informed consent, and the majority of prospective patients will go on to enroll in care.

Finally, it is worth remembering that establishing the pregnancy is the easy part. Raising a child is long hard work. Evaluating the whole life of the prospective patient, noting her financial and social supports, and ascertaining her general health and likelihood of longevity are also important aspects in counseling older women wishing to become mothers.

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Genetic Aspects of Donor Selection

7

Stephen Brown

Key Points

- Physicians often act as the intermediary between the egg donor and the recipient and by necessity accept the responsibility for ensuring that a low risk of serious genetic illness exists among the parties involved.
- Donation programs should adopt a position on genetic testing of donors which neither permits unacceptable risk nor is unfairly paternalistic in spirit.
- Obtaining a routine karyotype from a gamete donor is not necessary since the likelihood of discovering a balanced translocation is only 1 in 500.
- Soon it is likely that full genomic sequencing testing of donors will be affordable making this approach to screening feasible.

When the first edition of this book was published in 1997, oocyte donation was relatively new, and little had been written about the genetic screening of oocyte donors. No guidelines from professional societies yet existed, and there was no general consensus about what sort of screening was appropriate. Over the past ~13 years, much has happened – both in the world of oocyte donation as well as in genetics. There are now reasonably well-established and accepted guidelines for oocyte donor screening, and studies that have looked into recipient preferences for genetic screening have also been published. In addition, the number and type of genetic tests that one may consider in the context of egg donor screening have increased over the past decade.

Recipients, being mostly highly educated and successful people, are typically upon focused donor "quality," and many have very specific ideas about which attributes they would like their donor to possess (or not possess). Many recipients are willing to pay more money for eggs from women with desirable attributes, such as academic achievement and musical or other talent. They also tend to be aware that testing for a variety of genetic disease is becoming increasingly available, and many are keenly interested in knowing which genetic screening and/or testing has been performed. Therefore, it is important for professionals involved in the process of egg donation to have carefully considered genetic screening and testing.

From a biologic perspective, sperm donation and egg donation are similar; however, there are many aspects of oocyte donation such as its expense, shortage of available donors, and an inability to easily store eggs that make it difficult to reject potential donors as freely as one might reject sperm donors. This adds to the need to

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consider genetic aspects very carefully. The goal of this chapter is to discuss the following topics:

1. The role of the physician in the genetic screening of donors
2. Guidelines for oocyte donor screening
3. The pros and cons of new genetic tests
4. Commonly used genetic screening protocols (Appendix A)
5. Information that may be given to recipients about how donors are screened (Appendix B)

Role of the Physician in Egg Donor Selection

In the "natural" state, the process of choosing the other "donor" of gametes for one's children is one of life's most emotionally charged processes. It is also one of life's most irrational processes. Most people probably make many decisions about the genetic backgrounds of those they choose to have children with, but those decisions are mostly unconscious. In general, at least in our society, we do not make a specific effort to minimize the risk of genetic disease when we choose a partner for having children. In fact, if we carefully screened our partners for their reproductive fitness, we would probably reject all potential partners who would eventually need assisted reproductive technology.

In our society, each person has the right to choose a reproductive partner. This right even extends to the possibility of deliberately increasing the couples' risk of genetic disease in the offspring. For example, a couple in which both partners have a heritable form of deafness may well prefer to have a baby with a genetic form of deafness, a baby which most of us would think of as being severely handicapped. Or, consider the couple in which the man has oligospermia on the basis of a Y-chromosome microdeletion. Such couples frequently choose to go ahead with assisted reproductive techniques which, if it results in the birth of a male child, will virtually guarantee that their genetic condition is passed down to future generations. On the other hand, most if not all couples will try to avoid a serious risk of having a severely disabled child.

Since as a society, we believe that people have the right to procreate with whom they wish, we might think it most fair and morally safe to try to recreate this "natural state" in the setting of ART by leaving all decisions about the genetic aspects of gamete donors to the recipients themselves. If one adopts this point of view, the physician becomes merely a technical facilitator in the interaction between donor and recipient. Clearly, this model will not work since there are many complex medical issues in judging donor suitability, and this is especially true for egg donors. Also, there is the problem of maintaining donor confidentiality while attempting to match donor and recipient for ethnic and other characteristics. The donor and recipient typically cannot interact with each other. Therefore, the physician is in the middle of the interaction between them and, as the intermediary, by necessity accepts the responsibility of trying to do what "any reasonable" recipient would or should do in order to reduce their risk of serious genetic disease. Can any of us imagine doing nothing to reduce the risk of genetic conditions that we all would consider highly deleterious?

On the other hand, the idea of minimizing genetic risk can be taken to unpleasant extremes that are repugnant to us all. The following statement occurred in a discussion about semen donor selection in 1952. "It is just as necessary to investigate the family lineage of a human donor as it is for the workers at stud farms to select prize males based on ancestry to obtain a better grade of offspring. An effort should be made to learn of the physical stock from which the donor was descended – whether the parents and grandparents were healthy and lived their normal span of years or not. Donors should have no family history of syphilis, insanity, dementia, cancer, diabetes, epilepsy or any other inheritable or familial disease. The occupations of the donor's ancestry should disclose individuals with at least normal backgrounds. Queries should be directed to the donor attempting to learn of any morons, mongolism, cretinism, dwarfism, mutism, or any other undesirable hereditary manifestations." Weisman [1] quoted by Fraser and Forse [2]. Because this statement equates humans with farm animals, it

recalls the appalling atrocities of the eugenics movements of the early part of the past century. However, it is interesting to consider which aspects of this statement we agree with and which we do not. Where the selection against genetic disease drifts into unfair judgments about who should and who should not be allowed to reproduce is a matter of opinion. For instance, there are sperm banks that advertise sperm from especially successful men. Is this morally reprehensible? Or, should a donor be excluded because of a personal or family history of a behavioral variant such as homosexuality? How much myopia or dental malocclusion is too much? These questions may become particularly poignant when the potential donor is related to the recipient or to her husband. To exclude a woman's own sister as an egg donor because her (their) brother has schizophrenia or because their parents both have severe hypertension may present problems.

With that said, it seems clear that a gamete donation program should adopt a position regarding the genetic screening of donors which neither leads to unacceptable risks nor is unfairly paternalistic in spirit. In the case of oocyte donation (as opposed to sperm donation), the expense and lack of availability of donors may temper the degree of genetic selection. The ASRM published its most recent guidelines in 2008 [3], and there have been others preceding [4]. Such lists and guidelines have all been designed with the idea of doing what is reasonable to diminish the risk of transmission of genetic disease without unnecessarily excluding acceptable donors. Our own guidelines at the University of Vermont are presented below, and Appendix A contains our egg donor genetic assessment form. We note that the guidelines that we presented in the first edition of this book are very similar to those in the ASRM guidelines published more than 10 years later.

As a practical matter, we have found that lists of genetic conditions for which donors should be excluded are a bit dogmatic and that many situations arise which call for individualized consideration. An example of this kind of problem might be the donor who is in every way ideal for a given recipient except that she had a prior child with a chromosome abnormality. In this case, the tiny risk of recurrence (and the ability to test for it) is outweighed by the fact that the donor is ideal in every other way. Similarly, a donor who is in every way ideal but turns out to be a carrier of a recessive condition for which the perspective father is not a carrier might well be acceptable [5]. In this and other such cases, it is important to have a good grasp of underlying genetic principles as well as the availability of a formal genetic counselor.

Guidelines for Oocyte Donor Screening

The following are the guidelines that we use in our oocyte donor program.

The following list applies to the donor herself:

1. She should not have a *serious malformation of multifactorial origin* such as cleft palate, spina bifida, heart malformation, and clubfoot. Such malformations have a recurrence risk between 1 and 5 %. It is worth remembering that the word "serious" here may be a matter of opinion. Even dental malocclusion and myopia are probably inherited in a multifactorial manner. In our program, "serious" is taken to mean the life of the affected offspring is permanently impaired or the treatment for the problem (e.g., open heart surgery) is of major medical significance.
2. She should not have any *serious autosomal dominant Mendelian disorder* since the risk of transmitting illness to the offspring is 50 %. Although this is obvious in the case of neurofibromatosis or Marfan syndrome, it may not be obvious in other cases. For instance, a family history of early renal failure in a parent or sib may prompt a renal ultrasound and a new diagnosis of adult polycystic kidney disease. Such cases will not happen frequently, but they serve to demonstrate that a careful general history is much more important than a simple question of "do you have a genetic disease?"

   Recessive Mendelian disease may also exclude donors. The risk of transmission is low (since

it is unlikely that the recipient will also be a carrier) but still represents an avoidable risk. As a practical matter, most if not all prospective donors that are affected with recessive illnesses will be excluded because of poor general health.

3. She should be tested for carrier status for *Mendelian disorders that are common to her ethnicity*. Clearly this necessitates cystic fibrosis (CF) screening of Caucasians and a "Jewish" disease panel in donors who are of Ashkenazi background, a sickle cell test for donors of African and Mediterranean ancestry, and a complete blood count (CBC) for people of Asian ancestry (looking for evidence of thalassemia). As noted previously, carrier status does not exclude outright someone from egg donation, but it should prompt further discussion and focused testing of the prospective father.
4. She should be free from *diseases that are known to have a major (non-Mendelian) genetic component*.

   This list is large and perpetually enlarging. Conditions that clearly fall into this category include juvenile diabetes, rheumatoid arthritis, epilepsy, severe asthma, schizophrenia, and bipolar affective disorder. When present in one parent, the risk for the offspring is between 5 and 15 % for all of these conditions. Should a donor be excluded because she has easily controlled, exercise-induced asthma or because she wears glasses? Common sense dictates not, and efforts to establish hard and fast rules to govern these decisions are likely to fail.
5. She should not have a *chromosome rearrangement* that could result in unbalanced gametes.

   We do not routinely recommend karyotyping of donors since the likelihood of finding a balanced translocation is only about 1/500 [6]. However, if there is a family history that suggests the possibility of a chromosome abnormality (e.g., multiple miscarriages or stillbirth), then ordering a karyotype may be warranted. In this context, the issue of repetitive miscarriage should be mentioned. If a potential donor gives a history of several miscarriages, her risk of having a chromosome abnormality is increased, and a karyotype should be obtained or else she should be excluded. It is interesting to consider what to do with those potential donors who have normal chromosomes and a history of multiple miscarriages. The best policy is probably to exclude such donors although it is difficult to establish a rational genetic basis for this [7].
6. She should be under the age of 35 years.

   By using donors under this age, the risk of trisomy is significantly reduced.

The following list applies to the donor's first-degree relatives (parents, children, and siblings). The potential donor shares an average of 50 % of all her genes with her first-degree relatives. A pregnancy from her donated oocyte is the second-degree relative of her first-degree relatives and would share an average of 25 % of all genes with her first-degree relatives.

1. No major malformations should be present.
2. Autosomal recessive disease should not be present, unless the causative mutations are known and can be specifically tested for in the donor herself.
3. Autosomal dominant conditions should not be present.

   For some conditions (e.g., Marfan syndrome), it may be obvious that a sibling is unaffected; however, for other conditions, the diagnosis may be complicated by late age of onset, variable expression, and variable penetrance. Huntington's disease is a good example, and adult polycystic kidney disease is another. Because of these problems, the most conservative approach is to exclude such donors. The list of autosomal dominant conditions now should include breast and/or ovarian cancer if it is present in two first-degree relatives.
4. X-linked diseases should not be present in male relatives unless carrier status can be specifically excluded.
5. Chromosome rearrangements should not be present unless the donor has been shown to have a normal karyotype.
6. As for the donor herself, diseases that are known to have a major (non-Mendelian) component should not be present in first-degree relatives. In practice, this is the most

problematic area of donor genetic screening. The degree of risk of a multifactorial condition is sharply lower for second-degree relatives than for first-degree relatives, but it is still generally in the range of 1 % [8]. In most instances, this is enough to exclude a donor. For example, if the prospective donor's sibling has a major psychiatric disorder, the risk to the offspring is substantial. But, should a donor be excluded because her sibling has multiple sclerosis (MS)? Here, the reasoning is less clear. In the case of MS, the risk to first-degree relatives has been estimated to be 2 % [9]. The risk to second-degree relatives would be expected to be considerably less than 1 %, which many recipients might be willing to accept. These cases should be considered on an individual basis with the help of a geneticist if necessary.

In summary, the above guidelines are intended to minimize a couple's risk of having a severely ill or disabled child through gamete donation. It is inevitable that many situations will arise which are not specifically addressed here. As is often the case in medicine, there is no "right" answer in many of these cases. The decision to use or exclude a donor must always be made on the basis of a common sense assessment of risk versus benefit.

Patient Education

It is our policy at the University of Vermont to inform patients in our oocyte donation program about our guidelines and methods behind donor genetic screening. This is done, in part, because we have found that many recipients are quite anxious about the unknown genetic risks which they are incurring. Most feel reassured to have their anxieties confronted directly and forthrightly. Another reason for patient education relates to the fact that 2–3 % of babies are born with a malformation detectable at birth [10]. An even greater percentage will be eventually diagnosed with some genetic condition. These statistics are unlikely to change despite all of our efforts to screen the parents and the donors. Parents of affected children from gamete donation programs will naturally ask whether or not this event was preventable. Our goal is to assure prospective parents beforehand that all reasonable efforts were made on their behalf. We encourage our patients to read the following brief discussion of our donor genetic screening protocol. If patients have concerns and questions that go beyond our expertise, we refer them to a geneticist.

New Genetic Tests and Evolving Technology

Microarrays

Since the publication of the first edition of this book in 1997, it has become clear genomic copy number changes are an important cause of developmental disability and malformation. Likewise, genomic copy number variations are now known to be an important contributor to phenotypic variation. This raises the question of whether or not it would be useful to screen oocytes donors by microarray. Clearly, the finding of a genomic copy number variation that conferred major risk of illness would make a donor undesirable.

In practice, most copy number changes that result in disease occur de novo, and parents of affected children are not themselves carriers of the relevant genomic change. Thus, screening donors would not be effective. Also, an attempt to screen donors by microarray would uncover a large number of cases in which the prospective donor harbors a genomic alteration of unknown significance. This would lead to the exclusion of perfectly acceptable donors. Yet another reason not to use microarray to screen donors is the fact that balanced chromosome rearrangements are not detected by microarray. Thus, there are several good reasons not to routinely use microarrays to screen oocyte donors.

Avant-Garde Testing

A look at egg donor websites gives immediate insight into the fact that recipients are often willing to pay more for "desirable" eggs. For instance,

women in Ivy League colleges may command a higher price than those who have been less academically successful, and women in famous professional schools may command even higher prices. The amount that recipients are willing to pay "extra" for eggs that are perceived as particularly desirable can run into thousands of dollars. Of course, the willingness to pay more for highly desired eggs is predicated on the assumption that intelligence, success, and good looks are all heritable and that the chances of having a successful child are improved by obtaining "good" eggs.

For the time being, buying and selling services in this way, albeit highly controversial, is unlikely to have a major effect on outcome. The desired ends of intelligence, good looks, and success are only vaguely heritable, and their heritability is poorly understood. However, in the near future, that may change. It is now possible to perform full exomic sequencing for under $1,000, and companies willing to perform such sequencing are readily available. Within the next several years, it is likely that full genomic sequencing will cost less even less, making full genomic sequencing of egg donors entirely feasible as well. It is therefore likely that full genome sequencing can and will be used to test whether potential egg donors harbor serious mutations in known disease genes and disease-risk loci. If the genetic determinants of intelligence and other desirable traits are identified, genomic analysis will be used to identify these as well.

Of course, this type of genetic testing raises many serious ethical and moral questions, and thus, it seems likely that individual egg donor programs, as well as professional societies, will soon be forced to consider what genetic testing is morally and ethically acceptable. At what point does avoiding disease genes (which we generally agree is acceptable) turn into an effort to positively select desirable traits, the foundation of eugenics.

Editor's Commentary

Recipients of donor gametes are always interested in the pedigree and genetic background of their donor. Obviously, these factors are of grave importance to everyone. Yet, it represents a major burden to egg donation programs to warrant that any baby will be completely normal and forever free from disease. This is something every recipient wishes to hear, but no one can or should guarantee. Also, it seems that no matter what information is provided to patients, it is never enough. Often, the inquiries relate more to the fear of the unknown than to an understanding of the biology. Furthermore, there is a preoccupation with controlling all the variables and a general belief that we can assess the patients and their donors and predict the biologic outcome; sort of like following the recipe and baking a cake!

Steve Brown, M.D. offers sage advice regarding the practical aspects of genetic testing in an increasingly sophisticated clinical arena. As he touches upon in his narrative, eugenics is being practiced here. Following the published professional guidelines is certainly necessary and requisite in order to avoid dangerous outcomes. I believe local, regional, and national differences also exist in the actual practice of screening and matching donors that relates to the varying demographics of the population. Undoubtedly, patients in Manhattan will be different from those in Burlington, Vermont, or for that matter Valencia, Spain. At least, commonality related to the basic tenets of safe practice can be agreed upon.

My main message to patients regarding genetics relates to the natural variation of biology which we term phenotype. I tell them to look at their siblings and remember that despite common genotypes there exist obvious differences in appearance, personality, and talents. There is no way possible to predict these things; never has and never will be. Sometimes patients seem to forget all of these obvious life lessons when they become obsessed with pursuit of the "perfect donor." It is our job to keep everyone focused on reality.

Appendices

Appendix A

Genetic Screening Form for Oocyte Donors and Partners of Recipients

Name:_____

Date:_____

Birthdate:_____/_____/_____

Pregnancy history: (please list all the times you have been pregnant and the outcomes) _____

_____

Family ethnic background:_____

_____

Please indicate all relevant information in the following tables. When the requested information is unknown, please say so. If comments are needed, please make them. Remember that we are interested in your genetic background. If any relevant family member is adopted, please say so.

Relation	Age if living	Age at death	Cause of death
Grandfather (pat)			
Grandmother (pat)			
Grandfather (mat)			
Grandmother (mat)			
Father			
Mother			
Brothers			
Sisters			

Family Genetic History

	Self	Mother	Father	Siblings	Comments
Familial conditions					
High blood pressure					
Heart disease					
Deafness					
Blindness					
Severe arthritis					
Juvenile diabetes					
Alcoholism					
Schizophrenia or manic depression					
Epilepsy					
Alzheimer's disease					
Other (specify)					
Malformations					
Cleft lip or palate					
Heart defect					
Clubfoot					
Spina bifida					
Other (specify)					
Mendelian disorders					
Color blindness					
Cystic fibrosis					
Hemophilia					
Muscular dystrophy					
Sickle cell anemia					
Huntington's disease					
Polycystic kidney disease					
Glaucoma					
Tay-Sachs disease					

Please take the time to explain any other problems or conditions in your family history which you feel could pertain to the health of future generations.

Appendix B: Genetic Information for Recipients

Basic Genetic Principles for Participants in Gamete Donation

It is our policy to inform all participants in the oocyte or sperm donation program about our reasoning and methods for the genetic screening of donors. We do this in part to reassure you that we do everything that is reasonably possible to minimize the risk of transmission of genetic diseases and conditions. In addition, we want all participants to be aware of the limitations of genetic screening.

Human genetic disease can be divided into three major categories. The first of these is chromosomal: All of our genetic information is contained in 23 pairs of chromosomes that are present in all the cells of our bodies. Errors in the number of chromosomes can occur during the production of sperm and eggs. A well-known example of this category of genetic illness is Down's syndrome. Chromosomal disorders in general do not run in families. Rather, they happen more or less at random with the main risk factor for occurrence being increasing maternal age. Because of the association of chromosome abnormalities with maternal age, all of our oocyte donors are under the age of 35. While chromosome abnormalities can be tested for in pregnancies by maternal serum screening and amniocentesis, we cannot eliminate the risk of their occurrence. Luckily, the chance of having a baby affected with a chromosomal disorder is quite low (about 1/300–1/1,000).

The second major area of genetic disease is "single gene disorders." These are conditions that are caused by an abnormality in a single gene, and these can be further divided into two groups, recessive and dominant. With recessive single gene disorders, both parents must be carriers in order to have an affected child. When both parents are carriers, the risk of having an affected child is 1 in 4 or 25 %. Cystic fibrosis and sickle cell anemia are two well-known examples. Some of these disorders occur in specific ethnic groups (White Europeans are frequently carriers of cystic fibrosis. African Americans are frequently carriers of sickle cell anemia, and Jews of European decent are frequently carriers of Tay-Sachs.) For this reason, we test potential donors for those recessive conditions for which they are at increased risk. In addition, we question potential donors about the presence of any of these conditions in their families. For many rare conditions, there is no carrier testing available. Luckily, the chances of both parents being carriers for the same rare gene are very low.

With dominant single gene conditions, only one parent must have the abnormal gene. We ask all donors about the presence of such conditions in themselves and in their families. Donors from families with dominant genetic conditions are excluded.

The third major area of genetic disease is called "multifactorial." What is meant by this term is that the trait or condition in question is under some level of genetic control but that there are other factors such environment and chance involved as well. An example of this is the common malformation of cleft lip and/or cleft palate. There are probably several genes as well as environmental factors involved in this condition. Close relatives of someone with cleft lip and palate are at increased risk of having cleft lip and or palate, but the degree of that risk does not fit any simple model. Many other malformations as well as perhaps most common diseases fall into the category of "multifactorial." The list of things inherited in a multifactorial manner would include diabetes, heart disease, high blood pressure, some forms of cancer, and even such things as myopia and dental malocclusion. Behavioral traits can be inherited in a multifactorial manner as well. The list here probably includes severe mental illnesses such as schizophrenia as well as conditions such as alcoholism and even homosexuality. We screen all potential donors by asking them if they or any family members have any relevant conditions. When the potential donor or her immediate relatives have any of these conditions, they are excluded.

By following the above guidelines, we believe we have done everything reasonably possible to insure the good genetic health of babies born from egg donors. There is no doubt that the measures we take go way beyond what most couples who undertake "normal" parenthood do to insure good genetic health of their children. However, it would be unrealistic to believe that it is possible to prevent all genetic disease. Most malformations occur in the absence of any family history. The same is true for many dominant and recessive single gene conditions and for chromosome abnormalities. The good news is that the risk for genetic disease and malformation is, in general, quite low.

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Part II

Practical Aspects of Clinical Care

Synchronization of Donors and Recipients: Practical Aspects of Clinical Surveillance

8

Julie M. Sroga and Steven R. Lindheim

Key Points

- The donor–recipient cycle has provided a unique model to separately evaluate prescribed sex steroids allowing for an understanding of the isolated effects of each hormone's alteration on endometrial development and physiology.
- Successful implantation is the end result of a series of dynamically complex signals that occur between the cleaving embryo and the maturing endometrium to ensure apposition, adhesion, and ultimately penetration of the blastocyst.
- The length of prescribed estrogen administration prior to the addition of progesterone does not appear to be an influential factor in the outcome of an oocyte donation cycle, whereas the duration of progesterone exposure is key to whether or not an embryo will implant.
- There is insufficient evidence to recommend any one particular protocol for endometrial preparation over another with regard to pregnancy rates in oocyte donation.

Embryo implantation in the human results from three key events, which include development, synchronization, and signaling between the embryo and endometrium. These occur through a series of coordinated genetic and hormonal events regulating intracellular signaling in both the host uterus and implanting blastocyst [1]. Coordination of these events is crucial for success in any reproductive cycle, but in donor–recipient cycles, embryo development and endometrial priming occur at different trajectories and in separate environments. These cycles offer unique clinical challenges for the reproductive endocrinologist who must choreograph hormonal manipulation to align the recipients' endometrium with the retrieved, fertilized, developing, and ultimately transferred donor embryo. This synchrony of events also offers the clinical scientist the ability to study endometrial receptivity during the early stages of human reproduction and implantation [2, 3].

In this chapter, we will review the regulation of endometrial receptivity by the stages of ovarian hormone production and the implanting blastocyst, which has led to clinical protocols for the management of donor-oocyte and recipient cycles. In addition, we will characterize the clinical protocols for donor–recipient synchronization based on the recipients' reproductive state including strategies for pituitary downregulation in both the donor and recipient, ovulation induction protocols for the donor, optimizing uterine receptivity, and troubleshooting for when asynchrony occurs.

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The "Window of Implantation"

Improvement in IVF (in vitro fertilization), embryo transfer (ET), and laboratory techniques have resulted in increased pregnancy rates in both non-donor- and donor-assisted reproductive technology (ART) cycles, yet implantation rates remain disappointingly low. This is likely to be the result of transferring embryos into a non-receptive uterus [4]. Over the past several decades, researchers have begun to unravel the complexities of the peri-implantation window in various mammalian models [1]. However, details of the collaborative interactions between the human endometrium and blastocyst still remain largely unknown due to the lack of in vitro models for human implantation and ethical constraints of researching the early human embryo [3].

Molecular, genetic, and hormonal factors guiding implantation can be evaluated as those driving endometrial development and receptivity separately from those functioning from within the embryo [1, 5]. In most mammalian species, including humans, the timing of implantation has a specific temporal relationship from the time of luteinization transitioning from a pre-receptive phase to a receptive phase (window of implantation), followed quickly to a refractory or non-receptive phase [1]. During the pre-receptive phase, embryos within the endometrial cavity can survive until transition to the receptive state occurs. Once transition occurs to the refractory phase, embryo survival is negligible. Understanding the hormonal control of this short window of receptivity is crucial for coordinating and troubleshooting donor–recipient cycles.

Ovarian Hormonal Regulation of Endometrial Development and Receptivity

Production of ovarian estrogen and progesterone is crucial to endometrial preparation, activation, and regulation necessary for embryo implantation. The sequence of these cyclic events in mammals is relatively fixed. Progesterone is known to be critical for both implantation and maintenance of pregnancy, whereas ovarian estrogen requirement is species-specific with its role in humans largely unknown [4]. However, studies indicate that estrogen is necessary in endometrial priming and development prior to ovulation [6] and may play a significant role in blastocyst activation and competence which is necessary for successful implantation [7].

Estrogen Priming of the Endometrium

The donor–recipient cycle has provided a unique model to separately evaluate ovarian steroid hormones allowing for an understanding of the isolated effects of each hormone's alteration on endometrial development and physiology [6]. The long recognized role of estrogen, specifically estradiol, has been understood as inducing endometrial proliferation during the follicular menstrual phase or in the absence of progesterone such as in anovulatory women. However, estrogen priming of the endometrium plays a significant role for subsequent progestational effects to occur in order to prepare for implantation [8]. Specifically, estrogen induces expression of both estrogen receptors (ERs) and progesterone receptors (PRs) within the endometrium [9]. Estrogen activity on the endometrium is regulated through two isoforms protein estrogen receptors (ER), ERα and ERβ. Expression of ERα predominates during the follicular phase with expression correlating with the proliferative activity of the endometrium, but these levels decline following ovulation prior to implantation [8]. ERα is more abundant throughout the endometrium, where ERβ predominates within the glandular epithelium and vascular epithelium [8]. Like ERα, ERβ levels also decline during the secretory phase due to progesterone-induced downregulation of both ER isoforms. The decline of ER, specifically ERα, at the time of implantation may be physiologically important, and this trend has been noted across many species [8].

Exogenous administration of estradiol at doses equivalent to endogenous estradiol levels in a natural cycle induces staining of both ER and PR within endometrial glands and stroma. To achieve proper priming of the endometrium, all that is needed is sufficient duration of exposure to

estrogen to surpass a minimal threshold level, and superseding this duration does not appear to be detrimental to endometrial development. Navot et al. reported on the flexibility of length of estrogen treatment by evaluating pregnancy outcomes following different durations of estrogen exposure in donor–recipient cycles. They noted that adequate estrogen exposure could range from 5 days to 6 weeks without compromising endometrial receptivity or pregnancy outcomes [10]. Other studies have also confirmed that prolonged estrogen exposure does not negatively impact pregnancy outcomes when given up to 14 weeks of estrogen therapy [11–13]. However, significant breakthrough bleeding often occurs after 8–9 weeks of usage; therefore, it is advisable to discontinue estrogen therapy after 9 weeks to optimize cycle outcomes [11]. In summary, estradiol endometrial priming is necessary to induce molecular changes necessary for implantation. However, the duration of estrogen therapy has a wide temporal window in which it can be prescribed prior to the initiation of progesterone supplementation.

Progesterone Regulation of the Implantation Window

The secretory phase, initiated by ovulation, follows a controlled sequence of events with defined histological changes, historically referred to as "dating" of the endometrium [14]. Progesterone is known to antagonize the action of estrogen inducing its effects on tissues through progesterone receptor (PR) isoforms PR-A and PR-B. Specifically, progesterone induces regression of ER and epithelial PR while maintaining stromal PR concentration [6]. Unlike estrogen priming, progesterone treatment initiates a very short and specific window of receptivity that remains for only 24–48 h [15]. Gene mutations in PR-A cause infertility in rodent models [1], while treatment with RU-486, a progesterone antagonist, prior to entering the receptive phase can postpone the endometrial window of receptivity. However, once the endometrium enters the receptive phase, no therapy can prolong or reverse the sequence of events [16, 17]. Furthermore, once the non-receptive phase has been entered, it becomes detrimental for blastocyst survival and implantation [1, 18].

In rodent models, the window of implantation is less than 24 h, whereas in humans, this window appears to be slightly broader [1]. From human clinical trials, Navot et al. reported 40 % pregnancy rates from cleavage stage embryos transferred between days 17 and 19 days (day 15 defined as the first day of progesterone administration), while no pregnancies occurred if ET occurred early (<day 16) or late ≥20 days [18]. This defined the optimal time of ET between 3 and 5 days post-progesterone exposure. However, some authors argue that the window may be less stringent than initially thought with as little as 3 days of progesterone exposure prior to blastocyst competence [19, 20]. As such, defining the exact time the human endometrium enters and leaves the receptive phase has proven very challenging.

To better define this "window," research has focused on identifying peri-implantation biomarkers within the endometrium as well as defining the temporal relationship between the expression of these biomarkers and progesterone exposure. Pinopodes (also called uterodomes) are progesterone-dependent organelles that appear as membrane projections in the endometrial epithelium from days 20 to 21 of the natural menstrual cycle [21, 22]. The exact mechanism of pinopode function is still unknown, but appears to have a role in facilitating blastocyst adhesion. Pinopode appearance can be positively correlated with serum progesterone concentrations [23] with appearance of pinopodes occurring between day 6 and 8 of progesterone therapy. The duration of pinopode expression occurs for approximately 48 h within the human endometrium in all types of cycles with fully developed pinopodes existing for little as 1 day [21, 24]. In donor-oocyte recipients, determining the most receptive day (i.e., expression of fully developed pinopodes) may improve clinical pregnancy rates [25, 26]. Many argue that pinopode expression should be considered as a biomarker for endometrial receptivity. However, the timing and duration of pinopode expression can vary among individuals as much as 5 days [26–28]. Nevertheless, pinopode detection may prove to be useful in determining the optimal timing for ET, but further research is needed to better understand their specific role and relationship to progesterone initiation.

Although the specific sequence of molecular events which follow progesterone administration are not fully understood, studies support progesterone's role via PR in the secretion of substances that transcriptionally activate genes key in blastocyst apposition, attachment, penetration, and decidualization [1, 4]. Progesterone is known to promote prostaglandin E_2 (PGE_2) production which in turn stimulates synthesis of insulin-like growth factor binding protein-1 (IGFBP-1) and raises stromal aromatase activity [29, 30]. PR expression is maintained within the uterine stroma even after downregulation of PR in the endometrium [31] which supports progesterone's role in stimulating stromal differentiation allowing decidualization, which is a vital step in conception. As important as progesterone is for initiating these events, activation and signaling from the blastocyst must also occur for successful implantation.

Embryo–Uterine Crosstalk

Successful implantation requires apposition, adhesion, and ultimately penetration that result through a complex series of events and signals between the endometrium and blastocyst. Initially, apposition occurs, which is an unstable adhesion of the trophoblast layer of a competent blastocyst to the luminal epithelium of the endometrial surface [32]. This is followed by an adhesion stage where there is a localized increase in the stromal vascular permeability at the luminal epithelium site of blastocyst attachment [33]. Lastly, the embryonic trophoblast invades through the luminalepithelium into the stroma. This establishes a relationship with the maternal vasculature, which initiates signaling for endometrial stromal cells and endometrial extracellular matrix to undergo decidualization [1, 33].

These events happen through highly orchestrated endometrial and embryonic "crosstalk" signaling. Endometrial signaling occurs through HOX gene upregulation, which is essential for endometrial growth, differentiation, and receptivity. Both HOXA10 and HOXA11 mRNA are expressed in human endometrial epithelial and stromal cells, and their expression is significantly greater during the mid- and late-secretory phases, coinciding with the timing of embryo implantation and high circulating levels of estrogen and progesterone [34–37]. Following successful implantation, the decidua of the early pregnancy continues to express high levels of HOXA10 and HOXA11 mRNA [35, 36]. The HOX genes also regulate other downstream target genes leading to molecular and morphological markers specific to the implantation window including pinopodes, integrins, and IGFBP-1. Decreased expression of HOX genes during the secretory phase is associated with lower implantation rates in infertile conditions including patients known to have endometriosis, PCOS, hydrosalpinges, and uterine fibroids [38–41].

The competent blastocyst also appears to play an active role in its attachment and invasion, interacting with the endometrium through cell-to-cell interactions to mediate endometrial cell proliferation and differentiation. This occurs through the secretion of cytokines and growth factors including leukemia inhibitory factor (LIF) (a member of the interleukin six family of proteins), heparin-binding epidermal growth factor (HB-EGF), integrins, mucin 1 (MUC1), Wnt signaling, and β-catenin proteins each effecting receptivity and implantation [42–44].

Endometrial LIF secretion appears to be regulated by prokinextin1 (PROK1) in the mid-secretory phase of the menstrual cycle. In the mouse model, LIF-null mothers result in blastocyst implantation failure, whereas LIF-null blastocyst embryos transferred into a wild-type pseudopregnant uterus have normal implantation [45] but subsequent embryo demise during the prenatal period. This suggests that maternal LIF is critical not only for implantation but for embryo development [46]. While LIF is essential to implantation in the mouse model [4, 47], its role in human implantation remains unclear, which appears to be dysregulated in women with unexplained infertility and recurrent implantation failure [48, 49]. However, administration of r-LIF fails to improve pregnancy outcomes [50]. In vitro studies not only suggest that LIF mediates the expression of other adhesion molecules

[51], but PROK1 upregulates HB-EGF gene expression and cyclooxygenase-2 at the site of apposition in the uterine epithelium and on the implanting blastocyst [52].

Cell adhesion molecules also appear on both the endometrium and embryo during the time of implantation and contribute to blastocyst attachment [42]. Integrins have been studied in both humans and animals and appear to play a role in embryo–uterine crosstalk [44, 53]. Expression of the integrin αvβ3 is upregulated by HOX genes during the implantation window [53–55] and appears to be reduced in some fertility compromising disorders including endometriosis and unexplained infertility [54, 56], though other studies have not corroborated these findings [56, 57].

Several other signaling processes in the endometrium are only activated by the implanting blastocyst including the downregulation of MUC1 by the blastocyst in the uterine epithelium. MUC1 is increased from days 7 to 13 of the menstrual cycle [58] and remains upregulated 1 week following ovulation [59]; however, the specific function of MUC-1 in human implantation still remains largely unknown.

Wnt proteins are a large group of cysteine-rich molecules that contribute to blastocyst activation and competency [60] and also appear to stimulate LIF expression from the uterine epithelium [1, 3]. Uterine Wnt signaling is induced strictly at the sight of embryo attachment immediately prior to implantation, and this signaling by the activated blastocyst is necessary to promote its own attachment to the uterine epithelium [61]. Reduction in the Wnt/β–catenin signaling pathway while not affecting blastocyst formation results in impaired implantation as seen in reduced litter sizes in the murine model [4, 60, 61].

Implantation involves a complex array of signaling from both the endometrium and developing blastocyst. While many of these signals have been described, their precise and coordinated role remains unclear. Continued investigation will hopefully unravel their role in implantation and may provide better insight into treating infertility disorders and optimizing embryo–uterine synchronization in oocyte donation cycles.

The Recipient Cycle

The process of implantation of a fertilized ovum in the human uterus is determined by careful synchronization of embryonic and endometrial development and is primarily related to cyclic steroid hormone production. In oocyte donation, coordinated artificial endometrial growth is obtained through the delivery of prescribed estrogen and progesterone provided to the recipient during ovarian stimulation of the oocyte donor and is mandatory in establishing an optimal endometrial milieu to which the resulting embryo may implant.

To coordinate these complex events, the strategies for recipient uterine preparation can be divided into two distinct groups of women. The first group is women with functioning ovaries including patients with poor oocyte quality, multiple failed IVF attempts, transitioning menopause, carriers of genetic abnormalities, and those with inaccessible ovaries. The second group is women without ovarian function due to premature menopause (naturally, after surgical castration and iatrogenic chemotherapy induced), gonadal dysgenesis, and physiologic menopause.

The first reported pregnancy using oocyte donation was in a natural cycling 42-year-old female, where menstrual cycle synchronization of the donor's ovulatory cycle was achieved by monitored changes in urinary and plasma luteinizing hormone (LH). Unfortunately, the pregnancy aborted at 9 weeks [62]. This highly serendipitous synchronization process was subsequently altered by cryopreserving an embryo that was later transferred. However, once again, the pregnancy ended in spontaneous abortion, this time at 24 weeks [62]. Ultimately, the first viable pregnancy occurred in a 25-year-old female with premature ovarian failure where oral estradiol valerate (Progynova, Shering, Sydney, Australia) and intravaginal progesterone pessaries (Utrogestan, Piette, Brussels, Belgium) were given [63]. Since this sentinel event, a number of strategies have successfully been used in clinical practice to synchronize the donor and recipient cycles, the latter hinging on three components: those with and

without ovarian function, flexibility in artificial follicular phase length [10, 13, 64], and pinpoint progesterone initiation. Numerous estrogen and progesterone protocols varying in delivery route, daily dose, and active substance will be reviewed.

Women with Ovarian Function

In women who maintain ovarian function, synchronization between donor and recipient cycles is more complex secondary to the coordination of two hormonal cycles. An uncontrolled LH surge in the recipient woman can induce transition of the endometrium into the receptive phase creating asynchrony where an embryo is not yet available for transfer.

Historically, synchronization of the donor and recipient's LH surges has been used for coordination of cycles [65]. This involved several months of monitoring recipient cycles for an LH surge and luteal endometrial biopsies for detecting endometrial adequacy in order to best coordinate the cycles [66]. Others have described administration of estradiol starting with menstruation for 2–4 weeks during their follicular phase followed by progesterone administration the day of or prior to retrieval in the oocyte donor [67]. However, this approach did not eliminate a premature LH surge and luteinization altering the window of receptivity resulting in cycle cancellation. Since described by Lutjen et al. [63] and its successful application by Van Steirteghem et al. [68], embryo cryopreservation was used to overcome cycle synchronization issues. However, given the issues of embryonic loss after cryopreservation and thawing and the overall compromised success compared to fresh ET, embryo cryopreservation has precluded its use as an ideal standard of care.

GnRH Agonists (GnRH-a)

Since the late 1980s, the standard of care in autologous IVF cycles has been the suppression of the hypothalamic–pituitary axis using GnRH-a to prevent a premature LH surge. This approach has optimized IVF outcomes [69] and has become the standard for optimal cycle coordination in oocyte donation cycles [70,71]. GnRH-a downregulation typically requires 1–3 weeks for complete ovarian suppression and includes intranasal, intramuscular, and subcutaneous formulations (Table 8.1).

Table 8.1 GnRH-agonist route of administration and dosing for ovarian suppression

GnRH-a	Route of administration	Dosing
Buserelin	Intranasal	600 μg daily[a]
Leuprolide acetate	Subcutaneous	1 mg daily[a]
Leuprolide acetate	Intramuscular	3.75 mg monthly[b]

[a]Devroey and Pados [72]
[b]Fletcher et al. [73], Surrey et al. [74]

To minimize any initial agonist (stimulatory) effect that may result in ovarian follicular cyst and hormone production, GnRH-a can be initiated in the luteal phase of the previous cycle to avoid delays in cycle coordination between the donor and recipient. Others have reported the use of early follicular phase norethindrone acetate and GnRH-a in autologous IVF cycles which also minimizes the agonist effect and enhances cycle programming [75,76]. Both of these long GnRH-a protocols have been successfully applied to recipient cycles.

GnRH Antagonists (GnRH-ants)

In contrast, GnRH-ant induces an immediate decrease in circulating gonadotropin concentrations and does not exhibit agonistic effects [77]. Since its introduction into clinical practice in the late 1990s, GnRH-ants have primarily been used in autologous IVF cycles [78], with increasing use in the oocyte donor IVF cycle. They have a number of advantages as compared with GnRH-a including an immediate suppression of pituitary gonadotropins obviating the prolonged period until pituitary suppression becomes effective.

However, their routine use in clinical practice has not yet gained wide acceptance as pregnancy, and implantation rates have been reported to be lower in autologous IVF cycles [79, 80] and

oocyte donation cycles [81, 82] as compared with GnRH-a cycles. The concern lies with the known presence of GnRH receptors outside the pituitary that have been identified including the ovarian follicle and endometrium [83–85]. Any adverse effect of GnRH-ant might be attributable to a direct effect on granulosa cell function, ovarian steroidogenesis [86], embryonic development [84], and possibly endometrial development. The latter has been reported to include altered endometrial histology, earlier expression of progesterone receptors, or altered autocrine and paracrine mitotic programming [83].

As such, while oocyte donation studies have failed to demonstrate any negative impact of GnRH-ant on oocyte or embryo quality compared to those treated with a GnRH-a [87, 88] including a recent meta-analysis [89], its application in recipient cycles has only been reported in two studies [77, 90].

Prapas et al. assessed the direct effects that GnRH-ant exerted on endometrial receptivity in menopausal oocyte recipients who used GnRH-ant during their endometrial priming until the oocyte donor received hCG [77]. Similarly, each donor ($n=49$) received GnRH-ant for ovarian downregulation. Oocytes were then equally shared between two different matched recipients who were randomly allocated to pituitary downregulation with GnRH-ant ($n=49$) or without GnRH-ant ($n=49$). No differences were seen with respect to pregnancy rate (55 % vs. 59 %), implantation rate (26 % vs. 24 %), or endometrial thickness, suggesting that GnRH-ant does not adversely affect endometrial receptivity in oocyte recipients.

Simon et al. assessed the impact of GnRH-ant on endometrial development in 31 oocyte donors who were treated with a combination of rFSH and GnRH-ant started on day 6 of rFSH treatment and continued until the day of hCG administration at doses 0.25 or 2 mg/day [90]. Endometrial biopsies performed 2 and 7 days after hCG administration were compared to those using a long GnRH-a (buserelin) protocol and from cycles following an LH surge of a previous natural cycle. All the parameters studied were comparable in groups 2 days following hCG. On the other hand, 7 days following hCG, endometrial dating, steroid receptors, the presence of pinopodes, and the expression pattern of receptivity genes were comparable in GnRH-ant and natural cycle groups, while those taking GnRH-a, endometrial dating, and pinopode expression suggested an arrested endometrial development. This suggests that no relevant alterations in endometrial development in the early and midluteal phases in women occur using standard- or high-dose GnRH-ant, and the previous concerns raised about GnRH-ant's adverse effects on endometrial receptivity do not appear to be warranted. As such, the mainstay for pituitary downregulation remains GnRH-a; however, GnRH-ant is another option particularly for women who are averse to using GnRH-a.

Patients with Ovarian Failure

In patients without ovarian function, the production of estrogen and progesterone has ceased. Thus, hypothalamic–pituitary downregulation suppression is not necessary, and only exogenous estrogen and progesterone therapy is typically required to mimic a natural cycle.

Clinicians should recognize that women with premature and primary ovarian failure occasionally have intermittent ovarian function, which may appear at the most inopportune time, and therefore these patients should never be assumed to be menopausal. For women with premature ovarian failure, it has been estimated that close to one-half of affected women have evidence of follicular activity, approximately 25 % ovulate, and 5–10 % have been known to conceive spontaneously after the diagnosis is established [91, 92]. In those with Turner's spontaneous pregnancies have been reported in 2–5 %, mainly in those with 45 X/46XX mosaics [93, 94]. Thus, the possibility of spontaneous ovarian folliculogenesis should not be overlooked.

Follicular Phase Priming

Previous work has provided insight into the variable length of the artificial "follicular" phase that

still permits recipient–donor synchronization. By convention, approximately 2 weeks of estrogen priming has become the standard prior to progesterone administration. Since gonadotropin-stimulation oocyte donors speed follicular development, estrogen administration in the recipient often is commenced several days prior to any attempt at ovarian stimulation in the donor and continued with progesterone therapy once the donor is set up for oocyte retrieval [70, 72].

The length of proliferative estrogen administration prior to progesterone does not appear to be an influential factor in the outcome of an oocyte donation cycles as reported in a number of clinical trials. Navot et al. assessed the morphological difference in the endometrium from midluteal and late-luteal biopsies and found no differences between short protocols (minimum 6 days of estrogen therapy), long protocol (21–35 days), and control (14 days). This has allowed greater flexibility in synchronizing recipient and donor cycles without seemingly compromising pregnancy outcomes [10]. Younis et al. suggests the optimal duration of estrogen administration is 12–19 days with pregnancy rates >50 %. However, if the length of exposure fell outside this window, then pregnancy rates were adversely impacted (7 %) [13]. Michalas et al. reported optimal pregnancy rates (43–54 %) with 6–11 days of estrogen exposure, but estrogen exposure >11 days negatively impacted pregnancy outcomes (16–33 %) [12]. As such, successful outcomes have been reported to occur with regimens <5–6 days and >80–100 days [95], though abnormal breakthrough bleeding, reduced pregnancy outcomes, and higher rates of early pregnancy loss appear to occur as compared with the traditional 10–14 days of proliferative endometrial development [10].

Routes

Estrogen supplementation can be administered with oral, transdermal, subcutaneous, and vaginal formulations. Estradiol valerate and micronized compounded formulations are the most widely used estrogens for recipient replacement cycles (Table 8.2).

Table 8.2 Estrogen replacement routes and dosing in recipient cycles

Estrogen	Route of administration	Dosing
Estradiol valerate	Oral	4–8 mg daily[a,b]
17-β estradiol	Oral	4–8 mg daily[a,b]
Estradiol patch	Transdermal	50–200 μg q 3 days[a,b]
Estradiol pellet	Subcutaneous	100–250 mg placed ~6 weeks prior to ET[c]

[a]Dosing can be constant or in a stepwise fashion increasing every 3–5 days
[b]Devroey and Pados [72]
[c]Dmowski et al. [96]

In oral formulations, estradiol exposure to the intestinal milieu and hepatic portal circulation occurs, converting it to estrone, estriol, and conjugated forms. Therefore, as much as a 30 % decrease in the active steroid is delivered to target tissues has been reported [97, 98]. In comparison, transdermal administration of estrogen results in more physiologic estradiol to estrone ratios [99] and is not associated with any changes in serum lipoproteins, clotting factors, or renin substrate. However, studies suggest that more fluctuations in estrogen concentrations and less of a steady state are seen [99]. Regardless of the differences, clinical outcomes appear to be similar using either formulation [100, 101], though no randomized clinical trials have compared either's clinical efficacy. Intravaginal estradiol administration is not preferred during endometrial preparation as this route has been associated with poor patient compliance, attenuated absorption, and further compromised with the addition of vaginal progesterone [72, 100].

Dosing

Adequate endometrial preparation can be achieved with oral estradiol (valerate or compounded 17-beta estradiol) or transdermal regimens. Various hormone replacement regimens have been employed to prepare the recipient endometrium [10].

Originally described was the sequential steroid replacement protocol to simulate the natural menstrual cycle [66, 102, 103]. Other simplified

protocols utilize a fixed dose of estradiol without the physiological variation of hormonal concentrations seen during the normal menstrual cycle, as clinical outcomes are not compromised [67, 103, 104].

Role of Luteal Phase Estrogen

The role of luteal estrogen support remains controversial. Study of rodent models demonstrates the need for luteal estrogen in implantation and decidualization [1], but in other species, luteal estrogen is not required for successful pregnancy outcomes [105].

The role of luteal estrogen in humans and primates remains unclear. In autologous IVF cycles, pregnancy, implantation, and miscarriage rates are similar in patients using luteal progesterone and estrogen compared to progesterone alone [106, 107], though corpus luteum function continues to produce luteal estrogen that may be necessary for implantation. At present, there are no clinical trials in humans that have assessed the need and requirements for luteal estrogen, but standard fresh donor–recipient cycles and cryopreserved embryo replacement protocols typically utilize luteal estrogen.

Progesterone Timing Route of Administration

While blastocyst culture continues to evolve as the standard for ET, cleavage ET classically occurs between days 17 and 19 of the recipient's artificial cycle. This has been shown to be the most appropriate window of receptivity of the endometrium [18, 66].

Vaginal or intramuscular administration of progesterone is recommended for progesterone replacement in the recipient (Table 8.3), in contrast to oral preparations due to insufficient absorption from hepatic first-pass metabolism [72]. Many support vaginal preparations including suppositories, gel, and the ring over intramuscular treatments for enhanced patient satisfaction, and these have been shown to have a similar endometrial secretory pattern to the natural cycle [109]. Progesterone and estrogen therapies are administered together throughout the iatrogenic luteal phase and if pregnancy results, are continued until approximately 8–10 weeks of gestational age until the fetal–placental unit assumes production [70, 110] (Table 8.3).

Table 8.3 Progesterone replacement routes and dosing in recipient cycles

Progesterone	Route of administration	Dosing
Progesterone in oil[a]	Intramuscular	50 mg daily
Progesterone suppository[a,b,c]	Intravaginal	100 mg three times daily[b] 200 mg three times daily[c]
Progesterone gel[d,e]	Intravaginal	8 % gel two times daily

Some clinicians may start IM progesterone at 25 mg the day prior to oocyte retrieval in the donor then step-up to 50 mg the next day

[a]Devroey and Pados [72]

[b]Endometrin® or micronized progesterone 100 mg capsules

[c]Prometrium® or micronized progesterone 200 mg capsules

[d]Yanushpolsky et al. [108]

[e]Crinone® 8 % gel

Overall Recommendations for Optimizing Endometrial Preparation

While there appears to be flexibility in endometrial preparation, rigid study design is limited to suggest the optimal approach. A Cochrane review of randomized controlled trials ($n=22$) by Glujovsky et al. evaluated the most effective endometrial preparation for women undergoing transfer with either embryos from donor oocytes or frozen embryos with respect to live birth rates [111]. No significant benefit was demonstrated when using one GnRH-a over another or vaginal compared to intramuscular progesterone administration. The authors concluded that there is insufficient evidence to recommend any one particular protocol for endometrial preparation over another with regard to pregnancy rates after embryo transfers. While, there is some evidence to suggest a lower pregnancy rate and a higher cycle cancellation rate when progesterone supplementation is commenced prior to oocyte retrieval in oocyte donation cycles, adequately powered studies are needed to evaluate for the optimal treatment regimen.

Recipient Monitoring and Markers of Endometrial Receptivity

A number of direct methods have been used to assess uterine receptivity including histological dating, immunohistochemical methods for measurement of endometrial sex steroid receptor concentrations, scanning electron microscopy assessing pinopode expression, and more recently, cytokines, growth factors, and integrin molecules (see section "Embryo–Uterine Crosstalk") [14, 112–115]. Indirect measures of uterine receptivity have also been extensively evaluated including ultrasonography and Doppler ultrasound, each of which has been positively correlated with implantation and pregnancy rates.

Endometrial Biopsy and the Mock Cycle

Since originally described by Noyes et al. [116], who characterized the morphologic changes of the endometrium to each phase of the menstrual cycle, it has long been advocated that the endometrial biopsy is critical in the screening evaluation of the infertile couple [117–120]. This long-standing notion was to confirm ovulation and to assess the histological maturation of the endometrium to distinguish fertile and infertile couples. This has always been followed by "corrective" hormonal treatments to help infertile women. Recent work from the National Cooperative Reproductive Medicine Network raised this question in a prospective multicenter study to distinguish the ability of histological dating to discriminate between women ($n=847$) of fertile and infertile couples [121]. After detection of a urinary LH surge, subjects were randomized to biopsy in the mid (days 21–22) or the late (days 26–27) luteal phase. The proportion of out-of-phase biopsies (2-day delay in histological maturation of the endometrium) was similar in fertile and infertile women in either the midluteal (fertile, 49 %, vs. infertile, 43 %) or late luteal phase (fertile, 35 %, vs. infertile, 23 %). The authors concluded that histological dating of the endometrium does not discriminate between women of fertile and infertile couples and should not be used in the routine evaluation of infertile couple. Currently, the use of histological endometrial dating to determine endometrial receptivity in oocyte donation cycles remains controversial and is not utilized as the sole determinant of receptivity.

Mock Cycles

As such, the use of preparatory or mock cycles in recipients undergoing fresh donor-oocyte IVF has also been used as a clinical marker of receptivity, though its use remains controversial. Often a timed endometrial biopsy is obtained prior to an actual attempt at oocyte donation. The patient follows a prescribed regimen of hormone replacement similar to that planned for the actual transfer. Typically biopsies occur on the 21st day of medications or 7 days after beginning progesterone. This date coincides with the period known as the "window" of embryo implantation, giving an opportunity to survey the intrauterine environment during this critical interval. Three studies are detailed here reviewing this subject.

Sauer et al. reported that approximately two-thirds of biopsied samples were within 2 days of sampling (d-21); however, almost a third had stromal to glandular dysynchrony with the glandular component lagging behind the stromal component [87]. A lack of adequate estrogen stimulation was rarely seen (2 %), though all cases had subsequent normal biopsies after estrogen priming. Interestingly, no correlation was seen between measured endometrial thickness and histological response. The authors, nonetheless, concluded that the importance of performing an endometrial biopsy in women preparing for oocyte donation went beyond confirming the histological response to hormone replacement therapy as additional information including patient compliance was gained and provided an opportunity to review upcoming cycle treatment plans.

Two other studies specifically examined the impact of mock cycles in oocyte donation cycles on pregnancy outcomes. In a study of 36 women, Potter et al. identified 25 % (5/20) of patients >40 years of age had out-of-phase biopsies, which were subsequently in-phase on repeat endometrial biopsies with adjusted progesterone doses [122]. In contrast, 100 % ($n=16$) women <40 years of age had in-phase biopsies. Pregnancy rates did not

differ statistically between the two age groups. The authors concluded that mock cycles with endometrial biopsies might be beneficial in the older reproductive-age women but not in younger women undergoing ovum donation cycles. Jun et al. evaluated the use of preparatory cycles and compared ongoing-delivered pregnancy rates among patients who underwent mock cycles ($n=50$) with those who proceeded immediately to their actual oocyte donation cycle [123]. Pregnancy rates were similar in women with (42 % [21/50]) and without (43 % [21/48]) mock cycles. In women who underwent a trial cycle, adequate endometrial biopsies were observed in 76 % in pregnant groups compared with 86 % in non-pregnant groups.

Thus, although many IVF programs still perform mock cycles, the potential risks, benefits, and costs should be weighed against the overall lack of data supporting its use.

Ultrasonography

Endometrial thickness and its echogenic pattern is an easy, noninvasive technique that has been used as a surrogate marker of uterine receptivity and a predictor of pregnancy outcome prior to the embryo transfer. Overall, it is generally accepted that a correlation exists between endometrial thickness and uterine receptivity with significantly higher pregnancy rates in those with greater endometrial thickness and certain type of echogenic pattern in both autologous-oocyte and donor-oocyte cycles [124–131], while a thin endometrial stripe is associated with a reduced embryo implantation potential [128, 132, 133]. Others have even reported an adverse effect of an increased endometrial thickness [125]. Conversely, other studies have not shown sonographic assessment of the endometrium to be of any benefit in the characterization of uterine receptivity in IVF patients [134–139].

The echogenic pattern of the endometrium has also been suggested as a predictor of pregnancy outcome [129, 131, 140, 141]. In the proliferative phase, a trilaminar or triple layer with altering hyperechoic and hypoechoic layers should be seen, while after ovulation and/or progesterone administration, the endometrial patterns change to a homogenous hyperechoic pattern. Therefore, some suggest in autologous IVF cycles that if a homogenous hyperechoic patterns is visualized, it may suggest premature luteinization and altered endometrial receptivity [131, 140], though other studies report no alterations in pregnancy rates despite echogenic pattern [128, 133].

In oocyte donation cycles, where the possible adverse supraphysiologic effects of ovarian hormones upon the endometrium are eliminated [142–144], the correlation between endometrial thickness pattern and pregnancy outcome has been assessed in a few clinical trials. Noyes et al. retrospectively analyzed 343 oocyte recipient cycles and found that clinical pregnancy and live birth rates were significantly lower when endometrial thickness was <8 mm than when endometrial thickness was >9 mm [130]. Zenke and Chetkowski reported in recipient pairs with discordant outcomes ($n=41$) that endometrial thickness <8 mm 1 week prior to oocyte retrieval was found in failed cycles [128].

In contrast, a retrospective review of 465 oocyte donor cycles revealed no correlation between ultrasound appearance of the endometrium the day before embryo transfer and pregnancy outcomes [145]. A matched pair analysis of 365 recipients with discordant outcomes also suggested that endometrial thickness measured on cycle day 15 or 16 was not a significant finding [135]. Each of these studies used cleavage stage ET or a mixture of cleavage- and blastocyst-stage transfers [128, 130, 135, 145–147], whereas Barker et al. standardized to blastocyst ET ($n=79$) [148]. As such, endometrial thickness was still not different in either the late proliferative or mid-secretory phase in pregnant and non-pregnant cycles.

Nonetheless, despite the many reports (some conflicting), the endometrial thickness and endometrial pattern are reassuring as a marker of endometrial receptivity and pregnancy outcomes. On the other hand, literature suggests that couples should not be discouraged from undergoing an ET in oocyte donor cycles regardless of the endometrial thickness or its morphologic pattern. Certainly many studies are limited due to single measurement or measurements at differing in relation to the ET. A uniform agreement by

investigators to assess endometrial thickness and pattern in a more rigorous and standardized fashion would perhaps enable the clinician to gain further insight into endometrial thickness and its relative importance.

Doppler Flow

Imaging with uterine artery Doppler Flow assesses the pulsatile index (PI), which is a measure of the variability of blood vessel velocity, has been utilized to determine endometrial receptivity in ART cycles. Steer et al. investigated the PI grouped as low (1.00–1.99), medium (2.00–2.99), and high (>3.00) in 82 women immediately prior to ET in autologous IVF cycles and reported no pregnancies in those with a high PI [149]. This has been corroborated by others where decreasing pregnancy and implantation rates in 108 patients were seen in those with a PI > 2.50 [150]. In contrast, others have reported that changes in PI could not predict outcomes following ET [151].

Other indices including vascular index (VI), vascular flow index (VFI), vascular flow intensity, endometrial volume, and uterine resistance index (RI) have also been examined as markers for endometrial receptivity. Studies have shown a correlation with these indices including the association of lower VI and VFI with higher pregnancy and implantation rates [152, 153], while others report no correlation between pregnancy outcomes with uterine or spiral artery blood flow indices [133].

As such, the use of Doppler Flow imaging in assessing endometrial receptivity remains unclear. Further investigation may provide insight into its use as another noninvasive marker to identify optimal endometrial receptivity.

Biomarkers of Endometrial Receptivity

Endometrial sampling during mock cycles prior to the egg donation cycle has been utilized not only for histological dating but also to examine other biomarkers of receptivity including pinopode and integrin expression. As previously discussed (see section "Embryo–Uterine Crosstalk), endometrial and blastocyst signaling results in both pinopode and αvβ3 integrin expressions around the time of implantation. While studies have shown these to be altered and even absent in those with endometriosis and unexplained infertility [20, 54–56], other studies in both autologous-oocyte and donor-oocyte cycles have demonstrated conflicting data using these as markers for endometrial receptivity [21, 25, 26, 28, 57].

As further identification and understanding of these implantation markers biomarkers are elucidated, they may also help predict occult implantation deficiency and pregnancy outcomes. Future treatment including endometrial stem cell and gene therapy for direct treatment of dysregulated endometrial proteins or transcription factors may ultimately improve implantation and clinical outcomes [154].

The Oocyte Donor Cycle

Donors typically initiate controlled ovarian hyperstimulation (COH) after the recipient has begun estrogen therapy as follicular recruitment is often accelerated. In order to synchronize the donor's cycle, various regimens utilizing oral contraceptive pills (OCP), GnRH-a, and GnRH-ant have been used and will be reviewed (Fig. 8.1).

Oral Contraceptive Pills

The OCP and progestin-only pills (POP) have been widely used to synchronize IVF cycles [155]. Short-term OCP therapy is typically initiated in donors to coordinate COH cycle starts with that of the recipient [70]. They serve several purposes including contraception protection, reduce ovarian cyst formation, and shortened time for prolonged pituitary suppression [155]. OCPs typically are initiated the cycle prior to the planned COH start and discontinued several days prior to COH. Concerns regarding optimal COH stimulation and pregnancy outcomes have been raised.

With respect to COH stimulation, the optimal length of use of OCPs and washout period (time from last pill to COH) in IVF cycles remains controversial. Some suggest that the length of OCP administration should be minimized (12–16 days) in order to avoid over-suppression of the

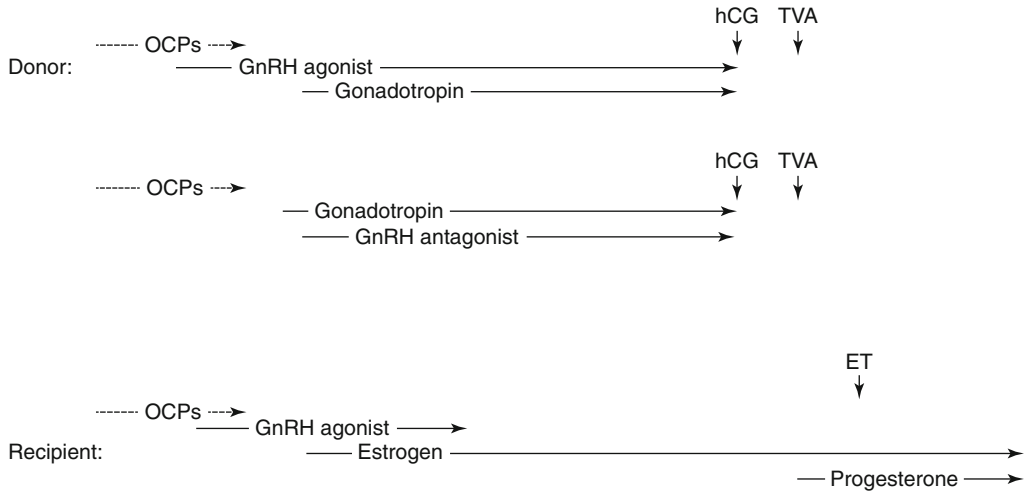

Fig. 8.1 Donor–recipient synchronization using GnRH-a and GnRH-ant in oocyte donor (Based on Klein and Sauer [70]. With permission from Elsevier)

pituitary–ovarian axis [156] and prolonging COH [157]. Cedrin-Durnerin et al. evaluated FSH and LH levels in IVF cycles using OCP pretreatment and reported the optimal washout period to be 5 days [158]. Shorter washout periods of 2 days demonstrate comparable pregnancy rates [159] but had longer stimulation cycles.

The use of OCP has historically been used with GnRH-a protocols; however, recent debate has focused on their use with GnRH-ant protocols [156]. Two recent meta-analyses in autologous IVF cycles using GnRH-ant suggested a decrease in pregnancy outcomes with OCP pretreatment when compared with no OCP pretreatment. However, the effect size was small and had many confounding variables including the type of OCP which were included in this analysis [160].

A recent randomized controlled trial ($n=263$) of normal responder autologous IVF cycles compared those using 12–16 days OCP pretreatment with COH–GnRH-ant with a washout period of 5 days to those using long GnRH-a alone for pituitary downregulation [156]. No differences were seen with respect to fertilization, clinical pregnancy, or live birth rates, but OCP pretreatment with COH–GnRH-ant resulted in shorter duration of COH compared to those using GnRH-a alone.

While no clinical trials in oocyte donors have assessed OCP pretreatment with clinical outcomes, its use for cycle synchronization does not appear to compromise recipient outcomes. It is typically recommended to use an OCP with at least 20 μg of ethinyl estradiol to prevent ovarian recruitment. Lower estrogen components and progestin-only pills (POP) more frequently will result in follicular recruitment and result in delayed cycle starts using either GnRH-a or GnRH-ant protocols.

Pituitary Suppression with GnRH-a or GnRH-ant

To allow for optimal synchronization between donor and recipient cycles, pituitary suppression in the oocyte donor is also necessary to prevent a premature LH surge. Long GnRH-a protocols have historically been used to induce pituitary suppression in oocyte donor cycles [71] to reduce premature ovulation, enhanced oocyte recruitment and pregnancy outcomes compared to non-GnRH-a cycles. Protocols using GnRH-a as a "flare-up" have also been described to shorten the duration of medications with similar pregnancy outcomes [161, 162].

In the past 10 years, GnRH-ant have increasingly been utilized for pituitary downregulation in oocyte donors as they offer the advantages of obviating the prolonged pituitary downregulation required with GnRH-a and a reduction in the incidence of ovarian hyperstimulation syndrome (OHSS) [163–166].

As previously discussed, concerns of decreased pregnancy and implantation rates were initially reported with GnRH-ant donor cycles [81, 82], as lower estradiol levels are often seen and thought to impact oocyte maturation and competency [167]. Newer variations in the use of GnRH-ant including its delay until lead follicles are at least 12–14 mm and additional gonadotropins (FSH and LH step-up) have been described [168, 169]. A recent meta-analysis has suggested similar clinical outcomes using with either GnRH-a or GnRH-ant (live birth rate 0.86, CI 0.69–1.08; ongoing pregnancy rate 0.87, CI 0.77–1.00) in donor-oocyte cycles giving clinicians the reassurance of either option without compromising clinical outcomes [170].

Controlled Ovarian Hyperstimulation (COH) in Oocyte Donors

The ultimate success in oocyte donation cycles is equally dependent upon the recruitment and development of multiple follicles from COH, which lead to the development of multiple and high-quality embryos for selection for ET. While the selection of the optimal stimulation protocol is beyond the scope of this chapter, much like in autologous cycles, noninvasive markers of ovarian reserve including age [171], early follicular phase FSH [172–174], estradiol [175,176], inhibin B [177, 178], and anti-mullerian hormone [179–181] have been used in an attempt to select the optimal ovum donor who will yield the highest number and best quality oocytes. In addition, a growing number of studies including two meta-analyses [182–186] suggest that antral follicle count ((AFC) 2–10 mm in both ovaries) in the early follicular phase correlates with ovarian reserve [187]. AFC appears to be useful in selecting optimal oocyte donors and allows for tailoring gonadotropin dosage particularly where concerns exist for both adequate COH response and ovarian hyperstimulation syndrome.

Special Considerations

Overcoming the Thin Endometrium

Thin endometrial lining, as previously discussed, is believed by many to result in poor pregnancy outcomes in both autologous-oocyte and donor-oocyte cycles. Several therapies in addition to supplementing with higher doses of estrogen have been proposed to address this issue.

Aspirin (ASA) has been investigated in oocyte recipients and frozen embryo recipients with conflicting results. In a small RCT, 28 recipients undergoing mock cycles who failed to develop an adequate endometrial thickness (≥8 mm) were either randomized to receive or not receive ASA. While implantation rates significantly improved in those treated with ASA (24 % vs. 9 %), no difference was noted in endometrial thickness between groups [188]. Nonetheless, the impact of ASA on endometrial thickness remains controversial, including a recent meta-analysis which found no improvement in clinical outcomes [111].

Vaginal sildenafil (Viagra) is a phosphodiesterase-5 inhibitor that enhances nitric oxide vasodilatory effects and has been reported in a few small clinical trials to improve uterine blood flow, endometrial thickness, and pregnancy outcomes [189–191]. There is also data to suggest that vitamin E in doses of 600 mg/day increases uterine capillary blood flow and results in improved endometrial thickness [190, 191]. Vitamin E in combination with pentoxifylline (anti-fibrotic therapy) also has been shown to result in improved pregnancy rates in with the face of thin endometrium [192].

Turner Syndrome (TS) Recipients

It is well known that women with TS have obstetric complications characterized by a high rate of hypertension, preeclampsia, and premature delivery [193, 194], but they also have a potentially

high risk of death during pregnancy from aortic rupture or dissection [195]. Currently, guidelines recommend thorough cardiologic screening before undergoing oocyte donation treatment [196, 197] with consideration for elective single embryo transfer to minimize obstetrical complications related to multiple gestations. A recent large series has also suggested lower ongoing pregnancy rates and a higher early pregnancy loss rate following ET compared to matched women undergoing oocyte donation which is consistent with previous reports [194, 198]. While it is unclear if it is related to uterine hypoplasia–hypovascularization, other factors including autoimmune thyroiditis or the increased prevalence of a heterozygous form of adrenal 21-hydroxylase deficiency, which has been reported in these patients, should be considered [199, 200].

Oocyte Donors with Levonorgestrel-Releasing Intrauterine Device (LNG-IUD)

Questions have arisen as to the impact of cycle coordination and/or removal in oocyte donors that present with a LNG-IUD. Suppression of ovarian function occurs in approximately 55 % of LNG-IUD users within the first year of use [201], but after which, many women will have normal ovulatory cycles including a high frequency of follicular growth and rupture [202]. With respect to oocyte donation cycles, some have suggested that a LNG-IUD may lower the fertilization potential of oocytes. A small study ($n=7$) did not show any adverse effect on fertilization, cleavage, or pregnancy rates when utilized in oocyte donors [203] suggesting that removal may not be required for oocyte- and recipient-cycle coordination.

Conclusion

Egg donation has provided many patients the ability to achieve pregnancy with success rates approaching 50–60 % per cycle. Donor–recipient cycles have certain challenges not seen in autologous IVF cycles; thus, the clinician must understand embryo–uterine biology, optimal protocols for donor and recipient coordination, as well as overcoming potential obstacles. Egg donation cycles have provided invaluable information in our understanding of human embryo implantation and successful synchronization of donor and recipient cycles. Continued research will gain further insight to determine optimal endometrial receptivity, improve implantation efficiency, and minimize multiple rates associated with assisted reproduction.

Editor's Commentary

One of the pleasant surprises discovered during the development of the clinical methodology of oocyte donation relates to the simplicity of synchronizing the donor and the recipient. Early investigators trying to align the menstrual cycles of spontaneously ovulating donors and recipients were hampered by the unpredictable nature of the spontaneous ovulatory cycle, and its variable quality of expression, resulting in many cancelled attempts and undoubtedly more than a few bad outcomes. Needless to say, it would have been nearly impossible to do this once donors were placed on ovarian hyperstimulating medications. Even the initial years of using hormone replacement therapy in recipients were plagued by doubt as to the adequacy of steroid delivery as patients were required to undergo mock cycles with endometrial biopsies, blood tests to evaluate whether "physiologic" levels of steroid had been attained, and were prescribed complicated roadmaps of hormones given in accordion-like fashion to mimic the ups and downs of normal ovarian secretion. Thankfully, that era is far behind us.

Sroga and Lindheim detail the complexity of the events that are presently believed to occur within the uterus at the time of implantation. It is indeed a highly dynamic environment. The intricacies of the cellular and biochemical interactions constantly

remind me of the absurd logic that suggests that a single clinical measure, such as a random serum estradiol or progesterone level or transvaginal ultrasound, will predict whether or not a transferred embryo might implant. Unfortunately, many patients and ill-advised doctors do ascribe to the value of these surrogate endpoints, and it denigrates the sacrifice and hard work of the hundreds of human subjects who undertook ritual testing to assure us of the sanctity of the regimens we now prescribe. After 30 years, what we do know is that there are many ways to prepare a uterus to receive and implant a transferred embryo, and perhaps, the simpler we make it, the better.

As egg freezing becomes vogue, the process will become even more facile, as only endometrial preparation will be needed and donors can be managed autonomously. In the meantime, a prescribed course of estrogen, probably any formulation will do, with the timely addition of progesterone will allow pregnancy to occur in humans of most any age and circumstance.

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9 Preparing the Endometrium to Maximize Success: The Dynamics of Artificial Cycles

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Key Points

- The sole administration of E2 and progesterone optimizes endometrial receptivity and carries clear messages that eluded our original and long-held views on endometrial receptivity and its hormonal control.
- Hormonal replacement of pregnant recipients is typically prescribed at constant doses until the tenth week of pregnancy at which time the placenta autonomously supplies all necessary hormones to support the gestation.
- The duration of exposure to progesterone rather than its serum levels controls the endometrial changes leading to endometrial receptivity.
- There is ample evidence that vaginal and intramuscular progesterone is equivalent for establishing endometrial receptivity in both regular ART and DE-ART.

In vitro fertilization (IVF) was developed for women with diseased or absent Fallopian tubes. Rapidly however, the clinical successes witnessed in IVF opened in their wake the doors to the until-then uncharted realm of oocyte exchanges. Together with its variant for male factor infertility – intracytoplasmic sperm injection (ICSI) – IVF is now called the assisted reproductive technology (ART). Logically, therefore, we refer to oocyte donation – with either IVF or ICSI – as donor-egg ART (DE-ART).

Using donated oocytes for women whose ovaries have failed – in DE-ART – implied however that endometrial receptivity may be attained through the prescribed use of exogenous hormones. At the outset, at a time when results of general IVF were relatively meager, the need to rely solely on artificially prepared endometrium in recipients tarnished any prospect that DE-ART would be successful. Hence, the improbable and rapid unraveling that placed the results of DE-ART not only at par but most often above those of the corresponding regular ART programs was certainly a surprise [1–4]. Subsequently, hormonal treatments provided to recipients were further simplified without affecting

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results, as discussed below. Amazingly a quarter of century later, the E2 and progesterone cycles developed for DE-ART recipients in the 1980s are still the unchallenged provider of the most receptive endometrium possible [5]. The fact that the sole administration of E2 and progesterone optimizes endometrial receptivity carries clear messages that eluded our original views on endometrial receptivity and its hormonal control. The DE-ART's quarter-century history thus indicates that other hormones and growth factors produced by the ovaries – whether or not under the control of gonadotropins– are not necessary for endometrial receptivity to embryo implantation. The reciprocal principle is that ovarian substances other than E2 and progesterone – i.e., androgens – either do nothing or in certain circumstances may actually harm endometrial receptivity. As we discuss later, this bears relevance for general infertility patients at large [6].

In the wake of DE-ART's unexpected superior results, the E2 and progesterone regimens developed for recipients have become study models for endometrial receptivity. Summarizing the use made of E2 and progesterone cycles for over >25 years, we outline four different types of studies for (1) assessing the markers – echographic, histological, genomic, etc. – of endometrial receptivity [7]; (2) establishing the leeway existing for simplifying protocols and synchronizing donors and recipients in DE-ART [8, 9]; (3) benchmarking the efficacy of new E2 and progesterone products [10]; and finally (4) applying these regimens outside of DE-ART, as, for example, for frozen embryo transfers (FET) [11–14].

We will review here the state of the art of E2 and progesterone cycles, as they are currently used in DE-ART. Doing this, we will emphasize the practical options – types of preparation, doses, and route of administration used – that exist for synchronizing oocyte donors and recipients. Whenever appropriate, we will also mention the tenets drawn by a quarter-century history of donor-egg ART practice that apply to endometrial receptivity in ART at large.

Background and Objectives

Originally, Hormone Administration Duplicated the Menstrual Cycle Profiles

The original challenge for the emerging practice of DE-ART was to prime endometrial receptivity in women deprived of ovarian function with exogenous hormones – E2 and progesterone. Not knowing better, the mere logic called for duplicating the hormonal profiles of the menstrual cycle in DE-ART recipients. There was little to no information as to any degree of leeway regarding the duration and doses of hormones to be used for priming endometrial receptivity. Hence, the early hormonal regimens of DE-ART squarely reproduced the patterns of plasma E2 and progesterone levels seen in the menstrual cycle [2, 15, 16]. Particularly, the progressive increase in E2 levels of the late follicular phase was reproduced by administering progressively increasing quantities of E2 [1, 2, 15–17]. As discussed below, the doses of E2 administered varied according to the route of administration chosen and preparation used [15, 16]. In contrast, however, the quantities of E2 and progesterone administered for duplicating ovarian production during the luteal phase were generally kept constant. This actually mimicked the constant daily production rates of E2 and progesterone encountered throughout the luteal phase.

Hormone Administration in Early Pregnancy

Because the corpus luteum is not present – absent or inactive ovaries – hormonal treatment must be continued until the luteal-placental shift is safely established. Once pregnancy is confirmed by rising hCG levels, the early DE-ART groups purported increasing the doses of E2 and progesterone administered daily [17]. This aimed at mimicking the rise in the circulating levels of E2 and progesterone normally seen in early pregnancy [18]. Today, however, hormone administration is commonly not further modulated once pregnancy is established, as it

has been unequivocally demonstrated not to affect outcome [19, 20]. Today, therefore, hormone replacement in DE-ART is typically pursued at constant doses until the tenth week of pregnancy (12th week of theoretical amenorrhea). By then, E2 and progesterone production is primarily occurring in the placenta, and no significant E2 and progesterone production comes from the ovary. Yet, the corpus luteum does not become totally inactive as peptide production – notably relaxin – continues until delivery [21]. While relaxin was purported to be instrumental in uterine and cervical changes occurring prior to labor, no delays in labor and/or cervical dilation dysfunctions have been reported in recipients of DE-ART whose ovaries are absent or inactive [22, 23].

Hormone Administration and Gonadotropin Profiles

The early recognition of the efficacy of E2 and progesterone cycles in DE-ART led to the use of similar paradigms for priming frozen embryo transfers (FET) [11, 12]. Early on, E2 and progesterone cycles were used after ovarian function was suppressed with a GnRH agonist (GnRH-a) [11, 12, 24]. Numerous reports concluded similar pregnancy rates following FETs in patients prescribed E2 and progesterone for their artificial cycles compared to FETs in the natural cycle [25]. This indirectly implied that the gonadotropin levels – suppressed in FET following GnRH-a, at physiological levels in the menstrual cycle, and elevated in women with failing ovaries – bear no consequences on ART outcome. The findings made in DE-ART and FET of regular ART in controlled and natural cycles disclaim therefore the hypotheses of possible physiological effects of circulating LH on endometrial receptivity. The latter thoughts were drawn from observing LH receptors in the endometrium [26] and demonstrating in vitro effects [27]. Today, DE-ART cycles conducted in women whose ovaries have not totally failed make liberal use of GnRH-a prior to administrating E2 and progesterone for endometrial priming. This permits a reliable synchronization of oocyte donors and recipients.

Pursuing our attempt at simplifying the priming of endometrial receptivity in DE-ART and FET, we reported that ovulation could be reliably suppressed by E2 alone [13, 28]. This implies however that E2 treatment is precisely started on cycle day 1 or better 2–3 days before the onset of naturally occurring or induced menses. An early onset of treatment is necessary in order to prevent the inter-cycle rise in circulating FSH [29] and the ensuing risk of follicular recruitment. In our hands, we reported a risk of premature ovulation of <5 % when E2 treatment was started on day 1 for priming FET [13]. The efficacy of priming endometrial receptivity by E2 treatment alone in women with active ovarian function was later confirmed by others in a controlled randomized trial (RCT) [30]. Subsequently, we recommended that in all patients – not just in good responders having frozen embryos – E2 treatment (2 mg of micronized E2, BID) is started 2–3 days prior to menses (efficacy >95 %). We found that this approach prevents ovulation for up to 2 weeks, possibly longer [31]. It was impossible to determine whether the rare failures observed [13, 31] resulted from treatment escapes – FSH elevation and follicular recruitment despite E2 treatment – or errors. Practically, the assurance that no premature ovulation took place can be simply ascertained by documenting that progesterone levels are low just prior to administer exogenous progesterone.

For fresh DE-ART transfers in women with functioning ovaries, even a ≤5 % risk of cancelling the embryo transfer – possibly higher due to ovarian dysfunctions – may appear excessive however. Cycle anomalies are indeed likely to be more frequent in women undergoing DE-ART precisely because of the underlying cause of infertility and lack of ovarian reserve. Yet, the trend for cryopreserving oocytes and constituting oocyte banks in DE-ART programs will likely lead to physicians primarily using simple E2 and progesterone cycles in DE-ART in a near future. In these cases, documenting premature ovulation will only bear the consequence of cancelling transfer with no adverse impact on final pregnancy outcome.

In women with absent or failed ovaries, reproducing the menstrual cycle levels of E2 leads to

LH surges occurring as early as day 8 [32]. A similar advancement in the LH surge was also encountered in women whose normal ovarian function was suppressed by exogenous E2 for priming FET [33]. In the menstrual cycle, the LH surge normally occurs later on cycle day 12–14. This different timing of LH surges despite similar E2 profiles indicates that in the menstrual cycle, the growing follicle actively delays LH surge by producing an anti-gonadotropin surge substance [34]. The message regarding receptivity in DE-ART however is that the endometrial receptivity is not affected by gonadotropin levels and whether or not the ovaries are functional [35].

Endometrial Changes Induced by E2 and Progesterone

Endometrial Priming by E2

By necessity, the follicular and luteal phases of the menstrual cycle were replaced by the E2 only and E2 and progesterone steps of DE-ART treatments. Implicit in this strategy is the fact that all the other products of ovarian function, most notably androgens and peptides, were ignored in DE-ART. The E2-only step of DE-ART treatment aims at inducing endometrial proliferation and priming the subsequent response to progesterone [8, 32]. The latter implies the development of ER and PR in endometrial glands and stroma [36]. Tissue proliferation characterized by cellular mitoses in endometrial glands and stroma is assessed clinically by measuring endometrial thickness on ultrasound. Practically, dual thickness of ≥7 mm, not different from findings made in the menstrual cycle [37], is considered as optimal. Endometrium of 5–7 mm has been shown capable of fostering the development of normally evolving pregnancies, even if possibly – not certainly – with poorer ART outcome. Endometrium <5 mm is generally held as incapable of maintaining receptivity and normal pregnancy development even though positive outcomes have been sporadically reported [38, 39].

As noted above, endometrial proliferation is associated with the development of the proper pattern of ER and PR expression. ER alpha (aER) has been shown to be necessary for the priming of PR. Nuclear PR (nPR) – now known to be of two types, A and B – accounts for the majority but not all of progesterone's effects on the uterus and is regarded as instrumental to endometrial receptivity [40]. Indeed certain effects of progesterone are nPR-independent, particularly the uteroquiescent properties exerted by progesterone on myometrial cells [41]. These non-genomic effects of progesterone are exerted through binding to membrane receptors [42], metabolites of progesterone such as allopregnanolone binding to the $GABA_A$ membrane receptor complex, or indirectly [43].

Progesterone and Endometrial Receptivity

Once the endometrium is properly primed by E2, the addition of progesterone triggers a sequence of morphological changes that characterize the luteal phase of the menstrual cycle [44]. This sequence of changes is actually so strikingly regular that early investigators in the field proposed that the luteal phase endometrium can be timed accordingly [44]. Remarkably, these findings made in the early 1950s have not been challenged to date, even if further methods of endometrial assessment – including "omic" science [45–47] – have since been added.

We now realize that the morphological changes reported by early investigators actually sequentially affect first the glandular epithelium and later the stroma. Indeed, the endometrial transformations that characterize the first half of the luteal phase take place in the glandular epithelium. These are epitomized by the development of subnuclear secretory vacuoles, which push the glandular nuclei toward the cellular apex thereby conferring a characteristic palisade-like aspect [6, 44] (Fig. 9.1). Conversely, the secretory transformations that characterize the second part of the luteal phase occur in the stroma [6, 44]. Initiated by the development of stromal edema, these changes ultimately lead to the predecidual transformation of stromal cells, which undergo

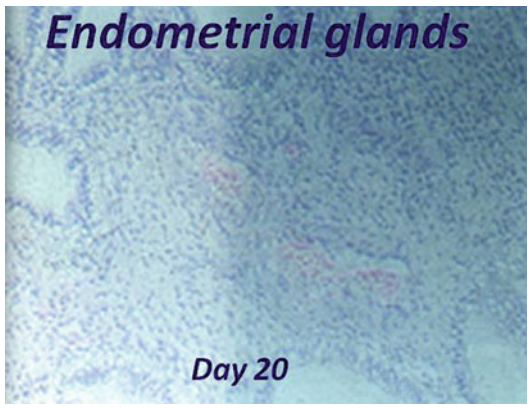

Fig. 9.1 Day 20 endometrium (sixth day of progesterone exposure)

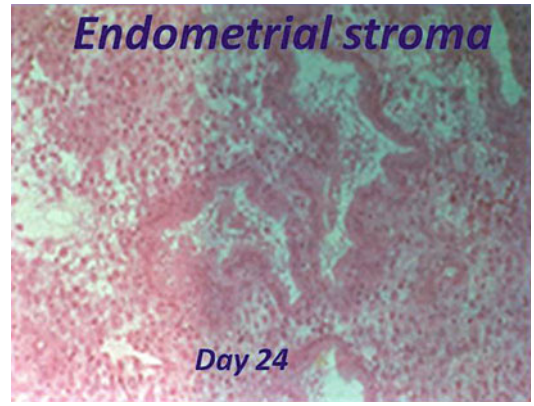

Fig. 9.2 Days 24–26 endometrium (10th–12th day of progesterone exposure)

epithelioid transformation (Fig. 9.2) [6, 44]. Predecidualization first starts in the vicinity of the spiral arteries as early as day 23 of a 28-day cycle or day 9 of progesterone exposure. The process later expands in a centrifuge manner to ultimately affect the full thickness of the endometrium, reaching the surface by day 26 (day 12 of progesterone exposure).

We have learned since the original description of Noyes and Haman [44] that the two constituents of the endometrium have different sensitivities – or threshold of responses – to progesterone [6]. The glands respond to minimal progesterone elevations, including the slight progesterone elevation encountered in the late follicular phase of the menstrual cycle. On the contrary, the stroma shows lesser sensitivity to progesterone with a far higher threshold for a full deployment of changes [6].

The Window of Implantation (WOI) Concept

Early work on DE-ART has defined the best timing for embryo transfers [1, 48]. There is now a consensus for recognizing that it is the duration of exposure to progesterone rather than its levels that control the endometrial changes leading to endometrial receptivity [48]. For cleaving-stage embryos, the optimal timing for embryo transfer is on the third to fourth day of exposure to progesterone [6, 48, 49] and 1–2 days later for blastocysts [28]. This time period is known as "the window of implantation (WOI)." From the heydays of DE-ART, we have known that a certain flexibility exists at the onset of the WOI with even DE-ART successes reported when embryo transfers occurred before any exposure to progesterone [1, 16, 50]. Conversely, the closure of the WOI is notoriously abrupt with no pregnancies reported when cleaving embryos are transferred after the fifth day of exposure to progesterone [1, 16, 51]. This led to the governing principle for endometrial receptivity in DE-ART stating that embryos can wait for the endometrium, but not the opposite. Stated differently, early transfers by reference to WOI are not optimal but bear certain chances of being successful, whereas late transfers have no chance at all.

Endometrial Responsiveness to Progesterone

Originally, the uterus – the endometrium in particular – was seen as passively responding to hormones. According to this view, all that counted for optimizing endometrial receptivity was to foster an ideal profile of circulating hormones – E2 and later, E2 and progesterone. The implication therefore was that endometrial effects simply followed the hormonal profile. The generally recognized observation that outcomes of DE-ART are essentially unaffected by the recipient's age

[5, 52] strongly comforted this perception. The latter obviously implied that no anatomical disruption of the uterine cavity – i.e., fibroids with submucosal extension – impaired hormones' action and thus, receptivity [5]. Generally, DE-ART data have supported the proposition that the endometrium passively responds to the circulating levels of E2 and progesterone in an age-independent manner.

Recently, however, different paradigms of endometrial responses to hormones have been identified in certain infertility conditions, most notably endometriosis and polycystic ovary syndrome (PCOS). In endometriosis, the eutopic endometrium was reportedly altered independently from the E2 and progesterone profile [53– 56]. These alterations have been linked in part to a documented state of progesterone resistance associated with endometriosis [57, 58]. Likewise, the testosterone elevation encountered in certain cases of PCOS may alter endometrial response to progesterone [59], including altering the expression of HOXA10 genes [60, 61].

Interestingly, the endometrial alterations reported in endometriosis [62–64] are corrected by ovarian suppression [56, 65, 66]. Ovarian suppression by analogs of GnRH (GnRH-a) or oral contraceptives is intriguingly equally effective, in spite of the difference in estrogenic environment achieved by these two approaches. In regular ART, the outcome can be normalized in endometriosis by either 3–6 months of GnRH-a [67] or 6–8 weeks of oral contraceptive (OC) taken continuously [68]. That endometrial morphology and ART outcome can be normalized by ovarian suppression (GnRH-a or OC) explains the report of normal implantation rates in DE-ART recipients with endometriosis [69]. The same probably applies in PCOS patients in whom ovarian suppression restores endometrial responsiveness to progesterone by blocking androgens. Hence, progesterone resistance as seen in endometriosis or PCOS is probably of limited concern in DE-ART, thanks to the fact that ovarian function is either absent or suppressed in this paradigm.

Endometrial receptivity is affected in recipients of DE-ART in cases of hydrosalpinx, as also demonstrated in regular ART patients [70]. Salpingectomy by laparoscopy, which restores normal receptivity [71, 72], should be proposed in donor-egg recipients similar to recommendations for women undergoing regular ART. When salpingectomy is technically difficult, proximal tubal clipping [73] or obliteration by trans-uterine placement of Essure devices [74, 75] should be considered.

Unexpectedly, Bodri et al. reported racial differences in DE-ART outcomes [76]. In their findings, the authors observed that the black race was an independent risk factor for not achieving an ongoing pregnancy after oocyte donation. Rather than an inherent racial difference, we believe that this observed difference in outcome likely results from an increased incidence of fibroids and/or past uterine surgery for fibroids in black women. In this study, black women were also significantly heavier than their white counterparts, a fact that may also hamper the outcome of DE-ART [77].

The Donor-Egg ART Regimens as Study Model

The recognized efficacy of E2 and progesterone treatment regimens designed for DE-ART for priming optimal endometrial receptivity led to using them as study platforms. The first objectives of these studies were to delineate the respective roles of E2 and progesterone and that of their ratio in priming endometrial receptivity. The prevailing principle in the early days of ART was that the E2 to progesterone ratio might correlate with endometrial receptivity. Along these lines, the unphysiologically high levels of E2 in regular ART were seen as responsible of the suboptimal implantation rates [78]. Using the treatment regimens designed for DE-ART as a study model, we demonstrated that luteal E2 levels – E2 produced in conjunction with progesterone – had no impact on endometrial morphology [32]. Further studies concluded that even extreme alterations in the E/progesterone ratio were without consequences on endometrial morphology [79, 80].

Epigenic Effects on the Endometrium

In a recent review, Munro et al. outlined the facets of endometrial regulation occurring in the menstrual cycle that likely result from epigenic modification [81]. Epigenic adaptations lead to stably inherited phenotypes without alteration in the DNA sequence. Changes in DNA activity without altered DNA sequence primarily result from DNA methylation and posttranslational modification of histone tail [82, 83]. Today, one commonly admits that 10–20 % of genes show DNA methylation patterns in tissue-specific forms of gene expression [84]. Evidence that epigenic changes are at the base of the endometrial alterations encountered in endometriosis has been accumulating. In animal models, injection of large amounts of E2 increases the degree of epigenic alterations, which revives the concerns about E2 overexposure.

Hormone Preparations Available and Regimens of Proven Efficacy

Choosing Between E2 Preparations

In general, estrogens can be administered either as native E2 molecules or synthetic products such as ethinyl E2 (EE). Synthetic estrogens were designed to maintain their bioactivity when taken orally by resisting enzymatic degradation during their first pass through the liver. Synthetic molecules such as EE however should not be used in DE-ART. This restrain is motivated by concerns regarding epigenic alterations through unphysiologically high estrogenic effects as encountered in the past with diethyl stilbestrol (DES) [85, 86].

Through micronization – the fine grinding of E2 crystals – the currently available E2 preparations were made readily and nearly totally absorbed when ingested orally [87, 88]. Oral E2 is however intensely metabolized during the first liver pass [88]. Because of this, the amounts delivered orally need to largely surpass – by 20–40 times – the normal daily ovarian production rates for achieving peripheral effects similar to those seen in the menstrual cycle. As illustrated in Table 9.1, daily doses varying from 2 to 6 mg BID have been used in donor-egg regimens for replacing the ovarian production of E2, which typically amounts to 0.05–0.5 mg/day. These oral E2 regimens lead to circulating levels of E2 that closely shadow those seen in the menstrual cycle. With the intense metabolism of E2 during the first liver pass, the larger fraction of orally ingested E2 is converted into estrone (E1) and subsequently E1 sulfate [88]. As a result of this, the circulating levels of E1 are elevated to pharmacologically high levels, commonly seven to ten times above those of E2 [87, 88]. In the menstrual cycle, the circulating levels of E1 increase as a result of E2 production but always remain below those of E2 with therefore E2/E1 ratios always >1. The pharmacological levels of E1 achieved as a result of administrating E2 orally were however not found to cause any harm in DE-ART [87, 88].

Over the past 30 years, various systems have been developed for delivering E2 transdermally that are commonly called “skin patches” [89]. These systems deliver set amounts of E2 per 24 h – commonly a number in micrograms that defines their strength – directly into the peripheral circulation [90]. Transdermal systems delivering E2 or “patches” are worn for 3.5 or 7 days, depending on the products [89]. While weekly systems appear practical, we have not used them because of their pharmacokinetics, which shows decreasing delivery doses toward the end of the week. The administered doses are modulated by the size of the transdermal system used and the number of systems worn simultaneously. The E2-to-E1 ratio remains >1 irrespective of the dose administered, as seen in the normal menstrual cycle [90]. E2 can also be administered transdermally from gels applied on the skin once a day [91]. The principle is that E2 diffuses to the superficial layers of the skin where it is stored and released progressively toward the dermal vessels. Skin gels are not commonly used for hormone administration in DE-ART, primarily because of the difficulty at precisely determining the dose administered.

Because they avoid the first liver pass, transdermal administration of E2 is not affected by

Table 9.1 Estrogen and progestin products and treatment regimens available

Product	Onset	Stop	Route	Dose	Plasma levels
Micronized E2	After ovarian suppression Cycle day 1 or better day 25 of previous cycle	At time of luteo-placental shift (8–10 weeks after embryo transfer)	Oral	2–6 mg BID	60–200 pg/mL
			Transdermal	2×0.1 mg/day	60–200 pg/mL
			IM	25–50 mg/day	~1,000 pg/mL
			Vaginal	Low dose	
				Estrace® cream 0.1 mg BID physiological levels	60–200 pg/mL
				High uterine conc.	1,000–2,000 pg/mL
				High dose	
				Estrace® tablets 2 mg BID	
				Very high ut. Conc.	
				Vag E2: Used in non-responding endom., should not be used casually	
Synthetic estrogen (i.e., ethinyl E2)	Not used in DE-ART	Not used in DE-ART	Not used in DE-ART	Not used in DE-ART	Not used in DE-ART
Progesterone	After 10–100 days of estrogen treatment	At time of luteo-placental shift (8–10 weeks after embryo transfer)	Oral	NA: not inducing predecidualized endom	Not reliable Not recommended
	3–4 days prior to ET		Transdermal	NA: poorly absorbed and metabolized in skin	NA
			IM (peanut/sesame oil preparation)	25–50 mg/day	20–50 ng/mL
	Commonly on evening of retrieval in donor		Subcutaneous (aqueous preparation)	25 mg/day	20–50 ng/mL
			Vaginal	300–600–800 mg/day (bioadhesive gel 90 mg/day)	5–15 ng/mL
Synthetic progestin dydrogesterone	Same as progesterone	Same as progesterone	Oral	10 mg BID	Dydrogesterone
				Not recommended in DE-ART, no predecidualization of endometrium	Not measured by progesterone assays, not commonly measured

factors that influence hepatic metabolism, as, for example, barbiturates and other inducers of cytochrome P-450-related enzymes [90]. Transdermal administration of E2 is therefore preferred when other medications are taken concomitantly, as notably sleeping pills, tranquilizers, antidepressants, and antiepileptics, or in case of smoking [92]. Conversely, the efficacy of transdermal skin patches may be hampered by obesity [93] and hot and humid weather. The doses of E2 used orally or transdermally are summarized in Table 9.1.

Intramuscular (IM) or Vaginal Progesterone

In DE-ART, progesterone is administered by intramuscular injections or vaginally. Oral preparations of micronized progesterone show evidence of good absorption. In menopause, these preparations are effective at antagonizing the endometrial proliferations induced by E2. Due to the intense hepatic metabolism during the 1st liver pass however, full secretory transformation of the endometrium cannot be achieved with oral progesterone irrespective of the dose used [94]. Hence, oral progesterone is simply not an option for hormone administration in DE-ART. Likewise, oral dihydrogesterone was ineffective at triggering predecidual changes in a DE-ART treatment model [95] and therefore should not be used in DE-ART.

Injectable preparations of progesterone existed long before the advent of ART and DE-ART. These compounds consist of oil (sesame, peanut, etc.) solutions designed to be injected intramuscularly. The doses used in regular ART for luteal support are also effective at triggering the luteal changes of the menstrual cycle in DE-ART regimens [96]. These doses (25–100 mg/day, with 50 mg most commonly used) are equal or superior to the mean daily production rates of progesterone by the corpus luteum (25 mg/24 h). IM injections are however painful, difficult to be self-performed, and may produce sterile abscesses, a serious complication of ART and DE-ART treatments.

Transdermal administration of progesterone is not feasible primarily because of the high doses needed. Indeed, the daily production rate of progesterone (25 mg/24 h) is 50 times superior to maximum E2 production in preovulatory time (0.5 mg/24 h) and 500 times baseline production rates (0.05 mg/24 h). Hence, oral and transdermal administrations of progesterone are not practical options. In an effort to avoid the inconvenience of daily IM injections, clinicians have therefore looked at delivering progesterone vaginally, the last remaining option [35, 97]. From the outset, vaginal progesterone was found to be highly effective at priming endometrial receptivity in spite of relatively low – sub-physiological – plasma levels of progesterone. Intrigued by this discrepancy between plasma levels and endometrial effects, Sauer's team compared endometrial tissue and plasma concentrations pending on whether progesterone was administered vaginally or by IM injections [98]. Plasma concentrations of progesterone were markedly higher following IM injections, whereas the opposite was seen for endometrial tissue concentration [98]. This comparison was later repeated but in women undergoing hysterectomy so that endometrial tissue could be obtained while ascertaining that samples were not contaminated by vaginal progesterone [99]. This aimed at rebutting the contention that the high endometrial tissue levels reported by Miles et al. might have resulted from contamination when sampling the endometrium vaginally [99]. Ultimately, it was demonstrated that the direct vagina to uterus, a functional portal system – the first uterine pass effect – truly existed between the vagina and the uterus [100]. Various methodological approaches provided converging evidence that the identified first uterine pass effect takes place through a countercurrent exchange with vein-to-artery transfer [101]. Such transport is dependent upon the special arrangements of the vasculature of the uterus and upper one-third of the vagina and thus is restricted to this area (Fig. 9.3) [102].

Clinically, there is now ample evidence that vaginal and IM progesterone is equivalent for priming endometrial receptivity in regular ART and DE-ART [96, 103, 104]. The choice between

IM and vaginal progesterones is thus made on the basis of personal preferences. The currently available progesterone preparations (Fig. 9.4) include (1) soft gelatin capsules containing 100–200 mg of micronized progesterone (sold under the names of Utrogestan® or Prometrium® by Besins or Solvay Pharmaceuticals, respectively), (2) inserts (Endometrin®, Ferring Pharmaceuticals), (3) polycarbophil-based gel containing 90 mg of micronized progesterone (Crinone®, Watson Pharmaceuticals), and (4) similar pharmacy-compounded products containing 100–200 mg of progesterone. Soon this choice will be complemented by a subcutaneous aqueous progesterone preparation – progesterone IBSA [105]. This will offer progesterone supplementation in a clinically sound self-injectable form that has lesser side effects than IM preparations.

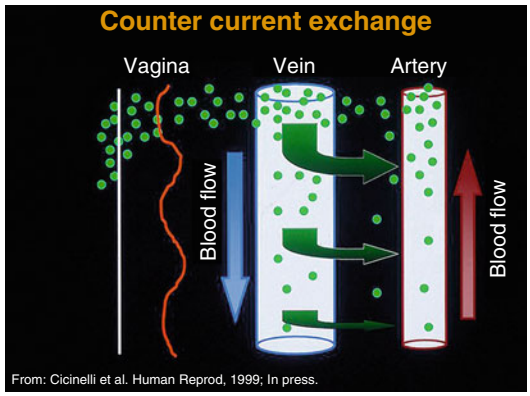

Fig. 9.3 First uterine pass effect. Substances such as, for example, progesterone absorbed from the upper third of the vagina are electively transported toward the uterus through an effective functional portal system. This direct transport, or first uterine pass effect (FUPE), results in higher tissue concentrations of progesterone when progesterone is administered vaginally as compared to by IM injections. The functional portal system linking the vagina and the uterus relies on countercurrent exchanges with vein-to-artery diffusion made possible by the great proximity of these vessels in the upper part of the vagina (From Cicinelli and Ziegler [100])

Simplified Regimens of Proven Efficacy

Early in the course of DE-ART, hormonal regimens administered to recipients aimed at duplicating the hormonal profiles of the menstrual cycle. Rapidly however, simplified regimens have been proposed that are equally efficient at priming endometrial receptivity in recipients whose ovarian function is inactive or suppressed [106]. These approaches administer constant rather than modulated E2 doses in the intent of duplicating the preovulatory rise in E2 [107]. In a further attempt at simplifying the synchronization of oocytes of donors with recipients, the flexibility in the duration of the E2 priming phase has been challenged. Experimental data indicated no differences in outcome when the E2 priming phase of treatments administered to recipients extended from 10 to as long as 100 days [106].

Fig. 9.4 Progesterone preparations. The most commonly available progesterone preparations include (1) vaginal gel (Crinone® 8 % (90 mg), Watson Pharmaceuticals), (2) inserts (Endometrin® 100 mg, Ferring Pharmaceuticals), (3) capsules (Utrogestan 100 or 200 mg, Besins Health Care, in the USA, Prometrium®, Abbott Pharmaceuticals), and (4) injectable (IM) preparations (progesterone injection, 50 mg/mL, Watson Pharmaceuticals)

GnRH-a in Women with Functioning Ovaries: Mandatory or Optional?

Progressively, DE-ART has been offered not just to women with absent or failed ovaries, but also to women whose ovaries are still functioning but not sufficiently for regular ART. Over the years, the latter group constituted a progressively larger proportion of DE-ART activity to the point that today, they actually constitute the majority. Indeed, DE-ART has universally become the logical next step for regular ART patients who have failed therapy because of an insufficient ovarian response to gonadotropins [108]. In women whose ovaries are still functioning, it is necessary to block ovarian function before administrating E2 and progesterone in order to avert the risk of premature ovulation. Logically, GnRH-a has been commonly used for suppressing ovarian function in these cases. Yet, E2 alone was shown to be >95 % effective at preventing inter-cycle FSH elevation and follicular recruitment when initiated on cycle day 1 [13] or better 3–5 days before menses [31]. But while >95 % reliability at preventing premature ovulation is fine in FET – as transfers just need to be postponed – it may be unacceptable for synchronizing fresh transfers in DE-ART. Hence, ovarian suppression using GnRH-a prior to E2 and progesterone administration remains the generally preferred treatment option in women undergoing DE-ART whose ovaries are still functioning. As discussed below, the rapid development of frozen oocytes banks made possible through oocyte vitrification protocols [109–111] will probably change these practices further.

Assessing Endometrial Receptivity

Endometrial receptivity has been typically assessed by endometrial biopsies using conventional histology criteria [112] or gene expression [113]. Originally, endometrial biopsies conducted in the menstrual cycle for the purpose of identifying luteal phase defect were performed in the late luteal phase [114, 115]. Typically, biopsies are performed in the late luteal phase on menstrual cycle day 24–26 aimed at witnessing the proper predecidual transformation of the endometrium.

We know today that the predecidual changes reflect the response of uterine stroma to progesterone, the least receptive constituent of the endometrium to progesterone. Hence, hormonal regimens – i.e., oral micronized progesterone or dydrogesterone – that fail to induce the predecidualization of stromal cells [95] should not be used in DE-ART. Paradoxically, certain of these preparations such as oral dydrogesterone [116] may appear sufficient in regular ART, in the presence of endogenous progesterone [117]. Practically however, preparation not satisfying the stringent rule of triggering predecidual changes should not be used in DE-ART and probably not in regular ART either.

Markers of receptivity on ultrasound have included endometrial thickness, echogenic appearance and vascular development, and resistance of sub-endometrial tissues. From the early days of ART, endometrial thickness was seen as a direct marker of endometrial proliferation induced by estrogen [118]. Interestingly, endometrial thickness in the menstrual cycle or following physiological hormonal replacement in DE-ART recipients is not different [33]. Therefore, this indicates that exposure to menstrual cycle levels of E2 for the duration of the follicular phase induces a state of maximal endometrial proliferation that is not exceeded by higher E2 levels. Presently, technical improvements of ultrasounds offer 3D reconstruction and volume rather than thickness measurement of endometrium [119], which improves intra- and interobserver precision of measurements [120]. Practically, endometrial thickness of less than 7 mm is predictive of lesser outcomes in DE-ART, but is characteristically of little prediction when thicker. Endometrium of less than 5 mm is usually not compatible with pregnancy development, but exceptions have been reported.

Endometrial appearance on ultrasound or echogenicity varies throughout the menstrual cycle. Typically, the endometrium changes from being lesser echogenic or "blacker" than the surrounding myometrium in the follicular phase to more echogenic or "whiter" in the luteal

phase [37]. Full changes in endometrial echogenicity [39] take 4 days to complete at the time of the follicular-luteal transition [37]. The time course of these changes parallels the coiling of endometrial glands induced by progesterone of which echogenicity appears to be a direct marker [80]. Practically however, endometrial echogenicity is of little use today in DE-ART. Artifact causing erroneously hyperechogenic endometrium in the follicular phase mainly stems from an intermediary position – between ante- and retroversion of the uterus. This indeed affects the gland-to-ultrasound-beam angle and in turn echogenicity.

Endometrial and more importantly, sub-endometrial blood flow has been assessed by a refinement of ultrasound, Doppler flow measurement, for the past 20 years. While estrogen increases uterine blood flow by reducing resistance [121], attempts to link blood flow to endometrial receptivity have essentially failed. The story took nearly 20 years to unravel due to the constant addition of new technical refinements in ultrasound-based blood flow measurements that have in general challenged the prior data [122]. Practically however, 3D-based operator-independent measurement of sub-endometrial blood flow failed to prospectively predict implantation chances [123–126]. Most importantly for DE-ART, 3D-based power Doppler fails to predict pregnancy chances in DE-ART-like FET cycles [127].

Uterine contractility has been assessed using ultrasound-based direct recognition of contractile events [128]. In regular ART, an inverse correlation was seen between uterine contractility at the time of transfer [129] and pregnancy chances in ART. These findings reinforce the concept that uterine contractions exert unfavorable effects of uterine contraction on ART outcome. Interestingly, in hormonal regimens used in DE-ART, exogenous progesterone was shown effective at inducing uterine quiescence within 4 days [41], as seen in the normal menstrual cycle [41]. Practically speaking, anomalies in uterine contractility encountered in ART are linked to COS and not encountered in DE-ART [128].

Need for Adjunct Therapy

Adjunct therapies are commonly used in ART [130]. As most of these aim at improving ovarian response to COS, they are generally of lesser interest in DE-ART. An exception to this rule exists for metformin, which was shown to revert insulin resistance existing in the endometrial tissue [131]. Of note, metformin has been shown to reverse insulin resistance and aromatase activation in endometrial tissue encountered in patients with endometriosis and PCOS [132]. Similar claims were made for antioxidants such as notably catechin contained in green tee, which reverted endometrial lesions in an experimental endometriosis model [133].

New Developments: Hormonal Treatments for Managing Oocyte Banks

A quarter-century history of DE-ART has allowed mastery over the synchronizing of endometrial receptivity in recipients with oocyte retrievals in donors. Recently, however, a single innovation – the reliable cryopreservation of oocytes through vitrification or slow freezing – has led many investigators to envision drastic changes in the management of DE-ART. Indeed, multiple reports suggest that oocyte cryopreservation can be reliably achieved by vitrification without reducing the efficacy of fresh oocyte donation [111, 134]. These findings are paving the way toward establishing new cryopreserved oocyte banks, which are bound to improve the ease and efficacy of DE-ART.

Another direct advantage of using oocyte banks for DE-ART relates to the possibility of quarantining oocytes in order to exclude the possibility of viral contamination. Further work will determine whether the early results of vitrification obtained with open systems – where gametes are in direct contact with liquid N2 – are similar if safer closed systems are used, as the closed system approach is likely to be mandated by regulatory agencies.

A prospective trial demonstrated that progesterone treatment can be withheld in the recipient until the day prior to, of, and even after oocyte warming [135]. This opens the possibility of initiating progesterone treatment only after documenting that the warmed oocytes fertilized, thus permitting an optimal use of donated oocytes. Indeed, in the event that the donated oocyte(s) fails to fertilize, it is possible to simply warm up and inseminate new oocytes while delaying the onset of progesterone accordingly.

Summary

In summary, donor-egg ART (DE-ART) has now been successfully practiced for over a quarter of a century. Through unexpected twists in the rules thought to govern the hormonal control of endometrial receptivity, the sole replacement of E2 and progesterone actually induces the best possible endometrial receptivity. Most astoundingly, the surprise bounty of clinical observations made during the early days of DE-ART has held true to the current day. Today as earlier, the outcome of DE-ART is at best equaled by regular ART but never surpassed. The primary lesson of DE-ART is that the optimal timing for embryo transfer is controlled by the duration of progesterone exposure, not the amounts administered nor the plasma levels reached. E2 treatment is necessary for a preliminary priming of the endometrium leading to glandular and stromal proliferation and the development of estrogen and progesterone receptors. Measurements of endometrial thickness are taken as satisfactory evidence of sufficient estrogen priming. The recent breakthroughs in oocyte cryopreservation – by slow freezing as well as vitrification – will likely lead to the development of true egg banks as long been the practice for banking sperm. Early data reported with this approach suggest that the ultimate efficacy of DE-ART – the number of pregnancies per oocyte retrieval – will be markedly boosted by reverting to systematic oocyte banking.

Conclusion

During its quarter-century long history, DE-ART has taught us some of the fundamentals of human reproduction, and it has became a key clinical tool for treating infertility related to failing ovarian function. The essence of DE-ART's lesson is that following sufficient estrogen priming (10–100 days), endometrial receptivity – WOI – is controlled by the duration of exposure to progesterone, not hormonal blood levels. Optimal DE-ART outcome is brought by transfers of cleaving- or blastocyst-stage embryos on the third to fourth and fifth day of progesterone exposure, respectively. Remarkably, uterine response to hormones and endometrial receptivity to embryo implantation remain unaltered in aging women, provided that local processes such as fibroids are excluded. The practical implication of the DE-ART's primary lesson is thus that oocyte quality is the primary factor affecting ART outcome [136]. It is likely that certain ominous consequences on ART outcome reported with poor sperm quality can be overcome by good quality oocytes, as provided by DE-ART.

Recent advances in the method of oocyte cryopreservation by slow freezing [137] and vitrification [138] are likely to lead to the development of oocyte banks. This will greatly facilitate and enhance the clinical efficiency of DE-ART, as well as modify – in essence, simplify – the treatments administered to the recipients. We foresee that in a near future, hormonal treatments prescribed to recipients of DE-ART will rival the simplicity with those currently used for FET. Endometrial alterations encountered in cases of endometriosis or PCOS are corrected or reduced, respectively, by ovarian suppression that accompanies hormonal treatments of DE-ART. Impairments of endometrial receptivity resulting from hydrosalpinges and possibly obesity do remain however. As in regular ART, hydrosalpinges call for salpingectomy, proximal clipping, or obturation by Essure device. Endometrial alterations encountered in obesity also seen in DE-ART may respond to metformin treatment.

Editor's Commentary

The proverbial question, "Is it the chicken or the egg," has been at the heart of research efforts in egg and embryo donation throughout its existence. Egg donation has allowed us to separate the two out from each other and learn a great many things about human reproduction. As very well described in this thorough treatise of the subject matter by Dom de Ziegler, M.D., various preparations have been manufactured and applied, in various doses and using differing schedules in an effort, to produce a receptive endometrial environment for embryo implantation. Amazingly, almost all of these schemes are efficacious, as long as an adequate exposure of progesterone exists and of course, the embryos are replaced at the right time. Research efforts at development taught us much about basic reproductive biology, and as Dom mentions, many of the clinical lessons learned were then exported for use in patients going through IVF with their own autologous gametes.

Unfortunately, many of the basic tenets learned years ago are being ignored today. It is not uncommon for contemporary patients to undergo daily blood tests for a variety of hormones, serial ultrasound examinations to assess their endometrial thickness, and to have their medications "adjusted." All of these efforts promote the myth that the endometrium must be carefully watched and controlled through pharmacologic manipulation and every patient blog implies that if you do not provide these services that you are essentially committing malpractice. This sad illusion creates a dependency on the doctor and generates a significant amount of revenue, but I firmly believe that it does not represent "good medicine." The evidence-based medicine clearly demonstrates that such adjunctive measures are unnecessary, add extra cost and also create a great deal of patient anxiety, and therefore in my opinion should be abandoned.

For many years, countless numbers of women endured mock cycles with endometrial biopsies in order to secure the knowledge which serves as the basis for today's clinical recommendations. Surprisingly, simplification has won the day. We owe it to these research subjects and patients to practice what we preach and not be tempted by the easy money generated through excessive testing that neither improves their outcome nor lowers their expenses.

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Blastocyst Versus Cleavage Stage Embryo Transfer: Maximizing Success Rates

10

Eric S. Surrey and William B. Schoolcraft

Key Points

- There is an emerging need to maximize the likelihood of live birth while minimizing the risk of multiple gestations, and the American Society for Reproductive Medicine has stated that in most cases of oocyte donation, only a single blastocyst stage or no more than two cleavage stage embryos be transferred.
- The development of highly specific sequential and nonsequential embryo culture systems as well as meticulous attention to air quality and laboratory technique has allowed for routine successful development of embryos to the blastocyst stage.
- Evaluation of embryo quality and number at the pronuclear and, perhaps more importantly, at the cleavage stage of development may serve as an imperfect predictor for blastocyst development potential.
- Proteomic and metabolomic assessments of spent culture medium may soon represent dynamic means of creating a unique profile of biomarkers to predict blastocyst viability.

Over the last decade, progressive refinements in the evaluation of ovarian reserve, controlled ovarian hyperstimulation regimens, embryology laboratory culture systems, as well as embryo transfer and cryopreservation techniques have resulted in significant improvements in assisted reproductive technology (ART) outcomes. With these advances, an emerging need to maximize the likelihood of a live birth while minimizing the risk of multiple gestations has attained paramount importance, particularly in the case of oocyte donation. Recently published guidelines from the American Society for Reproductive Medicine have stated that in the case of a young oocyte donor with favorable prognosis, only a single blastocyst stage or no more than two cleavage stage embryos be transferred [1]. However, in a recent analysis, Martin et al. suggested that even in "best" prognosis oocyte donors from whom at least two donations had resulted in live birth, the live birth rates per oocyte retrieved and per embryo transferred were only 7.3 and 24.6 %, respectively [2]. Given this staggering degree of attrition even in the best prognosis patients and the need to decrease the numbers of embryos transferred, it is critical that clinicians

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and embryologists obtain as much information as possible about the developmental and implantation potential of embryos considered for transfer.

The shift to more widespread transfer of blastocyst as opposed to cleavage stage embryos in good prognosis patients (including oocyte donor recipients) has represented one of the key factors in improving outcomes. Indeed, the debate in oocyte donation has shifted from the question of whether blastocyst stage transfer is feasible to whether blastocyst stage transfer should be standard and cleavage stage transfer the exception. We will provide evidence to support this contention in this chapter.

Why Blastocyst Stage Transfer?

There are a host of potential advantages to the use of blastocyst stage embryo transfer in the oocyte donation model (Table 10.1 and Fig. 10.1). Perhaps the most important is the fact that the embryo can be transferred into the uterus at the appropriate developmental stage. The tubal environment to which the cleavage stage embryo is exposed in vivo is significantly different with regard to nutrients and pH than the uterus to which the blastocyst stage embryo is exposed, and therefore, transfer at an earlier developmental stage may inhibit embryonic development [3]. Secondly, uterine contractility progressively decreases in the luteal phase from the day of hCG administration with the most profound decline occurring between 4 and 7 days [4]. This would theoretically result in a more quiescent state at the time of blastocyst transfer which could aid implantation. Thirdly, it appears that full activation of the genome of the embryo does not occur until after the cleavage stage [5]. Extending embryo culture would allow identification of embryos with an inherent developmental block.

The benefits of extended embryo culture are clearly dependent on the culture system. The development of highly specific sequential and nonsequential systems as well as meticulous attention to air quality and laboratory technique has allowed for routine successful development of embryos to the blastocyst stage in vitro [3, 6].

Table 10.1 Advantages of blastocyst culture and transfer in oocyte donation

Enhanced synchrony with uterine environment
Transfer into a more quiescent uterus
Enhanced developmental information
Increased implantation rates
Full activation of embryonic genome

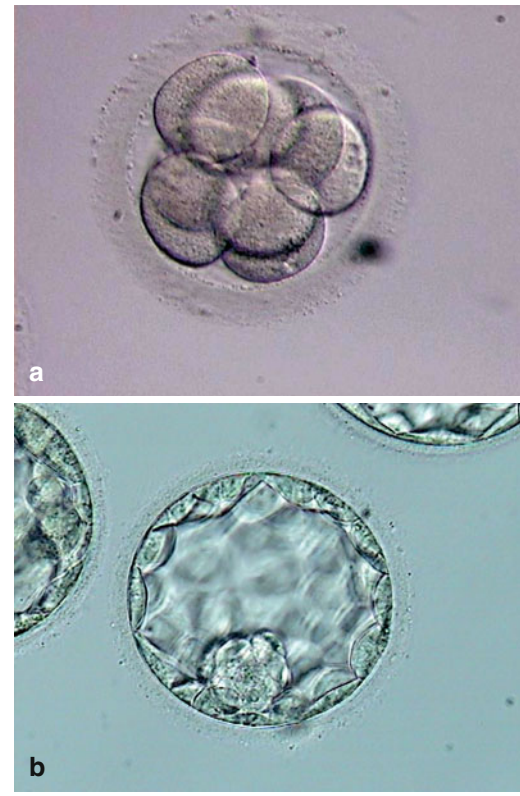

Fig. 10.1 (**a**) Photograph of high-quality eight-cell embryo derived from an oocyte donor 3 days after oocyte aspiration. (**b**) Photograph of high-quality expanded blastocyst derived from an oocyte donor 5 days after oocyte aspiration

Perhaps the most compelling reason in favor of blastocyst transfer is the significantly higher pregnancy and implantation rates achieved in comparison to cleavage transfer. The bulk of evidence has been obtained from IVF cycles employing autologous oocytes, which shall be presented first. However, one can only assume that outcomes obtained from oocytes derived from younger women without inherent fertility problems

(oocyte donors) would only be higher which is confirmed by the small number of trials addressing this specific population.

Blastocyst Transfer: IVF Outcomes

Two studies both published in 2004 evaluating elective single embryo transfer (eSET) in good prognosis patients are illustrative of the potential advantage of blastocyst transfer. Thurin et al. randomized 611 women less than 36 years of age with at least two good-quality embryos to eSET or double embryo transfer, of which 97.2 % underwent transfer on day 2 or 3 (the majority on day 2) [7]. The implantation rate for the first eSET was 33.6 %. In contrast, Gardner et al. randomized 48 women with similar baseline characteristics and at least 10 follicles >12 mm in diameter on the day of hCG administration to elective single or double day 5 blastocyst stage embryo transfers [8]. In this case, the implantation rate for the single blastocyst transfer group was 60.9 %.

A host of prospective randomized trials have compared cleavage to extended stage embryo transfer, the majority of which demonstrated improved outcomes with the latter [9–24]. One of the few trials which reported lower live birth rates with blastocyst transfer noted similar implantation rates for both groups [15]. Interestingly, all blastocyst transfers in this study were performed on day 6, which may be a confounding variable. Indeed, others have demonstrated that day 5 blastocysts may be better synchronized with endometrial development than more slowly developing embryos transferred on day 6, resulting in higher pregnancy rates with day 5 transfer [25, 26].

Perhaps more telling are the results of prospective randomized trials comparing elective single cleavage to blastocyst stage embryo transfer. Papanikolaou et al. randomly assigned 351 women under 36 years of age to transfer of a single cleavage stage (day 3) or blastocyst stage (day 5) embryo [27]. The study was terminated after an interim analysis demonstrated significantly higher ongoing pregnancy rates (58 % vs. 41 %, $P=0.02$; 95 % CI 1.06–2.66) and live birth rates (56 % vs. 38 %, $P=0.01$; 95 % CI 1.09–2.18) per embryo transfer procedure in the blastocyst group. Subsequently, Zech and coworkers performed a similar study of 227 women ≤36 years of age undergoing a first or second IVF cycle, resulting in ≥5 fertilized oocytes [28]. A significantly higher implantation rate per embryo transfer was achieved with blastocyst transfer (35.6 % vs. 23.7 %, $P<0.05$). Guerif and coworkers recently completed a prospective study of 478 couples assigned to day 2 eSET or single blastocyst transfer on day 5 or 6 [29]. It is important to note that patients were assigned on a "voluntary basis" which represents a confounding variable. Nevertheless, the delivery rate per fresh embryo transfer was again significantly higher after single blastocyst transfer (36.7 % vs. 25.1 %, $P<0.01$) (Table 10.2). It is interesting to note that a recent meta-analysis of live birth rates after elective single cleavage stage embryo transfer in prospective randomized trials described a live birth rate of 26.7 % [30].

Table 10.2 Comparative implantation rates (IR) resulting in live birth after elective single cleavage (eSET) or blastocyst stage (eBT) embryo transfer

First author (Ref.)	eSet		eBT		*P*
	N	IR/ET (%)	*N*	IR/ET (%)	
Papanikolaou [27]	176	43	176	58	0.04
Zech [28]	99	23.2	128	32.8	<0.05
Zech [28][a]	86	25.6	76	40.8	<0.05
Guerif [29]	243	25.1	235	36.7	<0.01

[a]Excellent-quality embryos only

Two recent meta-analyses addressing this issue with different designs and reaching different conclusions have been published. An updated Cochrane review evaluated randomized trials of early cleavage (day 2/3) versus blastocyst (day 5/6) stage transfers [31]. Sixteen of the 45 identified trials met inclusion criteria and were analyzed. Interestingly, there was no difference in live birth rates per couple in seven randomized clinical trials (day 2/3: 34.3 % vs. day 5/6: 35.4 %; OR 1.16, 95 % CI 0.74–1.44). This phenomenon held true for "good prognosis" patients as well. There was also a greater likelihood of having no embryos to transfer in the blastocyst

group, although this phenomenon was not significantly different for good prognosis patients. This analysis did not evaluate implantation rates per se.

In a more recent meta-analysis, eight randomized trials met stricter inclusion criteria of truly randomized design, transfer of equal numbers of embryos between the two groups and included only studies which had been previously published as full text in a peer review publication [32]. In this analysis, live birth rates were significantly higher after blastocyst versus cleavage stage transfers (OR 1.39, 95 % CI 1.10–1.76, $P=0.005$). Given the design of this meta-analysis with equal numbers of embryos transferred in each group, these data would more closely approximate an assessment of relative implantation potential.

Clearly, there are weaknesses with both analyses. The most critical of which for the purpose of this discussion is the fact that neither address outcomes of oocyte donor cycles. Even subset analysis of "good" prognosis patients cannot be compared to oocyte donors [31]. The average age of oocyte donors would be presumably less than that of IVF patients, and more importantly, oocyte donors would have no underlying history of infertility. In addition, outcomes from day 5 and 6 blastocyst transfer were typically combined, which represents a confounding variable as previously described [25].

Blastocyst Transfer: Oocyte Donation Outcomes

As previously mentioned, the outcome data for blastocyst versus cleavage stage embryo transfer in the oocyte donation model is limited. We are aware of no prospective randomized trials specifically addressing this patient subset.

Schoolcraft and Gardner reported a retrospective series of 229 patients undergoing oocyte donation at the Colorado Center for Reproductive Medicine, of whom 116 underwent day 3 transfer and 113 underwent day 5 transfer [33]. Mean ages of donors and of recipients were similar between the groups. The average blastocyst development rate was 58.7 %. Implantation rates resulting in documented fetal cardiac activity per embryo transfer were significantly higher in patients receiving a blastocyst transfer (65.0 % vs. 41.6 %, $P<0.01$). Clinical pregnancy rates per retrieval were also significantly higher after blastocyst transfer (87.6 % vs. 75.0 %, $P<0.05$) despite transferring a significantly lower mean number of embryos (Table 10.3 and Fig. 10.2). These results were confirmed by Shapiro and colleagues who reported a mean implantation rate of 52.8 % with a 66.7 % ongoing pregnancy rate in 47 donor cycles after blastocyst transfer on either day 5 or 6 [34].

Table 10.3 Oocyte donation: day 3 versus day 5 embryo transfer: cycle characteristics

	Day 3	Day 5	*P*
No. of donor cycles	116	113	–
Donor age (mean ± SEM)	28.8 ± 0.44	27.8 ± 0.41	NS
Recipient age (mean ± SEM)	39.9 ± 0.43	41.3 ± 0.41	NS
Blastocyst development (%)	–	58.2	–
Embryos transferred (mean ± SEM)	3.2 ± 0.05	2.1 ± 0.04	<0.01
Embryos frozen (mean ± SEM)	5.2 ± 0.59	5.6 ± 0.43	NS

Adapted from Schoolcraft and Gardner [33]

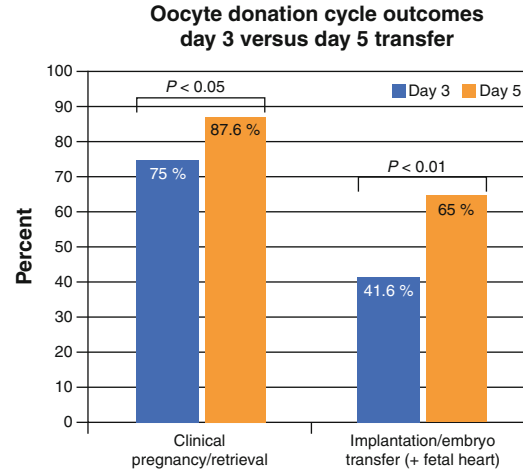

Fig. 10.2 Oocyte donation cycle outcomes comparing day 3 versus day 5 embryo transfer in a large retrospective series (Adapted from Schoolcraft and Gardner [33])

A more contemporary review of all oocyte donation cycles performed at the Colorado Center for Reproductive Medicine from 2004 through 2009 revealed that the implantation rate from 236 day 3 transfers was 45.4 % and that of 828 day 5 transfers was 72.5 %. The ongoing pregnancy rate after cleavage stage transfers was 70.3 % in comparison to 87.4 % after blastocyst transfer.

A recent retrospective analysis compared cleavage (day 3) to blastocyst (day 6) stage embryo transfer in 93 consecutive oocyte donation cycles [35]. Once again, significantly higher implantation rates (64 ± 6 % vs. 27 ± 7 %, $P < 0.01$) and clinical pregnancy rates (73 % vs. 40 %, $P < 0.01$) were obtained after blastocyst transfers. Even after oocyte vitrification, implantation rates in oocyte donor cycles after blastocyst development and transfer were extremely encouraging [36].

In contrast, Soderström-Anttila and Vilska reported upon a 5-year experience with elective cleavage stage embryo transfer in both anonymous and non-anonymous oocyte donation cycles [37]. An implantation rate of 43.2 % per embryo transfer was reported. Previously, Mirkin et al. reported a 22 % implantation rate with day 3 transfers in oocyte donation cycles [38].

There are several important confounding variables in the aforementioned trials. The lack of appropriately designed prospective randomized trials is a weakness. However, given the retrospective data from oocyte donors and prospective trials derived from good prognosis IVF patients, there is little to suggest that day 3 transfer is more advantageous in the oocyte donation model given an appropriate embryology laboratory setting. The combination of outcomes from day 5 and 6 blastocyst embryo transfers in these trials remains problematic. Although Shapiro et al. have demonstrated that clinical pregnancy rates from day 5 blastocyst transfers are superior to day 6 transfers in autologous IVF cycles, they noted the opposite phenomenon with oocyte donor cycles [26]. This may reflect a higher degree of synchrony between embryo and endometrium based on the specific endometrial preparation protocol employed. These data have not been confirmed, and one would remain concerned that transfer of more slowly expanding blastocysts may also reflect compromised developmental potential.

A third confounding variable, which has not been addressed in any of the aforementioned trials, is the impact of male age. It can be assumed that in the average oocyte donation cycle, paternal age would be elevated in comparison to "good prognosis" IVF cycles. Several studies have suggested that increasing paternal age (particularly >50 years) is associated with an adverse outcome in oocyte donor cycles [39, 40]. Both trials demonstrated a deleterious effect on blastocyst development rate. However, this finding has not been universally demonstrated [41].

The Case Against Blastocyst Transfer

Given the aforementioned evidence in favor of blastocyst transfer in the oocyte donation model, there remain several arguments which have been historically made in opposition to this approach:

1. A high percentage of otherwise viable embryos on day 3 fail to develop to the blastocyst in vitro and would be "lost" for transfer.
2. Cryopreservation of supernumerary blastocyst stage embryos results in lower survival rates than at earlier developmental stages, resulting in a decline in overall cycle efficiency.
3. Transfer of embryos at the blastocyst stage may be associated with an increased risk of monozygotic twinning.

We will address each of these issues.

The contention that viable day 3 embryos will not survive in vitro to the blastocyst stage and would have a greater likelihood of surviving in the uterus clearly cannot be directly tested since the same embryo cannot be evaluated in two places at once. The failure of embryos to develop in vitro may indeed be secondary to a suboptimal laboratory environment. However, in an optimal laboratory setting, this phenomenon may also be due to embryos with inherent genetic and metabolic impairment leading to arrested development. Other factors to consider would be those of advanced paternal age, severe sperm abnormalities, and the impact of cycles with an older (typically known) donor. In their meta-analysis, Blake et al. reported

that the likelihood that couples would have no embryos to transfer is significantly higher for blastocyst versus cleavage stage embryos [31]. However, when these investigators limited their analysis to good prognosis IVF patients, this difference was not statistically significant (OR 1.58; 95 % CI 0.65–3.82). These trials did not include oocyte donation cycles, a situation with a presumably better prognosis than "best case" autologous IVF patients. Indeed, we had previously reported that 58 % of fertilized donor oocytes undergoing extended culture in sequential medium reached the blastocyst stage, of which 84 % were felt to be of high quality [33].

It is not necessary to commit to blastocyst transfer in all cycles without exception, however. Evaluation of embryo quality and number at the pronuclear and, perhaps more importantly, at the cleavage stage may serve as an imperfect predictor for blastocyst development potential. Neuber et al. reported a high correlation between pronuclear symmetry, early cleavage, and subsequent blastocyst development [42]. Dessolle and coworkers created a predictive model for failed blastocyst development based on fertilization technique, female age, as well as number and quality of day 3 embryos [43]. This view has not been uniformly accepted in that others have suggested that morphologic assessment of embryos at the pronuclear or cleavage stage is poorly predictive of the likelihood of blastocyst development [44, 45].

The ability to efficiently cryopreserve supernumerary embryos enhances the overall efficiency of any given oocyte aspiration procedure. If outcomes with blastocyst stage cryopreservation were significantly compromised compared to pronuclear or cleavage stage freezing, then benefits of fresh blastocyst transfer would be neutralized. Meta-analyses have reported that the rate of embryo freezing was higher at days 2–3 versus days 5–6 [31, 32]. However, these reports only suggest that more embryos were available for cryopreservation at earlier developmental stages, as would be expected, but not that outcomes were enhanced from subsequent transfers. Guerif and coworkers previously noted that in their program, fresh elective single blastocyst transfer pregnancy rates were higher than elective cleavage stage embryo transfers, but once frozen embryo transfers were included, cumulative delivery rates were not significantly different between the two groups [29].

However, outcomes from blastocyst cryopreservation are not consistent among laboratories, and published reports cannot be universally applied. In addition, it is important to note that results from earlier studies may not reflect currently employed techniques. Veeck et al. reported a 76.3 % survival rate of blastocysts cryopreserved using slow-freeze techniques with an ongoing clinical pregnancy rate of 59.2 % [46]. In a retrospective analysis from this same group, clinical pregnancy rates (64.2 % vs. 37.4 % vs. 42.1 %, $P<0.05$) and implantation rates (38.5 % vs. 15.2 % vs. 17.1 %, $P<0.05$) per transfer were significantly higher after transfer of thawed blastocysts in comparison to thawed cleavage or pronuclear stage embryos [47]. There is disagreement among investigators as to whether there are differences in outcomes from blastocysts cryopreserved on day 5 versus day 6 when transferred to an appropriately prepared endometrium [26, 48]. An alternative approach for clinics uncomfortable with blastocyst slow-freeze techniques is to freeze supernumerary embryos at the pronuclear or cleavage stage and then allow subsequently thawed embryos to grow to the blastocyst stage before transfer. Employing this approach with oocyte donors, Shapiro and colleagues reported similar implantation and pregnancy rates as with fresh transfers [49]. The disadvantage of this approach is the inability to select embryos for fresh transfer from the full cohort of embryos which could have a deleterious impact on the success of the fresh embryo transfer.

The introduction of successful blastocyst vitrification has significantly improved the efficiency of cryopreservation and enhanced outcomes due to the elimination of intracellular ice crystal formation [50, 51]. In a recent review and meta-analysis, Loutradi et al. reported a post-thaw blastocyst survival rate that was significantly higher using vitrification as opposed to slow-freeze techniques (OR 2.2, 95 % CI 1.53–3.16) [52]. At the Colorado Center for Reproductive

Medicine, we have reported a 97.8 % survival rate after blastocyst vitrification even after trophectoderm biopsy [53]. In fact, some investigators have reported significantly higher pregnancy and implantation rates in nondonor IVF cycles after transfer of vitrified and warmed blastocysts than after fresh transfer [54]. This may be due to the presence of a more receptive endometrium in the prepared frozen embryo transfer cycle. However, in the case of oocyte donation cycles, endometrial preparation of the recipient would be similar for a fresh or frozen transfer cycle making this issue less relevant.

The final concern which has been raised regarding blastocyst transfer is the question of whether prolonged culture is associated with any inherent increased pregnancy risks. Several investigators have suggested that the incidence of monozygotic twinning may be increased after blastocyst versus cleavage stage embryo transfer [55–57]. This has been attributed to a possible increase in the hardness of the zona pellucida due to prolonged in vitro embryo culture. It is interesting to note that in two more recent studies, the incidence of monozygotic twinning was no different between blastocyst and cleavage stage transfers [58, 59]. This change may be reflective of advances in culture medium. In addition, these data are not derived from oocyte donation cycles, and therefore, we are forced to extrapolate to that model.

Blastocyst Selection: Is Morphology Enough?

Although it would appear from the evidence provided that implantation rates with blastocyst transfer are significantly enhanced over day 3 transfer in both autologous and donor IVF cycles, the results remain imperfect. In an effort to maximize success while minimizing multiple pregnancies, elective single embryo transfer clearly is ideal. Thus, enhancing the accuracy of embryo selection techniques is critical to achieving this goal.

Assessments of morphology and developmental rate have been the mainstays of this approach. We have previously discussed the merits of day 5 versus day 6 fresh blastocyst transfers. Employing a morphologic grading system based on the degree of blastocyst expansion along with the development and architecture of both the inner cell mass and trophectoderm, Gardner et al. demonstrated a relationship between blastocyst grade and implantation [60]. When two top-quality blastocysts were transferred (≥3AA) (69 % of patients), the implantation rates were significantly higher than the 15 % of patients who had only lower-scoring blastocysts (<3AA) transferred (69.9 % vs. 78.1 %).

In the setting of oocyte donor cycles, the predictive value of morphologic assessment is even less clear. In reviewing all oocyte donor cycles performed at the Colorado Center for Reproductive Medicine from 2004 to 2009, we noted that implantation rates after transfer of expanded but not perfect blastocysts were similar to those transferred which were felt to be perfect in quality and not dramatically different than in the small number of patients with only morulae available to transfer (Table 10.4).

In the best of circumstances, blastocyst morphology is not completely predictive of outcome. New tools, the details of which are beyond the scope of this chapter, may add additional information regarding the embryo in order to enhance the selection process. Aneuploidy screening may represent one of these approaches. The incidence of aneuploid embryos increases significantly with age, a phenomenon which one would assume would be negated with the use of a young oocyte donor. Indeed, Fragouli et al. noted a low aneuploidy rate (3 %) using comparative genomic hybridization techniques after polar body biopsy of oocytes derived from donors with an average age of 22 years [61]. However, these data do not reflect the impact of advanced paternal age, which is more commonly associated with oocyte donation cycles and may play a role in increasing the incidence of aneuploid embryos despite a high percentage of euploid oocytes. Exciting new validated techniques allowing for comprehensive chromosomal screening of blastocyst stage embryos have been shown to increase implantation rates by 50 % compared to contemporary

Table 10.4 Oocyte donation outcomes and blastocyst quality at Colorado Center for Reproductive Medicine (2004–2009)

Stage	Cycles	Total embryos transferred	Ongoing pregnancy (%)	Implantation (%)
Only morulae	7	21	100	71.4
Only early (1,2,2/3)[a]	29	66	69	53
Only advanced but not perfect (AB, BA, BB)[a]	93	189	84.9	72
Only perfect (AA)[a]	453	866	91.6	77.6

[a]Based on scale described by Gardner et al. [60]

autologous IVF cycles [62, 63, 64]. These techniques have primarily been employed in couples with recurrent implantation failure, unexplained recurrent pregnancy loss, and advanced maternal age and not in the oocyte donation model or in the average younger infertile patient. However, if the value of this approach is confirmed in appropriately designed prospective randomized trials, a case could be made for future investigation of this technique in other models as well. Indeed, analysis of blastocyst gene expression may take us beyond simple aneuploidy screening in creating a profile which predicts implantation potential [65].

In addition, noninvasive approaches to the assessment of the viability of embryos which may be morphologically similar are areas of intense investigation. Proteomic and metabolomic assessments of spent culture medium may represent dynamic means of creating a unique profile of biomarkers to predict blastocyst viability [66, 67]. If validated, these approaches would certainly have application in the oocyte donation model as well.

Summary

Oocyte donation represents the most consistently successful therapy in the assisted reproductive technologies. As success rates have improved, multiple pregnancy rates have also increased. As a result, the need to more effectively select a single embryo for transfer without compromising efficacy has become a critical issue. Extending embryo development to the blastocyst stage has represented a clear advance in this regard. Refinements in culture medium and laboratory techniques as well as increased competence in vitrification technology serve to reinforce this approach. New technologies in genomics, proteomics, and metabolomics will allow clinicians and embryologists to create a profile of the implantation potential of an embryo which extends beyond an assessment of morphology alone. The question, therefore, has shifted from which situations would be appropriate for blastocyst transfer to which situations, if any, would not be appropriate for blastocyst transfer in oocyte donation cycles.

Editor's Commentary

Blastocysts have taken center stage in egg and embryo donation since the first report of a birth in 1984. John Buster, M.D. at Harbor/UCLA, noted during the early uterine lavage experiments that only recipients of recovered blastocysts became pregnant and that the implantation and pregnancy rates of these transferred embryos were remarkably high. Of course, the efficiency of uterine lavage and natural cycles prevented the development of embryo transfers along these lines. Development of the in vitro methods proceeded, and for the next two decades, cleavage stage embryos became the focus and the practice in both conventional IVF and oocyte donation.

By the mid-1990s, it was becoming increasingly clear that we had a multiple birth problem in our recipients. Remarkably, and looking back in retrospect, at that time, the standard was still to transfer up to five

cleavage stage embryos. However, high-order multiple births were becoming commonplace, and many of the recipients were also older, making the resulting pregnancy even greater risk. Thus, it was fortunate that in addition to improvements in embryo cryopreservation, the development of extended culture systems that allowed growth up to the hatching blastocyst stage emerged. Finally, a return to the original premise of embryo donation could be realized, that being the transfer of a single healthy-appearing blastocyst to a well-prepared and synchronized uterus.

Drs. Eric Surrey and Bill Schoolcraft nicely summarize the improvements in clinical outcomes resulting from transitioning to a blastocyst transfer policy for embryo transfer. No different from the lessons of three decades ago, when it comes to predicting pregnancy at the time of embryo transfer, it boils down to selection. Further diagnostic testing beyond the current embryo morphology assessment promises to add further to the efficiency of the process. The ultimate goal of routinely transferring a high-quality preimplantation embryo is now at hand, and with national success rates consistently above 50 %, it is time to reexamine whether more than a single embryo should ever be placed into the uterus of a recipient.

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Strategies to Minimize Multiple Births in Recipients of Egg Donation

11

Gerard S. Letterie and Nancy A. Klein

Key Points

- Multiple gestations constitute *the* major complication of donor IVF, yet they are almost entirely preventable by utilizing single embryo transfer in all but the most extraordinary cases.
- Mandated dissemination of practice-specific pregnancy rates allowed patients to select ART programs based solely on apparent success rates, with little insight as to the variables that influence outcomes as well as a lack of emphasis on the perils of multiple births.
- Programs have continued the practice of multiple embryo transfer in part due to pressure to maintain high pregnancy rates that appeal to patients who are often faced with a significant financial burden associated with IVF.
- The impact on cost considerations may ultimately be the impetus for change in practice pattern, as third-party payers and government regulators begin to weigh in on the debate, imposing restrictions on medical practice in order to limit their financial exposure.

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Multiple gestation is increasingly considered a complication of in vitro fertilization (IVF). No longer held is the view that pregnancy should be pursued at all costs and that multiples are simply another inevitable consequence of infertility treatment. Improved techniques for embryo culture and selection, a better understanding of the substantial risks of multiple embryo transfer, and increased regulatory scrutiny have led to a reconsideration of the definition of *success* in assisted reproductive technology (ART). The well-documented hazards of multiple embryo transfer together with a broader definition of adverse outcomes that include harm to the potential child(ren), mothers, families, health-care systems, and society are force vectors that encourage a revision in ART practice.

Multiple gestations constitute *the* major complication of donor IVF (DIVF), yet they are almost always preventable. This complication is especially problematic in DIVF cycles where the implantation rates are known to be high and the consequences of maternal and neonatal complications in the older population are more acutely felt. Given substantial supportive data, single embryo transfer (SET) is now a viable option that should be considered routine in all but the most extraordinary circumstances of DIVF treatment. The suggestion to reduce the number of embryos transferred in order to reduce the incidence of multiple pregnancy has been the subject of considerable debate. In spite of obvious benefits, the concept of SET has met resistance from both recipients and providers of infertility treatment.

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A policy of routine SET for all DIVF cycles should be the standard; establishing such a standard would increase patient and provider acceptance and would not necessarily preclude individualized care in certain clinical situations where transfer of more than one embryo could be reasonably considered (e.g., when few or no high-quality embryos are available). It can be argued that the high implantation rates that characterize egg donation cycles justify a recommendation to transfer no more than two embryos regardless of the clinical circumstances.

The setting of DIVF poses additional unique challenges that influence the drive to transfer more than one embryo. The majority of recipients are older, often nulliparous, women who are often starting their families late, with only a single or limited opportunity for pregnancy, due both to personal and imposed age limits. There is often a strong motivation to have a sibling, ideally genetically related, particularly when their children may find themselves as caregivers for aging parents at a relatively young age. Future opportunities for siblings, particularly full genetic siblings, may be limited by recipient age or donor availability. Compounding this issue is the limited access to donors, resulting in the need to share oocytes among recipients (resulting in fewer embryos to cryopreserve) or potentially long waiting times (particularly for recipients seeking a donor of a certain ethnic minority). In known donor situations, recipients may also feel pressured to limit the number of donation cycles out of a desire to limit the risk or inconvenience to the donor. Recipients of cryopreserved embryos for donation or adoption may present a special circumstance in that there is often an agreement between the recipient and donor(s) or agency wherein all surviving embryos are transferred. Patients at high risk for complications of a multiple gestation or those unwilling to take this risk should be discouraged from agreeing to thaw more embryos than they are willing to carry, with thorough informed consent as to the health consequences if each transferred embryo implants.

The objective of this chapter is to redefine success for our patients and to describe the framework for effective voluntary implementation of SET which can result in high pregnancy rates and a near elimination of multiple gestations. We will review the clinical experience that supports routine adoption of an SET policy, the obstacles to garnering patient and provider acceptance, and recommendations for strategies to maximize healthy outcomes for patient and child.

Multiple Births: Scope of the Problem

Public Perception

The news media are portals for insight about the latest technology, medical devices, and therapeutic trends and hold considerable sway in shaping the public's perception of medical options. In a recent survey, 75 % of those polled relate that they rely on media coverage for medical information that weighs heavily in their decision-making [1]. In some settings, information derived from the media is held side by side to that offered by medical providers. There are several reasons for this power. News media, whether written or televised, present information in a format designed to appeal to our patients: easily accessed, conveyed in understandable language, and illustrated by personal vignettes to which they may relate. These aspects would be an ideal educational format for patients when the coverage is even handed and balanced. However, the lack of scrutiny in data quality and presentation, both overt and subtle, can undermine this opportunity. Contemporary agendas of the news media have evolved away from a traditional vehicle for informing the public as a watchdog to a venue for attracting audiences. In this capacity, multiple gestations are a treasure trove. The public is engaged by stories of goodwill, science, and family. Multiple gestations combine all three aspects in a single package, and the appeal has increased markedly in recent years.

The fascination with multiple pregnancies on the part of both the lay press and the public is long standing and predates any assisted reproductive technology. In the 1930s, the Dionne quintuplets captivated nations [2]. The sensation caused by these children found appeal across a wide spectrum

of interests; in fact, the intrigue was so great that the Canadian government saw fit to develop a theme park called "Quintland." The Dionne quintuplets found their way as poster children in a widespread marketing campaign for Carnation Milk. The success of this marketing campaign was no doubt related to the high visibility and attention that the quintuplet phenomenon could attract. In 1983, the Pisner quintuplets (four boys and one girl) were delivered in Maryland. *Washingtonian Magazine* caught the wave of excitement with feature articles profiling family life with five healthy children. In these early examples, scant attention was given to the complications of high-order multiples, portraying the children only as cute, healthy, and engaging. The fascination with multiple gestations has endured time and superseded the potential scorn of a more prudent society, as evidenced by the ongoing media coverage to the McCaughey septuplets who remain the subject of popular annual updates [3]. The exception to this positive media spin was the birth of octuplets after IVF in 2009. Although this case brought scrutiny and criminal charges to the treating physician, it was likely only the extreme circumstances of this single mother receiving public assistance that finally drew broad attention to this *iatrogenic* catastrophe [4].

As compared to high-order multiple gestations, the much more prevalent epidemic of twins has received little scrutiny in the lay literature and media. In fact, a recent article in the *New York Times* admonished the practice of selective reduction of twins with only a passing reference to the increased medical risks of twins and no suggestion that most of these are preventable complications [5].

Consequences of Multiple Gestation Pregnancies

Medical Risks

Although the risks of extreme prematurity in high-order multiple pregnancies are generally well understood, the risks associated with twin pregnancy are widely underestimated. Although many twins are born at or near term, as many as 60 % are delivered before 37 weeks due to either preterm labor or medical indications, with 10 % delivered <32 weeks [6]. Average gestational age for twins is just over 35 weeks compared to nearly 39 weeks for singletons [7]. Twins born after IVF experience a significantly higher incidence of perinatal mortality [8] and significantly greater risk of serious sequelae such as cerebral palsy [9] compared to IVF singletons. Elevated maternal risks associated with multiple gestations include hypertension, gestational diabetes, operative delivery, and hemorrhagic complications. DIVF patients often are already at high risk for these obstetrical complications, with compounding effects of age, higher incidence of uterine pathology such as fibroids, and risks potentially inherent to IVF including lower birth weight, preterm birth, and placenta previa observed even in singleton IVF pregnancies [10, 11]. Certain subgroups, such as patients with Turner's syndrome or those with chronic underlying medical illness, have additional risks that may be life-threatening. Furthermore, there is evidence of a detrimental effect when multiple embryos are transferred even in singleton pregnancies, where lower birth weight and/or preterm birth is increased when more than one embryo is transferred [12, 13].

Cost

Though it is accepted that multiple births add significant costs per infant due to the increased incidence of prematurity and corresponding perinatal and neonatal complications, the long-term costs of such sequelae are largely unknown. Based on 2006 economics, it was estimated that the mean additional cost incurred is approximately US $51,600 per preterm infant. These additional costs are limited to the perinatal and neonatal period [14]. Potential long-term disabilities and cost of ongoing medical care could potentially greatly compound the financial burden to society. A prospective cohort study of IVF twins and singletons has been proposed in the Netherlands (the TwinSing study) to investigate health outcomes and associated costs through the first 18 years of life [15]. Such investigations should prove invaluable to guide provider, patient, payer, and governmental reproductive

Fig. 11.1 Number of twin deliveries annually and rate as percent of all births in the USA, 1980–2006 (Reprinted from Chauhan et al. [6], Copyright (2010), with permission from Elsevier)

decision-making. The emotional toll on a family of multiple gestations is less well characterized but nonetheless imposes a significant impact on quality of life.

Incidence and Trends in ART Practice

The incidence of multiple gestations has risen substantially over the past three decades, predominantly due to the increased utilization of ART. While the incidence of high-order multiple gestations (triplets and more) has fallen significantly, the incidence of twins rose steadily from 1980 to 2004 after which there has been a plateau (Fig. 11.1) [6]. In the 1980s and early 1990s, most IVF cycles were associated with relatively low embryo implantation rates. Transfer of multiple embryos was considered necessary to maintain acceptable pregnancy rates and was considered standard of care. Even so, implantation rates were highly variable and unpredictable, resulting in high rates of multiple gestations including high-order multiples. Furthermore, many early programs lacked the ability to cryopreserve remaining embryos not selected for transfer. As the number of IVF programs increased, competitive and entrepreneurial influences among ART providers soon followed. In 1992, the Fertility Clinic Success Rate and Certification Act (FCSRCA) was passed, requiring that success rates of all US ART programs be made available to the public, though this was generally not enforced until 1995 when the CDC began publishing ART data. Though intended to serve as a "regulatory" force in ART practice, dissemination of practice-specific pregnancy rates provided another opportunity for patients to select ART programs based on their apparent success rates, often with little insight as to the variables that influence outcomes as well as a lack of emphasis on healthy outcomes or multiple pregnancy rates. Too often, data have been interpreted with a restricted view, defining success in terms of clinical pregnancy rates and ignoring the significance of multiple gestations.

As implantation rates improved, there has been a gradual reduction in the number of embryos transferred. Publication of practice guidelines by the Society for Assisted Reproductive Technology (SART) in 1998 coincided with a sharp reduction in the percentage of procedures where four or more embryos were transferred [16] (Fig. 11.2). There was a corresponding decrease in the incidence of high-order multiple pregnancies and increased percentage of singleton live births; however, adoption of these more conservative guidelines has been ineffective in reducing the rate of twins. Even at the time of the 2009 guidelines published by SART, SET was recommended as the standard only in the best prognosis cycles (Table 11.1) [17]. A substantial number of programs have continued the practice of multiple embryo transfer; this practice is in part related to considerable pressure to maintain high pregnancy rates that appeal to patients who are often faced with a significant financial burden

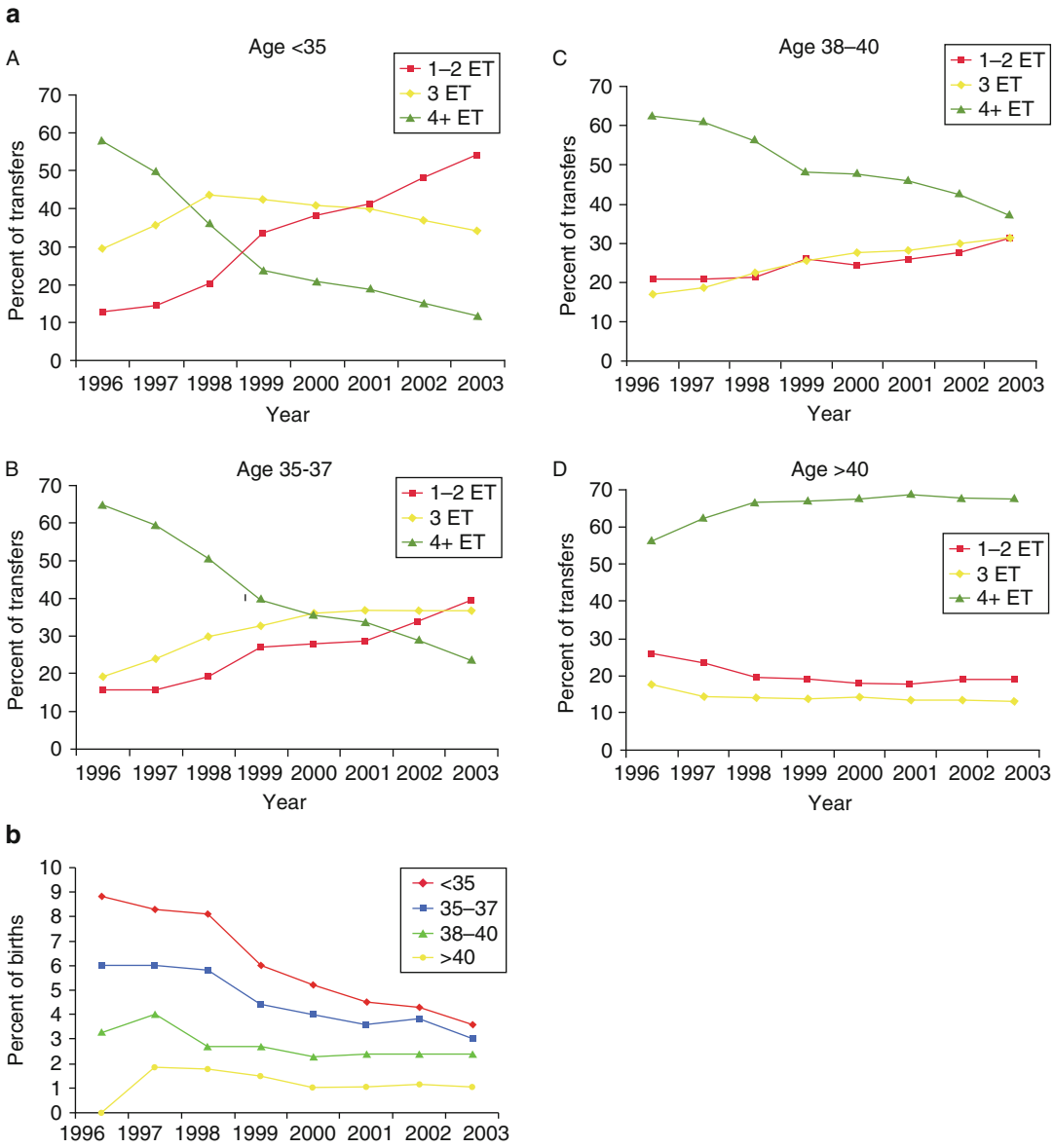

Fig. 11.2 (**a**) Percentage of cycles for each year in which a given number of embryos were transferred (ET): *red squares*, 1 or 2 embryos; *yellow diamonds*, 3 embryos; and *green triangles*, R4 embryos. (**A**) Women <35 years of age, (**B**) women 35–37 years of age, (**C**) women 38–40 years of age, and (**D**) women >40 years of age. The percentage of women with R4 embryos transferred declined for each of the first 3 age groups [17] (**b**) Percentage of HOM births for each year in age groups of women <35 years, 35–37 years, 38–40 years, and >40 years. Percentage of HOM births declined in the <35 and 35- to 37-year-old group [17] (Reprinted from Stern et al. [16], Copyright (2007), with permission from Elsevier)

associated with IVF treatment. Lack of insurance coverage or other subsidies for infertility treatments places many patients under considerable pressure to undergo as few treatments as possible.

The European Society of Human Reproduction and Embryology consensus meeting held in 2002 concluded that a twin pregnancy should be considered a complication of IVF [18]. However,

Table 11.1 Recommended limits on the numbers of embryos to transfer according to 2009 SART guidelines [17]

	Age			
Prognosis	<35 years	35–37 years	38–40 years	41–42 years
Cleavage-stage embryos				
Favorable	1–2	2	3	5
All others	2	3	4	5
Blastocysts				
Favorable	1	2	2	3
All others	2	2	3	3

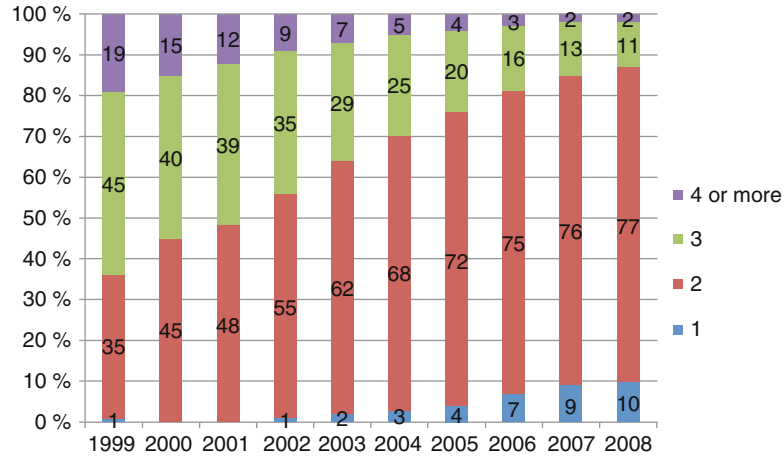

Fig. 11.3 Percentages of fresh, nondonor, ART cycles with transfer of 1, 2, 3, or 4 or more embryos (women <35 using autologous oocytes with cryopreserved embryos) reported to the CDC from 1999 to 2008 [19]

particularly in the USA, adoption of elective SET has been slow. In 2008, only 10 % of embryo transfers to women under 35 involved the elective transfer of a single embryo (Fig. 11.3) [19]. While the number of triplet and higher gestations has declined dramatically, there has been no reduction in the incidence of twin pregnancy due to the relatively low percentage of cycles where only a single embryo was transferred (Fig. 11.4).

Good prognosis patients, including donor egg and embryo recipients, are subject to the highest incidence of multiple gestations, due to the high implantation potential of embryos and the accepted practice of transferring multiple embryos. In 2009, of 6,843 DIVF pregnancies reported in the USA, 39.2 % were twins and 3.2 % were high-order multiple gestations including triplets and more (in 5.2 % of reported pregnancies, the number of fetuses was unknown) [20]. Out of the 5,894 live births, only 60.1 % were singleton, 38.6 % twin, and 1.3 % triplets or more, for a total multiple pregnancy rate of 39.9 %. An average of 2.0 embryos were transferred in the 10,151 fresh DIVF reported in the USA. Because data are not collected, the incidence of multifetal reduction in this population is unknown. With a small but growing proportion of elective SETs, these data indicate that in a significant proportion of cycles, three or more embryos were transferred.

Not all multiple pregnancies can be prevented with SET due to monozygotic twinning. An increase in the incidence of monozygotic twinning has been observed in IVF pregnancies compared to spontaneous conceptions, particularly when extended culture and blastocyst transfer are performed [21, 22]. The incidence of monozygotic twinning has been reported to be as high as 3.3 % in DIVF cycles [23], and although rare, monozygotic triplets and even quadruplets have also been reported in ART pregnancies.

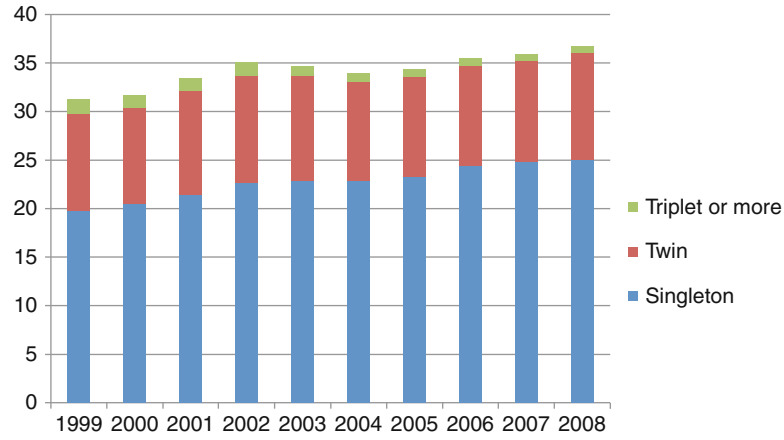

Fig. 11.4 Percentage of transfers resulting in live births and multiple birth rates for fresh, nondonor, ART cycles reported to the CDC from 1999 to 2008 [1]

Strategies to Prevent Multiple Births

Single Embryo Transfer

Improved embryo culture and embryo selection techniques have resulted in significant improvements in embryo implantation over the past several years. As a result, good prognosis patients such as DIVF recipients may now enjoy success rates with SET that are roughly equivalent to those with two or more embryos transferred while dramatically reducing the risk of multiple gestations. The term "elective SET" is generally reserved for the practice of transferring a single high-quality embryo when there are multiple high-quality embryos available for transfer (as opposed to cycles where only one embryo is available).

SET Outcome

Several investigators have compared outcomes after SET compared to two- or double-embryo transfer (DET), including several randomized controlled trials [24–30]. Results demonstrate that for cleaved (day 2 or 3) embryos, live birth rates are lower with SET than DET. However, as expected, there is a dramatic reduction in the incidence of twins when only a single embryo is transferred. A meta-analysis of eight randomized trials comparing day 2 or 3 elective SET with DET found that the live birth rate per embryo transfer was lower after a fresh elective SET (27 %) than DET (42 %) [31]. However, when pregnancies from subsequent frozen single embryo transfer were included, there was no significant difference in cumulative live birth rate per oocyte retrieval (38 % vs. 42 %). In contrast to results of trials comparing SET and DET on day 3, studies comparing elective SET and DET in blastocyst transfers found no significant difference in live birth rate when one versus two embryos were transferred [32–34]. A randomized controlled trial comparing elective SET and DET in blastocyst transfers demonstrated no significant difference in ongoing pregnancy rate (61 % vs. 76 %, respectively), whereas the high incidence of twins with DET (47 %) was eliminated with SET (0 %) [24]. The discrepancy in SET outcome after day 3 versus day 5 transfer presumably results from better embryo selection on day 5 – arrested embryos are eliminated, and blastocysts possess differentiated components allowing evaluation of multiple morphological features (such as inner cell mass, trophectoderm, and degree of expansion and/or hatching). It is important to include information about the increased risk of monozygotic twinning when counseling DIVF patients [23]. In light of this phenomenon, an even stronger argument for SET can be made.

Results of nonrandomized studies comparing SET to DET outcomes were summarized in a recent ASRM Practice Committee Opinion published in October 2011 ([33–38], Table 11.2).

Table 11.2 Results of nonrandomized studies comparing single embryo transfer (SET) to double embryo transfer (DET) [35]

Study	Gerris [36]	LeLannou [37]	Henman [38]	Criniti [33]	Stillman [34]
Embryo stage	Cleaved	Cleaved	Blastocyst	Blastocyst	Donor blastocyst
SET IR (%)	35.1	27.6	45	76	63
SET PR (%)	35.1	27.6	45	76	63
DET IR (%)	36.5	23.8	42	66	59
DET PR (%)	50	37	57	79	71
Twin rate (%)	41	37	44	62	54

Although some investigators have reported equivalent ongoing pregnancy rates with SET versus DET [33, 34], caution should be used in interpreting nonrandomized studies due to the inherent bias of physicians and patients to choose SET when the overall number and quality of available embryos are superior. Nevertheless, these studies demonstrate that in appropriately selected patients, there is no advantage to DET when a singleton live birth is the goal, supporting the concept that in these patients (including the majority of DIVF recipients), SET should be standard.

At Seattle Reproductive Medicine, we have adopted a policy to recommend SET in DIVF recipients if there is at least one high-quality blastocyst available on day 5. From January 2009 through December 2010, 352 DIVF recipients were offered SET. The average number of embryos transferred overall was 1.4 per transfer procedure [39]. There was no significant difference in pregnancy rate between the single- and double embryo transfer groups (75 % vs. 69 %), yet the twin rate was significantly reduced (0.8 % vs. 58 %, $p<0.001$). There were two triplet pregnancies due to monozygotic twinning in the DET group. In spite of these data, uniform patient acceptance of SET has been difficult to accomplish; however, our recent approach is to present SET as the routine (default) practice, resulting in an increased number of patients electing single embryo transfer (from 35 % in 2009 to 50 % in 2010).

Embryo Selection

In addition to extended culture and blastocyst transfer, several other methods of embryo selection have been proposed. Advances in preimplantation genetic screening through single nucleotide polymerase assay or comparative genomic hybridization have resulted in enhanced implantation rates even in older patients where the incidence of aneuploidy is high [40]. This technology has not yet been broadly applied in part due to cost, limited availability, and inaccurate results due to mosaicism especially when a single blastomere is biopsied on day 3. Trophectoderm biopsy on day 5 may reduce this risk by examining multiple cells; however, this requires embryo cryopreservation and transfer in a subsequent cycle unless results are immediately available within a 24-h time frame [41].

Concerns about the effects of extended culture on imprinting have not been substantiated in human embryos to date. However, not all laboratories have optimal success with blastocyst culture. Improved ability to select cleavage-stage embryos with the highest implantation potential would be expected to improve SET outcome when performed on days 2–3. Proposed methods of embryo selection have included examination of the embryo secretome (proteomics) [42], cumulus cell gene expression [43], meiotic spindle assessment [44], and serial, standardized morphological assessment made possible with time-lapse videography [45, 46]. Optimal embryo selection is a fundamental component to allow DIVF programs to allow for eSET without compromising cycle outcome.

Improving Efficiency and Cost

Prerequisites to gaining patient acceptance of SET and ensuring its success include the ability to provide optimal culture conditions and endometrial preparation, identify the best embryo for transfer, and maintain a successful embryo cryopreservation program. A robust quality assurance

program is integral to developing and maintaining a high rate of success. The most effective strategy to improve the cumulative live birth rate per donor retrieval is the availability of embryo cryopreservation followed by frozen embryo transfer (FET). Success rates from FET in most programs are significantly lower than corresponding fresh pregnancy rates – in 2009, the live birth rate from frozen embryo transfers in DIVF cycles was only 34 % compared to 55 % with fresh embryos in spite of a similar number of embryos transferred (average 2.1 and 2.0 embryos per transfer, respectively) [20]. Improvements in embryo survival and implantation rates have been achieved using newer vitrification methods. Continued improvements are needed to optimize success and corresponding patient acceptance. Even though cumulative SET pregnancy rates (i.e., fresh SET followed by cryopreserved embryo transfer) are similar to those with multiple fresh embryos transferred, patients are wary of the additional financial and emotional burden of multiple treatment cycles as well as the lengthened time to conception.

Financial incentives that bundle the cost of eSET followed by FET in unsuccessful cycles may serve to increase patient acceptance of eSET. Programs that offer discounted repeat cycles or refunds for an unsuccessful treatment course may also provide incentive to DIVF recipients and reduce the pressure to make clinical decisions based on individual cycle success rates alone.

Another approach to improve efficiency and reduce the cost of DIVF involves sharing the oocytes from a single donor oocyte retrieval among two or more recipients. Commonly, 20 or more oocytes may be retrieved in a single donor cycle, often resulting in remaining cryopreserved embryos that ultimately will not be used by the recipient. By sharing oocytes from one donor with two or more recipients, access to donor oocytes and cost-effectiveness can be greatly improved. However, matching and coordinating multiple recipients for a fresh embryo transfer are logistically cumbersome, and fewer embryos are available for cryopreservation. Recent technological advances in oocyte freezing through vitrification have made the possibility of utilizing frozen and stored donor oocytes a reality. A recent meta-analysis of randomized controlled trials utilizing oocyte vitrification demonstrated improved survival, fertilization, and embryo development compared to slow cool methods [47]. Even more encouraging are the results of a randomized clinical trial comparing outcomes in DIVF cycles utilizing fresh versus previously vitrified oocytes [48]. There were no significant differences observed between the vitrified and fresh oocytes in the ongoing pregnancy rate per randomized patient (43.7 % vs. 41.7 %, respectively), embryo implantation rate (39.9 % vs. 40.9 %, respectively), or proportion of top-quality embryos obtained per inseminated oocyte. While these promising results forecast significant advances in the efficiency and accessibility of DIVF treatment, to date, there has been limited experience with elective SET in oocyte vitrification cycles. Further experience and confidence in oocyte vitrification methods are needed to allow wide application of SET in DIVF cycles utilizing banked oocytes.

Role of Multifetal Reduction

Multifetal reduction (MFR) is an option that was initially described in 1986 to manage high-order multiple pregnancies and is sometimes considered as recourse in the event that greater than two embryos implant. The procedure is most often considered as an option for triplet and higher-gestation pregnancies, where an irrefutably high probability of complications is present. The reduction of twin to singleton pregnancies has created an even greater level of controversy even though medical outcomes are improved for the mother and child(ren) [49]. Unfortunately, the availability of this option sometimes serves only to postpone or minimize an honest appraisal of multiple pregnancy risk. Many patients may consider MFR an ethically acceptable practice only to find that they are philosophically or emotionally unprepared to make a decision to proceed. Discussion about MFR should be included in the informed consent process when transfer of more than one embryo is considered. Although the goal

of MFR is to protect the health of the mother and her prospective offspring, it should be utilized only in the rare circumstances where judicious treatment decisions have nonetheless resulted in a high-risk multiple gestations.

Prevention of Multiple Births: Revising the Standard of Care

Role of the Provider

Reliable information about the risks of multiple gestations is ideally provided by the patient's physician. Expectations and a slanted understanding of multiple gestations create a dynamic every reproductive endocrinologist faces on a daily basis: more than a fair share of patients express interest in multiple gestations. In fact, a substantial portion of patients surveyed report they consider twins to be their desired, optimal outcome [50]. This may be in part related to costs and a one-stop shopping attitude: a multiple gestation for many couples offers the opportunity to have a modern-day family of four (or more) in one broad sweep with what they perceive to be a minimal financial impact at the front end. Face-to-face counseling enhances understanding and can usually place multiple gestations in their proper clinical perspective. However, this is often a time-consuming and uphill challenge, as their opinions are shaped by a number of information streams. Our counseling and discussions are but one line of information and an increasingly diluted one at that.

The fundamental basis for gaining patient acceptance of SET is education, ideally provided by the physician. Such counseling provides the best defense against misconceptions regarding the risks of multiple pregnancy as well as the limited advantages of multiple embryo transfer on pregnancy rates. Understandably, a comprehensive discussion of the nuances of DIVF treatment and outcomes is a daunting, time-consuming task. In a 2008 survey of physicians affiliated with IVF centers registered with SART, only 34 % of respondents routinely discussed eSET with their patients [51]. A randomized trial found that more patients elected single embryo transfer after watching a DVD that included patient testimonials than those who received the same factual information in a written brochure [52]. The position that a singleton pregnancy is the intended outcome of DIVF should be conveyed in specific, supportive, and unequivocal terms. The role of the primary physician in fulfilling this goal is paramount and relies on his/her ability to instill a sense of confidence by thorough comprehension and presentation of facts as well as establishing a nurturing relationship that earns the patient's trust. Infertility patients, owing partly to the vast amount of information available via social networks and the media, see themselves much more as consumers of a product rather than recipients of health care. It is our obligation to keep the shift from a primary focus on pregnancy rates alone to the health aspects and risks of ART.

Role of the Media

As the number of higher-order multiples and the intrigue with ART increased, the press paid more attention. The McCaughey septuplets became a media spectacle and point of discourse on multiple gestations. The parade of news articles and the public's response ushered in a new era of media's interest in multiple gestations. Various episodes followed describing families with high-order multiples. The story lines appeared to emphasize the promise and minimize the peril of multiple gestations and ART.

News reports on multiple gestations were compiled from two major newspapers for the year 1999–2000, and data from these were reported in abstract form. The articles were reviewed with attention to outcomes, data contained, attributed sources of quotes and recommendations, literature citations, and outcomes [53]. Approximately half of the articles contained only interviews with families, with no scientific or medical data. Only 15 % described potential adverse outcomes in specific, quantitative terms, and only 2 % included discussion of long-term follow-up. The subjective, between-the-lines impression was one of a "two is better than one"

mentality and that other than number, multiples were really no different from singletons. Perhaps not by design, the hard edge of the clinical reality was softened. Specific descriptions of developmental or motor delay or perinatal morbidity and mortality attributable to prematurity were minimized. The media present an opportunity to disseminate factual data; the goal should be to educate the public in understandable and intelligent terms the potential negative impact of high-order multiples on the well-being of the children. Unfortunately, experience suggests that this goal is rarely accomplished.

The education of the media will be, in part, the burden of the profession to bear. Reliable characterization of adverse outcomes (redefining adverse outcomes as any multiple pregnancies) is required. The intentions of our profession to promote health of the children and families should be clearly presented. There should be a movement away from the idealized concept of multiple pregnancies and toward a balanced, realistic picture of the consequences of higher-order multiples. The profession has been successful at an awareness campaign regarding the impact on maternal age on fertility. No less vigorous a campaign could effectively change perceptions and enhance the counseling and understanding of our patients. This education should be clear, explicit, and supportive of the patient's interests in achieving a pregnancy but also designed to dissuade the patients from an interest in multiple pregnancies.

Role of the Government

The early days of ART practice were unregulated and relatively off the radar of bioethicists and healthcare legislators. The observation in 1990 of a commission of the Academy of Ethics in Medicine that the clinical care in IVF was dotted with unfavorable outcomes drew scant attention. However, as the practice of IVF evolved, multiple European countries passed legislation to regulate the number of embryos transferred. Over the past two decades, the landscape has changed dramatically, with pressure from various agencies to restrict the number of multiples births and the resulting observation that this in fact can be accomplished with a positive impact on outcome and patient care. Government regulation has become a reality in many countries with variable results, including both improvements and adverse consequences in clinical outcome. These efforts share a common theme of restricting the number of embryos transferred, whether by restricting the number of oocytes inseminated, the number of embryos transferred, or both. These changes may be a result of the public's desire to regulate IVF and growing concern over the use and misuse of the technology as portrayed in the popular press and media. Practitioners of ART would do well to pay attention to pending legislation and regulation.

The profiles of various forms of government regulation convey the spectrum of regulations on care. Three statements can be made regarding legislation in this field: it appears to be region specific with certain laws prompted by the religious or political climate; adverse outcomes can result from legislation; the most effective legislation appears to strike a balance between regulation for the public good and maintenance of judicious clinical care (including acceptable pregnancy rates).

European Experience

The European experience suggests that in a reasonable local political climate, the number of embryos transferred can be successfully influenced without sacrificing pregnancy rates. In some countries, interest in the regulation of IVF is based on religion, while in others it is primarily based on the need to restrict medical expenditures. Germany was one of the more extreme countries in adopting regulations for IVF, beginning with the Federal Embryo Protection Law in 1990 [54]. This law mandated that all fertilized oocytes subjected to in vitro culture be transferred and the number for transfer was restricted to no more than three. In 1990, Britain's parliament passed the Human Fertilization and Embryology Act, establishing a statutory licensing authority to oversee IVF. In several European countries, legislation mandating that the number of embryos be restricted has dramatically increased the utilization of SET while lowering the incidence of multiple gestations.

A Belgian law implemented in 2003 which provided reimbursement for up to six IVF cycles if certain restrictions on embryo number were adhered to: in the first year, the rate of SET increased from 14 to 49 %, while the rate of twins fell accordingly from 19 to 3 %. The overall pregnancy rate was unchanged (36 % vs. 37 %) [55]. According to ESHRE, in 2006, SET rates were highest in countries with mandatory limits on the number of embryos transferred, including Sweden (69.6 %) and Belgium (49.2 %) as well as in countries such as Finland (54.7 %) with subsidized fertility treatments where SET has become the standard of care [56, 57].

Countries prohibiting cryopreservation or destruction of fertilized human oocytes have confronted high rates of twins and triplets. In Italy, a law passed in 2004 dictated that all fertilized oocytes must be transferred and cryopreservation and destruction of embryos were prohibited. As a result, elective SET was uncommon, with a resulting high incidence of multiple pregnancies. This law was subsequently repealed due to the observations that multiple pregnancies increased and certain clinical profiles (male factor, for instance) were poorly served. Whereas the overall triplet rate reported by ESHRE in 2006 was 0.9 %, there was marked disparity among countries, ranging from 0 % in Sweden to 50.9 % in Italy, almost certainly due to the discrepancies in legislation [56].

Canadian Experience

In August 2010, legislation was passed in Quebec to regulate ART and control reproductive healthcare issues. The aim of the program was to promote SET in sequential cycles. According to this legislation, multiple embryos could be transferred in cases with a poor prognosis, but physician justification is required. Prior to the introduction of the program, the elective transfer of only one embryo was used in only 1.6 % of the cycles in the Quebec area, resulting in a multiple pregnancy rate of 25 % [58]. In the early days of this program, the overall clinical pregnancy rate was 32 % per transfer and 50 % of the transfers involved a single embryo transfer. The multiple pregnancy rate was only 3.7 %. These observations suggest that a single embryo transfer can result in acceptable pregnancy rates with a remarkable diminution in multiple pregnancy rates.

US Experience

Despite studies to identify the most cost-effective means to achieve IVF pregnancy while restricting the number of embryos transferred to one, multiple embryo transfer remains the standard of care in the USA. Factors influencing this tendency likely include increased number of providers and programs with consequent competition for both donors and recipients in the marketplace as well as continued patient preference for twins. In general, there is no consensus that Federal regulation in the USA will improve patient care.

Concern over medical expenditures is prompting the interest in the USA to reduce the multiple pregnancy rate; the observation of lower multiple pregnancy rates in mandated states suggests that there may be a role for government regulation in limiting the number of embryos transferred. IVF pioneers during the mid to late 1970s and early 1980s confronted multiple attempts at regulation, yet most providers felt that any government intervention was inappropriate. Concern that government regulation would be overly burdensome and onerous led to the concept of self-imposed regulation, ultimately resulting in the formation of the Society for Assisted Reproductive Technology (SART). Government initiatives followed, as several states passed legislature mandating insurance coverage for IVF. While SART has provided some assurance to government regulators and insurers that the profession is capable of policing itself, the recent attention to the continued high incidence of multiple births has called this into question.

US legislation could take several different forms. Overly stringent statutes may not serve the patient's interests best; reducing multiple pregnancy risk should be balanced by the need to control the number of embryos and optimize pregnancy rates. Legislation could be a single national policy or state-by-state laws defining standards of care. Regional discrepancies could result in medical tourism, with patients migrating

to states or countries with more liberal or nonexistent statutes. In some cases, this could result in compromised quality of care and/or lack of follow-up. Appropriate counsel regarding the need to maximize pregnancy rates for optimal patient care should be balanced against the need to protect the welfare of the patient (i.e., to reduce complications of pregnancy and adverse perinatal and neonatal outcomes).

The experience in several countries in Europe lends credence to the idea that multiple births will be reduced when the number of embryos transferred is restricted by law. There has been a movement to a defined policy of single embryo transfer for all DIVF cycles. Isolated restrictions and exceptions could apply, for example, where an overall lower number of oocytes and embryos or no embryos are available for freezing, where it would be reasonable to apply a policy to transfer no more than two embryos regardless of circumstances.

Role of Payers

The direct relationship between number of embryos transferred, multiple gestations, and related high costs is more recently coming to the attention of third-party payers. In fact, the impact on cost considerations may ultimately be the impetus for change in practice pattern, as third-party payers begin to weigh in to the debate, imposing restrictions on medical practice in order to limit their financial exposure. Given that the transfer of multiple embryos poses potential maternal, prenatal, neonatal, and potential long-term complications, insurers are motivated to limit their financial liability by restricting the number of embryos transferred. With the increasing contributions by private and governmental agencies to the funding of ART treatment, regulation by these agencies will become more common.

There is an early though increasing movement among insurance companies to impose mandates on clinical practice. For example, the concept of a "center of excellence" could be tied to reimbursement. Such a designation would require review of a clinic's practice patterns, including the number of embryos transferred and multiple pregnancy rates. Clinics falling below a certain standard would either be ineligible for any insurance coverage or participation or subject to a reduced percent of reimbursement. Awards may be tied to number of embryos transferred and to the rate of multiples with subcategories for twins, triplets, and higher, with the goal to offset the high expenses of neonatal care.

Initiatives calling for more insurance benefits should be accompanied by the expectation that insurers will become more involved in medical decision-making. By design, if overly simplistic, these benefits could impact patient autonomy and potentially increase the number of ART cycles necessary to achieve pregnancy in patients with a less favorable prognosis. The strong influence of cost on patient and provider acceptance of SET is exemplified by the high SET rates in countries with government subsidies for ART, especially if funding is predicated on the adherence to strict limits on number transferred.

Conclusions

Attempts to improve pregnancy rates in the early days of IVF translated to transferring multiple embryos. Even with technological advancements and improvements in embryo implantation rates, progress has been impaired by the inability to precisely and reliably predict the single best embryo for transfer, leading to the continued practice of transferring more than one embryo per IVF attempt. Though we are much better today than even in the recent past, this qualitative approach to embryo selection leads to the continued practice of transferring more than one embryo per IVF attempt. This practice is intended to improve cycle effectiveness and pregnancy rates but has been accompanied by the unwanted side effect of a higher likelihood of multiple embryo implantation and pregnancy. As a result, multiple births have increased over the last two decades to epidemic proportions exposing the field of ART to justified criticism.

The need to predict implantation potential and improve embryo selection is the focus of continued research, with promising results on

the horizon. In the meantime, practitioners of ART are faced with the need to reduce multiple pregnancy rates. Although the problem is complex in nature, some simple solutions can be implemented immediately in DIVF cycles. These solutions include education of patients and the public regarding the risks of multiples and ultimately a voluntary practice of SET. Live birth rates are similar when one versus two blastocysts is transferred, and the risk of twins may exceed 60 % with DET. While SET birth rates are similar when embryos are transferred on day 5 of embryo culture, there is a lower pregnancy rate observed compared to DET when embryos are transferred on day 3. This difference is eliminated when subsequent cryopreserved embryo transfer is performed. Contemporary aims in our field have been to define the risks and complications related to multiple pregnancies and to convey these risks to patients, so that intelligent decisions can be made regarding elective SET. In the USA, education of patients has been shown to change their attitudes regarding their preference for more than one embryo transfer. The ethical obligation for restricting the number of embryos has also emerged as another rational motivation for restricting the number of embryos transferred; providers of DIVF have a responsibility of nonmalfeasance to patients. With oversight within our profession, we may be able to forestall, if not completely avoid, the need for government and insurer regulation.

Editor's Commentary

Pregnancies have been celebrated and sensationalized in recipients of donor eggs and embryos from the very beginning. What has gone largely unnoticed is the consistently high number of multiple births experienced in the recipient population. Many of these pregnancies are dangerously complicated, and the resulting families can also be problematic. As Letterie and Klein clearly point out, this problem is entirely iatrogenic and correctable but perhaps requires more willpower than what our profession is willing to exhort.

Guidelines are guidelines, and the ASRM recommendations are neither enforced nor associated with any meaningful professional penalty if ignored, and they are being ignored. I agree that pressures on practices to exhibit high success rates are enormous as physicians compete for patients in the world's most fierce marketplace of assisted reproduction. Patients are also complicit in promoting the concept of "pregnancy at any cost" in their desperate quest to have a baby. When confronting patients with the perils of multiple births and the logic of performing single embryo transfer, I have often heard in response what I have come to term the Scarlett O'Hara rebuttal; "I can't think about this right now. I'll go crazy, if I do. I'll think about it tomorrow!"; translation, I'll take the risk now and worry about the consequences later.

The consequences are often quite grim. Bad outcomes affect children, their parents and families, and society at large. Professional emphasis has largely been focused on the complications of pregnancy and preterm births. These problems have been defined by death and disability and cost to the health-care system. But most newborns survive, and whether "intact" or not, the problems created by birthing multiple children at once do not end at delivery but continue on indefinitely. These are *forever* complicated families.

The European view of defining twins as a "complication" of assisted reproduction is disputed by many American practitioners, but in my opinion, it is really the correct one. We have a problem in this country, and we, as caregivers, need to recognize it and take active steps to fix it. The epidemic of multiple births is iatrogenic, and if physicians continue to ignore the problem that

we created, then it is inevitable that forces outside of medicine will mandate change through regulation and professional liability lawsuits. We must all try harder to promote a policy of single embryo transfer and condemn those who refuse to adhere to our professional guidelines.

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What Is the Outcome and Fate of Frozen Supernumerary Embryos Resulting from Egg Donation?

12

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Key Points

- While a shared egg donation cycle does not appear to impact upon fresh cycle pregnancy outcome, it does decrease the likelihood of having supernumerary embryos available for cryopreservation.
- Although recipients approach their donor oocyte treatment with a desire to cryopreserve embryos for attempts at creating a genetic sibling in the future, most only return to use their cryopreserved embryos after failing their original fresh transfer.
- A known relationship with the donor, familial or colloquial, may generate a stronger kinship to the resultant embryos and appears to motivate the recipient to undergo a subsequent frozen donor embryo transfer.
- Approximately one in five recipients allow embryos to remain in cryostorage indefinitely most likely to avoid making a final difficult decision regarding their fate.

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Cryopreservation of supernumerary embryos affords patients the potential opportunity to achieve multiple pregnancies from a single fresh IVF cycle or to at least have a second chance at success if the first attempt failed. In addition, the availability of frozen embryos reduces overall patient cost and increases the cumulative odds of pregnancy per case. Embryo cryopreservation is of particular importance in oocyte donation cycles because the number of embryos available frequently exceeds that which is acceptable (or desirable) for embryo transfer. Furthermore, limited resources specific to oocyte donation, including donor availability and cost, augment the appeal of cryopreservation. Despite the desire to cryopreserve supernumerary embryos at the time of the fresh donor oocyte transfer, more often than not, patients do not return to use their surplus embryos. Analysts estimate that as of 2003, over 400,000 embryos from all sources remained in storage facilities in the United States [1]. As the number of IVF procedures has only grown over the past decade, we speculate that this number has nearly doubled.

Disposition decisions can be difficult; consequently, frozen embryos may remain in storage for years awaiting a "verdict." Therefore, we assessed the factors that could potentially impact a recipient's likelihood to use her frozen embryos as well as factors that could affect the success of the frozen embryo transfer. We also addressed the various disposition options for embryos created by oocyte donation: donation to science/research, donation to an infertile couple, and

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embryo discard. Lastly, we reviewed the feasibility of donor oocyte banks and the impact these banks might have on the disposition of frozen embryos.

Background

According to SART data, the past 5 years has seen a steady increase in both the number of fresh and frozen donor oocyte cycles [2]. Of the 72,296 donor egg transfers performed in the United States from 2005 to 2009, 25,546 (35.2 %) involved frozen embryos. Although fresh donor egg cycles have consistently shown higher success rates than their frozen counterparts, approximately one-third of frozen donor oocyte cycles produces at least one baby [2]. There is a trend toward a higher frozen success rate over the past 10 years, and this is likely a result of improved freezing protocols, general laboratory techniques, and embryo transfer principles. The implementation of vitrification for embryo freezing, as opposed to slow freezing, has also improved embryo survival and pregnancy rates for cryopreserved embryos and oocytes [3–5].

Are There Factors That Impact Upon the Success of a Frozen Donor Oocyte-Embryo Cycle?

There are several factors that have been implicated in the success or failure of a recipient's frozen embryo cycle. As in a fresh donor oocyte transfer cycle, the recipient's uterine lining appears to play a pivotal role in the embryo's ability to implant and develop. A receptive endometrium is generally established using exogenous estradiol and progesterone. Measurement of the uterine lining is often used as a noninvasive tool to assess uterine receptiveness; there have been several studies demonstrating that a thin endometrium (the definition of which varies) is detrimental to embryo's ability to implant. While others have shown the correlation between thickness and success to be weak, measurement of the lining remains a universal component in the assessment of uterine suitability [6–9]. Although the majority of studies analyzing endometrial thickness and donor oocyte cycle outcome have been conducted in patients undergoing fresh donor cycles, the findings may be translated to frozen cycles as well. Dessolle et al. studied factors that were predictive of pregnancy, specifically in recipients of frozen embryo transfers. In concordance with previous work done on fresh donor oocyte cycles, an endometrial thickness <8 mm negatively impacted pregnancy rates [10].

Other anatomic factors can affect embryo transfer success. For instance, the presence of a hydrosalpinx has been consistently demonstrated (in both donor and autologous fresh and frozen IVF cycles) to impair the ability of an embryo to implant and thus affect the success of a cycle [11], be it a fresh or frozen. Soares et al. examined the impact of a hydrosalpinx on fresh oocyte donation cycles and, as expected, found that the presence of a hydrosalpinx was associated with a poorer outcome [12]. Subsequent studies confirmed the results, and thus it is recommended that recipients with a hydrosalpinx undergo salpingectomy before undergoing a fresh or frozen donor oocyte cycle [13].

Another factor affecting recipients' success is uterine pathology. Asherman's syndrome and submucous myomas have repeatedly been demonstrated to interfere with a recipient's ability to achieve pregnancy [9, 14, 15]. Moomjy et al. looked at the impact obstetric, gynecologic (specifically Asherman's syndrome), or congenital variables had on implantation efficacy or delivery outcome in donor oocyte recipients following a fresh embryo transfer. They noted that Asherman's syndrome, despite surgical correction, negatively affected the ongoing and delivered pregnancy rate [14]. Similar results have been reached by others, both in the donor and non-donor population, demonstrating that Asherman's syndrome (even after hysteroscopic correction) significantly impacts one's ability to conceive. Furthermore, in those with a history of Asherman's syndrome who do achieve pregnancy, there appears to be a significantly higher incidence of antenatal complications including preterm delivery, intrauterine growth restriction, placenta accreta, placenta

previa, and uterine rupture [16]. The impact of myomas on fertility is widely debated; however, it is generally accepted that large myomas and those located within the uterine cavity have a detrimental effect on ART outcome [17]. Although there is a paucity of data exclusively examining the impact submucous myomas have on the outcome of a donor oocyte cycle, based on the IVF literature, it seems prudent to remove intracavitary lesions before initiating a fresh or frozen donor oocyte cycle as they likely will negatively impact success [18].

Embryo quality, whether fresh or frozen, clearly plays an integral role in the success of donor cycles. While oocyte donors are presumably fertile women, even among young donors, a marked difference in egg quality may exist [19]. Additional factors such as the recipients' age, donor age, recipient body mass index (BMI), coexistent medical and gynecologic conditions, gravidity, and sperm quality have also been cited as contributors to outcome.

The practice of using the eggs from one donor for two recipients provides a model to more thoroughly study the recipients' role in success, because the source and quality of the oocyte become a constant variable. Zenke and Chetkowski performed a case–control study of 134 embryo transfers in which two recipients were matched to one donor. They identified 41 recipient pairs with discordant outcomes and found that pregnant patients had a significantly lower incidence and lesser severity of uterine pathology [20]. Furthermore, prior pregnancies, a thick endometrium (>8 mm), and a higher number of good-quality embryos were also associated with a significantly higher likelihood of pregnancy [20]. Recipient age, BMI, preexisting medical conditions, endometriosis, oocyte number, total motile sperm, ICSI, fertilization rate, number of 2PN zygotes, and the presence/absence of supernumerary embryos available for cryopreservation did not significantly affect a recipient's chance for pregnancy. More recently, Bodri et al. studied 444 recipients (222 pairs) sharing oocytes from the same donor with discordant outcomes [6]. They studied recipient age, obstetrical (gravidity and parity) and gynecological variables (previous uterine surgery, uterine fibroids, uterine malformations, endometriosis, history of tubal infertility), previous oocyte donation cycles, duration of estrogen replacement, received cumulus-oocyte complexes, mature oocytes, fertilized oocytes, transferred embryo scores, mean embryo score, transfer difficulties, and semen parameters. No factor investigated in their study was associated with a discordant outcome in recipient pairs sharing oocytes from the same donor [20]. Of note, the authors did not analyze endometrial thickness and its impact on cycle outcome. Although these studies were performed in recipients undergoing a fresh donor oocyte cycle, we feel the results can be extrapolated to frozen donor oocyte-embryo cycles because the recipients' factors and treatments are virtually the same in either case.

The impact the length of time of embryo storage has on the success of frozen embryo cycles (both donor and autologous IVF) has also been questioned. In a retrospective cohort analysis of frozen donated embryo transfers, no significant difference in pregnancy or implantation rates was found, suggesting that storage time does not impact on frozen embryo success [21]. Similar results were reported by Riggs et al.; they evaluated the impact of cryopreservation storage duration on embryo survival, implantation competence, and pregnancy outcome. Their subjects included both IVF patients and donor oocyte recipients, and they found that there was no significant impact on the duration of storage on clinical pregnancy, miscarriage, implantation, or live birth rate in either group [22]. Lastly, there is some data regarding the relationship between the outcomes of the fresh and frozen-thawed embryo cycles. Our group at NYU has demonstrated similar live birth rates (48.6 % vs. 39.6 %, $p = .34$) from frozen embryo transfers for recipients who succeeded or failed their fresh transfers, suggesting that the outcome of a fresh donor egg cycle does not appear to predict success in a frozen cycle [23]. In contrast, previous research analyzing the effect of a prior fresh donor oocyte transfer has on the outcome of a subsequent fresh transfer demonstrated that the success of the second attempt was associated with success of the initial attempt [24]. This was confirmed by two

subsequent, albeit smaller, studies [25, 26]. Although the numbers of patients included in the above studies are small, such information is helpful when counseling patients as this may impact their decision to return to use cryopreserved embryos.

The impact a shared oocyte donation cycle has on pregnancy rates, both in a fresh and frozen donor oocyte cycle, has long been debated. Although the practice of shared cycles reduces patient cost and wait time, some potential recipients are reticent to proceed with this option for fear of reduced success rates. This concern is further compounded by a desire to obtain a multitude of high-quality embryos suitable for cryopreservation to be used in the future to create a genetic sibling. The demand for donated oocytes has increased due to delayed childbearing and the associated effect on ovarian reserve. In addition, DE is becoming more of an option for those who have had multiple fertility treatment failures, in part due to an increase in the social acceptance of the process. A shared donor oocyte program offers a solution to this "egg efficiency" problem. Our group recently performed a retrospective analysis to examine whether there is a difference in pregnancy outcomes between women undergoing a shared ($n=656$) versus exclusive ($n=225$) donor oocyte cycles and did not find a difference in the clinical pregnancy rates among these groups [27]. Although the exclusive group had significantly more oocytes (19.5 vs. 11.6) and fertilized embryos (11.9 vs. 7.3) when compared with the shared group, the pregnancy rates were quite similar (58 % vs. 56 %). In fact, Glujovsky et al. recently demonstrated that the minimum number of mature oocytes that must be allocated to a recipient in a shared egg donor cycle to achieve an acceptable pregnancy rate was four [28]. Similar to Mullin et al., they did not find any statistically significant difference in pregnancy or miscarriage rate in patients who had received 4, 5, 6, 7, and ≥8 mature oocytes. Such results lend credence to the practice of sharing donors [27, 28]. Despite comparable fresh pregnancy rates from shared and exclusive donor oocyte cycles, investigators in both studies did note a significant difference in the average number of excess good-quality embryos available for cryopreservation [27, 28]. In fact, Mullin et al. showed cryopreservation was performed in 56 % of exclusive donor cycles as compared to 36 % of shared donor cycles [27]. Thus, while pregnancy rates appear to be similar in shared and exclusive cycles, cryopreservation is more likely to occur in exclusive cycles. In summary, although frequently studied, the factors most important in determining outcome in a recipient's frozen embryo cycle remain debatable; however, uterine lining/endometrial receptiveness and embryo quality appear to be the most significant factors influencing outcome. While a shared donation cycle does not appear to impact upon fresh cycle outcome, it does decrease the likelihood of having supernumerary embryos available for cryopreservation. Furthermore, fresh donor oocyte cycle outcome does not appear to predict the frozen embryo transfer outcome.

What Determines Why a Recipient Elects to Return and Use Their Frozen Embryos?

The above factors can be predictive of a recipient's likelihood of achieving pregnancy with frozen embryos; however, why a recipient elects to return to use such embryos is less well defined. While many couples site embryo cryopreservation as an advantage and often a determining factor for choosing an exclusive rather than a shared cycle, in reality the literature suggests that the majority of couples do not return to use their stored embryos. We set out to answer the following questions: were the surplus frozen embryos from donor cycles being used, who were the recipients that were most likely to use their embryos, and were these frozen embryos used to expand their families by creating genetic siblings? In short, does the perceived patient benefit, an "insurance policy" of banked embryos, in fact become reality [23]? Analyzed were 829 fresh donor embryo transfer cycles performed during the study period of 1/2000–12/2004; 444 recipients delivered a viable infant(s) following a fresh transfer. Of these successful women, 177 (40 %)

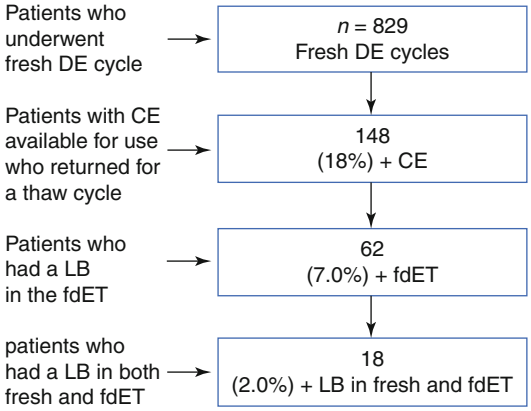

Fig. 12.1 Outcome of patients who underwent both fresh and frozen donor egg (DE) cycles. *CE* cryopreserved embryos, *fdEt* frozen donor embryo transfer, *LB* live birth

had supernumerary embryos cryopreserved; however, only 37 (21 %) returned for a donor frozen embryo transfer by August 2009. In contrast, of the 385 women who failed their fresh attempt, 128 (33 %) had supernumerary embryos cryopreserved and 111 or 87 % returned for a donor frozen embryo transfer by August 2009. While in total 44 (40 %) of these transfers resulted in a live birth, 13 % of women who did not become pregnant in their fresh cycle did not use their frozen embryos. Surprisingly, of the 829 women who underwent fresh transfers, only 18 (2 %) had children from both the fresh and frozen embryos [23]. Thus, the outcome of the fresh donor oocyte cycle appeared to dictate which patients returned to use their frozen embryos. Overall, only 49 % of the recipients with supernumerary cryopreserved embryos returned to use their embryos by August 2009. Calculations revealed that at the time of the study's conclusion, approximately 222 embryos remained in storage without a disposition [23] (Fig. 12.1).

In the above study, there were no differences between the mean age and the number of predonation children between those who did and did not return to use their donor oocyte-frozen embryos. However, patients who returned to use their cryopreserved embryos were significantly more likely to have received a directed donation and to have delivered a singleton gestation compared to those who did not return (9.5 % vs. 3 %, $p = .03$; 81 % vs. 19 %, $p \leq .001$, respectively) [23]. This data demonstrates that although recipients approach their donor oocyte treatment with a desire to cryopreserve embryos for a genetic sibling in the future, most only return to use their cryopreserved embryos after failing their fresh embryo transfer. Additional factors that we found to influence a patient's decision regarding donor oocyte-embryo disposition include the source of the oocyte donor (anonymous vs. directed) and the type of the gestation (singleton vs. twin) resulting from the fresh embryo transfer. We speculated that a relationship with the donor, be it familial or colloquial, likely generates a stronger kinship to the resultant embryos and therefore motivates the recipient to undergo a subsequent frozen donor embryo transfer. Similar conclusions were drawn by Sehnert and Chetkowski; they compared the disposition decision for cryopreserved embryos between patients that underwent donor oocyte cycles to those that underwent autologous IVF cycles [29]. They found that the majority of women (regardless of oocyte source) elected to utilize their embryos (they did not analyze frozen embryo disposition with regard to fresh cycle outcome). For those that elected to dispose of their embryos, their decision differed significantly based on oocyte source, as donor oocyte recipients were more likely to donate their excess embryos to other couples (68.8 %) rather than discard them (31.2 %). In contrast, patients undergoing IVF (autologous oocytes) were more likely to destroy (80.9 %) cryopreserved embryos rather than donate them to another couple (19.1 %) [29]. This study, as well as that performed at our facility, further highlights the importance patients place on genetic similarities and its role in frozen embryo disposition.

Except when using donor sperm, donor egg embryos contain only half of a couple's genetic content, and therefore, based on the above results, it may be psychologically easier for a couple to donate or eventually discard their supernumerary embryos. Klipstein et al. studied gender differences among couples choosing an embryo disposition [30]. Although this study was performed in couples undergoing their first IVF cycle, interesting

gender differences were identified which may help in understanding why recipients make their particular decision regarding frozen embryos. The authors found a gender bias in reproductive choices toward frozen embryos but not toward frozen gametes. With regard to frozen gametes, couples were concordant in their decisions to allow or refuse donation for research or discard. However, once the gametes were used to create embryos, couples reverted to traditional gender-based societal roles when making disposition decisions for their frozen embryos [30]. In the case of death or divorce, the majority of couples granted the female partner greater control/claim to the couple's frozen embryos. As this study involved patients undergoing conventional IVF, there were no donated gametes. It would be interesting to repeat this study in an oocyte donation population, where the genetic kinship between oocyte recipient and embryo is distant; in these cases where the male partner maintains a stronger genetic relationship to the frozen embryo, does the gender bias disappear, does it stay the same, or is it reversed?

Multifetal pregnancies played a significant role in a recipient's decision to use cryopreserved embryos in the study performed at our center. Of the 81 recipients whose fresh transfer resulted in a twin delivery, 74 (91 %) did not return to use their cryopreserved embryos; thus, to them two children likely represent a complete family [23]. Overall, the number of patients returning to expand their family with cryopreserved embryos was quite small. Thus, according to our previously reported data, while patients may initially be concerned with the number/presence of embryos available for cryopreservation, the majority are satisfied with one successful outcome. Although we reported on patient age and previous obstetrical history, we did not have access to additional demographic data such as socioeconomic status, religious and cultural beliefs, and medical history. Such factors may also impact on a recipient's decision to use the supernumerary embryos and thus must be considered when counseling patients on embryo disposition.

In an ethnographic qualitative interview study of 58 couples who had conceived using donor oocytes and having at least one frozen embryo in storage, Nachtigall et al. attempted to ascertain what couples thought about their embryos and how they approached a decision regarding their disposition [31]. They tape recorded interviews with 58 female recipients and 37 male partners (husbands) and subsequently analyzed them for themes. The authors asked the following open-ended questions about embryo disposition [31]:

1. Have you decided what to do with your frozen embryos?
2. When did you realize that making a disposition decision would be a question for you?
3. What decision have you made or what options are you considering?
4. What factors have influenced your decision/consideration on this subject?
5. How do you feel about your decision/consideration at this point in time?

The 58 couples that agreed to participate were predominately white, highly educated, and affluent. At the time of the interview, 42 (72 %) of the couples had neither made a decision nor were in the process of making a decision regarding their embryo disposition. Of the 16 who had made a decision regarding embryo disposition, 7 had donated their embryos to research/science, 5 had their embryos destroyed, 2 donated their embryos to another couple, and 2 used them for another attempt at pregnancy. The authors' analysis of interview transcripts revealed that the disposition decision is a process and follows four temporally sequential stages: stage 1 (reassurance) (when undergoing IVF treatment, couples are reassured by having large numbers of eggs), stage 2 (avoidance) (once childbearing is completed, most couples spend very little time thinking about their frozen embryos), stage 3 (confrontation) (when couples actually begin to confront the disposition decision, their reaction is frequently one of discomfort and uncertainty), and stage 4 (resolution) (those couples who were able to come to an agreement frequently expressed a profound sense of completeness and resolution) [31] (Table 12.1). In addition, the investigators found that the factor that most significantly contributes to the difficulty of the disposition decision is the complex manner in which couples

Table 12.1 The "stages" of emotions associated with a decision regarding embryo disposition

Embryo disposition: four sequential stages	Emotion	
Stage 1	Reassurance	When couples undergo IVF, they are "reassured" by having large #s of eggs
Stage 2	Avoidance	Following completion of childbearing, most couples rarely think about their frozen embryos
Stage 3	Confrontation	When confronting a decision on disposition, couples frequently feel uncomfortable and uncertain
Stage 4	Resolution	After finally making a decision on frozen embryo status, couples report a sense of completeness and resolution

conceptualize their embryos. While almost all couples viewed their embryos as "having the potential for life," some saw them as nothing more than biologic material, while others saw them as living entities with the ability to experience pain and discomfort. Thus, they could not envision subjecting embryos to destruction or donation for scientific research. Furthermore, many patients viewed the embryos as "virtual children" and felt it was their responsibility to protect them and their interests [31]. As guardians of their welfare, they felt conflicted over the decision to donate these "little children" to other infertile couples; would these couples provide for "their children" in the manner in which they would? In addition, while the remaining embryos were without the genetic input from the mother, they harbored the same genetic source as the couples' other children (borne after fresh donor oocyte transfer). Thus, they feared the possibility that this "sibling" could meet and initiate a relationship with their child. Other elements that impacted the recipients' conceptualization of the frozen embryos, and thus their decision-making process in this study, were the concept of a "genetic or psychological insurance policy" [31]. Recipients stated a sense of reassurance knowing that the frozen embryos could potentially provide medical benefit to their living children as well as becoming "potential replacements" for their living children (conceived through donor oocyte) if they should die. The last element identified by the researchers in how recipients conceptualize their embryos was what the frozen embryo symbolized—years of infertility that dominated and in many instances plagued a couple's life. Thus, while for some patients this emotion motivated them to empathetically donate their surplus embryos to another infertile couple who were also wrestling with the same diagnoses, others felt compelled to "use them all up" because they symbolized "unfinished business" [31].

The data garnered in these interviews suggests that decision-making involving supernumerary embryo disposition is a dynamic process that occurs in stages. Couples are initially focused on their immediate goal of becoming pregnant. They are so eager to achieve this goal that they consider surplus embryos to be a bonus. Uncertainty and difficulty regarding future disposition of supernumerary embryos do not enter their minds at that time. However, after pregnancy is achieved and childbearing is potentially completed, avoidance of the decision at hand predominates. As time passes and a decision is required, patients may become conflicted and confused. Although there are several disposition options, patients often find selecting one to be very difficult. Based on the data provided by this study, the manner in which female recipients and their partners conceptualize their frozen embryos guides their decision-making.

Similar conclusions were also reached in an earlier study by Robertson who assessed the ethical and legal issues that surround human embryo donation. Here, the two major determinants of a couples' willingness to donate their surplus embryos were their interpretation of "embryo status" and their comfort with being unable to contact their "genetic offspring" [32]. Although the latter work was not done specifically in donor oocyte recipients, the conclusions were similar to

that reached by Nachtigall et al. [31, 33, 34]. Thus, disposition decisions are tailored by several "recordable" facets, some which have already been studied and likely by others which have not. The former includes the source of the oocyte, the outcome of the fresh donor oocyte cycle, and the number of infants delivered, and the latter socioeconomic status, religious and cultural beliefs, and medical history. In addition, the recipient and her partner's conceptualization (e.g., biologic material vs. "little children") of the frozen embryo complicate the algorithm and significantly impact the choice a couple makes [31–34].

To Whom Do Recipients Donate Their Embryos?

Recipients are routinely given several options when deciding on how and to whom to "dispose" of their frozen embryos. Options typically include the following: use the embryos in future attempts to conceive, donate the embryos to science/research or an infertile couple, discard the embryos, or store the embryos indefinitely while contemplating the above possibilities. However, even after a decision is made, patients may change their minds. In fact, Klock et al. demonstrated that 82 % of couples (donor egg recipients and IVF patients) who had initially elected to donate their embryos to an infertile couple and 88 % of couples who had originally chosen to donate their embryos to research rescinded their decision when the time to donate approached [35]. Vacillating decisions highlight the changes in expectations and evolving circumstances couples often experience as they progress through the infertility process when approaching embryo disposition. Returning to the research performed at our center on the fate of cryopreserved donor embryos, we found the following additional information concerning frozen embryo disposition. Of the 305 recipients with cryopreserved embryos, 117 (38 %) thawed all of their embryos for use in a frozen embryo transfer, 63/305 (21 %) had embryos remaining in storage without a disposition, 52/305 (17 %) patients donated their surplus embryos to science/research, 66/305 (22 %) elected to thaw and discard their embryos, and 7 (2.3 %) had their embryos transferred to another facility for personal use or embryo donation [23]. The percentage of patients electing to maintain embryos in storage without a disposition is lower than that reported by other authors. This may be a reflection of the study period (time interval allotted to return to use frozen embryos was a maximum of 7 years) and the patients studied (mean age of the recipient in this study was 42 years). However, our data demonstrates that approximately one-fifth of recipients will likely allow embryos to remain in cryostorage indefinitely without a disposition [23].

Frozen embryos are essential to the continuance of stem cell research and scientific advancements as well as for the potential treatment of other infertile couples. The option to donate supernumerary embryos for scientific experimentation, particularly stem cell research, varies across the country. However, the majority of IVF centers can inform patients of facilities that would willingly accept discarded embryos. Early data demonstrated that couples were four times more likely to discard their frozen embryos than to donate them. There were also earlier studies that indicated little willingness to donate to science [33], but more recent data suggests that this option has garnered momentum becoming increasingly popular. Public awareness surrounding stem cell research has likely motivated patients to participate in this process. Hug recently reviewed 67 scientific publications regarding the possible donation of surplus embryos for medical research [36]. Studies evaluated included both IVF patients and donor oocyte patients. This review demonstrated that factors positively impacting a couple's decision to donate their surplus embryos to research included the following: knowing the research purpose, being well informed about bioscience and about the potential benefits of the research, being at the end of their IVF treatment, having poor-quality embryo, and being altruistic [36]. In contrast, being at the beginning of infertility treatment, not knowing the aim of the medical research, having good-quality embryos, and considering frozen embryos to be children appear to

hinder a couple's willingness to donate their embryos to science [36]. Additional studies demonstrated that patients who elect to donate their surplus cryopreserved embryos to science/research are more likely to have delivered a child in their fresh IVF cycle [37]. Consideration of the above factors may provide practitioners with insight into how best to counsel patients on embryo disposition, specifically with regard to research/scientific purposes.

It has also been shown that in addition to how patients (recipients and IVF patients) conceptualize their embryos (tissue vs. child), perceptions of the medical team play a role in their decision-making process [38, 39]. The more comfortable patients are with the medical team, the more apt they are to donate their embryos for scientific studies. For example, Provoost demonstrated that most patients knew very little about the option of donating embryos to science; however, after being appropriately counseled by the medical team regarding the procedures that would be performed (e.g., would not allow embryo to develop into a child), they were more willing to donate [39]. Based on such findings as well as data from a recent study by Nachtigall et al., it seems that if patients, specifically recipients, were more appropriately counseled regarding the procedures surrounding scientific donation and more comfortable with the scientific/medical team, more patients would elect to donate their embryos for research [34].

Destruction of embryos remains an option for both recipients and IVF patients. However, many view this practice as a "waste" and an action that hurts rather than helps both the individual as well as society as a whole [33]. Those electing to discard their embryos often cite ambivalence toward the cryopreservation process or partner disagreement toward disposition; thus, discarding provides a definitive outcome. Melamed et al. reported that most couples who chose to discard embryos stated it was "a last minute decision"; in addition, the majority did not agree with embryo research and were unable to donate their embryos to another couple [40]. Hammerberg and Tinney showed that although most couples preferred to donate their embryos to science/research or other couples rather than to discard them, those that elected disposal cited "not wanting a full sibling to existing children" and "opposition to embryo research" for choosing to dispose of their embryos [41]. In contrast, patients whose decision-making was influenced by religion were much less likely to have their embryos discarded. Therefore, countries that are predominantly Catholic (e.g., Brazil, Italy) have a very low incidence of embryo discardation [40].

De Lacey interviewed 12 couples and 9 women who had discarded supernumerary frozen embryos to better understand the decision-making dynamics that motivate a couple/individual to discard rather than donate their embryos [42, 43]. While most patients describe a desire to donate unused embryos at the outset of treatment, in reality most elect to discard of them. The participants in this study described their initial plan of embryo donation to be "idealistic rather a purposeful decision." Their views were transformed because of two events: becoming a parent and a change in how they viewed embryos (before freezing was a chance to become pregnant and post freezing was a "virtual" child in storage) [43]. The impact of these events changed their opinion regarding the frozen embryos compelling them to discard rather than donate their embryos [43]. In another interesting study by De Lacey, 33 patients who discarded embryos and 15 who donated embryos (all patients had done IVF, no recipients were included) were interviewed. They found that both groups identified adoption, tissue donation, and termination metaphors when asked about frozen embryo status; all were influential in a patient's decision-making process [42]. Those who elected to proceed with embryo donation emphasized the metaphor of pregnancy termination, while those who discarded their embryos emphasized the metaphor of adoption [42]. Although at first glance these seem contradictory (the decision and the metaphor), after further consideration the harmony between the motivation and the action is uncovered. Those that donate liken discarding their embryos to terminating a pregnancy, while those that discard embryos equate donation to "giving their unborn child up for adoption" [42].

Many recommend that, based on the high demand for embryos (for scientific research or

infertile couples), practitioners should discourage the practice of embryo destruction. The literature suggests that counseling pre- and posttreatment would reduce the incidence of this practice. For example, Nachtigall et al. demonstrated that patients desire more information, guidance, and/or psychological support when deciding on embryo disposition [34]. Such information relayed at the outset of the cycle (be it donor or IVF) may be more helpful in ensuring that embryo disposition does not default to indefinite storage or discard but rather promote embryo donation to science/research or infertile couples.

Despite the multitude of options, most patients find the decision a difficult one, and therefore, it is not surprising that most elect to leave their embryos in storage indefinitely. The decision, to not make a decision, however, is not only costly but eventuates in a plethora of unused embryos without a disposition, a situation that impairs current laboratory storage principles and protocols. Although the studies cited were done on a mixed cohort of patients (IVF and donor oocyte recipients), the results can be extrapolated to the recipient population. Thus, in summary, it would be best for IVF centers to implement definitive embryo disposition options, policies, and procedures at the outset of the initiated cycle so that patients are armed with the tools necessary to make appropriate decisions.

Is Embryo Donation a Viable Option for Recipients?

Although not routinely performed in all IVF centers, embryo donation to another infertile recipient is a viable option for using frozen embryos. It provides infertile couples with the opportunity to reproduce without obtaining a fresh oocyte source (autologous or donor). Embryo donation is, however, the least common disposition decision made and often represents the most difficult choice for a couple [44, 45]. While some view it as a "form of adoption" and liken the process to "saving a child," others are reluctant to embrace the process because they view the embryo not only as a potential child but also as a sibling to their existing children. In addition, they cite emotions of responsibility and thus are reticent to donate embryos for fear of how "their child" will be raised [45]. Several studies have shown that a lack of control over what happens to the embryos after donation not only hinders embryo donation but also creates an inability for couples to formulate a decision regarding the disposition of their inventory and therefore further perpetuates an atmosphere of ambivalence [31, 41, 43–46]. Sehnert addressed the practice of embryo donation, specifically as it relates to donor oocyte recipients. They found that the chief motivation behind the donation of embryos to other infertile couples was to perpetuate the altruism afforded to them by gamete donation [29]. It is apropos that those who were the recipients of donation would perpetuate this practice by donating their embryos to others. In a more recent study performed by Hill and Freeman, the authors used a larger study population to compare the final cryopreserved embryo disposition between patients and donor oocyte recipients [47]. Their results were similar to Sehnert and Chetkowski in that a higher proportion of patients with infertility used or stored their cryopreserved embryos for future use compared with donor oocyte recipients [29, 47]. Recipients were much more likely to donate to other infertile couples and were less likely to discard their remaining embryos compared with IVF patients [47]. In this study, as expected, the mean age of the IVF patient was significantly lower than that of the donor recipient; older age likely affects a patient's willingness to not only undergo an embryo transfer but proceed with pregnancy as rising age corresponds with rising antepartum and intrapartum risks.

Will Oocyte Cryobanks Alter the Fate of Oocyte Donation?

Advancements in reproductive medicine over the past decade have led to the development of successful oocyte cryopreservation. In fact, Grifo

and Noyes demonstrated comparable pregnancy/live birth rates between those undergoing oocyte cryopreservation cycles and age-matched controls using fresh autologous or donor oocytes [48]. Thus, this technique not only affords women facing impending sterility the ability to preserve their fertility but also allows for a more equitable distribution of oocytes. Recent data supports this practice offering results that are comparable to fresh donor oocyte cycles [48–50]. In a prospective randomized study, Cobo et al. evaluated the outcome of oocyte vitrification in an egg donation program by assessing the outcome of embryos created from vitrified and fresh oocytes in the same stimulated cycle [49]. They did not note a difference in fertilization rates, day 2 cleavage, and day 3 cleavage or blastocyst formation between the two groups. Furthermore, embryo quality on day 5 and day 6 was similar for the vitrification and fresh oocyte groups. Lastly, pregnancy rates, implantation rates, and miscarriage rates were comparable [49]. Similar results were reported by Garcia et al.; they also reported on the outcome of vitrified oocytes obtained via oocyte donation and compared it to fresh oocytes [3]. Again, there were no differences noted between the two groups with regard to embryo development, implantation rate, or clinical pregnancy rate [3]. Such results support the use of frozen donor oocytes and advocate for the implementation of donor oocyte banks as they would reduce donor cycle costs, waiting times, and screening limitations ultimately changing the practice of female gamete donation [51]. Furthermore, we speculate that this practice would reduce the number of unused embryos that remain indefinitely in cryostorage. In addition, it would assuage the ethical dilemmas recipients often cite when creating, storing, and finally deciding on what to do with their excess embryos. Moreover, recipients would still have the opportunity to utilize the same donor's oocytes to create a genetic sibling if so desired in the future. Although oocyte banks could potentially hinder the scientific research that is performed on such embryos, in our opinion, the benefit (limited number of embryos without a disposition) outweighs this "risk."

Conclusion

Despite the multitude of options that recipients are offered by their care providers regarding frozen embryo disposition, most patients experience difficulties when approaching this decision. The uncertainty surrounding the best "home" for these embryos is demonstrated in the overwhelming number of cryopreserved embryos that remain in storage indefinitely. Furthermore, as demonstrated by studies performed globally, patients delay their decision because they find it to be "the most difficult decision they have ever had to make," and they wish to "avoid making a decision to destroy embryos" [36, 52]. Thus, although patients are excited at the time of embryo cryopreservation and actually find the state of "no embryos available for freezing" quite disappointing, the presence of such embryos can create significant confusion and even distress later. Similar to the limitations inherent in embryo scoring systems, the disposition decision process is a fluid rather than a static process. Previous cycle outcomes as well as life events (e.g., divorce, financial instability, and death) greatly influence a couple's decision, and thus what one thinks at the time of donor oocyte cycle initiation can be quite different several years later. Although there is a dearth of studies performed exclusively on the attitude of donor oocyte recipients toward frozen embryo disposition, in many instances, we have extrapolated results from IVF patients, to better understand the factors that influence a recipients' decision regarding the fate of cryopreserved embryos.

Editor's Commentary

Advances and refinements in the methodology of assisted reproduction have benefited all patients undertaking IVF. Over the years, extended culture has improved, the ability to select embryos appropriate for use has improved, cryobiology has improved, and ultimately the number of

embryos needed to transfer has decreased. As a result, programs now have many high-quality embryos in cryostorage, and the question of what to do with these "leftover embryos" has emerged as a major concern of both our patients and society at large.

Although it may seem simple enough to require patients to provide us with an advanced directive regarding the final disposition of their supernumerary embryos, we all know that it is a very difficult process and a dynamic one. Patients often regard their cryopreserved embryos and speak of them as if they were living children, and this transference makes destroying embryos or donating them much more personal and complicated.

There are interesting differences among couples and within couples, as to how they work through these decisions, and all of us must have a healthy respect and appreciation for these differences. Even individuals seemingly comfortable with a disposition at the time of consenting may later struggle with their decision and change their minds. It is reasonable to assume that a transformation in thinking may regularly occur within all of our patients, and therefore, there is a need to continually readdress the original disposition, certainly before a final action is taken and preferably after a moratorium of time has passed. It is noteworthy that up to 20 % of patients will continue to store embryos without forming a final disposition, rather than have to make a final definitive decision.

Perhaps egg freezing will solve some of this problem, but certainly not all of it. There will always be embryos in cryopreservation and patients unable to decide their fate. As Fred Licciardi, M.D., comments, it is better to require patients to formulate a plan prior to creating the embryos and hope that downstream they are comfortable with it. Still, we can expect that many individuals will remain indecisive, and programs need to be prepared to deal with them and their embryos as well.

Donating embryos to a program for reproductive use or research is a very special gift indeed and should be acknowledged as such. It is also a gift that keeps on giving as future generations are impacted by the actions taken by single individuals today.

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Prenatal Considerations After Oocyte Donation

13

Zachary S. Rubeo and Lynn L. Simpson

Key Points

- Both general and condition-specific risks should be considered when caring for women who conceive through oocyte donation.
- There is a 2 % maternal mortality for women with Turner syndrome, or a 100-fold increased risk of death compared to the general population usually a result of aortic dissection or rupture.
- Patients of advanced maternal age (AMA) are at risk for hypertensive disorders, diabetes, fibroids, placental abnormalities, and prior operative deliveries, all of which predispose them to cesarean delivery.
- Prospective patients should be extensively counseled prior to the initiation of infertility treatments and postmenopausal women should undergo a complete cardiology consultation with echocardiography.

The number of pregnancies conceived through oocyte donation is on the rise [1]. In 2008, approximately 12 % of all advanced reproductive technology (ART) cycles involved oocyte donation – an increase from previous years [2]. While routine antenatal care may be appropriate for many of these patients, the *indication* for oocyte donation may dictate specific prenatal considerations. Once a pregnancy is established through oocyte donation, a healthy woman should be managed as any other gravid woman – with regular prenatal visits, routine prenatal labs, and appropriate ultrasound screening. However, patients who use oocyte donation as a means for achieving pregnancy because of a preexisting condition may require more specialized obstetric care. Both general and condition-specific risks should be considered when caring for women who conceive through oocyte donation.

General Considerations

Oocyte donation may offer the only chance for pregnancy in certain infertile couples. The indications for this procedure vary widely, including both

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primary and secondary ovarian failure as well as a history of unsuccessful in vitro fertilization (IVF) procedures. The field has advanced so significantly that success rates for these procedures are usually quite high and approach – and even surpass – success rates of other ART procedures [2, 3]. In general, the obstetric and perinatal outcomes after oocyte donation are good, although available literature suggests that certain complications may be more common in these patients. A large study comparing pregnancies conceived through oocyte donation to pregnancies conceived through IVF reported increased risks of first trimester bleeding, pregnancy-induced hypertension (PIH), and hospitalization at some point in the pregnancy but otherwise an equivalent obstetric course [4]. The perinatal outcomes between the two groups were similar; no differences in birth weight, prematurity, or intrauterine growth restriction were observed [4]. A similar study comparing nulliparous patients after oocyte donation to standard IVF demonstrated a significantly increased risk of PIH (26 % vs. 8 %); however, no difference in first trimester bleeding, gestational diabetes, premature labor, or low birth weight [5]. A recent meta-analysis similarly concluded that pregnancy conceived through oocyte donation increased the likelihood of developing a hypertensive disorder compared to pregnancies conceived using standard ART (OR 2.57, 95 % confidence interval, CI, 1.91–3.47) and to those who conceived naturally (OR 6.60, 95 % CI 4.55–9.57) [6]. Overall, there appears to be a 16–40 % risk of hypertensive disorders in pregnancies conceived through oocyte donation [4]. It has been speculated that pregnancies conceived through oocyte donation are considered "foreign" to the recipient, resulting in an inadequate maternal immune response to the conceptus and poor placental development, leading to an increased risk of PIH [5]. In the aforementioned studies, the mean age of the donor oocyte patients in comparison to the standard IVF patient was significantly higher, which may contribute to the higher risk of hypertensive disorders that accompanies advancing maternal age. Likewise, other obstetric complications noted in studies reporting on donor oocyte pregnancies may also be related to maternal age. In a comparison of outcomes of patients after oocyte donation and standard IVF who were *all above the age of 38,* there were no significant differences in preeclampsia, preterm labor, preterm premature rupture of membranes, intrauterine growth restriction, gestation diabetes, abnormal placentation, or oligohydramnios [7]. Thus, pregnancy-related complications may be more related to maternal age rather than from the oocyte donation procedure itself. Other preexisting medical conditions – such as Turner syndrome and malignancy – also impart risk on the pregnancy unrelated to the method of conception.

This review of the common indications for oocyte donation will highlight the specific prenatal considerations for the practitioner caring for these patients.

Advanced Maternal Age

Oocyte donation in patients with age-related infertility is the largest contributor to the increasing use of oocyte donation in ART centers [1]. In fact, the number of cycles of oocyte donation rapidly increased after it was established that live births in women of advanced maternal age could be achieved with oocyte donation [1]. According to the 2008 report on ART procedures in the United States, the number of ART cycles using oocyte donation rose sharply after age 40 (Fig. 13.1). According to CDC data, about 90 % of all donor cycles in women 48 years of age and older used donor oocytes [2]. The increased rate of oocyte donation in older women is due to the well-established fact that advancing maternal age is associated with a sharp decrease in natural fecundity, as well as an increase in chromosomal abnormalities and spontaneous miscarriage [8]. At age 30, the natural pregnancy rate remains >400 pregnancies per 1,000 exposed women per year and decreases to 100 pregnancies per 1,000 women by age 45 [9]. Correspondingly at age 45, the risk of Down syndrome is 1 in 30 with an overall miscarriage rate of 90 % [9]. Despite the biological trend toward infertility, many women – especially in developed countries – are postponing childbearing until later in life due to social and financial factors [8]. Data from the Centers for Disease Control and Prevention (CDC) confirm that older women having their *firstborn* child later in life has risen dramatically [10]. In 1975, the first birth rate for nulliparous women

was 19.8 per 1,000 among women aged 35–39, increasing to 44.5 per 1,000 in 1997 [10]. However, faced with the proverbial "biological clock," many women choosing to become pregnant later in life must turn to oocyte donation to achieve pregnancy.

It is a common misconception among patients that pregnancy is without risk if a young egg is used for oocyte donation. While the risk of fetal aneuploidy does decrease if the donor if young and healthy, AMA patients, traditionally defined as ≥35 years of age, can face significant maternal and perinatal risks beyond that of miscarriage and chromosomal abnormalities. Undoubtedly, many of the adverse outcomes seen in AMA pregnancies are a result of the increased risk of chronic medical disease associated with age [11]. However, even in the absence of chronic conditions, AMA patients experience more obstetric and perinatal complications than younger women. In a series of over a million women who delivered in the state of California, pregnancy complications such as preeclampsia, gestational diabetes, and placenta previa were more common in women >40 years of age [12]. Similarly, a prospective cohort study from Sweden reported higher rates of gestational diabetes, pregnancy-induced hypertension, severe preeclampsia, and placenta previa in women >40 years of age [13]. The 2005 First and Second Trimester Evaluation of Risk (FASTER) trial compared obstetric outcomes prospectively in over 36,000 women and also found older women had more complications (Table 13.1) [8]. Studies have also reported that older women are more likely to have less favorable perinatal outcomes and an increase in intrauterine growth restriction (IUGR) and low birth weight infants [8, 12, 13]. Available data all highlight the importance of vigilant screening and careful monitoring of the AMA patient for medical, obstetric, and perinatal complications.

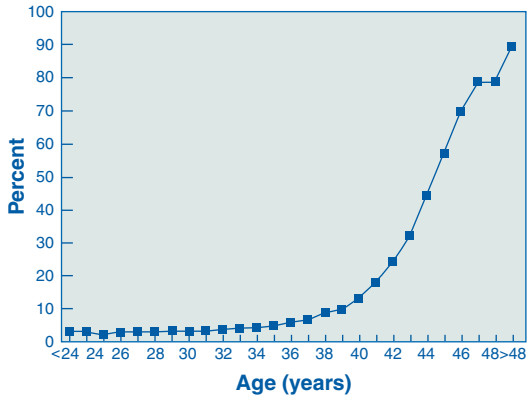

Fig. 13.1 Percentages of ART cycles using donor eggs, by age (US Department of Health and Human Services, Centers for Disease Control and Prevention [2])

In the following sections of this chapter, select complications of AMA pregnancies will be discussed in more detail.

Table 13.1 Obstetric and perinatal complications based on FASTER trial data

	Age 35–39 vs. age 35	Age ≥40 vs. age <35
Outcome	Adjusted OR (95 % CI, *p*-value)	Adjusted OR (95 % CI, *p*-value)
Gestational hypertension	0.8 (0.7–1.0, 0.02)	1.0 (0.8–1.4, 0.94)
Preeclampsia	0.9 (0.7–1.2, 0.60)	1.1 (0.7–1.6, 0.81)
Gestational diabetes	1.8 (1.5–2.1, <0.001)	2.4 (1.9–3.1, <0.001)
Placenta previa	1.8 (1.3–2.6, 0.001)	2.8 (1.6–4.6, <0.001)
Placental abruption	1.3 (0.9–1.8, 0.21)	2.3 (1.3–3.8, 0.002)
Preterm labor	0.9 (0.8–1.0, 0.15)	0.9 (0.7–1.2, 0.39)
PPROM	1.2 (0.9–1.5, 0.20)	1.2 (0.8–1.9, 0.41)
Preterm delivery	1.0 (0.9–1.1, 0.61)	1.4 (1.1–1.7, 0.001)
Low birth weight	1.1 (0.9–1.3, 0.17)	1.6 (1.3–2.1, <0.001)
Macrosomia (>4,500 g)	1.4 (1.1–1.8, 0.004)	0.8 (0.4–1.4, 0.38)
Operative vaginal delivery	1.1 (0.9–1.2, 0.57)	0.9 (0.7–1.2, 0.54)
Cesarean delivery	1.6 (1.5–1.7, <0.001)	2.0 (1.8–2.3, <0.001)
Perinatal loss	1.1 (0.6–1.9, 0.74)	2.2 (1.1–4.5, 0.03)

Adapted from Cleary-Goldman et al. [8]
OR odds ratio, *CI* confidence interval, *PPROM* preterm premature rupture of membranes

Hypertensive Diseases in Pregnancy

The rate of hypertensive disorders of pregnancy ranges from 5–7 % of all pregnancies and accounts for 12–18 % of maternal mortality worldwide [6]. The cardiovascular risks of advanced age are responsible for a significant proportion of the morbidity associated with AMA pregnancies. Older women have approximately a four to five times higher chance of having chronic hypertension [12]. In part, this is related to decreased compliance of the arterial tree with age, leading to a chronically elevated afterload and an increased pressure during systole [14]. During normal pregnancy, blood volume increases by as much as 1 liter, which leads to a compensatory decrease in resistance in the maternal circulation and an increase in cardiac output. Thus, the physiologic pregnant state is one of high flow and low resistance, which may not be tolerated well by older women. With an already lowered compliance secondary to aging, it has been speculated that an older pregnant woman cannot mount the same compensatory cardiovascular response that a younger woman can achieve [14]. It is not surprising, then, to infer that PIH and associated hypertensive diseases of pregnancy, such as preeclampsia, eclampsia, and HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, are potential complications of AMA pregnancies. A large study examining the adverse obstetric and perinatal outcomes according to maternal age found woman aged 40–44 years to have an increased risk of pregnancy-induced hypertension (OR 3.29, 95 % CI 3.01–3.59) and severe preeclampsia (OR 1.40, 95 % CI 1.26–1.56) when compared to women aged 20–29 years [13]. Similarly, women aged >45 years old and greater had an increased risk of pregnancy-induced hypertension and severe preeclampsia (OR 6.38, 95 % CI 4.67–8.72 and OR 1.86, 95 % CI 1.17–2.97, respectively) [13]. Other large studies confirm an increasing risk of PIH with increasing maternal age [11, 12, 47].

Older women should undergo a complete cardiovascular assessment prior to initiation of the oocyte donation procedure. A comprehensive history should be ascertained, with special attention to preexisting cardiovascular risk factors and pertinent family history. In addition to a full physical cardiovascular exam, one may consider further testing including an electrocardiogram (ECG) and, in selected patients, a stress echocardiogram. Older women who become pregnant after oocyte donation should be monitored closely for early rises in blood pressure and new onset proteinuria. Preconception counseling and consultation with a maternal-fetal medicine specialist can help prepare and care for these patients during pregnancy.

Diabetes Mellitus

Similar to hypertension, there is an increasing rate of diabetes mellitus with advanced maternal age [15]. Insulin resistance is more common in older patients, but many affected adults are asymptomatic before diagnosis. Often, this early period of insulin resistance can lead to a hyperinsulinemic state and associated early microvascular damage [14]. Pregnancy is accompanied by rising levels of insulin-antagonizing hormones that further exacerbate insulin resistance, as reflected by elevated postprandial glucose levels. Older women with a decreased insulin reserve are more likely to have difficulty adapting to this physiologic change [14]. This increases the likelihood of gestational diabetes mellitus (GDM) in AMA pregnancies, further enhancing the risk of hypertensive disorders if there is coexisting vascular compromise. Overall, the incidence of GDM in the AMA population varies from 1.7–10.5 % with a fourfold increase related to age alone [12, 14]. Compared to women aged 20–29 years, the risk of gestational diabetes in women >45 years of age is 4.7 times higher and 3.4 times higher in women 40–44 years of age [13]. The FASTER data likewise found a significant increase in gestational diabetes with increasing maternal age (Fig. 13.1). With an increasing incidence of GDM in this population of older women comes a higher likelihood of antenatal complications. Risks of preeclampsia, macrosomia, shoulder dystocia, and birth injury are all increased in pregnancies complicated by GDM [15]. Although there is some debate regarding

universal GDM screening in pregnancy, selective screening of women with identifiable risk factors alone is estimated to miss close to half of all GDM patients [15]. Given this fact, all women – particularly those of advanced age – should be screened for GDM, and for patients with risk factors, early screening prior to the third trimester may be warranted. Normoglycemia early in gestation is important for normal fetal development, and thus prior to inclusion in any oocyte donation program, AMA women should be screened appropriately for preexisting diabetes mellitus.

Preterm Birth

Although the data on preterm birth in AMA pregnancies is conflicting, the majority of studies suggest that AMA imparts an increased risk of prematurity [13, 16]. Stratified by age, preterm births at <37 weeks, <34 weeks, and <32 weeks were found to be significantly increased for women ≥40 years (adjusted odds ratio 1.54, 1.57, and 1.65, respectively, for those aged 40–44 years old, and 1.63, 1.88, and 1.94 for those aged >45 years of age) [13]. Data from the FASTER trial adjusted for preexisting medical conditions demonstrated an odds ratio for preterm birth of 1.4 (95 % confidence interval 1.1–1.7) for women aged 40 years or above compared to women less than 35 years, suggesting that age alone imparts a risk of preterm birth [8].

Stillbirth

In 2005, the stillbirth rate in the United States was reported as 6.2/1,000, a decline from previous decades [17]. A large systematic review recently reported that the relative risk of stillbirth in older versus younger women ranged from 1.20 to 4.53, though the absolute risk still remains low [18]. Although it is tempting to assume that the risk of stillbirth is increased due to conditions associated with advanced maternal age such as hypertension and diabetes, there is likely a small inherent risk of stillbirth *independent* of these conditions and related to age alone [18]. This is supported by the observation that intrauterine fetal death (IUFD) is increased in women >45 years of age with an odds ratio of 3.76 (95 % confidence interval 2.22–6.40), independent of pregnancy complications or medical conditions [13]. A similar large study from Canada demonstrated a 1.8-fold higher risk of stillbirth in women aged 35–39 years of age and a 2.4-fold higher risk in women 40 years and over, even after controlling for a variety of other factors such as hypertension, diabetes, placenta previa, and multiple gestation [19]. Aging uterine vasculature and reduced uterine perfusion may be at the root of this increased risk, but currently there are no accepted guidelines to screen or antenatally test for such risk in healthy older women. In addition, the predictive value of age alone for stillbirth is low [20]. Although age alone may not support increased fetal surveillance, it has been proposed that if weekly antenatal testing were initiated, the rate of IUFD in elderly women would fall from 5.2 to 1.3 per 1,000 [21]. Based on this approach, a single fetal death would be avoided for every 863 antenatal tests performed, but an additional 71 inductions of labor and 14 cesarean deliveries would be required [21]. As no established guidelines exist at present, the initiation and frequency of antenatal testing is left to the discretion of the prenatal care provider and patient.

Preexisting maternal medical conditions regardless of maternal age do impart an increased risk of stillbirth. Older women have higher rates of hypertension and diabetes, but other medical conditions such as systemic lupus erythematosus, renal disease, thyroid disorders, and even obesity are increased in this population and have been associated with a risk for IUFD [22]. Screening older women who have conceived via oocyte donation for these various medical conditions can help guide management and antenatal testing in the prenatal period.

Peripartum Considerations

Beyond the antenatal issues described previously, there are certain peripartum issues to consider in managing AMA patients. A protracted labor

course is more common in elderly patients and lowers the likelihood of a vaginal delivery. It has been suggested that decreased efficiency of myometrial gap junctions, decreased number and function of myometrial oxytocin receptors, and thickening of the muscular layer of myometrial arteries may be responsible for such prolonged labors [16]. Contributing factors may also include less effective pelvic joint function and reduced abdominal wall expulsive forces [14, 16]. The cesarean delivery rate is higher as maternal age increases for a variety of reasons beyond simple labor dystocia. Other obstetric factors that AMA patients are at increased risk for – such as hypertensive disorders, gestational diabetes, fibroids, previa, and prior cesarean deliveries – all predispose older women to cesarean delivery [14]. Interestingly, a comparison of younger women with spontaneously conceived pregnancies and older women who conceived through oocyte donation found an increased risk of cesarean delivery *even after* controlling for such confounders, with a cesarean delivery rate of 71 % reported in older women with ART pregnancies [23]. In addition, there is an increasing trend toward cesarean delivery on maternal request in recent years [24]. Despite a lack of concrete evidence, it has been postulated that pregnancies in older women are considered "premium" due to the significant cost and difficulty in conception, and there exists an increased anxiety among practitioners and patients surrounding delivery [24]. For older patients considering vaginal birth, induction of labor is also more frequent, which also contributes to the high cesarean delivery rate in this population. Compared to women in their twenties, the OR for labor induction is 1.75 for women 40–44 years of age, and 2.47 in women ≥45 years of age [13]. Similar to cesarean deliveries, operative vaginal deliveries are also more common in older women, which may be related to the decreased expulsive forces generated during the second stage of labor [16].

In conclusion, pregnancy in the AMA patient after oocyte donation is certainly not without risk. As many donor oocyte pregnancies are a result of age-related infertility, it is especially important that obstetric providers dealing with such patients are mindful of these potential antenatal complications. With vigilance, AMA patients can have healthy maternal and fetal outcomes after donor oocyte pregnancies.

Turner Syndrome

Turner syndrome is a genetic condition that has sparked much interest with regard to oocyte donation. The syndrome affects 1 in 2,000 live births and is the only known monosomy (45,X) to be compatible with life [25, 26]. Turner syndrome patients are affected by short stature, webbed neck, and "streak ovaries." The absence of ovarian follicular development, due to a decrease in follicular number beginning as early as the 18th week of fetal life, results in primary ovarian failure and subsequent infertility [27]. In 5–10 % of patients, there will be enough follicular development in the ovaries to initiate menarche but not sustain it throughout the entirety of the reproductive years [27]. Therefore, spontaneous pregnancies only occur in 2 % of patients, with most women who desire conception needing to use oocyte donation [28]. Although achieving a pregnancy with oocyte donation is similar in patients with and without Turner syndrome, the miscarriage rate is reported to be higher at 25–50 %, even with young, healthy donated eggs [27, 29, 30]. Uterine factors, specifically hypoplastic uteri and decreased uterine perfusion associated with Turner syndrome, are suspected to contribute to this higher miscarriage rate [27, 29, 31].

In addition to difficulties with conception, patients with Turner syndrome have significant potential pregnancy risks (Table 13.2). The National Institutes of Health (NIH) reported on 250 women affected by Turner syndrome and found 30 % had bicuspid aortic valve and 12 % had coarctation of the aorta [26]. Cardiovascular disease is responsible for up to half of all deaths in patients with Turner syndrome, and 30 % of women experience congestive heart failure at some point in their lives [25]. Even in the absence of congenital heart disease, these patients tend to have higher arterial blood pressure at baseline as adults [25]. The most feared cardiac complication

Table 13.2 Factors to consider in patients with Turner syndrome after oocyte donation

Increased rate of miscarriage
Cardiovascular complications, including increased rate of maternal morbidity/mortality necessitating rigorous cardiology screening
Increased rate of cesarean delivery

in Turner patients is aortic dilation with the potential for dissection or rupture. The presence of aortic dilation can be particularly dangerous in pregnancy with the normal fluid shifts and cardiovascular changes stressing the walls of the aorta. Furthermore, it has been postulated that elevated estrogen levels during pregnancy may lead to remodeling of the aorta, making it more susceptible to dilation and dissection [32]. A review of donor oocyte programs found that there were four deaths among women with Turner syndrome, all from aortic dissection [33]. A report on pregnancy outcomes for 50 patients with a history of coarctation of the aorta demonstrated only one maternal death and that occurred in a woman with Turner syndrome [34]. Overall, it is estimated there is a 2 % maternal mortality for women with Turner syndrome or a 100-fold increased risk of death when compared to the general population [35]. Those not screened thoroughly for cardiovascular disease prior to ART are presumed to be at highest risk [35]. While preconception assessment by an experienced cardiologist can reduce the risk for women with Turner syndrome, these patients remain at risk for pregnancy-related hypertensive disorders, preterm delivery, and even maternal death [27, 28, 30]. The American Society for Reproductive Medicine (ASRM) published specific guidelines for caring for women with Turner syndrome because cardiovascular-related complications are so high in pregnancy [36]. The guideline suggests that these women be counseled extensively prior to the initiation of any infertility treatment and undergo a complete cardiology consultation with blood pressure monitoring, echocardiography, and possibly magnetic resonance imaging [36].

Once pregnancy has been established, Turner syndrome patients should be monitored very closely by a maternal-fetal medicine specialist, with proactive treatment of hypertension and periodic echocardiography in consultation with a cardiologist. Stable women with aortic root diameters of less than 4 cm may attempt a vaginal delivery with appropriate anesthesia, while those equal to or greater than 4 cm or progressively dilating should undergo a cesarean delivery prior to labor under epidural anesthesia [36]. Due to the potential for adverse cardiovascular events, a single embryo transfer should be considered in an effort to avoid a multi-fetal gestation that carries increasing hemodynamic demands and cardiovascular risk. Even in the absence of cardiovascular abnormalities, cesarean delivery may be warranted in patients with Turner syndrome. Short stature and a small pelvis can lead to cephalopelvic disproportion and labor dystocia. In the two largest series of patients conceiving after oocyte donation, all women with Turner syndrome were delivered abdominally [27, 30]. Overall, the cesarean delivery rate in this population has been reported to be as high as 85 % [33].

Malignancy

Infertility is one of the devastating effects that cancer treatment can have on young women. Pelvic radiation, chemotherapy, and surgical treatment can deplete ovarian reserve and lead to iatrogenic ovarian failure. However, in those with an intact and healthy uterus, pregnancy is still possible through oocyte donation with good success. In a report on 24 women, age 28–53 years of age, who underwent a donor embryo transfer after a variety of malignancies, all infants were born healthy, and all but one woman remained disease-free [37]. Overall, 66 % of infants were delivered via cesarean, and there were no neonatal complications [37]. In another report of 6 women who conceived through oocyte donation after being treated for Hodgkin's lymphoma with varying combinations of radio- and chemotherapy, 5 were delivered by cesarean for obstetric indications, and all infants were born healthy and remained so on follow-up [38]. While cancer treatment can adversely affect the ovaries, it may

Table 13.3 Effect of chemotherapeutic agents on maternal health

Chemotherapeutic agent	Side effect	Recommended preconception testing
Anthracyclines	Arrhythmias	EKG
	Dilated cardiomyopathy	Echocardiogram
	Coronary vasospasm	24-h Holter monitor
		Cardiology consult
Bleomycin	Pulmonary fibrosis	Pulmonary function tests
	Hypoxemia	Pulmonology consult
Platinum agents	Chronic renal insufficiency	24-h urine collection
		Creatinine clearance, basic metabolic panel

Adapted from Noyes et al. [41]

also have an effect on the uterus. Studies of pregnancy outcomes in patients after bone marrow transplantation, with either chemotherapy or total body radiation, found an association between abdominal radiotherapy and preterm labor and delivery of low birth weight infants [39, 40]. Irradiation of the uterus may result in decreased elasticity, decreased vascularity, and potentially abnormal placentation. Available data suggests that such patients treated in childhood have decreased uterine volume and decreased uterine blood flow when they reach reproductive age, but that they are often responsive to physiological sex steroid replacement [40]. The sequelae of these changes in the uterus have not been fully characterized, but it is known that spontaneous abortion is more frequent in cancer survivors [37]. Poor uterine perfusion may contribute to intrauterine fetal growth restriction, and scarring and fibrosis of the uterus may be responsible for abnormal placentation and possibly placenta accreta or percreta [41].

Specific chemotherapy regimens can also have serious and lasting effects on maternal health (Table 13.3). Practitioners caring for these women should consult specialists in oncology to review the potential maternal and fetal risks associated with administered chemotherapeutic agents. Ideally, preconception counseling should provide a comprehensive assessment of risk so that patients appropriate for IVF with donor oocytes can proceed. A multidisciplinary team of perinatologists, oncologists, reproductive endocrinologists, genetics counselors, and psychologists should be involved in the pre-pregnancy and antenatal care of these women.

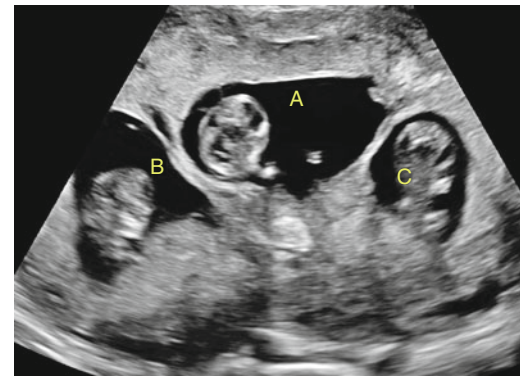

Fig. 13.2 Triplet gestation (A, B, and C) (Photo courtesy of Dr. Lynn Simpson)

Multi-fetal Gestation

Multi-fetal gestation is a significant risk for any patient undergoing ART, including IVF with oocyte donation (Fig. 13.2). Studies of multiple gestations following oocyte donation have reported an increase in preterm birth and neonatal complications related to prematurity [4, 42]. A large series of oocyte donation patients that included 232 pregnancies found that the preterm birth rate was 13 % in singletons, 56 % in twins, and 100 % in triplets, with IUGR being reported in 31 % of twins and 78 % of triplets [42]. Although the management of multi-fetal gestation after oocyte donation

does not differ significantly from pregnancies conceived spontaneously or through other ART methods, women should be well informed of the risks prior to conception and recounseled after a multifetal gestation is conceived. Elective reduction of a multi-fetal gestation remains an option for patients who decide the risks are too great and desire a singleton pregnancy.

Psychological Aspects

In addition to thorough medical screening, a psychological assessment of couples prior to inclusion in any oocyte donation program is recommended [43, 44]. Available data suggests that these patients are well educated, mostly white, and display low levels of depression and high levels of marital satisfaction [45]. Although there is a relative lack of literature on postpartum depression in this population, routine screening is recommended. Interestingly, women who conceived through oocyte donation reported less parental anxiety than those who underwent traditional IVF procedures, and the "bond" between mother and infant has been observed to be normal, or above normal, in the majority of cases [45, 46]. One dilemma faced by parents of these children is whether to disclose the method of conception to the child and other family members, and if so, when to disclose this information. While there is limited data on this issue, consultation with a psychologist may help parents with these decisions.

Conclusion

Pregnancies after oocyte donation generally have good outcomes if proper screening is undertaken prior to inclusion in an oocyte donation program. Increased vigilance by the practitioner is vital in these pregnancies due to the preexisting maternal medical conditions that often make oocyte donation a necessity and may place both the mother and the fetus at risk. A multidisciplinary team composed of a reproductive endocrinologist, obstetrician, maternal-fetal medicine specialist, and other pertinent medical practitioners can help to optimize both maternal and neonatal outcomes.

Editor's Commentary

Pregnancies and births following egg donation have often been heralded and sensationalized. Yet, typically not mentioned, but inherently important to each success, is the hard-working obstetrician who labors right alongside the patient to ensure a good outcome. Recipients are often "high-risk" pregnancies and are now known to also carry unique additional risks related to egg donation itself. This includes an increased incidence of hypertension, diabetes, preterm labor, small for gestational age infants, stillbirth, and placental abnormalities. Furthermore, a very high rate of multiple gestations has plagued egg donation throughout its history, further complicating outcomes.

I have been amused by the complacency young residents in training have developed in caring for these exceptional pregnancies. Recently, a 50-plus-year-old twin delivered at our medical center, and it was not even mentioned at the weekly M&M; no doubt such a pregnancy was not that unusual or noteworthy these days to this audience, but 25 years ago it would have been international headline news! Postmenopausal pregnancies are common enough now to virtually go unnoticed. Yet, they remain challenging cases to ensure that the ultimate goal of delivering a healthy baby and mother is achieved. I have long believed that this goal can only be reached through intense collaboration with our colleagues in maternal fetal medicine (MFM). Involving MFM preconceptionally provides the opportunity to fully assess the overall medical health of the patient and advise her as to the potential impact pregnancy might have on any underlying condition or illness. It also allows the patient to learn firsthand from her future caretaker exactly how they expect to manage complications should they present later on. Finally,

I am sure obstetricians do not appreciate being handed a complicated older patient mid-second trimester without advanced warning.

In their enthusiasm for parenthood, patients often downplay the risks posed by pregnancy. They find it strange that I tell them that pregnancy is a life-threatening condition. I have been sobered by the death of a pregnant 50-year-old, and I now feel compelled to remind them all of this risk. Before embracing a risk of mortality, I believe we must at least address whether or not it is reasonable to seek motherhood with each woman we treat. Since the care of our successes ultimately falls to the obstetrician and fetal-maternal specialists to manage, I strongly urge all reproductive endocrinologists to collaborate fully with them early on in the process of patient screening.

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14 Defining, Understanding, and Managing the Complex Psychological Aspects of Third-Party Reproduction

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Key Points

- Societal changes have contributed to the complexity of psychosocial issues that intended parents, donors, surrogates, and their children must consider. Relationships are no longer dyadic, but now a plurality exists among stakeholders who participate.
- Currently with commercial and professional services growing in popularity, the long-standing tradition of the anonymous donor remains in place, predicated upon the belief, right or wrong, that no relationship exists between the parties.
- Personal information regarding a gamete donor may ultimately play an important emotional role in persons conceived through sperm and egg donation, as children mature and try to understand what part genetics plays in their identity.
- There is no uniform model of a donor registry and each country that maintains one is patterned after unique cultural and legal influences that exist locally. The USA has no mandated federal registry of donors and relies upon small voluntary registries to serve this need.

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Allusions to third-party reproduction have existed since biblical times when Sarah and Abraham used Hagar as their surrogate to beget Ishmael. Surrogacy has come a long way since then; today it is a global business. Sperm donation has also been used since biblical days and has since evolved into a multimillion-dollar industry. Ovum donation is a relative newcomer to third-party reproduction, but its use has grown quickly since its introduction in the 1980s.

Prior to the existence of commercial sperm banks, a medical student could produce a specimen and donate his sperm with reasonable assurance of his anonymity since the physician performing the insemination brokered the arrangement. The introduction of commercial sperm banks and egg donor "agencies" (groups that recruit donors and match them with recipients) redefined identity privacy. It took the control of the identity of sperm donors out of the medical professionals' hands and opened the door to information sharing and identification. What promoted the changes in gamete donation and anonymity?

Third-party reproduction (gamete donation as well as surrogacy) and in vitro fertilization (IVF) have grown as a family building option; IVF now accounts for 1 % of all births in the USA. By 1998, 10 % of all assisted reproductive technology (ART) cycles involved donor ovum (7,756 cycles), and by 2005, the percentage of all ART cycles that involved ovum donation had risen to 12 % (16,161 cycles) and resulted in 5,043 live births, of which 59.2 % were singletons, 38.9 % were

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twins, and 1.9 % were triplets or more (http://www.asrm.org/). Estimates of babies conceived through sperm donation are much more difficult to estimate. The 1987 estimate of 30,000 babies does not account for the advancements in technology including IVF and intracytoplasmic sperm injection (ICSI.) Furthermore, the 1987 Office of Technology Assessment study has been severely criticized because the information was collected through a survey and was not based on actual data [1].

Not only were the numbers of children born through gamete donation increasing, but social change was also occurring at a rapid pace. In 2010, 66 % of children ages 0–17 lived with two married parents, down from 77 % in 1980; viewed by racial background, 75 % of White, non-Hispanic, 61 % of Hispanic, and 35 % of Black children lived with two married parents (http://www.childstats.gov/americaschildren/famsoc1.asp). Families are formed in many different ways – through divorce and remarriage, adoption, fostering, single parents by choice, etc. – and donor gametes or surrogacy became yet another choice in family building options. From the *New York Times* Magazine to Redbook, articles have been examining the option of donor gametes and surrogacy with regard to family structure and functioning. In addition, the portrayal of the family has changed tremendously since the days of "Father Knows Best." Today, same-sex parents are seen on network television shows. "Modern Family," a weekly sitcom, follows a same-sex male couple with an adopted daughter, a blended family with a mother, son, and stepfather, as well as a traditional married heterosexual couple with three children.

Both television and the print media have been enormous engines of social change. The Internet, however, has eclipsed them both. In gamete donation, the "Facebook Factor" has become a change agent unto itself. Donors historically gave little information about themselves other than a perfunctory profile. Currently, donors give a detailed personal and medical profile in addition to providing photographs; in some programs these photos are shared with the recipients. Most donors are of the age where Facebook is an integral part of the social fabric of their lives; a significant volume of information is now available to anyone surfing the Internet. The zeitgeist of anonymity has shifted to one of openness.

This social change has contributed to the complexity of issues that intended parents, donors, surrogates, donor-conceived persons, and surrogacy-gestated persons (as well as all their families) must consider. It is not a dyadic relationship between parents and donor or parents and surrogate; the relationship is now a plurality among all the stakeholders. The medical aspects of third-party reproduction are no longer the main focus. If everything goes well, the medical experience for all the participants is short lived. It is the "happily ever after" once they conceive and are discharged from obstetrical care that needs to be examined.

Types of Egg and Sperm Donation

As previously noted, there is no longer a "one size fits all" regarding gamete donation. Different options exist among and within sperm banks regarding donor identity – from anonymous to completely open from a young age. In addition, there are "Do It Yourself (DIY)" websites that completely bypass the medical, legal, mental health, and commercial industries (Newsweek, October 10, 2011 "You Got Your Sperm Where?"). These DIY sites allow for donors and recipients to make matches and arrange for home inseminations.

The American Society for Reproductive Medicine (ASRM) Ethics Committee [2] created a reference chart for understanding the range of relationships within gamete donation (Table 14.1):

From the beginning of gamete donation within the medical setting, anonymity was challenged. In the first published account of insemination performed by a physician using sperm donated by one of his medical students, anonymity was already compromised [3]. By publishing the report in a medical journal and offering information regarding the recipients (such as their occupation), many people in that small community could make an educated guess as to the recipients'

Table 14.1 Levels of gamete donor information sharing

Level 1. Non-identifying information
Donor provides non-identifying medical or biographical information
Level 2. Non-identifying contact for medical updates
Donor agrees to be contacted with anonymity intact by the program for medical updates and further information if requested
Level 3. Non-identifying personal contact
Donor agrees to have non-identifying contact when the child reaches a certain age and both agree to the disclosure
Level 4. Identifying personal contact
Donor agrees to have identifying information shared with the offspring when the child reaches the age of maturity and both agree to the disclosure

Adapted from [2]

identity. Nonetheless, the medical community advocated for anonymous donation with no relationship among any of the stakeholders. The sperm banks further promulgated this anonymity and lack of relationship. When ovum donation began, most ART programs also offered anonymous donors. Currently, with commercial egg banking growing, the same anonymous donor model is still in place, predicated upon the belief that no relationship exists among the stakeholders.

Another major social change in play is the fact that more intended parents began telling their children that they were donor conceived. Historically, parents did not disclose the donor's contribution to the child's conception (Benward, Braverman, Galen 1). Unlike today, intended parents rarely were referred for mental health psychoeducational counseling and frequently physicians offered the advice to "just go home and forget all about it." This has changed radically; the ASRM Practice Guidelines and Ethics Statements strongly encourage mental health counseling to address these considerations and issues.

Once parents began to disclose information about the use of donor conception to their children, the question of what relationship and meaning the donor has to the donor-conceived person began to gain more attention. Common sense dictates that children will have varied responses to this information, but that many will be curious about their donor origins. Currently, the only research that exists to address this issue has come from surveys from the Internet [4, 5]. For example, the website www.donorsiblingregistry.com states that its purpose "is to assist individuals conceived as a result of sperm, egg or embryo donation who are seeking to make mutually desired contact with others with whom they share genetic ties." The danger of drawing conclusions from these studies is to deduce that they are a representative voice. These surveys focus attention on a valid voice of the donor-conceived community and shed valuable insight into how these relationships function for the donor-conceived persons. However, the donor-conceived persons who do not participate on the website or on other forums may have a very different perspective on these relationships.

These studies suggest that donor-conceived persons very adamantly believe they should be told of their donor origins at a young age. Donor-conceived persons over age 18 were interested in obtaining more information about medical history, sense of identity, and family history, whereas younger donor-conceived persons were interested in similarities with siblings and with donors [4]. These recent studies still beg the question of whether curiosity and information seeking also denote seeking a relationship. These studies and available websites all lead to the question regarding what relationships exist or might exist among the donors, donor-conceived person, intended parents, and other family members.

Relationships Within These Types of Relationships

Theoretically, in an anonymous donation, there is no active relationship among participants. However, as some of the surveys have shown [4, 5], there is a relatedness that may or may not be construed as a relationship. This also begs the question of whether there is no relationship between donor and donor-conceived person just because there is no communication or contact. For the purposes of this discussion, relationship

will be defined as the interaction among participants.

In a very strict anonymous donation, the supposition is that there is no relationship or no need for a relationship. The only relationship is between parents and donor-conceived children, and the donor is relegated to the role of an outsider to the family (levels 1 and 2 in the chart). It has been argued that this role has the function of allowing the donor to function in several capacities: the shadowy and ambiguous figure of "another man," the intelligent medical student, or the altruistic donor as a family man and father who wants to help infertile men father children [6]. Many have argued that the anonymity protects the male in heterosexual couples [6, 7].

In the level 3 of anonymous donation, the donor has agreed to some type of contact when the donor-conceived person is a specific age, typically age 18. With the introduction of contact, the new question arises about what relationship status is conferred. There is a range of relationships that can be expected or inferred. This can be mitigated by agreements by the donor and recipient(s) but can easily be circumvented by a child or adult who was never party to this agreement. For example, when a sperm donor and recipient know each other and agree that he will remain uninvolved in the child's life, the child may choose to pursue a relationship independent of any agreement. The donor and recipient may remain in agreement, but the donor-conceived person may force changes in that agreement.

Genetic heritage is an important influence in many aspects of individual traits. It is the degree to which genetic heritage influences these traits that is open to debate. Information on the donor may play an important emotional role to donor-conceived persons as they mature and try to understand what role genetics may play in their identities. Many have argued that gamete recipients, when disclosing their stories to their children, minimize the significance of genetic connections by emphasizing that the donor-conceived person was very much wanted and loved.

Others have argued that being loved and wanted is an emotion independent of the desire to know one's own genealogy. Wanting knowledge about oneself will, therefore, not be satisfied by just being loved and wanted. Anecdotal reports from donors have suggested this lack of knowledge about their origins leaves part of themselves forever unknown [1].

Resources have emerged to help guide intended parents about when and how to disclose their genetic origins to their children. The overall argument regarding adopted children posits that being open with children and telling their story "early and often" allow children to learn their genetic origins at developmentally appropriate ages when their cognitive development allows. From organizations like Resolve (http://www.resolve.org/family-building-options/donor-options/talking-to-your-children.html) to the American Fertility Society (http://www.theafa.org/mediafiles/talking-to-your-children-about-ovum-donation.pdf) to the Donor Conception Network (www.dcnetwork.org), parents have resources to guide them in the when and how of disclosing to their children the specifics regarding their conception. All these approaches advocate an open and age-appropriate discussion.

Other Complicating Issues

The dynamics of the management of relationships among recipients can be influenced by disparate variables. The age of intended parents often may differ by a decade or two from the donor's age. Single mothers in their late 30s or early 40s may use a sperm donor who is in his late teens or early 20s. Egg donor recipients are often in their 40s and come to egg donation because of age-related factors, while their donors are often in their early 20s. With the increasing number of identity release donors as well as the possibility of donors and donor-conceived persons meeting independently, will the fact that the donor is significantly younger than the recipient parents influence the interest or need for a relationship?

Another issue that may influence the relationship among all the participants in ovum and sperm donation relates to compensation of the

donor in the USA. There have been no studies that have explored whether this compensation influences the donor-conceived persons' feelings about their relationship to the donor or whether this engenders positive or negative feelings toward their parent(s) who paid for the donor. Donor-conceived persons would most certainly be aware that donors are typically compensated, and there appear to be no resources for parents to guide them in their discussion with their children about this subject.

Another area that can certainly have an impact on the relationship between donors to the donor conceived is the statistical likelihood of multiple children resulting from a single sperm donor, and ovum donors also may donate more than once or may have frozen embryos from a cycle donated to another recipient. Once again, no studies exist that explore the impact or meaning of multiple connections between a donor and donor-conceived persons. Common sense dictates that there will be differences resulting from a first contact between these parties to, say, the tenth contact. Add to this the fact that the donor's own children and the donor's partner may have their own independent feelings and reactions to this new relationship in their lives.

Recipient Parents

What does it mean to be biologically but not genetically related to your child? Recipient mothers who carry the pregnancy must work through these thoughts and feelings. Adoption has long since proven that a parent needs not have a genetic or gestational tie to love and parent a child. But are there different dynamics at play for the intended parents if there is a biological connection between only one parent and the child. Unlike adoption, couples must navigate the imbalance of one parent having a biological tie, while the other does not. With egg donation, the father has a genetic relationship, whereas the mother does not, while in sperm donation the mother has both a genetic and gestational tie to the child, while the father does not.

Donors

Donors have a genetic relationship with any child conceived; little is known, however, about whether donors view any other relationship or connection to those conceived or to the parents of those conceived. Studies have found that donors downplay the importance of a genetic tie [8, 9]. Known donors have reported having no desire to assert a relationship with any child conceived [10–12]. Anonymous or paid recruited donors appear to want information on whether a pregnancy was achieved [13–15] and would not object to contact at the age of majority [16]. None of the studies to date have addressed in depth whether donors view that a relationship exists. Although many agree to contact, the qualitative nature of that contact or what meaning the contact creates is not addressed in the current literature.

Are There Other Stakeholders and Those Implications?

Will the children born to the donor, as well as the donor-conceived persons, want any relationships? As mentioned previously, there is a growing voice of donor-conceived persons who answer affirmatively by seeking to have contact with their donor or their genetic half-siblings on websites like the Donor Sibling Registry or sibling registries within sperm banks. In addition, other individuals such as the donor's siblings, parents, and other family members might consider that a relationship exists with the donor-conceived person. The literature has not addressed whether these other stakeholders hold other opinions, and, if they do, what is the nature of the relationship to each stakeholder. Just as the nature of the term "friend" has changed due to social media such as Facebook, so does the nature of the term "relative" change as third-party reproduction has gained prominence.

Donor Gamete Registry

Discussing the purpose of a voluntary registry is not unlike discussing the interpretation of a Rorschach blot – each discussant projects what

he or she sees upon the image of the registry. Gamete donor registries exist in many forms worldwide. For example, the UK and many other countries require mandatory disclosure to offspring of the donor's identity at the age of majority. There is no uniform model of a donor registry; it has been left to each country with its cultural and legal influences to craft its own version.

Registries exist to maintain records. Yet, it is the type of information placed in the records that engenders controversy. Information about the donor may be divided into three categories: medical, psychosocial, and donor identification. The question of what type of information a donor registry would preserve must address this fundamental issue. Accompanying this question is whether the registry is voluntary or mandatory. Government registries are clearly mandatory.

In the USA, sperm banks, patient groups, and commercial enterprises have created small voluntary registries, but there has been no central registry yet created.

Reasons for and Against a Registry

There has been discussion in the USA about a donor registry for well over a decade. In 1998, *Fertility and Sterility* published two opposing points of view regarding a gamete registry [16–18] in the same year the subject appeared at the annual meeting as a scheduled debate.

Accompanying the growth in egg donation and embryo donation has been a change in attitudes about gamete donor conception. In its landmark statement, the Ethics Committee of the American Society for Reproductive Medicine recommended that disclosure is "ultimately the choice of recipient parents" but that "disclosure to offspring of the use of donor gametes is encouraged" [19]. This recommendation sets into motion part of the change in the consideration of a gamete donor registry. Simply put, if the majority of donor-conceived persons are aware of their donor conception, the very real possibility of increased interest and curiosity was more likely to occur. While no studies have been able to identify what, if any, information donor-conceived persons are going to seek regarding their donor, there is huge controversy about these three categories of donor-provided information.

Less controversial is whether the disclosure of medical information is favored. It is the standard of care for gamete donor recipients to receive a full medical history on the donor and his/her extended family. This information may be important to the donor-conceived persons for medical reasons or for more emotional reasons such as curiosity or identity.

Another area of functionality for a registry is the appropriate storage of records. ART clinics close or change owners each year, and the question of what happens to the donor records is critical for potential future inquires. ASRM practice guidelines recommend the permanent storage of records involving donor conception. The guidelines state "… in the opinion of the ASRM, a permanent record of each donor's initial selection process and subsequent follow-up evaluations should be maintained. To the extent possible, the clinical outcome for each donation cycle should be recorded. A mechanism must exist to maintain such records as a future medical resource for any offspring produced" [20]. As physicians retire or practices change hands, donor records may become a burden when practicing within guidelines.

Conflicting and Competing Needs

There are many stakeholders involved when a gamete donor registry is contemplated, including the donor, donor-conceived persons, recipients, physicians/medical programs, and society. Frequently the needs of all the stakeholders conflict when considering the role and function of a registry. The rights of donors who expect to be anonymous would not be protected should a registry collect and release identifying identification. However, donor-conceived persons might feel insufficiently informed if information that is fundamental in their identity formation is withheld. A single donor registry model cannot meet each stakeholder's needs. Consequently, when forming a registry, it must be made clear what needs are intended to be met.

Some have argued that any registry must include not only preservation of medical and general characteristics information but must include the mechanism for identification, such as websites for the donor-conceived (http://tangledwebsorg.wordpress.com). This argument is posited as a human rights issue. In this evaluation, the donor-conceived person's rights supersede those of the donor's rights or needs. This construct of a registry also conflicts with the medical professional's or bank's needs to honor the agreement they made with the donor to be anonymous.

Gestational Surrogacy: Psychological Considerations

Unlike gamete donation, gestational carrier or surrogacy has almost exclusively relied upon a known relationship. Since the 1980s, gestational surrogacy has grown as a family building option due to increased access by the medical community and intended parents to information on the Internet and through media coverage. For example, Hollywood frequently reports that its celebrity stars have used surrogacy. Gestational surrogacy began strictly for medical reasons, e.g., an absent uterus or medical danger to the mother. Over the last 10 years, however, surrogacy has also grown as a family building option for same-sex male couples.

The focus in a gestational surrogacy arrangement is on the relationship. Specifically, intended parents and gestational surrogates need to discuss the intended nature of their relationship both during the pregnancy and once the delivery occurs. As in most collaborative reproduction arrangements, there is a range of choices – from one of formality to one of friendship.

Gestational surrogates and intended parents need to explore whether they are congruent in their expectations of the relationship. Research on gestational surrogates and intended parents has been extremely limited. Researchers have found that gestational carriers and the intended parents were unremarkable with regard to any preexisting psychopathology [21]. More recent studies have examined the intended parents' and gestational carriers' experience and report no consequent negative issues or problems [22]. After delivery, gestational carriers were found to have no psychological problems from carrying and delivering a child for the intended parents.

There have been a few more recent studies that have examined the intended parents' experience [22, 23]. There are biased, small sample studies that have been reported on gestational carriers, and there has been one 2003 study that performed qualitative interviews of 34 women who delivered as gestational carriers [24]. In this study, the authors found that gestational carriers do not suffer psychological problems as a result of their participation. However, this study failed to distinguish gestational carriers from traditional surrogates, and 21 % of the sample was in a known relationship. This reduced the sample size of the gestational carriers.

Gestational surrogacy is built upon the basis that the surrogate and intended parent relationship should be mutually respectful and collaborative. Through consultations with the mental health professional, medical health professionals, attorneys, and recruiting agencies, each participant should receive counseling regarding their expectations for the relationship and the risks of not having those expectations met. Specific issues related to frequency and mode of contact should be discussed frankly. Discussions must be had and agreements must be made about the communication needs and commitments of each individual. Some groups are more formal in their approach and have a weekly scheduled phone call, Skype time, or in-person meeting, whereas others phone, text, and tweet multiple times in a day. Issues such as whether to become Facebook "friends" should be discussed, and these issues are often supported by the mental health professional.

Once the baby is delivered, the next stage of the relationship must be negotiated. Prior to pregnancy, intended parents and their gestational surrogates should have this discussion. However, the relationship may change over time, and the initial agreement may no longer prevail. A group that intended to be more formal may discover a deeper level of relatedness and wish to keep in touch beyond any previously agreed upon yearly greeting

card. Conversely, a group that finds they do not care for each other or where one participant is intrusive throughout the pregnancy may choose to terminate any contact once delivery is achieved.

Communication is the single most difficult challenge of the relationship. Most frequently, gestational surrogate relationships begin with participants who are unknown to each other, and the relationship grows over time.

Conclusion

Managing the relationships in third-party reproduction involves multiple considerations. Like looking through a prism, the issues are refracted by the angle through which they are viewed. Overall, the meaning of what relationships exist among all the stakeholders in gamete donation or gestational carrier or surrogacy is evolving within a rapidly changing world. Although many third-party reproduction arrangements are anonymous in nature, it remains to be seen whether anonymity exists in just a "snapshot in time" and will yield to social networking and the availability of information and contact on the Internet.

Editor's Commentary

Mental health care professionals from a variety of backgrounds and holding various degrees (Ph.D., M.D., MSW) have been a steadfast party to the development of egg and embryo donation from the very beginning. The careful screening of donors and recipients using many different techniques and tools to ascertain the intent of the participants and their overall mental fitness to participate has been vital to the success of the method. With the ever-rising number of cases and increasingly complex nature of the many "stakeholders," it is perhaps more important than ever to address the psychosocial status of all parties prior to embarking on a treatment course. As Dr. Braverman points out, it is essential to recognize that the pregnancy is just the beginning of a life journey, and careful preparation for the future of that child should occur early on in the process.

Dr. Braverman also referenced that I have never been a proponent of mandating a national registry for tracking gamete donors. This is not because I believe that secrecy and anonymity is the better approach. I have performed egg donation with both known and anonymous donors many times and with good results. Clearly, for some patients nondisclosure makes perfect sense, and for others it does not. Rather it is my inherent distrust in the maintenance and security of personal data by any government and how it ultimately might be used, or potentially corrupted and abused, that fuels my reluctance to endorse a national plan for sharing donor/recipient information. I prefer that patients safeguard their own health information, especially if it is going to be available to the public in perpetuity. Also, we have seen examples where legally mandated donor identity disclosure has essentially killed the practice of egg donation, as noted in the dramatic decline in the use of the method in the UK.

I believe asking a young unmarried, nonparous woman in her twenties to extrapolate how she may feel about disclosing her personal information or identity 10, 20, or maybe 50 years downstream in life to a child that she may or may not know existed is simply unrealistic. Furthermore, I think that many donors normally go through multiple changes in their attitude about having participated as they age, and it would be difficult to affirm from a survey at any age whether or not they will have a lifelong commitment to being maintained in a donor registry. I appreciate that my view is not universally shared, particularly among special interest groups that have been pushing for a national registry for nearly 20 years, but it is, after all, just my opinion. The debate goes on.

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15 Disclosure Decisions Among Known and Anonymous Egg Donor Recipients

Susan C. Klock

Key Points

- Egg donation allows recipients to gestate the pregnancy, contribute physiologically to the pregnancy, and psychologically bond to the developing fetus, which makes it uniquely different from adoption.
- Despite differences in disclosure decisions, the unifying theme underlying the reason for the decision was the *best interest* of the child and the child's well-being.
- Disclosing to children the nature of their donation origin appears to be a complex decision, influenced by a variety of factors, including donor type (anonymous or known), parental beliefs about the best interest of the child, and the child's age.
- Mental health professionals can provide a unique, neutral, productive environment to help all parties work through issues that arise from egg donation.

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The path to parenthood for some couples includes egg donation. Since the first report of a successful egg donation pregnancy over 25 years ago [1], the possibility of pregnancy and parenthood for women with premature ovarian failure, genetically heritable diseases, advanced maternal age, and other previously insurmountable conditions has become a reality. Egg donation has undergone substantial growth in the past 15 years. The Society for Assisted Reproductive Technology (SART)/American Society for Reproductive Medicine (ASRM) 1995 report indicated the initiation of 3,555 donor cycles, with 1,451 pregnancies and 1,206 deliveries [2]. By comparison, the 2008 SART/ASRM/CDC statistics reported 11,777 donor cycles initiated, with 6,843 pregnancies and 5,894 live births [3]. The rapid growth in the use of donor eggs has prompted an examination of the social and psychological aspects of this distinctive route to parenthood. As prospective parents consider egg donation treatment, they must consider many unique aspects of parenting related to egg donation. One of the many decisions in the transition to parenthood among egg donor recipients is the question of disclosure regarding the egg donor origin of the child. The decision to disclose to others in the social support network and, most importantly, to the child is based on many factors. The purpose of this chapter is to review the literature on disclosure among egg donation recipients and to discuss the clinical implications of these findings.

Egg donation is offered in roughly two thirds of countries surveyed by the International

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Federation of Fertility Societies (IFFS) but is prohibited in approximately one fourth of countries surveyed [4]. Countries vary in the acceptance of known or anonymous donors, the information obtained and stored regarding donor characteristics, and the ability of the donor child to find out identifying information about their donor. Some countries allow payment of direct expenses incurred during the donation process (e.g., parking, time off work, travel); other countries, like the USA, provide compensation for the donor [5]. Social customs and psychological factors vary by country and, as such, influence the presence of statutes and guidelines governing the practice of egg donation. In the USA, FDA regulations and professional society guidelines shape clinical practice [6, 7], but couples' individual beliefs and values guide their decisions regarding the disclosure of using an egg donor to conceive. The unique aspect of egg donation, which allows the recipient to gestate the pregnancy, contribute physiologically to the pregnancy, and psychologically bond with the developing fetus, makes it very different from sperm donation for the infertile man and adoption for the adoptive parent.

Egg donation is a unique path to parenthood with its own particular issues to consider in regard to disclosure decisions. Therefore, direct extrapolation regarding disclosure decisions from the sperm donation and adoption literature will not be included in this chapter, but instead the focus will be on the research findings and clinical experience solely with egg donor recipients. The following is a review of the clinical research regarding attitudes and intentions regarding disclosure in egg donation recipients.

Review of the Literature

Disclosure Attitudes and Intentions

The psychosocial research on oocyte donation began in the early 1990s to document this new treatment modality. Several studies have been conducted on varying aspects of disclosure in egg donation, and these studies are summarized in Table 15.1. In a survey of parental attitudes toward oocyte donation, Pettee and Weckstein sent questionnaires to 122 egg donor recipients in ten states and received 31 responses (25 % response rate) regarding parents concerns and attitudes [8]. They found that 55 % of respondents had used a known donor and 45 % anonymous donor. Among these parents, the primary concern about egg donation was the question of

Table 15.1 Studies of disclosure to the child and others among egg donation participants

Authors	Year	*n*	Age child	Donor type (%)	Disclose, child (%)	Disclose, others (%)
Pettee and Weckstein	1993	31	–	45 % anon	43	83
				55 % known	88	83
Soderstrom-Anttila et al.	1998	51	0–4 years	84 % anon	38	73
				16 % known		
Greenfeld et al.	1998	90	Pretreatment	71 % anon	52	58
				28 % known	88	97
Golombok et al.	1999	21	3.5–8 years	86 % anon	5	72
				14 % known		
Murray et al.	2006	17	12 years	–	35	–
Hahn and Craft-Rosenberg	2002	31	<6 weeks	100 % anon	56	85
Greenfeld and Klock	2004	90	2.8 years	77 %	59	80
				22 %	59	80
Van Berkel et al.	2007	44	3.5–4.0 years	100 % known	82	–
Hershberger et al.	2007	8	Pregnant	87 % anon	50	–
MacDougall et al.	2007	79	1–10 years	–	81	–
Soderstrom-Anttila et al.	2010	101	3+	85 % anon	61	71–86

disclosure to the child. Eighty-three percent of respondents had told at least one other person about using egg donation to conceive. In terms of disclosure to the child, of the 14 couples who used an anonymous donor, 6 (43 %) intended to tell their child, 1 (7 %) did not, and 7 (50 %) were undecided. Of the 17 cycles with a known donor, 15 (88 %) planned to tell the child and 2 (12 %) had decided not to tell. This study provided an early insight into the possible differences in disclosure decisions based on type of donor used and the type of relationship the recipient parents had with the donor.

Soderstrom-Anttila et al. investigated the health and development of 59 egg donor infants and 126 IVF infants between the ages of 0 and 4 years at a Finnish clinic [9]. Among the egg donor infants, 51 pregnancies were initiated, 43 with an anonymous donor and eight with a known donor. Roughly half of the parents who used an anonymous donor did not want any information about the donor and only 3 of 42 reported a desire to meet their donor. In terms of disclosure to others, 73 % of oocyte donation parents had told at least one other person and 90 % of IVF parents told at least one other person about their method of conception. In contrast to the number of other individuals told about the method of conception, 38 % of the oocyte donation parents (included were 2 of the 9 recipients who used a known donor) and 60 % of the IVF parents planned to tell the child about their mode of conception. At the time of the study, over half of both groups of parents believed that the child at the age of 18 should not have the right to obtain identifying information about the donor. The authors noted, "The parents must themselves decide what is best for them and this decision should be respected." But the authors also cited the hazard of unintentional disclosure because in this sample a majority of recipients had told others but a minority planned to tell the child. Therefore, the authors recommended that parents not tell other people if they do not plan to tell the child.

Greenfeld and colleagues were the first to specifically address the question whether attitudes toward disclosure were related to the use of an anonymous or known donor [10]. In a series of 90 consecutive recipients, 64 (71 %) who used an anonymous donor and 26 (28 %) who used a known donor, they found that 97 % of known recipients versus 58 % of anonymous recipients had told others about using egg donation. Eighty-eight percent of known recipients planned to tell the child and 52 % of the anonymous recipients planned to tell.

Hahn and Craft-Rosenberg examined the disclosure decisions of parents who conceived their child through egg donation [11]. In a study of 48 couples with an egg donor child at least 6 weeks of age, one or both parents from 31 families (58 respondents) agreed to participate in an interview and complete the study questionnaire. Approximately 56 % of parents indicated that they planned to disclose, 19 % were not and 24 % were undecided. The investigators found that parents had several concerns about disclosure and nondisclosure. A primary concern among parents was how and when to tell the child and the child's reaction to knowing of their donor conception. Parents were also concerned with the nondisclosure stance in terms of inadvertent disclosure or disclosure by someone other than the parents and the child's reaction to the information. Despite describing themselves as being *firm* in their decision and not changing their minds, both disclosing and nondisclosing parents had many worries about their decision. The undecided group mostly reported lack of consensus between parents as the reason for being undecided. Of note, among nondisclosing parents, none had told others about using donor eggs compared to 85 % of the disclosing parents. *Telling others* was a pervasive theme which was regretted and often affected the disclosure decision.

In a study of donor egg mothers, Greenfeld and Klock assessed disclosure attitudes in reference to the recipient using a known versus anonymous donor [12]. In this study 90 egg donor mothers (70 anonymous and 20 known donors) were queried regarding their knowledge about their donor and disclosure plans. The average age of the mothers was 44 years, and the average age of the egg donor child was 2.9 years. For the sample, an average of 0.5 years elapsed between the time the couple decided to use donor egg and the

time they were matched to a donor. For both anonymous and known recipients, *appearance* was the most important characteristic in their donor selection. In terms of telling others, 80 % of both anonymous and known recipient reported that they had told others about using a donor to conceive. When asked if they had to do it over again, would they tell others of using donor eggs? Sixty four percent of anonymous recipients and 46 % of known recipients stated that they would tell others.

Both disclosers and nondisclosers to others felt strongly about their attitudes toward disclosure. The parents who said *yes* they would tell others if they had it to do over again cited the importance of social support from others, demystifying the egg donation process to help other women and that openness was in the best interest of the child. Alternatively, the women who would not tell others if they had it to do over again stated that they believed it was in the best interest of the child not to tell others, primarily because it was the child's information and the child should be the first to know the information and because they were concerned about inadvertent disclosure. Regarding disclosure to the child, both groups (known or anonymous donor) were identical in their intentions: Ten percent had told the child, 49 % planned to tell, 31 % were not telling, and 10 % were undecided. The authors concluded that in this sample there were no differences in disclosure to others or the child based on the use of a known or anonymous donor. Despite differences in disclosure decisions, the unifying theme underlying the reason for the decision was the best interest of the child and the child's well-being. The majority of the sample reported that they had received counseling by a mental health professional as a part of their treatment process. Interestingly, most respondents stated that if any member of the treatment team made a recommendation regarding disclosure, it did not influence their decision.

More recent studies have sought an in-depth understanding of the disclosure decision among egg donation mothers. In a study from the Netherlands, where all egg donations are made on a known basis, van Berkel et al. (2007) [13] studied privacy and disclosure among 44 egg donor recipients compared to 62 IVF mothers whose children were between the ages of 3.5–4.0 years old. The investigators asked women about their attitudes and plans for disclosure and the reasons for their positions. In this sample, 47 % of donors were a family member, 36 % were friends, and 16 % were acquaintances. In terms of disclosure to the child, 18 % of egg donor and 12 % of IVF mothers indicated that they would never tell their child about their origin. Reasons given for this choice were as follows: the information was not important, they had an agreement with the donor not to disclose, and they did not want their child to have an *identity crisis* or *misery*. The majority of egg donor mothers indicated that they planned to tell their child but were unsure at what age. Common reasons given for disclosing were that the child had a right to know, that they had already told many other people so they felt a pressure to tell the child, and concerns over medical background information. The authors noted that after the donor child was born, contact between the donor and the parents/child was good and frequent. Half of the recipients saw their donors daily or weekly and described the relationships as positive. In three cases, problems in the donor relationship emerged due to too much interference on the part of the donor and that the expectations of the donor were greater than those agreed to at the time of the donation. Egg donor mothers had significantly more worries about the future than the IVF mothers. More egg donor mothers were worried about the unknown negative consequences of their mode of conception on the health of their child, future questions from the child about their origins, and future identity problems compared to IVF mothers.

In a qualitative study of eight pregnant egg donor recipients, Hershberger et al. elucidated the reasoning behind women's disclosure decisions [14]. The authors reported two broad themes which emerged from the interview data: (1) women engaged in *selective disclosure* choosing individuals to tell and the amount of information to disclose and (2) women felt a responsibility toward the resulting child which was a prominent

component of the disclosure decision. Of the eight women in the study, four planned to disclose, three were undecided, and one was not planning to tell her child. Even as responsibility and concern for the child's well-being was the primary concern of all the women, disclosure decisions varied. Additionally, women who had told others and who planned to tell the child reported the belief that a person has the right to know the information about their conception. The right to know was extended to the child but also to family members and health-care professionals. Among women who were not planning to tell the child or who were unsure, the duty to protect was a belief cited to avoid discord in relationships, protect the mother from remembering her infertility, protect the child from accidental disclosure, and protect the child from shame and stigma.

Another recent study by Soderstrom-Anttila et al. surveyed Finnish parents who had a child via egg donation between the years of 1992 and 2007 [15]. In this sample of 175 women, there were 206 deliveries of 243 infants. The questionnaires were sent to parents and assessed demographic information, disclosure decisions, and reason for disclosure decision. The response rate was 67 and 85 % of respondents had used an anonymous donor. Sixty-one percent of mothers and fathers reported that they had told or planned to tell the child of their egg donor conception. There was no difference in disclosure based on donor type, with 64 % of parents with known donors planning to disclose.

One hundred and one parents had children over the age of 3. In this group of parents, 28 (27 %) had already told their child. Thirty-eight of the 146 (26 %) children between 3 and 14 years had already been told, 18 % had been told between the ages of 7 and 9 years, and 76 % had been informed between the ages of 3 and 6. Most parents reported using the *seed planting* strategy indicating that a *nice person* gave a gift, a seed, or an egg to help create the child. Disclosure differed by age of child with 83 % of parents with children in the 1–3-year group indicating that they would disclose compared to 44 % of the parents with child in the 13–14-year group. In 16 % of couples, the mother and father disagreed with one another regarding disclosure. The most frequent reasons for telling were as follows: *it is natural to be open and honest* and *the child has a right to know*. Among those who planned not to disclose or were unsure, the most common reasons for nondisclosure were as follows: *it was unnecessary information* or it could be *harmful to the child*. In terms of telling others, 86 % of mothers and 71 % of fathers had told someone else about the use of donor egg. Not surprisingly, telling others and telling the child were highly correlated, but 71 % of parents who had already told other people had not yet told their child. Interestingly, only 31 % of mothers and 24 % of fathers are in favor of the Finnish law requiring open-identity donation.

Outcomes Based on Disclosure

It has been assumed through the experience with adoption and sperm donation that there would be a significant negative consequence for the child and the family if they opted for nondisclosure. Stories of negative experiences of donor offspring searching for their donor are readily reported in the popular media. It is impossible to know if these experiences are representative of the population of donor offspring. The stories of pain and anguish, grief, and feelings of not belonging are certainly poignant and highlight the potential difficulties in donor gamete conception, but the question remains: "are there any measureable, stable differences in the psychological well-being of donor offspring who are informed of the mode of their conception compared to those who are not?"

In 1999, Golombok et al. compared families created with IVF, donor insemination, oocyte donation, and adoption on measures of quality of parenting and well-being of the child [16]. In this sample, the children were between the ages of 3.5 and 8 years. Of the 21 egg donation families, 18 had used an anonymous donor and three had used a known donor. One of the 21 parents had told their oocyte donor offspring of their origin. Seventy-two percent had told family or friends, but 38 % stated they would *never tell* their child. Golombok et al. noted no differences in quality

of parenting or well-being of the child based on intention to disclose. When asked about their reasons for nondisclosure, 69 % of oocyte donation parents stated they would not disclose in order to protect their child, and 23 % stated they would not disclose to protect the mother's relationship to the child.

In a follow-up to this study, Murray et al. investigated parents' marital and psychological state and the parent–child relationship through a standardized interview and questionnaires when these same children were 12 years old [17]. No differences were found between groups (IVF, egg donation, donor insemination, and adoption) on measures of parental and marital adjustment. No differences were found between groups on measures of the children's socioemotional development, school adjustment, or peer relationships. In terms of disclosure, at the time of the study, 35 % of egg donor mothers, 11 % of donor insemination mothers, and 88 % of IVF mothers had already told or planned to tell their child of their mode of conception. Sixty-five percent of egg donor mothers reported never intending to tell their child or being undecided about telling their child. The majority of these mothers cited a desire to protect their child from the perceived negative effects of disclosure on the child's well-being. Among the 35 % of egg donor mothers who had told or planned to tell, the strong belief that the child has a right to know was the primary reason for disclosure.

These two studies are a unique contribution to the literature in that they followed the same families over time to assess parenting, child adjustment, and disclosure. While the sample sizes are small, the insights to be gained are important. The method of family building (IVF, egg donation, sperm donation) was not related to parenting quality indicating that the lack of genetic link among egg donor mothers and sperm donor fathers is not essential for the development of strong, positive family relationships. One difference that was observed between groups was that egg donor mothers reported that their partners were *less reliable* and less likely to share parenting load with them than the DI mothers. The authors speculated that the egg donor mothers' anxieties about the lack of a genetic link to their child as well as their strong motivation to have a child might compel them to take on the majority of the parenting load. There were no significant differences in psychological adjustment or functioning among the preadolescents in the study based on disclosure status. This finding does not support the view that there are negative consequences in the parent–child relationship or child development because of nondisclosure of the child's donor origin. Additional research of this type is needed to understand if this finding is replicated in other, larger samples of parents and children and at different stages of child development.

Shelton et al. were interested in examining whether there was variation in psychological adjustment problems among children conceived by assisted reproductive technologies from different conception groups (IVF, donor sperm, donor egg, donor embryo, and gestational surrogacy) [18]. Children conceived with nonrelated gamete donors or gestational carriers between the ages of 4 and 10 years were identified from 18 UK clinics and 1 clinic in the USA. Eight hundred and seven families (548 fathers and 792 mothers) were recruited: 386 IVF, 182 IVF with donor sperm, 153 IVF with donor egg, 27 IVF with embryo donation, and 21 with gestational carrier. Parents were asked to complete questionnaires about the child's psychological adjustment including symptoms of attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), depression, anxiety, somatization, peer relations, prosocial behaviors, and neurodevelopment disorders. The sample contained 394 boys and 375 girls with an average age of 6.8 years. There was a high level of agreement between the mothers' and fathers' reports of their child's adjustment. There was no association between conception group and mother reports of conduct problems, ODD, or ADHD. For fathers, there was a significant relationship between conception group and conduct problems, with fathers in the egg donation group rating the children higher in conduct problems compared to fathers in the IVF group or sperm donation group. None of the five conception groups had elevated levels of conduct or peer problems compared to British normative values. Disclosure to offspring

regarding the mode of their conception was not addressed in this study.

In summary, disclosure to the child regarding his or her oocyte donation origin appears to be a complex decision, influenced by a variety of factors, including donor type (anonymous or known), beliefs about the best interest of the child, and age of the child. Also, as can be seen by the review of the literature, the studies are limited by methodological problems such as small sample size, nonrandom sampling, and moderate participation rates. Other variables, such as the age of the child, consensus between parents, personal beliefs regarding privacy in general, and community values, can also affect disclosure. There may be an overestimation of disclosure due to the possibility that parents who plan to disclose may be more willing to participate in studies of disclosure. Finally, in studies in this area, *intention* to tell is used to assess *actual* disclosure. It is important to remember however that the *intention* to tell a child about their donor oocyte origin is not the same as *actually* telling. It is possible that some families intend to disclose but find barriers to disclosure that allow time to pass without the child being told. For parents who plan to disclose, the barriers to disclosure can be overcome with the help of information regarding strategies for disclosure and patient education materials. This information is the focus of the next section.

Clinical Implications

Helping couples navigate the disclosure decisions is an important part of the infertility counselor's role. Counseling donor recipients at the initial stage of considering this treatment option and selecting a donor through counseling families with children of different ages, the mental health professional can provide a unique, neutral, productive environment to help all parties work through issues that arise from egg donor conception. Pretreatment counseling is offered in many programs routinely and is recommended in the ASRM guidelines [7]. Klock and Maier [19] and Sachs and Burns [20] have provided useful recommendations regarding topics to cover in the pretreatment recipient counseling session(s). In pretreatment counseling, discussion of donor selection covers many physical and psychological characteristics including the choice regarding disclosure.

In pretreatment counseling, the participants' values and beliefs regarding the importance of sharing information should be examined. The relative value placed on disclosure or privacy in general day-to-day life can be discussed. For example, some couples maintain a more private stance regarding emotionally laden topics such as money, sex, or religion. For these couples, donor egg treatment may fall into the private category of information, and they opt not to discuss it with others. Alternatively, some individuals may describe themselves as *an open book* and may be more likely to discuss all range of topics, including donor conception, with people at all levels of their social support network.

A second topic to discuss in reference to the disclosure decision is the participants' beliefs about the relative contribution of genetics and the environment in the child's development. Specifically discussing the participants' beliefs about the relative contributions of genetics, gestation, the rearing environment, and the relationship with the parents can shed light on the parents' rationale for their disclosure decision.

Third, the counselor can guide the recipient to think about the knowledge of oocyte donation from the child's perspective, asking the recipient to imagine how they would feel if they had been conceived by a donor gamete and would they want to know that information about themselves. Also, in reference to the potential child, the recipient can be encouraged to think of the impact of the oocyte donation information over time. For instance, the consideration to tell a 2-year-old has a different meaning and consequences than telling a 12-year-old. All of these topics can be discussed with the recipient at the pretreatment interview. Some couples may feel that it is premature to discuss disclosure-related topics during pretreatment counseling, but it is helpful for the recipient to begin considering, weighing their beliefs, and discussing possible plans at this time. A recipient's refrain, "We will think about it if we get pregnant,"

should be followed up with more inquiry about their expectations, fears, and plans.

During the discussion of disclosure, the mental health professional can maintain a neutral position to allow full consideration of all possibilities. In addition, the mental health professional should remember that there might be few places where the recipients can discuss the full range of their thoughts and feelings without feeling judged or being told what to do; therefore, neutrality may be a relief while they come to their own conclusions. Also, it is unclear if couples follow the recommendation of mental health professionals regarding the disclosure decision; therefore, when a mental health professional takes a definitive stand one way or the other or tell the participants that they *have to* do something, it stymies the discussion. In addition, a rigid stance toward disclosure or privacy places the mental health professional in a position of convincing the participant about their position, implies that the couple cannot make the decision for themselves, and shuts the door to additional consultation in the future if the couple is in need of future support. The mental health professional can share data from the existing studies and can share recommendations for disclosure from the ASRM and other bodies, but ultimately the decision rests with the parents, and pretreatment counseling is an important part of the decision-making process.

After the pretreatment counseling, the recipients should have a preliminary plan regarding disclosure. Particularly with respect to family member donation, the wishes of the donor and the recipient have to be considered carefully, discussed with one another, and an initial plan made prior to beginning treatment. Then an agreement to discuss disclosure decisions and actions in the future can be put in place. In known donor cases, disclosure is frequently the starting point in the counseling after an initial count of how many people in the donor's and recipient's lives already know about the known donor arrangement, and their interconnected relationships usually highlight the impractical nature of privacy. Once the number of people who are aware of the donation is determined, then concrete discussions of the implications of that knowledge can be addressed directly. For couples using an anonymous donor, the preliminary plan may be for privacy or disclosure.

Posttreatment counseling is frequently requested by donor gamete families around when and how to tell the child. In a study by MacDougall et al., the authors interviewed 141 donor gamete couples, 79 who had used donor eggs to conceive [21]. In the donor egg group, 18 (23 %) had already disclosed, 46 (58 %) planned to, 8 (10 %) planned not to disclosure, and 7 (9 %) were unsure. Among the disclosing families, the investigators found two predominant strategies which they describe as the *seed planting* and *right time* strategies. The seed planting strategy was characterized by the belief that early disclosure is very important. The rationale from the parent's perspective was that the child would always know about their donor origin; therefore, the risk of a break in trust between parent and child would be minimized. In the seed planting strategy, parents wanted to promote a perception that donor conception was natural and matter of fact, within the context of the routine, daily family interactions. The seed planting strategy was initiated among the disclosing parents in this study when the child was between 3 and 4 years old. It typically began when the child asked where babies came from; it was more commonly initiated by the mother and was discussed in the course of daily activity.

The right time strategy was characterized by the belief that there is an optimal window in which to disclose to the child and that disclosing too early could confuse or upset the child. In the right time strategy, the parents view the disclosure as a single event of telling, instead of the gradual unfolding of the story. Many parents stated that they *just knew* when the time was right; others identified the right time when the child had the cognitive skills to understand the medical and technical aspects of the procedure. Parents who intended to tell identified the ages of 10–12 years, whereas those who had already told disclosed around ages 6–7 years.

The authors of this study noted that no matter which strategy the couple used, parents wanted to know what to say and have a narrative for disclosing. They identified five themes used in disclosure:

(1) *the helper* (the parents needed someone to help them have the child), (2) *spare parts* (one parent did not have the part that was needed to make a baby, and therefore, they got the spare part from someone else), (3) *families are different* (donor conception discussed as one of many ways families are made), (4) *labor of love* (the child was conceived because the parents very much wanted them), and (5) *nuts and bolts* (only describing the technical details to the child).

In clinical practice, mental health professionals often help parents develop a disclosure strategy. A useful resource for parents is the Donor Conception Network [22]. The Donor Conception Network has a series of four brochures with age-appropriate dialogues for the disclosure of donor gamete conception. These brochures, as well as other children's literature about donor gamete conception, are available on the Donor Conception website. These resources can be helpful to parents looking for a concrete way to communicate to their child about the child's egg donor origin. In posttreatment counseling, mental health professionals can help parents form their narrative for telling the child and help them feel comfortable discussing the topic in a natural, forthright manner.

There have been many developments in egg donation since 1984, but the disclosure decision remains a fundamental unanswered question in the psychological and social adjustment of the child and their family. It is incumbent on mental health professionals and social scientists to continue studying the psychosocial impact of egg donation on the well-being of children and their families. Large, representative, longitudinal studies are needed to fully understand this form of family building and its implications for child development.

Editor's Commentary

In my nearly 30 years of working with couples involved with gamete donation, perhaps the most common question asked of me relates to whether or not a parent should disclose the circumstances of the pregnancy with their child and, for that matter, with the rest of the world. It is an important question that deserves answering, but I rarely do. I say this because personally I think the question is unanswerable, and the right course of action depends upon a number of circumstances unique to the birth of that child and the family to which that child is born and immediately becomes a member.

Births invite community celebration, and it is vitally important for parents to know how best to prepare for this entrance when planning for a pregnancy that involves a third party. For some patients, open disclosure makes perfect sense, and I have seen many share the information openly with their family and friends even before achieving a pregnancy. In other cases, disclosure would be personally difficult if not impossible and potentially jeopardize their marriage, family, and community relationships. So, I tell my patients they must reach this difficult but important decision in the manner in which they approach other life decisions of similar magnitude, principally through deep introspection and open communication with themselves.

I believe good parents are relatively selfless when it comes to promoting the welfare of their child. I also believe that parents are very selfish when it comes to protecting them. For that reason I think that the decision as whether or not to disclose may take years of parenting in order to know when, if ever, to engage their son or daughter with this challenging information. I do not believe that infertile patients can suddenly think like parents and I also believe that raising a child has a profound influence on how you might address this question at a later point in time.

A neutral third party, separate from the infertility care providers, may be best suited to direct discussions on these matters, as even couples may have strong disagreements as to the course of action to take regarding disclosure. I tell patients that there

is no such thing as a good secret, and therefore, I believe working through these issues is best done without enlisting friends or family support, at least until the decision on whether or not to disclose is firmly made. I also tell them there are many ways to address this issue and that there is not one model for success. I have performed both anonymous and known gamete donation, and when approached with care and guidance, both approaches seem to work equally well.

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Risk and Complications Associated with Egg Donation

16

Daniel Bodri

Key Points

- The overall rate of complications experienced by egg donors appears to be less than 1 % and is remarkably consistent between studies conducted in different regions of the world and with different clinical practices.
- The low complication rate in egg donors could be diminished even further by the systematic implementation of protocols that use GnRH agonists for the induction of final oocyte maturation.
- An average of 230-mL blood loss should be considered normal during the first 24 h after an uncomplicated transvaginal oocyte retrieval.
- Primary patient-related risk factors for complications include young age, previous history of OHSS, PCOS, and exaggerated markers of high ovarian reserve such as high antral follicle count or elevated levels of AMH.

Short-Term Complications of Oocyte Donation

Oocyte donation has been practiced for more than two decades and currently has wide indications. This has led to an increased demand and a continuous growth of oocyte donation cycles worldwide [1]. Although serious short-term complications are expected to occur at a relatively low rate, it is universally recognized that ovarian stimulation and oocyte retrieval might involve significant inconvenience and discomfort, as well as risk of injury to the donor.

The short-term risk complications have a defined timeline which helps in their correct differential diagnosis. Significant intra-abdominal bleeding is detected during the first 24 h after oocyte retrieval and prompts close observation or surgical exploration. Smaller-scale, self-limiting intraperitoneal bleeding causes persistent lower abdominal pain during the first few days and might be detected with transvaginal ultrasound scanning. Other potential complications such as adnexal torsion or pelvic infections rarely occur during the first week after oocyte retrieval. In contrast, the symptoms of an early-onset ovarian hyperstimulation syndrome (OHSS) usually appear 3–9 days after hCG administration and can persist up to 10–12 days afterward. Despite their young age and potentially high ovarian response, donors appear to have lower probabilities of developing OHSS due to the absence of subsequent pregnancy. Nevertheless, cases involving oocyte donors with severe early-onset OHSS have been reported in the literature [2].

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Table 16.1 Short-term major complication rates in oocyte donor series

Author, year	Oocyte retrievals, *n*	OR-related complications, *n* (%)	Moderate/severe OHSS, *n* (%)	Total, *n* (%)
Sauer (2001) [2]	1,000	4 (0.4)	3 (0.3)	7 (0.7)
Bodri et al. (2008) [4]	4,052	17 (0.42)	22 (0.54)	39 (0.96)
Maxwell et al. (2008) [5]	886	5 (0.56)	1 (1.1)	6 (0.7)
Sahuquillo et al. (2011) [3]	972	3 (0.31)	–	3 (0.31)
All studies	6,910	29 (0.42)	26 (0.38)	55 (0.80)

Overall rates of short-term, serious complications reported in oocyte donation series published during the last decade are presented in Table 16.1. The four available retrospective studies published to date reported a total of almost 7,000 treatment cycles [2–5]. The overall rate of complications is less than 1 % and is remarkably consistent between studies which were conducted in different regions of the world (USA and Europe) with different clinical practices. Approximately half of these short-term complications (at a total rate of 0.42 %) were related to the oocyte retrieval procedure. This type of complication might be reduced by technological advances (such as changes in ovum-aspiration needle design) improving the overall safety of transvaginal ultrasound-guided oocyte retrieval [6].

The other half of short-term complications were OHSS-related (at at total rate of 0.38 %) which in turn can be directly influenced by each center's ovarian stimulation policy. Convincing evidence shows that in any oocyte donation program, OHSS rates are negatively related to the proportion of GnRH antagonist stimulated/GnRH agonist triggered cycles used [4]. This implies that the overall expected <1 % short-term complication rate could be at least diminished by a half (to the level of the residual oocyte retrieval risk) by the introduction and systematic implementation of protocols which use GnRH agonists for the induction of final oocyte maturation. From a good clinical practice viewpoint, the fact that there is a stimulation protocol which can significantly increase the safety and well-being of oocyte donors is of great importance. The rate of minor, short-term disturbances experienced by oocyte donors were evaluated in only two of the above-mentioned studies varied between 8.5 and 12.5 % [3, 5].

Complications Related to Oocyte Retrieval

Since the description of transvaginal ultrasound-guided oocyte retrieval, several observational studies conducted in non-donor IVF patients have evaluated the rate of complications related to this procedure. These studies have shown that the procedure can be considered as safe with rates of serious complications varying between 0.02 and 0.3 % for intra-abdominal bleeding, 0.01 and 0.6 % for pelvic infection, and 0.08 and 0.13 % for ovarian torsion. Cases of bowel, ureter, and pelvic vessel injuries were described as case reports [7–10].

Intra-Abdominal Bleeding

Minor vaginal bleeding that stops spontaneously or after local compression frequently can occur following oocyte retrieval in up to 8.6 % of the cases. It rarely requires other measures than local compression for <1 min; exceptionally vaginal tamponade or suture is applied [7]. On the other hand, intra-abdominal bleeding is a more serious complication which is usually caused by trauma of vessels of the ovarian capsule or bleeding from ruptured follicles. According to the estimation of Dessole et al., an average 230-mL blood loss can be considered normal during the first 24 h after noncomplicated transvaginal oocyte retrieval [11]. Retrospective, non-donor IVF patient series observed a rate of intraperitoneal bleeding or hemoperitoneum varying between 0.02 and 0.3 %, whereas no cases were observed in the prospective study of Ludwig et al. [7]. This complication was also described in case reports as a

consequence of coagulation disorders such as essential thrombocythemia [12] or factor XI deficiency [13]. The case report of Moayeri et al. [14]. described a patient with von Willebrand disease initially undetected by routine coagulation screening tests who presented a recurrent hemorrhage after oocyte retrieval. In oocyte donation series, intra-abdominal bleeding was one of the main oocyte retrieval-related complications at a rate of 0.1–0.35 % [2, 4].

Pelvic Infection

Whereas in the literature the rate of pelvic infections following oocyte retrieval in IVF patients was reported to be between 0.01 and 0.6 %, in existing oocyte donation series no pelvic infection was reported. This can probably be explained at least in part by the absence of important risk factors such as the history of pelvic inflammatory disease or hydrosalpinges and severe endometriosis among oocyte donors [15, 16].

Adnexal Torsion

Adnexal torsion is a very rare but serious complication related to ovarian stimulation. The presence of enlarged and at the same time mobile ovaries is recognized as a predisposing factor. Retrospective, non-donor IVF patient series report its incidence between 0.08 and 0.13 % in some cases involving the loss of the patient's ovary. In oocyte donor series, there are three reported cases series yielding a comparable low incidence of 0.02–0.3 % [4, 5, 17].

Other Rare Complications

Trauma to pelvic structures (bladder, ureter, bowel, large vessels, nerves) caused by the ovum-aspiration needle is a potentially severe complication of ultrasound-guided oocyte retrieval. To date, only case reports are published in the literature in non-donor IVF patients. Cases of perforated appendicitis were described by several authors. Several cases of ureter injury had been reported which often can represent a diagnostic challenge [7, 9, 10]. The much feared case of a large vessel injury was described in only one study with favourable resolution by conservative management. In comparison, a massive retroperitoneal hematoma following injury of a sacral vein and requiring surgical intervention was described by Azem et al. [18].

Anesthetic Complications

The rate of complications related to anesthesia in oocyte donors is low; a single case (0.1 %) of an adverse reaction to anesthetics was reported in the series of Sauer [2]. This might be explained by the fact that oocyte donors are usually young and healthy without any significant anesthesiological risk factors and are also thoroughly screened during their selection procedure.

Prevention and Management of Oocyte Retrieval-Related Complications

As a prerequisite for entering an oocyte donation program, a comprehensive donor screening and evaluation are recommended which apart from the exclusion of any infection or genetic risk also should include a complete screening for bleeding disorders. Additional tests might be needed in case of previous hemorrhagic complications. In order to reduce the risk of intra-abdominal bleeding during oocyte retrieval, an atraumatic technique is mandatory (avoiding repeated punctures of the vaginal wall, ovarian capsule, and follicles) [19]. A recent randomized clinical trial conducted in non-donor IVF patients evaluated the effect of reduced-size needle tip (17–20 G) on the overall pain experience after oocyte retrieval [6]. Although the degree of intra-abdominal bleeding was not evaluated, the authors have found significantly less vaginal bleeding, and patients also had significantly less pain. The risk of a pelvic infection following oocyte retrieval is low in oocyte donors, but it can be further reduced by

systematic screening and treatment of risk factors such as hydrosalpinges or undetected lower genital tract infections. The benefit of preventive antibiotics seems to be controversial, but they can be prescribed on an empirical basis after taking into account the potential side effects and the risk of an allergic reaction [16].

The postoperative observation following oocyte retrieval should be long enough (at least 2 h) to detect early alarm signs of short-term complications. Unstable blood pressure, tachycardia, or peritoneal irritation might be signs of significant intra-abdominal bleeding. Repeated transvaginal ultrasound scanning and serial hematocrit determinations are useful tools for confirming the suspicion. On the other hand, insufficient analgesia after oocyte retrieval might also cause similar symptoms such as hypotension, syncope, vagal reaction, nausea, and vomiting. After discharge from the unit, the ability to follow-up and access to a 24-h medical center for observation (in some cases for therapy of persistent severe pain) or eventual surgical intervention should be readily available. Significant intra-abdominal hemorrhage prompts a surgical—usually laparoscopic—intervention, and in almost all cases, conservative management is possible with no long-term consequences for the donor's health. In some cases, however, blood transfusion might be required [4]. In contrast, smaller, self-limiting intraperitoneal bleeding usually only needs observation during the first 24 h and outpatient follow-up afterward. For other less frequent complications (such as ovarian torsion or pelvic infection), the possibility of referring to a tertiary center, where diagnostic tools and surgical options are readily available, is recommended.

Ovarian Hyperstimulation Syndrome

Oocyte donors are only exposed to early-onset OHSS due to the absence of a subsequent pregnancy. This risk however should not be underestimated because donors are typically young women selected to have good ovarian reserve, and they frequently yield a large number of oocytes. It was estimated that donors who develop >20 follicles are exposed to a 15 % OHSS risk with the possibility of subsequent hospital admission [20]. The overall incidence of OHSS in the context of oocyte donation was addressed only by few studies. Sauer et al. reported a 1.5 % incidence of severe OHSS in a series of 400 long agonist donor cycles [21]. Despite high peak estradiol levels, no severe complications occurred, and hospitalization was not required. This relatively favorable course is due to the absence of a subsequent pregnancy, since unlike IVF patients, egg donors are exposed only to hCG-induced early OHSS. A more recent large randomized clinical trial which evaluated three different gonadotropin regimens (with a long agonist stimulation protocol and hCG trigger) including >1,000 oocyte donors reported a 5–7 % mild/moderate OHSS rate despite liberal cycle cancellation policy [22]. These studies highlight the fact that if effective preventive OHSS measures are not implemented, moderate/severe OHSS is expected to occur in oocyte donors in varying degrees depending on the type of stimulation protocol and triggering agent used.

Prevention of OHSS in Oocyte Donors

Several methods have been proposed for the prevention of clinically significant moderate/severe OHSS in non-donor patients undergoing ovarian stimulation for in vitro fertilization treatment (recently reviewed in Humaidan et al. 2010) [23]. Most of these can be easily applied in oocyte donors because any potential deleterious effect on the luteal phase can be disregarded. A didactical classification of different prevention strategies stratified by the time of their application (before stimulation, during stimulation, and after oocyte retrieval) is presented in Fig. 16.1 [24].

Identifying Risk Factors

Primary patient-related risk factors which are identifiable before starting ovarian stimulation include young age, previous history of high response or OHSS, PCOS characteristics, and

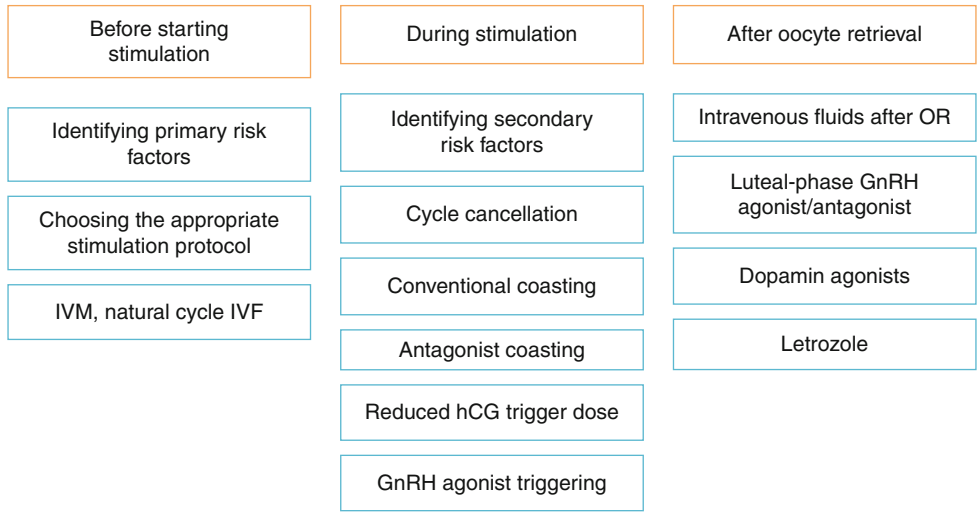

Fig. 16.1 OHSS prevention methods (Modified after Aboulghar (2009); Reprinted from Mohamed Aboulghar [24]. Copyright (2009), with permission from Elsevier)

markers of high ovarian reserve such as elevated antral follicle count (AFC) and serum anti-Mullerian hormone levels (AMH). In order to ensure high success rates, most oocyte donation programs have established donor age limits (usually <35 years old) although in some cases exceptions are made especially with "directed" known oocyte donation. The course of the donor's previous stimulation cycle is extremely useful but is not available for first-time donors. Oocyte donors with explicit PCOS syndrome are not ideal candidates, and their ovarian stimulation might be extremely difficult to manage with frequent cancellations for low response and longer duration of stimulation with an elevated OHSS risk. Therefore, it is questionable whether PCOS donors should be included at all in oocyte donation programs.

A recent large-scale European study evaluating >1,000 cycles stimulated with a long agonist protocol concluded that AFC was a useful, simple, and noninvasive tool for donor selection [25]. The authors have found that donors with AFC < 10 had a significantly higher cancellation rate for low response and fewer retrieved oocytes, but recipient pregnancy rates were not adversely affected. In contrast, cancellation rates for OHSS risk increased proportionally to higher AFC from 0.9 to 14 %. Similarly, AMH emerged as a promising serum marker of normal ovarian response or of elevated OHSS risk [26]. In the context of oocyte donation, recent studies have shown that AMH has a good correlation with the number of retrieved eggs and the need to decrease gonadotropin dose in order to avoid OHSS [27, 28]. A number of ovarian stimulation-related secondary risk factors exist such as follicular count on hCG triggering day, peak estradiol levels, and the number of retrieved oocytes, but they are of limited predictive value [29]. This is especially true for GnRH antagonist-based protocols where it was shown that compared to the follicular count on the day of hCG trigger, the peak estradiol level is less reliable at identifying OHSS-risk patients [30].

Personalizing Oocyte Donors' Stimulation Protocols

The choice of the most appropriate donor stimulation protocol is of paramount importance not only for optimizing ovarian response and to ensure high recipient success rates but also for establishing safe and simple stimulation for oocyte donors.

By extension from protocols used in non-donor IVF patients over many years, the classical long agonist regimen of stimulation was successfully applied to oocyte donors. It has offered the advantage of easy cycle programming which was

Table 16.2 Advantages and drawbacks of different donor stimulation protocols

Protocol type/triggering agent	Advantages	Drawbacks
Long agonist/hCG	Depot agonist	*OHSS risk*
		Longer duration
		Side effects
Short agonist/hCG	Less gonadotropin requirement (flare-up)	*OHSS risk*
GnRH antagonist/GnRH agonist	*No OHSS*	Higher cost
	Shorter duration	
	Depot antagonist	
No GnRH analogue or extended CC/GnRH agonist	*No OHSS*	LH surge?
	Shorter duration	Oocyte quality?
	Less expensive	

particularly important for donor-recipient synchronization [1]. Depot GnRH agonist preparations were also successfully used with this protocol offering the possibility of reducing the number of injections administered to the donor [31]. Although the short GnRH agonist protocol was found to be suboptimal in non-donor IVF patients, it has yielded good outcome when applied to oocyte donors [32, 33]. It has the advantage of shorter duration and of reducing the overall gonadotropin requirement due to the agonist's flare-up effect. On the other hand, it requires obligatory hCG triggering which carries an inherent OHSS risk [4]. Recently, a GnRH analogue-free stimulation protocol using extended follicular-phase clomiphene citrate (CC) administration was evaluated in a pilot study [34]. This innovative protocol takes advantage of the CC's ability of suppressing premature LH surges. Its main advantage lies in its cost-effectiveness and the possibility of oral administration, but recipient success rates still have to be evaluated in larger trial. The advantages and drawbacks of different donor stimulation protocols are summarized in Table 16.2.

Following their introduction into the clinical practice in the early 1990s, GnRH antagonists were also rapidly applied to stimulation of oocyte donors. Apart from the well-known advantages which contribute to donor commodity (shorter duration of stimulation and decreased gonadotropin consumption), the application of GnRH antagonists has also provided the possibility of substituting hCG with a GnRH agonist as the triggering agent for final oocyte maturation. A recent meta-analysis with a total sample of 1,024 donors summarized the findings of 8 randomized clinical trials which compared the use of different GnRH analogues for downregulation in oocyte donation [35]. The primary outcome measure was the rate of ongoing recipient pregnancies per randomized donor, and secondary outcome measures were the number of retrieved oocytes, the duration of stimulation, gonadotropin consumption, and OHSS incidence per randomized donor. As a main finding, this meta-analysis has found no significant difference in the number of retrieved oocytes (−0.6 COC, 95 % CI −2.26 to +1.07) or recipient ongoing pregnancy rates (RR 1.15, 95 % CI 0.97–1.36) between the two different protocols (Figs. 16.2 and 16.3). Moreover, with the GnRH antagonist protocol, stimulation duration was significantly lower (−0.9 days, 95 % CI −1.61 to −0.20), whereas gonadotropin consumption (−264 IU less, 95 % CI −682 to 154) and OHSS incidence (RR 0.62, 95 % CI 0.18–2.15) was also lower even if statistical significance was not reached due to sample size limitations. In practical terms, this means that currently available evidence suggests that in oocyte donors, GnRH antagonist-based protocols are as efficient as those based on GnRH agonists, but they are considerably safer (see section on "GnRH Agonist Triggering") and also have potential advantages for treatment simplification (possibility of using a single-dose GnRH antagonist protocol).

IVM/Natural Cycle IVF

In vitro maturation (IVM) has been recently evaluated in a prospective cohort study of 12 oocyte donors with PCOS or polycystic ovarian morphology [36]. After collecting an average 12.8 germinal-vesicle-stage oocytes per donor from

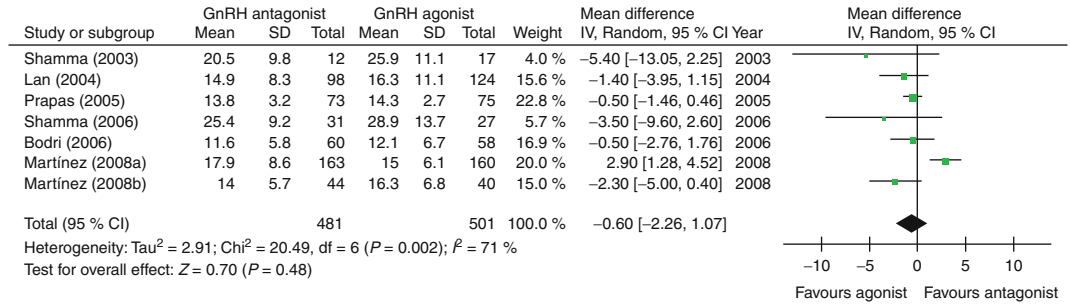

Fig. 16.2 Weighted mean difference for the number of retrieved oocytes (Reprinted from Bodri et al. [35]. Copyright (2011), with permission from Elsevier)

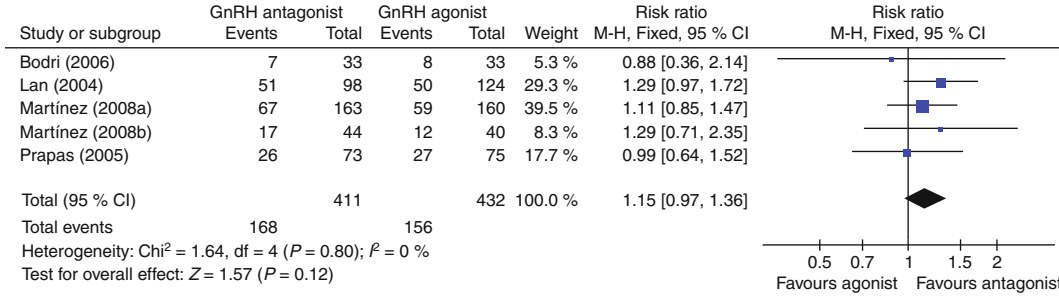

Fig. 16.3 Risk ratio for recipient ongoing pregnancy rate per randomized donor (studies with 1:1 donor-recipient ratio) (Bodri et al. [35])

unstimulated ovaries, comparable pregnancy rates (30 % live birth rates per cycle) were obtained compared to conventional donor IVF. Although this approach completely eliminates the risk of OHSS in the donor, the expected lower implantation rate of IVM embryos (18.2 %) hampers success rate in the recipient's cycle. Similarly, a single case report proposed the modified natural cycle IVF protocol in a 36-year-old donor by obtaining a healthy live birth in the recipient following single embryo transfer [37]. Although this approach eliminates any potential OHSS risk, it is hampered by the high risk of cycle cancellation and the failure of retrieving any mature egg from the donor.

Cycle Cancellation

Cycle cancellation by withholding hCG trigger practically eliminates the risk of any clinically significant OHSS but with the great drawback of also cancelling the recipient's cycle. Because spontaneous ovulation could still occur, cancelled donors should use efficient and reliable barrier contraception methods to avoid the risk of any unwanted pregnancy and subsequent late-onset OHSS.

Coasting

Coasting efficiently reduces the incidence and severity of OHSS both in oocyte donors and in non-donor IVF patients. It must be emphasized however that OHSS is not completely prevented and that prolonged coasting >4 days compromises oocyte quality and subsequent embryonic implantation rates [38, 39]. Recent data shows that in oocyte donor cycles where GnRH agonist trigger was used, elevated peak estradiol can be tolerated and coasting becomes unnecessary [40, 41].

Antagonist Coasting

In a randomized clinical trial of high OHSS-risk non-donor IVF patients stimulated with a long

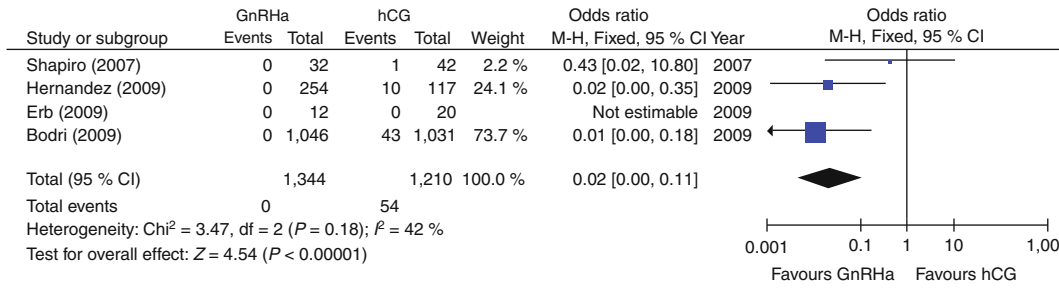

Fig. 16.4 OHSS incidence in oocyte donors after triggering with GnRHa versus hCG: retrospective cohort studies

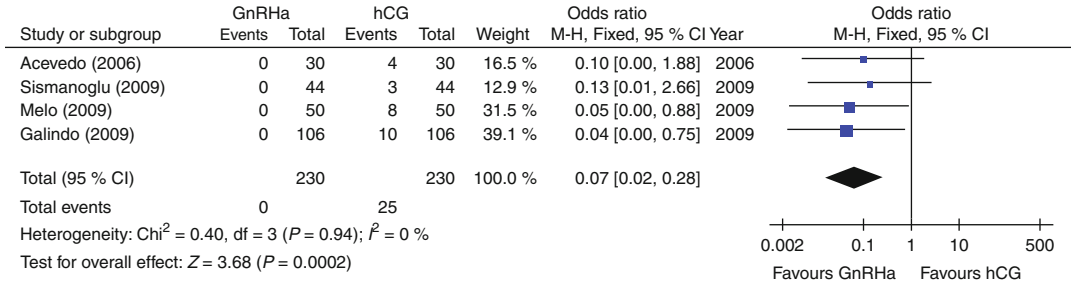

Fig. 16.5 OHSS incidence in oocyte donors after triggering with GnRHa versus hCG: randomized clinical trials

agonist protocol GnRH, antagonist coasting has resulted in more rapid estradiol decline, shorter coasting duration, and a higher number of good quality embryos compared to conventional coasting [42]. Although this method is readily applicable in oocyte donors stimulated with the agonist protocol, the exact degree of OHSS reduction or any potential deleterious effect on oocyte quality has yet to be evaluated in a larger trial.

Reduced hCG Dose

A recent systematic review that included a limited number of clinical trials concluded that in the high-risk non-donor IVF patient population, the incidence of OHSS was not reduced even with lower dose of urinary hCG (5,000 versus 10,000 IU) [43].

GnRH Agonist Triggering: Achieving an OHSS-Free Stimulation Protocol

Several retrospective cohort studies [40, 44–46] evaluated the outcome of oocyte donation cycles after the newly available GnRH agonist trigger. Although they varied largely in size (ranging from 32 to 2,077 cycles), all of them were concordant in finding no significant differences in key outcome variables such as the proportion of mature oocytes, fertilization rates, and subsequent recipient implantation and pregnancy rates. More importantly, no moderate/severe OHSS cases at all were detected after agonist trigger, whereas in the hCG group, its incidence reached 4.5 %. These retrospective series had an inherent bias between the examined treatment groups because agonist triggering was preferentially applied to cycles with a much higher ovarian response (Fig. 16.4). A number of methodologically more appropriate randomized clinical trials [47–50] have evaluated the same variables as retrospective series. They included a total number of oocyte donors ranging from 60 to 212 per study. No significant difference was observed in the number of retrieved oocytes (total and mature), fertilization rates, embryo quality, and pregnancy rates in corresponding recipients. OHSS cases only occurred in the hCG arm (between 7 and 16 %) (Fig. 16.5). This means that calculated OHSS reduction rates

after GnRH agonist triggering are especially high (OR 0.02–0.07) unparalleled by any other OHSS prevention method. A recent observational follow-up study performed in 102 high OHSS-risk oocyte donors examining biochemical and ultrasound signs of early-onset OHSS has even suggested the complete elimination of the syndrome (absence of hemoconcentration or ascites) after agonist triggering [41]. Moreover, data from both retrospective cohort studies and controlled clinical trials suggests that GnRH agonist triggering does not adversely affect the quality of retrieved oocytes or the implantation potential of resulting embryos. These findings suggests that GnRH agonist triggering is currently one of the most efficient and powerful ways of preventing OHSS in oocyte donors. However, excessive stimulation is still not recommended due to more discomfort and a higher risk of oocyte retrieval-related complications.

Intravenous Fluids

Although intravenous albumin administration for preventing the development of severe OHSS was first suggested almost two decades ago, clinical studies on its effectiveness still show conflicting results. A recent meta-analysis has concluded that currently there is limited evidence of the benefit of intravenous albumin at the time of oocyte retrieval. In contrast, hydroxyethyl starch markedly reduced (OR 0.12, 95 % CI 0.04–0.40) severe OHSS incidence in non-donor IVF patients [51].

Luteal-Phase GnRH Analogues

A recent, pilot study performed in 28 oocyte donors evaluated the luteal-phase administration of GnRH analogues (either GnRH agonists or antagonists) during 9 days following oocyte retrieval [52]. Although the only significant finding was a reduction in the amount of free pelvic fluid measured in the Douglas pouch, the authors suggested that both analogues are capable of inducing a pronounced luteolysis evidenced by a decrease in serum VEGF levels. In addition, this strategy has also been used in non-donor IVF patients undergoing freezing of all embryos or fresh embryo transfer [53].

Dopamine Agonists

Dopamine agonists used after hCG administration were recently proposed as a prophylactic treatment for OHSS prevention. A recent meta-analysis pooled the findings of four randomized clinical trials [54]. Although there was a significant reduction in overall OHSS incidence, it was only observed in the early-onset (OR 0.10, 95 % CI 0.03–0.33) and moderate OHSS (OR 0.38, 95 % CI 0.22–0.68) groups. A pilot trial successfully applied this strategy in high-risk oocyte donors achieving a significant albeit not complete reduction in moderate OHSS rates (from 44 to 20 %) [55].

Aromatase Inhibitors

Letrozole—an efficient oral aromatase enzyme inhibitor—was administered to oocyte donors during their luteal phase in two recent pilot studies causing a rapid, dramatic decrease in serum estradiol levels [56, 57]. Although OHSS incidence was not evaluated in these studies, it was suggested that letrozole could be used as an adjuvant to reduce supraphysiological estradiol levels in high-responder IVF patients, diminishing the risk of potential thromboembolic complications.

General Recommendations

Among the currently available preventive methods, only GnRH agonist triggering comes close to an almost complete (if not 100 %) prevention of early-onset OHSS. Antagonist coasting, luteal-phase administration of GnRH analogues, and/or dopamine agonists seem to be promising pharmacological strategies. Other methods have either limited or no efficiency (such as simple coasting, reduced hCG dose, intravenous albumin) or their effect has not been tested yet in sufficiently

Table 16.3 OHSS prevention methods in oocyte donors

OHSS prevention method	Advantages	Drawbacks
In vitro maturation	Complete prevention	Low embryo implantation rate
Cycle cancellation	Complete prevention	Cancelled recipient cycle, expensive
Coasting	Cheap	Incomplete prevention, compromised oocyte quality if prolonged >4 days
Antagonist coasting	Can be used in agonist protocol	Efficiency is not yet proven, expensive
Reduced hCG dose	Cheap	Inefficient
GnRH agonist triggering	Complete prevention	Only applicable in GnRH antagonist protocols
Intravenous albumin	–	Limited efficiency, potential side effects
Luteal-phase GnRH analogues	Can be used in agonist protocol	Efficiency is not yet proven, expensive
Dopamine agonists	Oral administration	Incomplete prevention, potential side effects
Aromatase inhibitors	Oral administration	Efficiency is not yet proven, expensive

large-sized clinical trials (IVM, HES, aromatase inhibitors) (Table 16.3).

Hence, in the context of oocyte donation, the first choice option is GnRH antagonist stimulation protocol coupled with GnRH agonist triggering. It is easily applicable in all donors independent of their ovarian response (both high and normoresponders), and according to available evidence, it does not adversely affect recipient cycle outcome. The application of GnRH agonist triggering has also important practical consequences. Given the fact that OHSS risk is greatly diminished or even eliminated, cycle monitoring could become less stringent (i.e., less need for repetitive estradiol assays or ultrasound monitoring), and in the future, stimulation surveillance could probably be simplified even further. In addition, after GnRH agonist triggering, cycle cancellation, or co-interventions, reducing OHSS risk (such as coasting) may become entirely unnecessary [40]. All these positive effects would allow a reduction in the workload of medical teams and greatly simplify the everyday management of oocyte donation cycles. Additional benefits include the shorter duration of the unsupported luteal phase (4–6 days), reduced ovarian volume, and diminished abdominal distension which altogether might substantially decrease the burden of treatment for oocyte donors [58, 59].

If for some well-defined reason (such as suboptimal outcome in a previous GnRH antagonist-treated cycle) choosing an antagonist protocol is not an option, a GnRH agonist protocol (long or short) with reduced FSH dose and mandatory hCG triggering might be recommended. Nonetheless, in high-risk patients with high follicular counts and elevated peak estradiol levels, antagonist coasting and/or luteal-phase GnRH analogue/dopamine agonist administration is also recommended.

Diagnosis and Management of OHSS in Oocyte Donors

In a recent review, a new practical and clinically oriented OHSS grading system was proposed based on more objective measurements compared to those that were previously established [23] (Table 16.4). The authors concluded that subjective OHSS symptoms show large individual variations and cannot be assigned to a particular OHSS grade. In contrast, transvaginal ultrasound is particularly useful in determining the extent of fluid shift into the pelvis and abdomen [41, 55]. Whereas mild OHSS can be accompanied by the presence of a small amount of liquid in the pouch of Douglas, the moderate form is characterized by a larger periuterine collection. Severe OHSS is characterized by observing large amount of ascites between the intestinal loops. Additionally, hemoconcentration (hct > 45 %) remains a very useful objective marker in detecting clinically significant moderate/severe OHSS which needs close attention and might require hospitalization.

Table 16.4 Proposed new clinical grading system for OHSS

	Mild	Moderate	Severe
Objective criteria			
Fluid in Douglas pouch	✓	✓	✓
Fluid around uterus (major pelvis)		✓	✓
Fluid around intestinal loops			✓
Hematocrit >45 %		✓[a]	✓
White blood cells >15,000/mm		±[a]	✓
Low urine output <600 mL/24 h		±[a]	✓
Creatinine >1.5 mg/dL		±[a]	±
Elevated transaminases		±[a]	±
Clotting disorder			±[b]
Pleural effusion			±[b]
Subjective criteria			
Abdominal distention	✓	✓	✓
Pelvic discomfort	✓	✓	✓
Breathing disorder	±[c]	±[c]	✓
Acute pain	±[c]	±[c]	±[c]
Nausea/vomiting	±	±	±
Ovarian enlargement	✓	✓	✓
Pregnancy occurrence	±	±	✓

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Note: The ± sign means may or may not be present
[a]If two of these are present, consider hospitalization
[b]If present, consider intensive care
[c]If present, consider hospitalization

As mentioned before, oocyte donors are only exposed to early-onset OHSS, and due to non-conception, the spontaneous resolution of the syndrome is expected after menstruation occurs. First symptoms usually appear 3–9 days after hCG administration but can persist up to 10–12 days afterward. This relatively benign outcome means that oocyte donors can usually be managed on an outpatient basis [60]. Nonetheless, if signs of potentially life-threatening severe OHSS are detected, such as oliguria, pleural effusion, or clotting abnormalities, hospitalization with more aggressive treatment options (thrombophylaxis, culdocentesis, and intensive care) are recommended [23].

In relation to the recently emerged option of substituting the hCG trigger, there is some debate in the literature as to whether clinically significant early-onset OHSS will occur at all after GnRH agonist triggering [61, 62]. In fact, following agonist trigger, a massive, irreversible luteolysis can be seen, and menstruation usually occurs 4–6 days after oocyte retrieval. Therefore, it is more likely that any early alarming symptoms (e.g., abdominal distension, pain, nausea, vomiting) occurring during this relatively short time period are likely related to ovarian retrieval-related complications rather than to "real" OHSS or at the most represents some kind of "aborted" clinical picture of moderate OHSS [41].

Potential Long-Term Consequences of Oocyte Donation

The link between ovulation-stimulation drugs and the risk of future reproductive cancers (e.g., ovary, breast, and endometrium) has been extensively studied, but any potential relationships are still poorly understood. Although most studies failed to demonstrate a "cause and effect" relationship and were somewhat reassuring, it seems that among infertile patients there may be an increased risk for ovarian cancer among nulliparous

women, particularly those patients with extensive pelvic problems related to endometriosis and chronic PID. Such patients also appear at risk for developing *borderline* ovarian tumors [63]. However, infertility itself is a strong inherent confounding factor which might only be controlled for by examining data on cancer incidence of fertile oocyte donors. Information is extremely scarce on the risk of tumors in women who underwent ovarian stimulation for oocyte donation. To date, only three case reports have been published, reporting the occurrence of colon and breast cancers a few years after individuals had participated in oocyte donation [64].

Similar to the debate regarding cancer risk, there is very limited data on the risk of developing future infertility in former oocyte donors. In a recent European study, 194 former egg donors were questioned regarding their fertility an average of 3.7 years after their stimulation cycle. The authors found that most women (95 %) who wanted to have children conceived spontaneously within a period of 12–18 months, suggesting that the donation procedure did not affect their subsequent fecundity [17]. Another retrospective study evaluated successive cycle outcomes in consecutive oocyte donation attempts up to nine cycles and concluded that ovarian response was maintained throughout [65]. These findings suggest that a stimulation-related decrease in ovarian reserve is unlikely.

With relation to potential short- and long-term consequences and also to reduce the risk of consanguinity among donor-conceived offspring, it is reasonable to set limits for oocyte stimulation cycles performed by the same donor. Currently, there are but few well-defined guidelines which are specifically related to oocyte donors. The American Society for Reproductive Medicine issued a practice guideline focused on repetitive oocyte donation in order to limit health risks to the oocyte donor [66]. They suggested that limiting the donor's participation to six stimulated cycles would be reasonable. In fact, a similar European guideline was also issued by the regional Health Authority in Barcelona, Spain, which fixed similar limit of oocyte retrievals per donor. Both in the USA and in Europe, there is an increasing awareness of possible short-term complications as well as for the need of long-term follow-up of oocyte donors [64, 67]. Hopefully, in the near future, governmental agencies and professional societies will start to work together in establishing compulsory donor registries which will permit conducting large-scale follow-up studies and could help to answer some of the remaining open questions about the long-term consequences of oocyte donation.

Editor's Commentary

We now know, and most ART practitioners generally believe, that egg donation is a reasonable risk activity and may be offered to healthy women who wish to participate. It certainly was not so obvious to us in the early 1980s, and in fact, the risks that were assumed by the human subjects agreeing to perform embryo donation at the Harbor-UCLA Medical Center would be considered unacceptable by today's standards. The first donors were only paid $250 to be inseminated with unprocessed ejaculated semen and then underwent a series of uterine lavages in hope of recovering the in vivo fertilized embryo! It is really incredible that no one was seriously injured in the initial efforts.

Comparatively, today's donors are much better off, even though they now typically undergo anesthesia in order to recover their eggs. The risks are largely no different than those faced by any patient undertaking ovarian hyperstimulation and egg retrieval for autologous use. The obvious issue thus becomes whether or not it is ethical to perform a procedure upon a young woman that carries a definable risk of injury for no known personal benefit other than payment for services rendered. This remains a contentious and hotly debated subject which has been present since the very first case and continues unabated today.

Daniel Bodri, M.D., provides a nice review of the published literature spanning three decades and multiple continents and defines the low risk of complications noted

in egg donors. More importantly, he summarizes several approaches which promise to further lower the risk. OHSS remains the biggest worry, and advances in screening, such as obtaining precycle serum AMH levels, and in the clinical practice, using GnRH triggers instead of hCG, offer hope for dramatically lowering the complication rate. Even so, we must not forget that the health and well-being of our egg donors must be as vigilantly safeguarded as our regular patients. It is therefore important to openly share and discuss all complications, both actual and theoretical, with these young women prior to their participation. I prefer to lose an occasional potential donor to fear and anxiety after hearing the procedural details than to have any one of them look back with regret and feel that they were taken advantage of by the medical system.

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Part III

Office Practice Management

The Role of the Donor Oocyte Nurse Coordinator

17

Karen R. Hammond

Key Points

- The nurse coordinator often has more patient contact and spends more time with both the oocyte donor and the recipient than any other individual in the practice.
- Coordinators facilitate the matching process and should communicate honest and realistic expectations with respect to donor characteristics, wait times, and success rates.
- In collaboration with the physicians, the coordinator directly reports the progress of the donor's cycle to the recipient and to the medical team at large so as to avoid unintentional scheduling conflicts.
- Accurate recordkeeping is fundamental to all aspects of health-care delivery and must be in compliance with local, state, and federal standards.

Coordinate – (*verb*) – \kō-ȯr-də-nāt\
To bring into a common action, movement, or condition; harmonize; to be or become coordinate especially so as to act together in a smooth concerted way

Merriam-Webster Dictionary

Perhaps in no other field of medicine is the interaction and coordination of the health-care team more important than in assisted reproduction, in general, and third-party reproduction, in particular. The nurse plays a pivotal role in the functioning of the entire team. As the primary contact for oocyte donors and their recipients, excellent communication, organizational, and clinical skills are essential.

The State Board of Nursing for each state in the USA establishes and controls the scope of nursing practice. The nurse is ultimately responsible for awareness and compliance with practice regulations in the state. This information is readily available by contacting the State Board of Nursing and for most states can also be found on their respective websites. Regulations not only vary between states, but also educational preparation and certification standards may differ among locales.

The nurse coordinator often has more patient contact with both the oocyte donor and the oocyte recipient than any other individual in the practice. They commonly function as the primary educator, the bridge for communication, and the clinical coordinator. Often the nurse sets the tone for patient perceptions and clinical practices and is responsible for the day-to-day running of the program. The coordinator can positively impact the

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experience of the donor and the recipient by enhancing an understanding of the risks, benefits, and overall process. Furthermore, if these activities are ignored or performed poorly, programs will suffer negative consequences.

Very little has been published with respect to the role of the nurse coordinator in oocyte donation. Of course, each individual assisted reproduction center will also have specific duties for the nurse coordinator and other nurses in the oocyte donation program unique to their particular locale. The purpose of this chapter is to provide an overview of the role of the nurse coordinator and detail the responsibilities assumed by this individual in an effort to optimize efficiency, success, and recipient/donor satisfaction in this area of practice.

Program Development

The percentage of assisted reproductive technology programs that offer oocyte donation in the USA has increased steadily in the last decade, from 84 % in 1999 to 92 % in 2008, while the number of fresh embryo transfers has almost doubled during the same time period, from 5,844 in 1999 to 10,151 in 2009 [1]. New programs continue to be established, and existing programs continue to evolve.

In developing a new program, the coordinator has a blank canvas on which to work. Practice decisions regarding everything from donor recruitment (including agency versus program-recruited donors, known versus anonymous), screening, selection, and information sharing to recipient recruitment, synchronization, and stimulation protocols must be established. Standard operating procedures (SOP) and policies must be written and implemented from which practice decisions are to be made. The coordinator is often responsible for writing much of the SOP and for maintaining the manuals, as well as initiating their periodic review and updates with the program director.

In an established donor program, the nurse coordinator is also responsible for maintaining the integrity and functionality of the program. Constant attention must be paid to local, state, and federal regulations and keeping an active vigil for modifications or revisions in the professional guidelines. As the program evolves and develops over time, policies and procedures, forms, and protocols must be maintained and updated. The coordinator should preserve these completed documents, as well as other pertinent donor records, within a system of secure archives.

Donor Recruitment

An ample donor pool is essential for a successful donor oocyte program to exist and thrive. Donors may be recruited directly by the program, accessed through donor agencies, or identified by recipients from friends or family members. In a recent survey of donor oocyte programs, the primary egg donor source was program-recruited in 77 %, agency-recruited in 18 %, and known donors in 5 % [2]. Each of these donor sources has intrinsic advantages and disadvantages. With each of the various methods of donor recruitment, medical and psychosocial issues, including whether anonymity will be maintained, must be addressed. Nevertheless, the donor is still considered to be a patient and, as such, should be afforded all appropriate rights and protections [3].

Program-Recruited Donors

Many programs elect to recruit and screen their own donors without the assistance of an agency. One advantage enjoyed by program-recruited donors relates to the development of an early relationship with the donor team. Typically, the coordinator plays a pivotal role in recruitment beginning with the initial advertisement. When a prospective donor contacts the office, the coordinator is generally the one who takes her call, provides an overview of the program, and performs the initial intake interview. The coordinator will then guide the patient through the screening processes, and this close working relationship will continue through the match and actual donation cycle. This progression of activity is not always

as straightforward or easy as it seems. In a 1998 publication by Lindheim and Sauer, the attrition rate from initial response to the advertisement to the actual acceptance of a prospective donor was more than 75 % [4]. Similarly, Gorrill and colleagues found an attrition rate of 82 % from initial response to donor acceptance that resulted in a cost per accepted donor of almost US$1,900 [5]. In short, donor recruitment is both time-consuming and expensive.

Agency-Recruited Donors

In an effort to minimize the program's time and expense related to donor recruitment, some programs prefer to utilize the services of agencies that specialize in donor procurement. Donor agencies often advertise that they possess a more extensive pool of available donors. This additional availability may be especially attractive for recipients who have particular racial, ethnic, cultural, or religious needs or for those patients who have other very specific requests, such as unique phenotypic characteristics, talents, or educational backgrounds. In general, while the ART program may incur lower expenses related to the recruitment of egg donors, the recipient patient will often incur higher fees when using an agency compared to donors provided in-house or self-selected.

Known Donors

Known donors are yet another source of oocytes. In this scenario, the recipient provides a suitable woman who is willing to donate her oocytes. Known donors are generally family members or close friends. Special attention should be paid to assure that the donor is independently willing to donate and that qualifications are not distorted in a manner in which the donor's health and recipient's chance for pregnancy would be compromised. Policies should be established and adhered to with respect to known donor qualifications, including whether the requirements should be the same as recruited donors, such as age minimum and maximum, parity, and body mass index. Unique psychosocial and legal issues must also be addressed [6].

Matching a Donor with a Recipient

Programs vary widely with respect to the process of donor matching to a recipient. Variations relate to the number of available donors, practice size, and program preferences. In general, donors are matched with respect to race, phenotypic characteristics, and other personal requests made by the recipient. Most programs ask recipients for a "wish list" of characteristics that they would hope to see expressed by their donor. Agencies and larger programs may have a catalog or list of potential donors from which to choose. Smaller programs may simply offer the recipient a choice of one or more currently available donors. Irrespective of the type of matching process, a protocol should be established, written, maintained, and periodically updated. The coordinator facilitates the matching process for the recipient and the program and should communicate honest and realistic expectations with respect to desired donor characteristics and wait times. Nonjudgmental discussion and feedback with the recipient can be very supportive.

Education

Patient education is among the most important and time-consuming roles of the coordinator. Accurate medication administration, precise scheduling of visits and procedures, and communicating clear instructions are critical to the success of a donor oocyte program and crucial to gaining patient satisfaction. The details and intricacies of the process may at times lead to information overload for both the donor and recipient, yet each has a different perspective and motivation for successful compliance. The mere sight of all of the medications and the thought of all of the appointments can be overwhelming to both. Nevertheless, each must be educated on the importance of following all instructions exactly to ensure synchronization is maintained.

Donor

Oocyte donors are generally young, healthy women who are gracious, altruistic, and wish to provide an amazing act of generosity. However, these women also lead busy lives with work or school or family responsibilities. Donors need to be assisted in incorporating the details of the donation cycle into their lives in order to minimize the risk of omission or error and to ensure compliance.

Most donors have never given a medication injection, much less self-administered an injection. Injection administration can be a daunting task. Written instructions, DVDs, web links, and return demonstrations may all be helpful adjuncts to teaching. As with all patients, some donors learn better with one instruction method than another. The donor's comfort level needs to be ascertained early on in the process and the instructions reinforced as needed. Contact information for office personnel who are able to assist the donor needing clarification on instructions should be provided for easy access at any time of the day, night, weekend, or holiday. After all, the recipient's entire treatment cycle is at stake, and services occur 24/7 regardless of the calendar.

Recipient

Many donor oocyte recipients have a long history of infertility and are often quite familiar with medications, self-injection, and attention to specific details associated with infertility treatment. On the other hand, some patients may present with other medical conditions (such as ovarian failure or significantly advanced reproductive age) that lead directly to in vitro fertilization with donor oocytes. Recipient medications are different from those used during standard in vitro fertilization therapy. For instance, instead of gonadotropins and hCG, recipients now take estrogen and progesterone. Therefore, instead of primarily subcutaneous injections, recipient medications are mostly administered orally, transdermally, intramuscularly, or vaginally. Some programs utilize practice or "prep mock" cycles, in which the recipient takes the medications and undergoes monitoring to insure correct administration and an adequate endometrial response. A mock cycle may permit adjustments in the dosages and routes of administration, as well as increase the recipient's comfort with the medication protocol as they gain familiarity with the drugs.

Staff

It has long been said that the best way to make yourself look good is to surround yourself with good people. This old adage certainly holds true for staff and personnel involved in the care of oocyte donors and recipients. The team approach to third-party reproduction has been utilized with success for many years. Everyone from receptionists, appointment secretaries, medical assistants, nurses, embryologists, and physicians comprises the team. Each member should be aware of his/her role in the program, as well as the roles of other members of the team [7]. The better educated and informed the staff, the more smoothly patient care will flow.

Donor Satisfaction

Since the initial costs of donor recruitment and donor education are high, programs benefit from donor retention. It has been shown that pregnancy rates are maintained over multiple sequential donations [8]. The American Society for Reproductive Medicine (ASRM) has recommended that the number of stimulated per donor donation cycles be limited to approximately six cycles and be further limited to no more than 25 children per population of 800,000. These guidelines are intended to reduce the health risks to the oocyte donor, as well as to minimize the likelihood of inadvertent consanguinity in the subsequent generation [9].

Donor satisfaction may be achieved in a variety of ways. After all, the donor is performing a generous act of altruism, and she should be treated with dignity and respect and subjected to as little inconvenience as possible. Appointments

should be scheduled at a convenient time with minimal wait. Some programs offer separate entrances and early or late appointments to accommodate the donor's personal schedule. Expressions of appreciation for their kindness also go a long way. Remember, a donor who has a worthwhile experience is much more likely to refer her friends for donation too. Donors can serve as a good source of recruitment when their experience has been a positive one.

Clinical Roles

The Food and Drug Administration (FDA) regulations [10] and the ASRM guidelines [11] provide the framework for donor testing, screening, and eligibility in the USA. The donor eligibility rule became effective on May 25, 2005 [9]. Although the ultimate responsibility remains with the program director, the coordinator generally orders the testing and performs the screening in compliance with FDA regulations and ASRM guidelines. The coordinator may also provide the required documentation necessary to present at the time of practice audits. To assist in this process, the Society for Assisted Reproductive Technologies (SART) has developed a uniform donor application form [12], a female donor physical examination form [13], a donor medical history interview questionnaire [14], and an interview key for the donor eligibility evaluator [15], all of which are available for download by SART members on the SART website, www.sart.org.

Synchronization

The oocyte donor and recipient cycles must be synchronized to achieve a successful pregnancy. While the length of recipient estrogen administration can be variable and can be prolonged after sufficient endometrial preparation has been achieved, donor medication schedules are much less flexible. In general, recipients begin estrogen administration about a week before ovarian stimulation begins in the donor. The coordinator must possess a keen understanding of reproductive physiology to ensure appropriate donor/recipient cycle synchronization has occurred and be able to sufficiently communicate the importance and rationale for this treatment scheme to the patients. Failed synchronization may result in the obligate cryopreservation of all embryos or cycle cancellation.

Monitoring

Many coordinators and nurses perform ultrasound scans for oocyte donors and recipients. In a position statement, ASRM supports nurses' performing limited pelvic ultrasound examinations, including for follicle size and number and endometrial thickness and pattern, after specific training and with ongoing supervision [16]. The additional clinical contact facilitates the development of a trusting relationship and is also time efficient. Venipuncture for laboratory testing may also be incorporated into the coordinator's role. However, all of these roles will vary among programs.

Once the monitoring results become available, the coordinator is responsible for discussing them with the physician to determine the next step in the treatment plan. In some programs, monitoring may be performed off-site. While convenient for the recipient or donor, differences in scheduling and time zones may complicate the retrieval of the results from the monitoring center. The treatment plan is, in turn, discussed with the patient and necessary appointments are scheduled.

Coordination and Communication

As the title implies, the primary function of the donor oocyte coordinator is indeed coordination. This coordination primarily consists of concise communication and precise recordkeeping.

Liaison

The coordinator is the liaison between all members of the health-care team and the patient. In collaboration with the physician and embryologist, the

coordinator maintains the responsibility of communicating the progress of each donor and recipient to the oocyte donation team, as well as the program at large. This communication is especially important if the program has different in vitro fertilization and donor oocyte coordinators so that scheduling will not be conflicted.

Anonymity

In an anonymous donor oocyte program, anonymity must be respected and maintained. To avoid an inadvertent meeting, all donor and recipient appointments should be scheduled in a fashion in which the two will never be in the office at the same time. It should be remembered that patients in the waiting room commonly talk to one another. If possible, the donor and recipient should be scheduled on different days, and both should be informed that there is a minimal risk of unintentional contact. Some recipients request to give a small gift or letter of appreciation to the donor. Use caution in permitting this gifting as the recipient may see the donor in possession of these items. If the recipient wants to give the donor a letter of appreciation, it would be prudent to require it to be received in an unsealed envelope for program review before passing it along to the donor. In an anonymous program, keep in mind that mutual anonymity is the goal.

Cycle Management

Clearly, coordination and communication of cycle management is crucial. Advanced arrangements for the best means of contact, such as telephone, secure email or messaging, or voicemail, should be made in advance of the treatment cycle. Precise communication regarding continued medication administration, dosage adjustments, and appointments is requisite. Keep in mind that the recipient will generally have fewer appointments and medications to manage than the donor. For these reasons, as well as reassurance, the recipient should be kept abreast of the donor's progress during the treatment.

Medical Records

Accurate recordkeeping is fundamental to all aspects of health care. FDA requires that records related to third-party reproduction be maintained for 10 years [10]; however, the ASRM recommends that permanent records of each donor's screening, test results, and treatment cycle outcome be maintained [10]. Data forms and logs are helpful to maximize the completeness of records.

Mandated Reporting

In 1992, a federal statute, the *Fertility Clinic Success Rate and Certification Act*, was enacted. Section 2 of this statute "requires each assisted reproductive technology (ART) program to annually report its pregnancy success rates to Centers for Disease Control and Prevention (CDC), along with the identity of each embryo laboratory used by the program, and whether the laboratory is certified under Section 3 or has applied for such certification" [17]. To comply with this statute, each program that performs ART procedures must report the data for each patient who begins an donor oocyte IVF cycle specific data for each patient who begins a donor oocyte recipient cycle to the Centers for Disease Control and Prevention. The data are then randomly validated, and the report is published annually and made available on the CDC website. SART member programs must report their data to remain in good standing with the organization. The coordinator is often responsible for accurately recording and reporting the required data, as well as serving as a resource for data validation visits.

Counseling

The coordinator is in no way a substitute for a mental health professional. Clearly, some degree of stress is normal for the oocyte donor and recipient. The coordinator should strive to be an empathetic listener and recognize conversation and behaviors that warrant referral to a mental health professional. Open dialogue with both donors and recipients in this regard is essential for supportive care.

Table 17.1 Resources for coordinators

Organization	Resource	Website
American Society for Reproductive Medicine	Professional organization	www.asrm.org
Nurses' Professional Group of ASRM	Professional group	www.npg-asrm.org
The American Fertility Association	Patient advocacy organization	www.theafa.org
RESOLVE: The National Infertility Association	Patient advocacy organization	www.resolve.org

Resources for Coordinators and Nurses

Professional organizations and continuing education conferences are excellent resources for donor oocyte coordinators, as well as other members of the donor oocyte team. Membership in ASRM includes certain journal publications, continuing education opportunities, resources, and newsletters. The Nurses' Professional Group (NPG) of ASRM also offers networking opportunities through message boards and discussion lists where members can pose specific questions to the entire NPG membership for answers and feedback. More recently, a certification course and examination for reproductive endocrinology nurses has been developed by the NPG and is available through the ASRM website. Program and individual SART membership is also available. Access to newsletters and uniform forms are among the benefits of SART membership. Professional educational conferences are also excellent sources of continuing education and peer interaction. Finally, collaboration with patient advocacy organizations, such as the American Fertility Association and RESOLVE, can be outstanding resources for providers and patients alike (Table 17.1).

Summary

The donor oocyte coordinator plays an essential role in the implementation and success of a donor oocyte program. Their roles include oversight of donor recruitment, matching a recipient with a donor, clinical management, donor and recipient education, and compliance with regulatory requirements. Excellent organizational and interpersonal skills, a commitment to excellence, and knowledge and utilization of available resources are important aspects of the job and help facilitate successful performance of the program.

Editor's Commentary

Nurses and donor egg coordinators have been involved in the development and delivery of egg and embryo donation services since 1983. Their work has largely gone unrecognized, but without their dedicated efforts, it is likely that none of the milestones in the history of the method would have been reached. These individuals must be focused; they must be committed; they must be obsessive; and they must be good at multitasking. They juggle many schedules and report to many people.

Nurses represent the mortar that holds all the component parts of the program together. They are juggling the interests of multiple parties: the donors, the recipients, and the program. At the same time they are providing vital services including clinical care, program liaison, and regulatory management. Coordinators view patients and donors from a different perspective than physicians and often will see or hear things within the practice that would otherwise go unnoticed. As a result they commonly put out fires before they start and keep the focus on the delivery of care.

Karen Hammond, DNP, CRNP, outlines the myriad of tasks that must be performed well in order to manage a donor/recipient cycle. Coordinators are, in many ways, the face of the program and provide a necessary continuity that reassures patients that all is well with their often unknown and

unseen donor. To be effective they must be good listeners and clear communicators. They must be nurses but also teachers. Attention to detail and appropriate documentation are also critically important skills given the increased regulatory surveillance placed upon egg donation by federal and state authorities. Perhaps most importantly, nurse coordinators provide time and project empathy, both of which are necessary to guide all parties through this somewhat convoluted clinical pathway to a common ground.

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The Finances of Egg Donation

18

Arthur J. McGrath and Mark V. Sauer

Key Points

- A number of strategies are used by patients to limit costs of egg donation which include splitting cycles, using frozen eggs and embryos, using health-care insurance, and borrowing with medical credit cards.
- A "split cycle" generally is not associated with the expected 50 % reduction in cost of the full fresh cycle cost as many recipient expenses are fixed cost and program operational costs are typically added.
- Required testing and screening of donors have increased in complexity and cost, and expenses are passed on to the consumer. Thus, egg donation today is approximately two- to threefold more expensive than it was in 1990, and generally three to four times more expensive than conventional in vitro fertilization.
- Historically American ART practices have been cash businesses not unlike cosmetic surgery centers where services are not covered by health-care insurance. However, the combination of using health-care insurance and cash/credit payment for ART treatment including egg donation has grown considerably over the past 15 years.

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Egg donation has always been a relatively expensive form of assisted reproduction. This is partly due to the obvious fact that in most cases, the donor receives financial compensation for the performance of her service, as well as the extra costs associated with screening the donor prior to her acceptance into the program. However, the discrepancies presently seen in cost between conventional IVF and donor egg IVF were not always so great. For instance, in 1990 patients were typically spending approximately $5,000–7,000 with medications for a cycle of in vitro fertilization, whereas egg donation averaged around $9,000–10,000. In 2012, including the cost of drugs, IVF

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in most American centers costs around $10,000, whereas a donor egg cycle commonly runs $25,000 or more per attempt.

Egg donation has become increasingly expensive due to several factors related to the egg donor portion of the treatment cycle and not to the process of IVF itself. In addition to normal medical services that must be paid for by the recipients, inflated donor compensation and state and federal regulatory requirements have steadily and substantially increased the cost of doing the business of egg donation over the last 20 years.

This chapter reviews the financial aspects related to egg donation including the costs incurred by the practice and addresses various means for covering the cost of care for patients. The overview also includes the financial impact on the method resulting from each of the following: different types of egg donation cycles, donor recruitment methods, methods of payment for egg donation cycles, and the costs of the component parts of an egg donation cycle.

Component Parts

The essential elements of egg donation include the stimulation of the approved egg donor with gonadotropins for an IVF attempt culminating in egg retrieval. The patient/recipient of the donated eggs is typically hormonally synchronized with the donor to facilitate a successful implantation in the recipient of the future embryos transferred. Most of the expense of an egg donation treatment cycle is associated with the services provided to egg donor. The following grid demonstrates the range of services listed by CPT code delivered to both the egg donor and recipient. These services are needed to complete a typical anonymous fresh egg donation cycle in which the donor's eggs are not split between recipient couples. The chart also indicates the frequency range for the delivery of the each of the services depending on the practice model, as well as the expected range of pricing for each unit of service (Table 18.1).

Types of Egg Donation Cycles and Financial Impact

Egg donation can be provided in several different clinical configurations in both anonymous and known donor formats with somewhat differing associated expenses:

1. Fresh full (not split) egg donor cycle
2. Fresh "split" egg donor cycle
3. Embryo adoption cycle
4. Frozen embryo transfer cycle
5. Frozen egg donation cycle

1. *Fresh full (not split) egg donor* cycles utilize all eggs retrieved for one recipient. The anonymous version of a fresh cycle would be the most expensive option as the maximum expenses are incurred with all eggs to one recipient and full compensation and screening expenses for the anonymous donor are passed on from the screening program to the patient. A fresh cycle utilizing a known donor can significantly reduce the cycle cost as donor compensation, recruitment, and screening costs can be taken partly and sometimes wholly, out of the bill. These reductions can range from 25 to 33 % of an anonymous fresh full cycle.

   Some individuals have further reduced their expenses by having the known donor utilize their own health-care insurance to cover the cost of the required pre-retrieval laboratory tests. This approach to cover testing costs has some risks involved for the egg donor as the coverage might later be determined by her insurance company to be invalid, thereby exposing the donor to either repayment of the coverage extended or, worse, the cancellation of her policy. The other intangible expense when utilizing known donors is the psychosocial one related to the complex emotional entanglements associated with known egg donation. Although the parties are screened psychosocially prior to participation, if problems arise afterward in the relationship, additional monies may be spent in mending the relationship.
2. *Fresh "split" egg donor* cycles usually divide the donor's eggs between two or more recipients. It remains unclear whether or not splitting

Table 18.1 Range of services provided during an egg donation treatment cycle

Procedures	CPT codes	Frequency range (visits)	Unit cost range ($US)
Anonymous egg donor			
Medical management	99213	4–8	$200–$300
Ultrasound studies	76830	4–8	$200–$300
Endocrine studies (blood)	82670/83001/83002	6–16	$75–$150
Venipuncture	36415	4–8	$10–$25
Egg retrieval	58970	1	$1,000–$1,800
Identification of oocyte	89254	1	$750–$1,500
Echo-guided aspiration	76948	1	$200–$350
Anesthesia (30 min)	99141	1	$400–$800
Donor compensation		1	$2,500–$10,000
Donor laboratory screens	FDA, locally required and standard of care testing	See chart on donor screening testing details	$1,500–$3,000
Donor Psych. evaluation	99274	1	$200–$1,000
Injection teaching	99211	1	$100–$400
Donor medical coverage	Various options for coverage for injury to egg donor	1	$250–$1,500
Donor recruitment and administration	Fees associated with recruitment non-laboratory screening of donors	1	$750–$3,000
Donor medication	Cost determined by stimulation protocol and formulary	1	$2,000–$4,000
Recipient	*Dx*: *628.8*		
Medical management	99213/99362	1–4	$200–$300
Ultrasound studies	76830	2–5	$200–$300
Endocrine studies	82670//83001/83002	4–8	$75–$150
Venipuncture	36415	2–4	$10–$25
Sperm prep	89261	1	$350–$550
Insemination of oocytes	89268	1	$450–$650
Culture and fertilization	89251	1	$1,500–$2,000
Extended culture	89272	1	$500–$1,000
Echo-guided transfer	76998	1	$200–$400
Embryo transfer	58974	1	$400–$600
Prepare embryo for transfers	89255	1	$200–$300

eggs between couples has a detrimental effect on the overall pregnancy rate of recipients. A 2006 paper from Argentina focusing on split cycles demonstrated an implantation rate per recipient couple of only 26.8 %, lower than what is typically seen in non-split attempts [1]. Furthermore, reducing the number of eggs per couple likely reduces the likelihood that a recipient will have supernumerary embryos for cryopreservation and later use (and reduced cost compared to attempting another fresh cycle). These factors need to be taken into consideration when considering the seemingly reduced cost of split cycles. Furthermore, a fresh split egg donor cycle is not the expected 40–50 % of the full fresh anonymous cycle cost as many of the expenses in a split cycle remain the same particularly for the recipient patient. Medical practices do not typically reduce expenses by the number of splits from the single donor as the number of eggs per split is an unpredictable process. The price is preset even though the outcome of the expected number of eggs is unknown. In order to

compensate for the unpredictable aspect of splits, the expected price is generally set at slightly more than half of the full fresh anonymous price. This type of cycle price might therefore range from $14,000 to $18,000.

3. *Embryo donation* refers to excess embryos created with eggs being frozen and at a later time donated to another couple generally in the anonymous context rather than through a known donation. This is typically the least expensive option as the donating couple has absorbed all of the expenses associated with creating the embryos that have been in cryostorage. Embryos created after 2005 are subject to FDA regulations and cannot be donated unless the gamete donors are screened according to FDA-published guidelines. The recipients of the donated embryos are often asked to absorb the costs of additional FDA testing of the donating recipient(s). There cannot be a charge for the donated embryos *per se* due to federal regulations forbidding the buying or selling of human embryos, and therefore, minimal administrative charges for storage and matching in addition to thawed embryo transfer fees would have most embryo donation cycles in the $4,000 to $8,000 fee range per attempt. One downside of embryo donation is the limiting nature of the demographics and phenotypes of the individuals that provided the gametes. Therefore, it is difficult to predict much about the expected phenotype, other than race and ethnicity, of the child that might result from embryo donation.
4. *Frozen embryo transfer* refers to the excess embryos often created with donor eggs that may be used later by a recipient in future frozen embryo transfer attempts. These cycles involve minimal monitoring and only require the thawing and transferring of the embryos. These cycle fees are in the range of $3,000–$5,000 per attempt.
5. *Frozen donor egg cycle* refers to eggs that have been frozen in advance of a patient directive and subsequently selected by recipients who then give consent to thaw and inseminate them with directed sperm to create embryos for transfer. This is a newer technology that may run into regulatory requirements and limitations not unlike sperm banks as essentially this cycle type represents the banking of eggs. Pricing of this model would fall into a category similar to the fresh split cycle noted above in that donor's eggs are split among two or more recipients. The advantage of this model is the avoidance of the complexity of simultaneously matching a donor with several and potentially demographically diverse recipients. With an egg bank, like a sperm bank, patients can schedule their donor selection and treatment timing at their leisure. The disadvantage of a frozen egg bank is the potential lower pregnancy rates associated with using frozen versus fresh donor gametes and the fact that not every program can successfully freeze and thaw human oocytes. Programs offering this approach have been able to balance the advantages and disadvantages and offer services in various types of packages in the $14,000 range.

Donor Egg Recruitment Methods

Donor egg cycles can use oocytes from a number of different egg recruitment methods in both anonymous and known formats:

1. Physician-based recruitment
   - Many American physicians in the field have their own recruitment and egg donor screening programs. These recruitment programs range from a handful of donors a year to hundreds of donors in a large pool. Physicians offer donor pools to patients either through phenotypic and demographic descriptives or occasionally photographs and demographic summaries. Historically, physicians have also provided discounted cost IVF to women who agree to share their retrieved eggs with other women recipients for an egg donation cycle, thereby reducing the price for both women. Physician recruitment costs can range from $1,500 to $3,000 often depending on the regional location of the practice.
2. Agency-based recruitment
   - There is a largely unregulated industry that recruits egg donors and makes

them available to potential recipients. Recipients who use agency-based donor eggs must then find a physician willing to accept, screen, and then stimulate the chosen agency donor. The relationship between the recipient chosen egg donor, recipient patient, treating physician, and recruiting agency creates a more complex treatment configuration for several reasons. First, the physician's ability to ensure anonymity, if desired, is compromised by an independent third-party agency. Second, the treatment itself and relations with the donor and recipient can become stressful by virtue of conflicting and competing agendas among the donor, recipient, agency, and treating physicians. Agency-based recruitment can have a dramatic range of cost depending on the difficulty of finding the type of donor requested by the potential recipient, and the fees charged by the agency for the services provided are not standardized. Not unexpectedly, pricing usually set at what the market will bear.

3. Patient recruitment
   - Patients may directly advertise for egg donor services in an effort to secure certain characteristics that they personally believe are more valuable or rare in egg donors such as high SAT, MCAT, LSAT, scores, graduation from Ivy League Schools, or certain attributes such as artistic or musical proficiency. These recruitment situations result in known donors that may be fraught with clinical management difficulties as the patient often must manage their own treatment-related stress and that of the expensive donor through a lengthy treatment process. As with agency donors, the women recruited directly by patients often create additional costs for recipients as these independent arrangements encourage agreements in which the "special qualities" sought by the potential recipient come at a higher price of reimbursement. The costs associated with personal recruitment, not the least of which are the emotional ones, are hard to value.

Methods of Payment

There are a number of methods currently being used in the USA to pay for egg donation treatment cycles:

1. Cash/credit
2. Health-care insurance and cash/credit
3. Health-care insurance
4. Medical credit cards
5. Shared-risk programs
6. Barter programs

1. Cash/credit
   - Historically, most ART centers in the USA have been cash businesses not unlike cosmetic surgery centers where services are not covered by health-care insurance. Over the last 25 years, about 15 states have enacted various types of mandates for infertility coverage by employers buying health-care insurance. Nevertheless, ART remains a largely cash payment business [2].
2. Health-care insurance and cash/credit
   - The combination of health-care insurance and cash/credit payment for ART treatment including egg donation has grown considerably over the last 15 years. Managed care contracts with health-care providers 10–15 years ago might have covered IVF services but would likely have specifically excluded reimbursement for egg donation. Over the last decade, perhaps resulting from member (patient) pressure, health-care insurance has increasingly covered the recipient/patient portion of an egg donation cycle when the patient has IVF coverage. This benefit can reduce the egg donation cycle out-of-pocket expense by as much as one third. If the ART practice is *in network* for gynecology services but out of network for IVF/ART services, the out-of-pocket patient expenses for an egg donation cycles might be reduced by 5–10 % for the cost of an egg donor cycle through coverage for services related to such things as ultrasound monitoring for recipient.
3. Health-care insurance
   - Over the last 25 years, a number of states have begun to mandate various levels of infertility diagnosis and treatment generally

for employers with over 50 employees. These state government-based mandates may include IVF but will generally not cover donor egg services [2]. Furthermore, many employers wishing to recruit or retain employees have purchased policies with coverage for ART treatment although rarely for donor egg treatment cycle.

4. Medical credit cards
   - Prior to the credit crunch of 2008, there existed a number of medical credit card opportunities for patients getting ART treatments including egg donation cycles. These arrangements charge administrative fees to the treating centers/physicians and certain payments and interest rates from the patient depending on the patient's credit score. These medical credit cards are tied to a treatment plan and a budgeted amount for the stated treatment including portions to be paid by the patient and the portion to be borrowed from the credit card. Failure to pay back the credit card company is generally the risk of credit card company rather than the health-care provider. Medical credit card companies have begun to reemerge for over the last 2 years postrecession although charging higher fees and with more stringent credit rating requirements.
5. Shared-risk programs
   - Shared-risk programs represent more of a unique restructuring of cost rather than a method of payment. Nonetheless, it is a way to preserve patient funds for future treatment attempts in the event that their cycle does not result in pregnancy. Shared-risk programs generally provide a limited number of treatment attempts, using either IVF or egg donation cycles, for fees set at a multiple higher than the cost of a single treatment cycle but significantly less than the cost of the maximum number of cycles included in the program. The "eligible" patient pays a flat fee amount regardless of the use of one or the maximum number of treatment cycles until achieving the "defined" outcome. If the defined outcome is not achieved, the patient receives a full refund. Generally, assessment fees to determine whether or not a patient is eligible are not refundable. The defined outcome can range from a live birth to a child living 1 month after birth [3]. Expenses incurred to become eligible can be considerable and represent fiscal elements to be aware of when assessing a shared-risk program. ASRM has developed ethical guidelines for the development of shared-risk programs [4]. However, these are merely recommendations and are not policed or regulated.
6. Barter program
   - As a way to reduce the cost of IVF and egg donation, physicians have given patients discounts on IVF cycles in exchange for sharing their eggs with another woman needing oocytes for an egg donation cycle. These arrangements are particularly complicated and require counseling and adequate informed consent of all parties since oftentimes the infertile woman donating her eggs fails to become pregnant while the recipient of her eggs achieves success. Furthermore, the practice of bartering suggests coercion and exploitation since women without financial resources are more prone to give away their eggs to women with the financial means to underwrite her cycle. In addition, equity questions may be raised as to how the bartering values are distributed between the parties. The potential for profiteering by clinics and physicians also exists [5].

Cost of Egg Donation

The component costs of an egg donation cycle include the general expenses of operating a medical practice such as facility, staff, and income for the provider as well as the following cost centers:

1. Recruiting and retention of egg donors
2. Screening of egg donors
3. ART support services (embryology)
4. Donor compensation (see article 5)

1. Recruiting and retention of egg donors
   - Recruiting and retaining the services of egg donors has become an expensive proposition in 2012 from its modest beginning in California in the mid-1980s. In the early stages, regulation was nonexistent, and a few physicians in the field managed egg donors and recipients forging what has become the basis of today's standard of care in egg donation. A 1999 study by Gorrill [6] found that the cost in Oregon to bring a donor into their program was $1,869.00 per accepted donor. In their study, 12 % of all inquiries entered the "active donor pool." About 10 % of the screening costs in this Oregon study related to obtaining an STD panel. These costs have increased significantly since that time with the addition of USFDA infectious disease screening requirements implemented in 2005. The 1999 costs of egg donation would need to reflect regional labor differences as well as inflation. The cost components for recruitment would remain largely the same as the Oregon study with the exception of new regulatory requirement addressed below.
2. Screening of egg donors
   - The medical screening of egg donors has three components:
     (a) Standard of care medical screening (ASRM guidelines)
     (b) State-specific regulatory required screening
     (c) Federal regulatory screening requirements
       (a) Standard of care medical screening
         - Standard of care screening indicated by national professional standards calls for the safe donation of oocytes from one individual to another. Safety in this context primarily relates to avoidance of the transmission of infectious disease. The American Society for Reproductive Medicine recommends screening for sexually transmitted diseases and questionnaires to assess family history for possible genetic diseases requiring further testing.

       (b) State-specific regulatory screening
         - Each state may or may not have its own regulation relative to egg donation.
           – New York State requires the tests indicated in the table below to be carried out within specified timetables.

       (c) Federal regulatory screening requirements
         - In May 2005, the US Food and Drug Administration (FDA) approved regulations to protect the public from infectious disease transmission through screening of oocyte donors (Code of Federal Regulation Title 21, Part 1271). These regulations are detailed and complex. The economic costs of these FDA regulations were reviewed by Baker [7]. The Baker review estimates ongoing costs per case for the implementation of the FDA regulations at about $3,500 including the cost of the tests themselves. The FDA-required tests are expensive and must be completed within specified time frames. The table below highlights the tests required by the FDA (Table 18.2).
           – In addition, there are substantial administrative costs accrued by programs in order to maintain accreditation with state and federal agencies and to be prepared throughout the year to remain in compliance with these regulations in view of unannounced and anticipated audits.
         - ART support services/embryology
           – Providing egg donation requires access an embryology/andrology laboratory facility which will handle the services including the entire CPT codes specific to elements of the cycle.

Table 18.2 Egg donor testing requirements by organizational entity

Test type	FDA required	NYS required	ASRM recommended	Practice-specific required options
HIV, types 1 and 2	X	X	X	X
Hepatitis B core AB	X	X	X	X
Hepatitis B surface AG	X	X	X	X
Hepatitis C virus (HCV)	X	X	X	X
Syphilis	X	X	X	X
Chlamydia trachomatis	X		X	X
Neisseria gonorrhoeae	X		X	X
Screening (questionnaire)	X		X	X
TSE	X		X	X
CJD	X		X	X
Sepsis	X		X	X
Vaccinia	X		X	X
Testing (*within 30 days of retrieval*)				
Donor, HIV, types 1 and 2	X	X	X	X
Donor, hepatitis B core AB	X	X	X	X
Donor, hepatitis B surface AG	X	X	X	X
Donor, hepatitis C AB	X	X	X	X
Donor, HIV-1/HBV/HCV, NAT	X		X	X
Donor, RPR w/REFL SYPH IGG	X	X	X	X
Donor, C. trachomatis, TMA	X		X	X
Donor, N. gonorrhoeae, TMA	X		X	X
Donor, West Nile virus (WNV)				X
General tests				
Toxicology				X
CBC				X
Blood type				X
AMH level				X
Genetic screening		X	X	X
Cystic fibrosis				X
SM atrophy				X
Fragile X				X

3. Donor compensation
   In 2007, Covington and Gibbons' anonymous e-mail survey of ART clinics found that average egg donor compensation in the USA was $4,217. Compensation was closer to $5,000 in the west and northeast regions and lowest in the northwest at $2,900 [8]. The 2007 ASRM Ethics Committee paper on "Financial compensation of oocyte donors" recommended that compensation greater than $5,000 required justification and did not find payment above $10,000 to be appropriate [9].

What the Market Will Bear?

Frustrated REI practitioners having trouble finding egg donors for their recipients may be tempted to raise egg donor compensation as a method of attracting more egg donors. The result of this practice is generally counterproductive in that all donors will migrate to the provider paying the highest compensation. This market tendency in turn compels the competitors in the region to match or exceed the recently raised prices in order not to lose their supply of egg donors for their patients. Thus, inadvertently, the price rise has increased the cost of egg donation treatment in the region for all patients and yet likely failed to solve the problem of the individual that initiated the raising of the compensation in the first place. Ironically, the price increase undoubtedly also pushed the treatment option out of reach for many patients. In the period of 2002–2008, egg donor compensation in New York City area experienced a series of increases from a 5-year-long base of $2,500–$ 5,000 and finally settled in at $8,000. Compensation has remained at the $8,000 level since the period of major increases until the present. However, let the price increaser beware!

Summary

Egg and embryo donation continues to grow in popularity in the USA with over 10,000 cycles performed in a variety of ways annually. Costs incurred by recipients are substantial, and a marked rise in price has occurred over the past 20 years. This increase in cost has been largely driven by the escalating price paid for the services of egg donors, as demand has outpaced the supply of women available to participate. Additionally, required testing and screening of gamete donors has increased in complexity and cost, and these expenses are also passed onto the consumer recipient. As a result, egg donation today is approximately two- to threefold more expensive than it was in 1990 and generally three- to fourfold more expensive than conventional in vitro fertilization.

A number of strategies are used by patients in an attempt to lower or limit costs which include splitting cycles, using frozen eggs and embryos, using health-care insurance, and borrowing with medical credit cards. All of these approaches have their advantages and disadvantages, and it is critically important that patients have a firm understanding of what they are paying for in signing up for egg donation services.

Editor's Commentary

Egg and embryo donation in the USA has always been an expensive proposition. This seems so obvious when comparing costs against other places in the world where assisted reproduction is a subsidized health-care benefit, and in a few of these locales, even egg donation is included. But, the fixed cost of American IVF plus the additional expenses of providing donor eggs makes the price tag for egg donation quite high. Considering that the median income for a full-time working woman in the USA is around $35,000 a year, it is not surprising that a $30,000 charge for a medical procedure is outside the range of affordability for the average person.

The cost of egg donation has risen disproportionate to the rise in fees charged to patients treated with conventional IVF. The principle of supply and demand has governed behavior in the marketplace and has driven up prices for donor compensation and overall professional services. Furthermore, the regulatory testing now required of programs by state and federal agencies in the screening and maintenance of their donor programs has added more expenses. All of these costs are passed onto the consumer, "simple economics." Unfortunately, these consumers are also our patients who are in desperate need of treatment. The "simple economics" has literally excluded many women from getting the care they need using this very specialized form of assisted reproduction.

The lay press and public have taken issue at times with our profession as a result of what appears to be selective care for the wealthy. It did not have had to evolve this way. In the late 1980s while at USC, I published the idea of the "split donor" cycle as a way to efficaciously deliver eggs to women in need while equally dividing the cost in order to make it affordable. Not surprisingly, programs embraced the *efficiency* of this approach, particularly since donor services were, and still are, in short supply; however, the *cost reduction* aspect seemed to get lost in translation. In fact, not long after this paper was published I remember a practitioner approaching me following a talk at a national meeting. He thanked me for proposing split cycles as it allowed him to "double the take." Clearly, this was not my intent.

There is some potential good news though. As Art McGrath points out, more and more insurance companies are at least partially covering donor egg treatment expenses. Furthermore, states mandating insurance coverage often require payment for basic donor egg services. These underwrites are not all inclusive, but every little bit helps. Finally, I do believe that egg banking will soon become reality and at least this method promises to lower overall cost while maintaining efficiency; we shall have to wait and see about that.

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Donor/Recipient Insurance Coverage: Protecting Against Unexpected Liability

19

Cary Lisa Dicken

Key Points

- Complications arise from egg donation and donors; recipients and programs offering services are at risk of incurring medical debt that is typically uncovered by standard health insurance.
- Disputes between various stakeholders will inevitably arise over personal liability for paying uncovered expenses, and all parties should sign agreements in advance of treatment related to specific fiscal responsibilities.
- Donor/recipient insurance programs have evolved to assist in defraying costs related to adverse outcomes; however, they are actually written as accident, disability, and death policies.
- Donor/recipient policies are not intended to represent primary health-care coverage and act as supplemental plans to existing coverage schemes.

Oocyte donation (OD) was originally intended for reproductive-aged women with premature ovarian failure and women with intractable infertility. However, currently OD serves the reproductive needs of a more diverse group of women, including women of advanced maternal age and postmenopausal patients. Despite oocyte donation being an expensive procedure, its popularity can be attributed to its high rate of success [1]. Oocyte donation is now more commonly performed than ever. Yet, inherent risks to both the donor and recipient still exist. Measures to protect all parties, including the IVF practices that offer such services, from potential expenses secondary to complications must be established to maintain a viable and operationally sound program.

History of Oocyte Donation

The first successful human pregnancies established using donor oocytes were reported in the early 1980s by two separate groups [2]. A team from the Harbor-UCLA Medical Center in Los Angeles, California, achieved a pregnancy using artificial insemination and in vivo fertilization of a designated egg donor with subsequent uterine lavage to retrieve the embryo prior to implantation [2]. Another team from Monash University in Melbourne, Australia, established a successful pregnancy using conventional in vitro fertilization (IVF) methodology and donated oocytes from an infertile woman who was undergoing treatment for her own infertility. The single embryo transfer into the synchronized estrogen- and progesterone-primed uterus of a woman with

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premature ovarian failure resulted in the first *egg donation* pregnancy [3]. Current practice considers IVF of donor oocytes and resultant embryo transfer to be a superior practice as it avoids the possibility of a retained pregnancy in the donor [1], a complication that no longer occurs in contemporary practice.

When donor oocyte cycles were first utilized clinically, eggs were often obtained from women undergoing IVF who donated *excess* eggs not used for fertilization. In this context, egg donors did not assume any additional risk. As practice changed and cryopreservation of supernumerary embryos became a reasonable and affordable option, women undergoing IVF chose to fertilize all their retrieved eggs in order to create embryos for future use. As a result, the women donating eggs changed. Currently designated egg donors undergo ovarian hyperstimulation and oocyte retrieval in order to harvest and donate all of their retrieved oocytes to specific recipients intent on their in vitro fertilization and embryo transfer [4].

Ovarian hyperstimulation solely for the purpose of egg donation has resulted in questions regarding who is fiscally responsible for problems and complications arising during the course of care. Specifically, when the eggs of an anonymous donor are used to assist another woman to conceive, who is the responsible party, the donor, the recipient, or the program? Presently in the USA, there is no standard policy to define these relationships. In fact, the USA, in comparison to other countries, lacks regulation regarding the conduct of reproductive technology. Our nation's general approach has been to let the private sector regulate egg donation through the marketplace and the courts and to make all professional guidelines voluntary [5].

Risks Associated with Oocyte Donation

Risks to Oocytes Donors

The medical risks associated with oocyte donation are largely secondary to ovarian hyperstimulation and the oocyte aspiration required for egg retrieval. The complications, therefore, are really no different than those experienced by infertile women undergoing traditional IVF [4]. Such risks include the development of ovarian hyperstimulation syndrome (OHSS), bleeding or infection secondary to transvaginal oocyte aspiration, anesthesia complications, and post-retrieval pain. Recent studies suggest that oocyte donors actually have a lower risk of developing OHSS compared to other women undergoing IVF [6]. This may be attributed to the fact that oocyte donors do not become pregnant, a condition known to exacerbate OHSS. A review of 1,000 consecutive cycles reported less than a 1 % rate of serious adverse events in participating oocytes donors [7].

Additional risks to egg donors, such as potential long-term adverse effects of egg donation on future fertility or the theoretical possibility of developing ovarian cancer, have yet to be clearly demonstrated. To date, studies do not demonstrate any adverse impact of egg donation on a donor's future fertility [6, 8]. Similarly, the association between assisted reproduction and ovarian cancer is questionable [9], and the overall effect of multiple cycles of ovarian stimulation on the development of gynecological cancers as a whole remains unclear [10, 11].

Risks to Donor Oocyte Recipients

The intended recipient of donor oocytes also assumes a certain amount of risk, which, in their case, is associated with pregnancy after IVF and embryo transfer. Even in those recipients who do become pregnant, donor oocyte IVF cycles can still result in abnormal implantation leading to spontaneous miscarriage or ectopic pregnancy. In addition, donor oocyte IVF cycles are associated with multiple gestation pregnancies as well as other complications associated with high-risk pregnancy such as hypertension and diabetes. Finally, despite the high rates of success, there is still the possibility that the recipient will not get pregnant.

Aside from the possible pregnancy complications and the potential for failure, the recipient must also accept a certain amount of risk related

to the selected egg donor. Although theoretical, the recipient potentially can contract a sexually transmitted disease from the embryos that were transferred. FDA regulations requiring full infectious disease testing within 30 days of oocyte retrieval do not preclude recent contraction of a sexually transmitted infection [12]. Therefore, the recipient ultimately faces some, albeit small, risk of exposure.

The recipient also assumes some risk by trusting that the reported genetic and medical history of the donor is accurate. A full psychological evaluation is required; however, no guarantee of the validity of the donor's stated history can be reasonably ascertained. An adverse outcome with the pregnancy or in a child born from donor oocyte IVF is possible if the donor is not completely truthful about her genetic and medical history or if the donor is not properly screened. The monetary compensation associated with oocyte donation clouds the issue further and may provide a negative incentive for full disclosure on the part of the donor and even the program offering her services.

Finally, the recipient also relies upon the donor to complete the agreed-upon treatment cycle and assumes some risk in the donor's ability to respond well or to be compliant with treatment. A legal contract or informed consent agreement to receive oocytes does not ensure an adequate response to ovarian stimulation or retrieval of oocytes for fertilization will actually occur. The recipient may also be responsible for additional unplanned costs should the donor require extra days of ovarian stimulation, if a problem arises with the synchronization of the donor and recipient cycles causing delays or the donor requires hospitalization due to illness.

Oocyte Donor/Recipient Liability

Both the oocyte donor and recipient assume certain risks when entering into an agreement to move forward with a cycle. Informed consent is essential for both parties so that a clear understanding of responsibility and ownership is established. Just as it is understood which party has rights to the oocytes, resultant embryos, and potential children, the individual financially responsible for any complications that may arise as a result of the cycle must also be established. Upon signing informed consent, both parties should have full disclosure of their individual risks and fiscal liabilities. In addition, consent forms should clearly state whether or not the donor and recipient will be compensated should the donor either not complete the cycle or not stimulate as well as anticipated.

As stated earlier, medical complications do occur during IVF. Oocyte donors and their recipients should only enter into an agreement after proper counseling by medical professionals knowledgeable of all aspects of the care. Donors assume the risks associated with the use of injectable gonadotropins and from the oocyte aspiration procedure. Diagnostic tests, such as serial ultrasound examinations and serum hormone levels, are also required for the timely retrieval of the eggs. The potential long-term consequences of oocyte donation must also be considered as a risk when counseling a potential egg donor. The overall impact of egg donation on future fertility as well as ovarian cancer remains unknown, but potential risks should be discussed. Additionally, the unlikely but significant risk of a severe complication requiring emergent surgical intervention, such as ovarian torsion, and the possible loss of an ovary as a result should be disclosed. Egg donors must be well informed of all known complications and side effects of medical procedures prior to initiating treatment. Equally as important, donors must have a clear understanding of who will be financially responsible for paying any extraneous treatment costs. The informed consent agreement between the IVF program, donor, and recipient must state which party will pay any additional fees and expenses incurred should a complication from treatment arise. In many instances, donors are named as the only responsible party. However, if this is the case, it must be unequivocal and well documented and, most importantly, appropriately consented.

Similarly, recipients assume a certain amount of risk when accepting a donor. The recipient must understand that despite the extraordinary fee associated with egg donation IVF, there is no guarantee of a successful pregnancy. Best

attempts are made to select women who are most likely to respond well to ovarian stimulation, yet the number and quality of eggs actually retrieved from a donor may not always be ideal. The recipient accepts an egg donor's history as being true, but there often is no proof of pedigree. The recipient must, therefore, acknowledge the possibility that any child born from the donor IVF cycle may inherit an undisclosed but potentially identifiable disorder. Although a complete medical screening for sexually transmitted diseases lowers the risk of infection and genetic screening minimizes the transmission of known genetic disorders, there is no guarantee of a *normal child*, nor can it be absolutely certain that sexually transmitted infections have not been passed to the recipient. Thus, patients may unknowingly be exposed to a sexually transmittable infection or receive an embryo with a genetic mutation.

Liability for any adverse outcomes resulting from donor oocyte cycles should be spelled out in the informed consent. In order to protect the three parties involved in the agreement – those being the donor, the recipient, and the IVF program – all potential risks and adverse outcomes must be fully explained, openly discussed, and clearly documented prior to cycle initiation. The informed consent should explain potential risks to all parties – medical, genetic, infectious, psychosocial, and pregnancy-related. In addition, specific individual fiscal responsibility for both known and unforeseen costs incurred during treatment must be disclosed and accepted by all parties.

Oocyte Donor/Recipient Insurance

In the USA, many health insurance companies either do not pay or have limited coverage for fertility treatment. Furthermore, infertility coverage at a national level is not mandated, and while some states have created laws mandating coverage of certain fertility treatments, these generally do not apply to egg donation. Only a few states have laws requiring insurance companies to have partial or full coverage of IVF treatments, which may defray the costs of egg donation [13]. Therefore, for the vast majority of patients in the USA, the intended parents are financially responsible for the cost of the entire cycle.

If the intended parents assume the financial responsibility for the donor egg cycle, should they also be held liable for any potential complications that arise from performance of the cycle? This should be decided in advance. Does the treating fertility office assume responsibility for extraneous costs of both the donor and recipient? If the oocyte donor was obtained through an egg donor agency, will that agency assume risks to the donor? Like many other at-risk relationships, obtaining coverage for and settlement of individual claims that might occur from performance of the service led to an interest in insurance underwriting the activity.

Presently, the recipients are asked to bear complete responsibility for all monetary aspects of the infertility procedure as well as any resulting complications. Typically, they will either independently purchase a short-term insurance policy to cover the specific assisted reproductive cycle or an insurance policy may be purchased by the treating office or the egg donor agency which passes the cost onto the patients as part of their global professional fee. However, this has not always been the approach.

In the early days of oocyte and embryo donation, the donors themselves were responsible paying fees to treat complications arising from treatment. This was indeed problematic for multiple reasons. First, the injured donor felt she was unjustly penalized by having to incur cost for a problem created by the doctor. Consequently, she often refused to pay these bills. Furthermore, when a donor utilized her own medical insurance plan, there was no guarantee that the company would pay the bill, seeing OHSS or egg retrieval as an infertility benefit that was not covered under her policy. These payments take away from the overall compensation she received. The inherent risks with oocyte donation, namely, ovarian hyperstimulation syndrome (OHSS), ovarian torsion, and complications from oocyte aspiration, may require prolonged and expensive hospitalization. Even in cases where the bills were paid, the donor's policy might later be cancelled, or her

premiums increased in price. Review of claims might later result in the insurance company asking for money back from the donor if indeed they determine that her insurance claim was improperly filed or falsely represented. In addition, like many Americans, donors are young women who commonly do not have health-care insurance and are generally ignorant of the high price of health care. Most have never been sick, let alone hospitalized, and are stunned to find out the enormity of the expense. The burden of responsibility for medical expenses resulting from complications of egg donation would be too much for most donors to personally bear. Potential liability for medical bills should impact upon the choice of whether or not to participate in all women considering egg donation. However, because known complications are relatively rare, most often they are willing to proceed, assuming that problems will occur in others, but not themselves.

For recipients, however, financial compensation to the donor and payment of her full treatment cycle are thought to represent the sum of their fiscal responsibility. Assuming any additional costs for medical problems arising from treatment was typically not documented in the drafted agreements. Recipients, therefore, did not enter into the relationship with the full awareness of potential significant additional costs. Having already paid a high fee, most recipients were uninterested in spending even more money for donor expenses especially when it was not stated in their informed consent. Additionally, paying out of pocket for medical bills generated from donor adverse events is often much more expensive than purchasing a short-term insurance policy.

To ensure that women would remain interested in participating in egg donation, insurance coverage – separate from one's own personal health insurance policy – was developed. However, defining the responsible party in the contract between the oocyte donor and recipient upon entering into the agreement became essential. Early interest on the part of insurance companies was sparse. When egg donation first started, very few cycles were performed, making the sale of short-term insurance policies marginally profitable and expensive to offer. Additionally, although the low rate of complications in oocyte donors was attractive, when complications occur, the treatments are expensive, further reinforced the nonprofitable nature of underwriting these policies. However, as egg donation grew in popularity and increasing numbers of cycles were performed, insurance companies realized the potential for profit based upon the volume of sales and began providing supplemental medical insurance policies specific to egg donation patients and the practices offering services.

A specific short-term health insurance policy purchased prior to the onset of a donor oocyte cycle is helpful in covering medical expenses incurred from complications. Insurance for oocyte donor/recipient cycles ideally should include coverage for related acute care as well as related long-term complications. The issue of financial responsibility ultimately becomes the burden of all participants, and the means by which the insurance is purchased varies. These options range from the IVF program purchasing an insurance plan which will be included in the overall cost of the cycle and paid by the recipient to the recipient or the donor agreeing to bear total financial responsibility and essentially paying out of pocket for incidental bills. There are several insurance companies from which a short-term *accident insurance* plan can be purchased. These plans offer single-instance coverage for a stated period of time and encompass various fertility procedures often not covered by a regular insurer. They are meant to act as supplemental coverage to existing health-care insurance policy, which is still used primarily to pay the bills. They are often combined with disability and death benefits to make them more attractive. These policies may cover multiple medical procedures occurring throughout a specified period of time. However, they are event specific, and therefore for subsequent cycles, additional policies must be purchased. There is typically no deductible; however, all claims are subject to review by the payer and not paid unless they can be justified under the specific policy.

Obtaining short-term oocyte donor insurance should not necessarily impact the personal health

insurance plan of an oocyte donor, but being an egg donor in and of itself may later impact the donor's ability to later obtain health insurance. Some companies may view a history of having been an egg donor as a preexisting or risky condition and therefore charge higher premiums for coverage or deny applications for coverage.

Despite the availability of short-term insurance plans, most fertility programs still require donors to have their own medical insurance to cover unplanned expenses. If complications develop, the donor's insurance will be billed; this is generally true for the donor insurance plans since they act as a supplemental payer. This returns the donor to the earlier paradigm whereby the high costs of medical bills may result in reduced coverage or refusal of payment for medical services by the primary provider. In these cases, the donor supplemental insurance kicks in with coverage usually up to $200,000.

The bottom line is that both the donor and recipient must fully understand their financial obligations prior to entering into treatment. If not clearly stated, both parties must clarify which party's insurance will be billed in the case of medical complications, who will be responsible for paying the insurance premium, how long will the short-term insurance plan last, and what happens if a complication arises outside that time period. Of equal importance, many donor/recipient insurance policies also offer insurance to the recipient to cover expenditures from a donor not completing the cycle or her fail to respond adequately to ovarian stimulation resulting in cancellation.

Oocyte Donor/Recipient Insurance Policies in the USA

Several insurance companies in the USA now offer short-term policies that can be used toward coverage of egg donor cycles. In addition, a few insurance agencies in the USA provide specific policies geared toward the more general use of assisted reproductive technology. These plans are intended to cover complications incurred by the egg donor during the IVF cycle, but they may also protect the recipients from their own medical expenses resulting from care not covered by their personal health insurance. Protection of both egg donors and recipients from unexpected medical expenses also indirectly benefits the IVF fertility centers and the egg donor agencies by preventing claims from disgruntled donors or recipients who received medical bills for iatrogenic complications. This impacts upon malpractice liability and may help keep claims against the practice down.

Insurance companies providing policies for assisted reproductive technologies offer both a combined egg donor/recipient bundled policy and egg donor-only or recipient-only plans. The donor-only or recipient-only coverage is least expensive. This flexibility allows the recipient to pay a premium only for the coverage desired and necessary and reduces their expenses. Current premiums for donor- or recipient-alone policies typically cost between $200 and $300, whereas a combined donor/recipient plan premium is usually $400–$500 per cycle. These policies only provide coverage for complications and expenses resulting directly from the cycle of treatment and typically have a maximum limit of $500,000 for combined complications of the donor and recipient and coverage up to $200,000 for egg donor-only or recipient-only policies [14–17].

Each insurance company dictates the time period for which expenses are covered. Some cover costs occurring within 90 days of the medication start date [17], whereas others may cover medical expenses incurred up to 30 days post-retrieval [15]. Many of the policies, however, state that coverage is only for medical complications that are *reasonable*, *usual*, *and customary* [14–17]. Complications defined in this manner are left to the interpretation of the insurance company payer and may therefore be disputed or denied upon review. Most of these policies do not mandate the accessing of any preferred provider network for required medical care resulting from retrieval and/or transfer treatment procedure-related medical complications. Donors and recipients are permitted to receive the necessary medical care from any approved physician and/or

qualified medical facility [14]. However, their primary insurance plan may dictate their basic coverage, and expenses incurred outside of network will be billed as such.

Another coverage option includes purchasing a blanket accident insurance policy from an insurance company that can then be applied toward egg donors and recipients. Like the other insurance policies, coverage starts when the egg donor begins synchronization treatment procedures for the cycle, and the accident expense benefit will cover any related medical expenses incurred within 90 days of the transfer. In addition, the accident blanket policy will continue to cover claims for up to 52 weeks. Like the assisted reproductive technology-specific plans, blanket accident insurance will cover up to $250,000 of incurred medical expenses if either the egg donor or recipient experiences medical problems as a result of the egg donation procedure. Premium costs for this type of insurance vary from state to state but range from $180 to $245 for *egg donor-only* coverage and $400 for combined *egg donor and recipient* coverage. These policies are valid in all states other than New York [18].

Some egg donor/recipient insurance policies specifically cover IVF programs and egg donor agency programs and protect them from unforeseen and costly medical expenses of matched donors that are a result of treatment procedure-related medical complications. These policies therefore are purchased by the fertility center or egg donor agency, not by the intended parents individually. These insurance policies are written for the benefit of insured IVF programs and egg donor agencies participating in egg donor cycles. Most medical expenses resulting from complications related to egg donor retrieval and recipient embryo transfer are covered. When the egg donor recipient liability policy is purchased by an IVF fertility center, the insured center identifies all participating egg donor recipient cycles that begin medications on a monthly basis to the insurance company. Only those cycles in which incidental expenses occur and require liability insurance coverage, as determined by the insured center or agency, are reported as a claim [14].

Summary

Since the first successful egg donation pregnancy in the 1980s, the use of donor eggs and in vitro fertilization to achieve pregnancy has grown enormously in popularity. Because egg donation most commonly utilizes anonymous donors, the intended recipients must also be aware of all the donor's risks of injury that may occur from undergoing assisted reproductive therapy. These risks include the potential to generate significant financial expenses from medical complications. Therefore, early documentation that delineates the specific financial responsibility of all parties is essential to protect all parties.

Complications from egg donation cycles are relatively rare, and in the earlier years of egg donation, the donor herself was deemed financially responsible for paying all additional medical expenses resulting from complications. Aside from cost, this became problematic for donors, as their own personal health insurance policies could be affected if used to cover costs of by participating. In addition, many donors were young women without health insurance who could not afford the cost of additional medical care. The need for specific insurance policies to provide supplemental coverage of adverse events to either the donor or recipient in an egg donation cycle was evident. As egg donation grew in popularity, with over 10,000 cycles performed annually in the USA alone, many insurance providers realized the potential for developing a new market of clients.

Most insurance groups offer short-term accidental coverage policies that can be purchased by the recipient to cover specific medical costs arising from complications during a donor egg cycle. Commonly, IVF fertility centers or egg donation agencies will actually purchase these insurance policies for either the donor or recipient individually or both together. The cost of this coverage will then be included in the total fees paid by the intended recipients for the performance of the cycle. These short-term insurance policies prevent unnecessary cost to the donor and avoid impacting her personal health

insurance coverage. In addition, the policy protects the recipient's medical insurance and offers additional supplemental coverage for expenses that may not be normally covered. It also ensures some insurance protection should the donor not complete the cycle or respond poorly and be cancelled. Finally, egg donor/recipient insurance may protect the IVF fertility practice and/or the egg donor agency from potential malpractice litigation by paying expenses for complications arising from care that might otherwise be settled in a court case.

Editor's Commentary

Egg and embryo donation has always been hampered by potential disputes arising from the inherently shared liability for expenses. Conflicts subsequently arise between parties when they go unpaid. One might argue that the donor, acting on her own behalf and paid as a free agent, assumes the risks of treatment for which she is paid and therefore also assumes liability for medical costs that might incidentally occur as a result of that participation. This tenet was largely operational during the first 10 years of practice. However, when donors are hospitalized or injured and expensive medical bills are incurred, it soon becomes apparent that the donor is not going to pay them and expects someone else to do so. If not, a malpractice suit likely follows as she attempts to gain further compensation to offset these additional costs.

Recipients have also been uncomfortable with the idea that the egg donor is responsible for her own medical bills and, rightfully so, as they too may be deemed responsible in the event that the donor defaults on her expenses. Because complications are relatively rare and minor problems are typically handled *in-house*, programs are often *self-insured* against claims for payment of bills of donors or recipients. However, when problems do arise, the costs can be very high and may include reimbursement for medical bills, time lost from work and family, and even disability claims. Few medical programs can afford these types of incidents and thus the need for an insurance policy to underwrite these expenses became apparent.

However, no different from purchasing any insurance policy, buyers need to carefully read the fine print. Most basic plans are actually limited, term specific, *supplemental* medical insurance, and combined with a disability and death benefit. It may be also helpful for insuring donors without any primary coverage, but again, the terms are very specific and the policy is not meant to function as universal health-care coverage. Commonly, policy buyers must be identified and occasionally issues related to privacy and HIPPA develop especially since the data is stored and banked by private insurance companies who cannot guarantee how this information may be shared in the future. However, despite these concerns, overall donor/recipient insurance sells because it provides an umbrella of coverage that is needed.

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Part IV

New Frontiers in Egg and Embryo Donation

Egg and Embryo Banking: Essential Elements for Maintaining High Rates of Success

20

Zsolt Peter Nagy, Antonio Capalbo, and Liesl Nel-Themaat

Key Points

- Vitrification is a process by which a liquid is solidified into a noncrystalline (glassy) phase by lowering the temperature and greatly increasing its viscosity. One of the main sources of cryogenic injury, ice crystal formation, is eliminated both within cells being vitrified (intracellular) and the surrounding solution (extracellular).
- Recent prospective randomized studies have found no significant differences between fresh and vitrified oocytes regarding their in vitro and in vivo developmental potential.
- It is clear that only a minority of morphologically normal oocytes produce pregnancies, suggesting that most of the problems leading to poor embryonic development and implantation cannot be detected using standard microscopic evaluation.
- Vitrification is less traumatic to cells and is therefore a more effective cryopreservation technique for human embryos than conventional slow-freezing methods.

Since the beginning of time, it has been the fantasy of men to freeze time. In no other field have we been closer to accomplishing this dream than in the cryopreservation of live tissues, gametes, and embryos. Cryobiology (the study of life at low temperature), as we know it today, has come a very long way to where we now have the ability to freeze and thaw living cells (basically freezing time) while maintaining viability, without any apparent detrimental effects.

The first successful mammalian embryo cryopreservation occurred in the 1970s [1], while the first human pregnancies were achieved relatively soon thereafter, becoming just the ninth mammalian species with normal offspring following the transfer of cryopreserved embryos [2]. Slow freezing is the original and most thoroughly studied method of cryopreserving gametes and embryos. In 1985, vitrification was demonstrated as an alternative to slow freezing in reproductive biology [3]. Since then, there have been several

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reports of the use of vitrification to cryopreserve human and animal oocytes and embryos. The technique has evolved over the years, leading to the development of novel tools that allow the use of submicroliter volumes, significantly increasing the cooling and warming rates, and subsequently efficiency (see review by Vajita and Nagy, 2006) [4].

Oocyte and embryo donation are well-established practices, currently applied in a wide range of cases, such as perimenopausal and/or menopausal women [5], poor-responder patients [6], couples with multiple unsuccessful IVF attempts [7], inability of patients to produce euploid gametes due to rare chromosomal disorders (e.g., homologous Robertsonian translocations [8]), or heritable genetic conditions coupled with a low response to ovarian stimulation (COH). Furthermore, male homosexual individuals or couples dependant on donor oocytes or embryos may now have a baby that is not adopted after birth. The biggest issue faced by potential recipients is finding suitable donor oocytes or embryos. Cryobanking, if performed appropriately, may help to circumvent this problem.

The most crucial prerequisite for a successful egg and/or embryo cryobanking program is the availability of an efficient cryopreservation protocol in addition to having suitable donors. Embryo freezing has been successfully applied for three decades, which explains why embryo banking was introduced into donation programs earlier than oocyte banking. So far, fresh donations have been the most common donation strategy. Indeed, cryopreservation of sperm and embryos has been an integral part of infertility treatment for some time now [2], and as a result, assisted reproduction treatments have become more flexible and effective.

Embryo donation and banking is associated with many ethical, legal, and psychosocial implications. The ability to efficiently cryopreserve oocytes has significantly reduced the need for embryo cryobanking in favor of oocyte banking, opening a new era in donation programs.

There have been various concerns about oocyte freezing, mostly related to its poor clinical efficiency. Until recently, literature on the donation of oocytes cryopreserved by slow freezing was difficult to find, indicating the limitations in clinical application of this technique and highlighting the need for a more efficient cryopreservation strategy. The overwhelming majority of recently published data showed that vitrification caused less cellular trauma and is a more effective technique for human oocyte and embryo cryopreservation than slow freezing [9–11]. Oocyte cryopreservation by vitrification can be performed successfully in a routine IVF program and does not seem to result in decreased developmental potential when compared to fresh cycles [12, 13]. It therefore is becoming the foundation for egg donation programs.

Many factors determine the overall success of a cryobank. In this chapter, we will discuss the advantages of banked materials over fresh donations, outline the most significant factors that determine success, and shed light on the strategies and clinical implications of cryobanks in the field of infertility treatment.

Advantages of Banking Versus Fresh Donation Cycles

Banking of oocytes and embryos has several advantages over fresh donation cycles and can lead to a general improvement in the clinical and logistic efficiency of infertility treatments. Although fresh donation is a proven in vitro fertilization (IVF) technology, it is hampered by several difficulties, such as limited donor availability, cost, the need to synchronize the donor and recipient cycles, travel requirements, and the inability to quarantine oocytes. Oocyte and embryo cryopreservation circumvents or mitigates all of the above-mentioned situations.

Commonly, all the oocytes or embryos from a fresh donation cycle are given to just one recipient. This is mainly due to the difficulty in synchronizing multiple recipients, as it is crucial that each has a receptive uterus for implantation. When banking, synchronization is no longer a problem, and donors can plan their donation cycle to fit their schedule and not be dependent on the recipient or vice versa. This benefit is

especially significant since a shortage in donor eggs and embryos exists in most countries for a variety of religious, ethical, regulatory, and financial reasons. As a result, cross-border reproductive care has emerged, whereby couples or individuals travel to other countries to receive the treatment that they cannot obtain at home.

Due to the medical impact of postponing childbearing, especially in developed societies, women of more advanced ages suffer frequently from diminished ovarian reserve. Consequently, a large demand for oocyte donation has developed, but this has not been accompanied by an increase in oocyte donors [14, 15]. This shortage has become a major problem for both recipients and fertility specialists. Cryobanking allows more efficient sharing of donor eggs and embryos between multiple recipients by improving the utilization of resources. It is thus possible to better select the donor population, resulting in a lower number yet higher quality donation cycles. Additionally, a donation sharing policy provides further prognostic information on oocyte and embryo quality from the analysis of previous IVF cycles from the same donation. This knowledge helps clinicians in the management of subsequent donation cycles, ultimately leading to an improvement in clinical outcomes in terms of pregnancy rate (PR) and reduction of twin deliveries. This aspect is especially important for older recipients who are at risk for developing severe complications resulting from multiple implantations when more than one embryo is transferred.

Another major drawback of fresh donation cycles is the production of supernumerary embryos that require frozen storage until further use or disposal. Unless the recipient fails to conceive, the odds that the frozen embryos will ever be used are low. Knopman et al. recently reported that only 21 % of recipients with supernumerary cryopreserved donor-oocyte embryos returned for transfer if succeeding with their fresh attempt [16]. Oocyte cryobanking dramatically reduces frozen-embryo storage and mitigates many of the related moral/ethical concerns.

Cryobanking eggs also provides the possibility of quarantining oocytes while testing donors for infectious diseases, as is the standard of care used by sperm banks. Consequently, the risk of transmission of potentially transmissible diseases could be further reduced.

Finally, the establishment of cryopreserved donor-oocyte banks considerably simplifies the logistics and means by which oocytes are donated. They provide oocytes that are immediately available, while meeting the recipient personal needs, and thus shortening or even eliminating the problem of long waiting time.

Principles of Reproductive Cryobiology

Currently, cryopreservation plays a significant role in most biological fields. Applications include the use of cryopreserved microorganisms in molecular biotechnology, preservation of frozen tissues for transplantation, cell culture, tissue engineering, a large array of research fields, and assisted reproduction in animals and human. In cryobiological applications, much lower temperatures are applied than what is found in the natural environments where reproductive cells have evolved. This ultra-low-temperature exposure can either destroy living tissue in a matter of seconds or preserve it for years and possibly centuries.

Regardless of the methodology used, the negative effects of cryopreservation procedures on cellular functions (generally referred to as "cryodamage") may impair the oocyte and embryo's ability to develop. These injuries may occur at every step of the cryopreservation procedure [17]. Because of the intrinsic complexity of the phenomenon and the inadequacy of investigation methods, the mechanism and reasons for cryodamage, as well as the specific protective mechanisms of cryoprotective agents (CPAs), are poorly understood. It is thus not surprising that the vast majority of existing cryopreservation techniques have been established empirically on the basis of rough morphological changes observed under a stereomicroscope, and efficiency has been justified by clinical outcomes (i.e., in vitro and in vivo survival and development).

The cooling rate used for oocytes and embryos reflects their size, permeability, and diffusion

characteristics, which is significantly slower than for somatic cells, erythrocytes, or sperm (1 to >100 °C/min). A controlled-rate cooling is used to regulate extracellular ice crystal formation, which is achieved by using a calibrated liquid nitrogen (LN_2) container or an automated machine. The best results are thought to occur at the fastest cooling rate at which a balance (equilibrium) is maintained between water loss (by diffusion) from the cell and the incorporation of this water into the extracellular ice crystals surrounding the cell (for a detailed description of principles of equilibrium cooling procedures, see reference) [18]. The controlled-rate cooling then continues to around −40 to −150 °C, and straws are subsequently plunged into LN_2 for final cooling and storage.

Although this strategy has been routinely applied with relatively good results for embryo freezing (for review, see reference) [19], this has not been the case with oocytes. The reasons for this difference in sensitivity between oocytes and embryos were investigated, but are beyond the scope of this chapter (for more information on the topic, see reference) [17].

It has now been more than two decades since the first report of oocyte cryopreservation using slow freezing [20, 21], and yet, widespread application of oocyte cryopreservation has been hindered by an inconsistent efficiency of the available slow-freezing cryopreservation methods [22]. Novel approaches to slow freezing have been introduced [23–27] with improved oocyte survival rates and subsequent embryo development. Although these studies describe an increase in oocyte slow-freezing success rate, they also show the limitations of the technique in terms of implantation rate per thawed oocyte. Very recently, reduced oocyte developmental competence was reported in frozen cycles when compared with sibling fresh cycles [28], confirming the negative impact of slow-freezing procedure on oocyte potential.

Vitrification is a process by which a liquid is solidified into a noncrystalline (glassy) phase by lowering the temperature and greatly increasing the viscosity. One of the main sources of injuries, ice crystal formation, is entirely eliminated both within the cells being vitrified (intracellular) and in the surrounding solution (extracellular). Whether vitrification will occur depends on the composition of the solution, as well as other factors, the most important being the cooling and warming rates. The phase transition to a glass state is a kinetic rather than a thermodynamic phenomenon, and the glass transition temperature may vary based on the conditions. To achieve vitrification of solutions, a radical increase in the cooling rates or the concentration of CPA is required. Therefore, by dramatically increasing the cooling rate, the CPA concentration could be reduced. As a result, a high cooling rate prevents chilling injury and allows the reduction of the CPA and thus mitigates toxicity.

Recent prospective randomized studies involving oocyte donation as well as the conventional infertile population undergoing IVF have found no significant differences between fresh and vitrified oocytes regarding their vitro and in vivo developmental potential [12]. The minimum volume vitrification method has proven to be the most consistent and efficient strategy to cryopreserve oocytes and embryos for all kinds of reproductive treatments, including cryobanking for donation cycles.

Elements That Determine Success

Technical Aspects

When determining efficiency of a banking program, the first and probably most important variable that must be considered is the survival of the eggs or embryos. Without having a dependable protocol for storage with high post-thaw survival rates, donor banks will not meet their foremost priority, which is to provide viable eggs and embryos to recipients, resulting in pregnancy and live birth. To accomplish this goal, there are numerous technical aspects to consider.

Cooling and Warming Techniques

During a cryopreservation cycle, eggs/embryos are cooled to a specific temperature (typically −196 °C when using liquid nitrogen), stored, and warmed

when needed. There are several ways to accomplish this. However, the most commonly used techniques all use LN_2 to cool the specimens to a desired temperature.

Slow freezing can be described as an attempt to create a delicate balance between various damaging factors, including ice crystal formation, fracture, toxic, and osmotic damage. During slow cooling, a gradual, often stepwise cooling rate is typically applied by exposure to LN_2 vapor or by automated freezing devices (see below) that use LN_2 to obtain a fixed cooling rate. The specimens are cooled gradually to −6 °C by placing the straws into the controlled-rate freezer. At about −7 °C, seeding is performed, which induces ice crystal formation in the solution, preferably far from the sample. There are slight variations in the subsequent cooling rates, but values are between 0.3 and 1 °C/min. Only when the desired temperature is reached (between −40 and −120 °C), the cells are submerged into LN_2 for final cooling and storage.

During vitrification procedures, eggs/embryos are exposed directly to LN_2 without significant prior cooling (typically only to room temp). This is a much quicker process and requires significantly less and cheaper equipment than with modern slow-freezing techniques. The direct submersion results in an ultrarapid cooling rate and formation of a glasslike phase instead of freezing. The warming method correlates to the method of cooling that was applied. For slow frozen, warming is typically achieved by thawing in a 37 °C water bath, whereas protocols that use vitrification required submersion of the eggs/embryos directly into warming media at 37 °C. Regardless of which method of cooling and warming is used, it is important that the cryopreservation media, carriers, and devices are compatible with the chosen protocol.

Cryopreservation Media

Cryopreservation media are formulated not only to serve as a carrier solution for the frozen or vitrified eggs and embryos but also to protect the cells from damage that may occur during cooling. In fact, most of the media consist of a basic medium, such as tissue culture medium (TCM) M199, supplemented with protein and CPA. The latter are especially important as they change the physical properties of the solution to prevent ice crystal formation, which may damage cell membranes and other organelles. Two types of CPAs, permeable (such as dimethyl sulfoxide and ethylene glycol) and non-permeable (such as sucrose) are typically used in combination to achieve maximum protection against cooling and subsequent warming. Oocytes and embryos are usually equilibrated in 1–2 mol/L solutions of permeable and non-permeable CPAs.

Slow-freezing and vitrification protocols usually include stepwise introduction of the CPAs as well as stepwise dilution to prevent osmotic shock. This means that several different media, usually made up of the same base solution with different concentrations of the CPAs, are used during cooling and warming procedures. These can be purchased in kits containing all the necessary solutions, or they can be made in-house. For a successful donor program, it is essential that the laboratory has access to cryopreservation media that allow sufficient survival rates, whether they use commercially produced or "homemade" media.

Cooling Devices

Storage of eggs and embryos by cryopreservation requires cooling of the medium (containing the eggs/embryos) to a temperature that is low enough to cease all physical, chemical, and thus metabolic activity that normally occur in cells. Traditionally, this is achieved by storage in LN_2 (−196 °C) and lately in LN_2 vapor [29]. Vitrification by super-rapid cooling using LN_2 slush (−205 °C) is a newer technique that can result in higher embryo survival compared to traditional LN_2 [30]. In the case of slow freezing, it is essential to cool the cells as much as possible before submersion in LN_2 to prevent cryodamage. Various devices can be used to accomplish this. These include a wide range of LN_2 containers, ranging from homemade Styrofoam boxes with calibrated shelves for vapor cooling to commercially available automated machines. The device of choice depends on the protocols used for cryopreservation. Slow-freezing protocols are

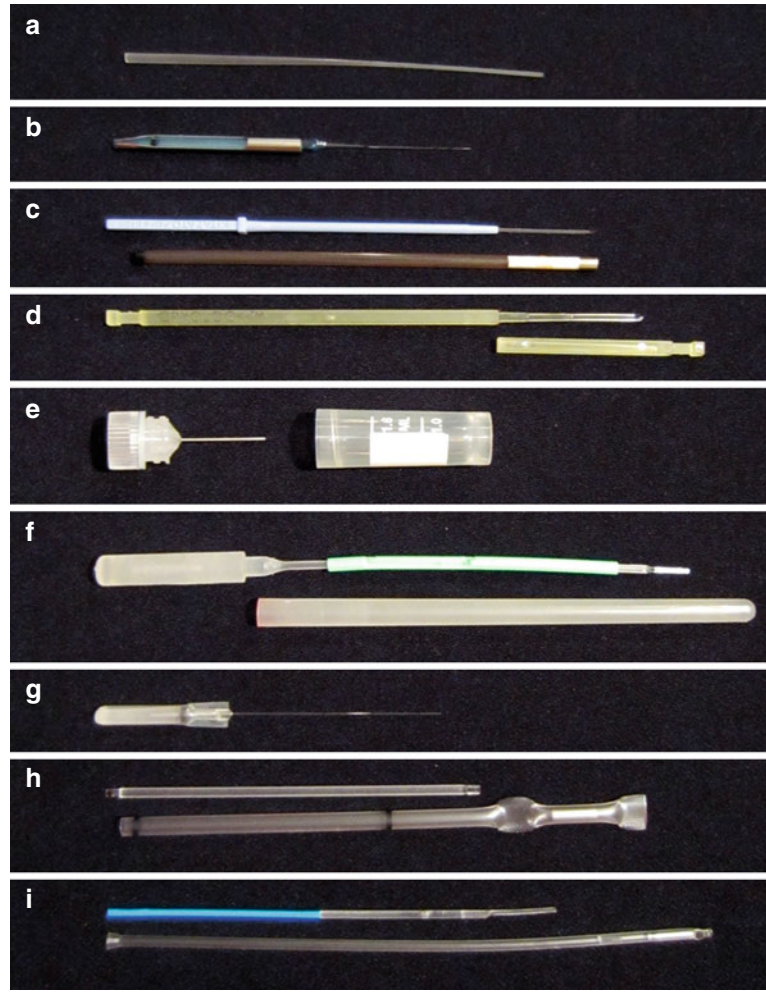

Fig. 20.1 Vitrification carrier devices; photo taken by Liesl Nel-Themaat

typically more dependent on these devices, as vitrification is typically performed by submerging the cells into LN_2 without significant prior cooling.

Carriers

When embryos/eggs are cryopreserved for storage, a suitable carrier is necessary to hold and protect the cells in a specified volume of cryopreservation medium. They should also be practical for operational purposes. During slow freezing, 0.25-mL plastic straws that can be sealed after loading are typically used. For vitrification, several different devices are commercially available, while there are a few that can be made in-house (Fig. 20.1). They differ from the classical straw in that they hold the embryos/eggs in a very small volume of cryopreservation medium, thereby allowing a rapid cooling rate and vitrification instead of freezing (for review, see [31]). Examples include the Open Pulled Straw (OPS, Fig. 20.1a), Cryotip (Fig. 20.1b), Cryotop (Fig. 20.1c), Cryolock (Fig. 20.1d), Cryoloop (Fig. 20.1e), and McGill Cryoleaf (Fig. 20.1f). These devices require direct submersion into LN_2, which brings some concerns about cross-contamination.

Recently, some devices were designed with a protective cap or sleeve that is sealed prior to vitrification, which therefore provides a closed

system. These include the Cryopette (Fig. 20.1g), Rapid-I (Fig. 20.1h), and High Security Vitrification system (Fig. 20.1i). The choice of carrier is based on each lab's preference, and no one device or vitrification protocol thus far has been proven superior to all others. However, it is generally accepted that vitrification results in higher survival rates than those obtained using slow freezing [32]. Regardless of the technique used, carriers should be appropriate for the type of cryopreservation that is performed.

Storage

After cryopreservation, eggs and embryos are placed into storage where they may remain for extended periods until a transfer is requested. This may be years after collection, and there is so far no indication how long oocytes and embryos remain viable if stored correctly, but theoretically, there is no time limitation. It is therefore of utmost importance that a dependable storage system is implemented. Traditionally, cells have been banked in LN_2 in large dewars that have to be filled on a regular basis to keep the LN_2 levels high enough to allow cryopreserved materials to remain submerged. However, this can be a tedious process, especially in larger programs with numerous dewars. Automated systems are thus a more practical approach. Dewars are connected to a computerized system and external LN_2 source that will automatically monitor and fill the dewars when needed.

Concerns with cross-contamination have prompted design of similar systems, in which the cells are kept in the vapor phase rather than being exposed directly to LN_2 [29]. One critical component of storage is tracking and identification of specimens. The most effective is an electronic database on a high security server and sufficient backup in case the main server fails. Storage of eggs and embryos should comply with whatever tracking system has been implemented. It is important that all the technicians that handle eggs or embryos to be included in the bank are fully trained and understand the storage procedure to prevent loss of specimens. Such a system allows easy and prompt location of specific eggs and embryos when needed and eliminate any chance of misidentification. Labeling of carriers at the time of cryopreservation should also be consistent with the storage system.

In cases where oocytes or embryos are vitrified in a location other than where warming is performed, safe transportation to the lab is essential. Typically, the specimens are transported in dry shippers, which keep them in LN_2 vapor. Recent studies did not observe any adverse effects of storing embryos [33] or oocytes [29] in the vapor phase.

Safety

In recent years, much emphasis was placed on the concerns with direct exposure of human eggs and embryos to LN_2 [34]. There is a theoretical chance that shared storage of materials that are exposed to the surrounding LN_2 may allow cross-contamination of viruses and possibly other microorganisms between specimens of different patients, as was shown in gametes, embryos, and other tissues [35–38]. This has prompted development of several "closed" vitrification systems, where direct exposure to LN_2 is prevented by sealing of the small straws or by placing a tight cap over the specimens (see section on carriers above). The downside of this approach is that the cooling rate is significantly decreased due to the larger volume of cryopreservation medium that is required with micro straws and the layers of air and plastic that is surrounding the cells in capped devices. This means that vitrification is less efficient and survival rates are potentially decreased when compared with "open" vitrification systems. However, the benefits of eliminating chances for cross-contamination may override this.

Another approach is to sterilize the LN_2, by means of ultraviolet irradiation [39, 40] or filtration [30]. Despite these concerns, to date, no case of disease transmission following transfer of embryos from either vitrified eggs or embryos contaminated by LN_2 has been proven. However, transmission of hepatitis B virus from embryos to recipients due to culturing embryos with contaminated serum has been documented [41]. Since there are currently no laws prohibiting open systems, it is the responsibility of each program to weigh the advantages and disadvantages

of open and closed systems before choosing a protocol.

Oocyte Banking

Donor Recruitment, Selection, and Management

Recruitment

Traditionally, for classical egg donation, the burden of finding a suitable donor caused significant stress for patients needing donor eggs [42]. With donor egg banks, however, recruitment of donors is the responsibility of the clinic. Advertising by means of newspapers, the Internet, radio, flyers, etc., is utilized to attract potential donors. In the USA, it is permissible to compensate egg donors financially, which creates a large incentive for many young women. The ASRM Ethics Committee published guidelines on solicitation of donors, which should be met [43]. A donor typically receives between $3,000 and $8,000 for a first donation. In many other countries, financial compensation for egg donation is not permitted, which makes recruiting donors much more challenging. Known, fresh donations will thus remain more popular in these countries, while anonymous donor incentives are truly for the greater good. Patients from countries with restrictive regulations may also opt for treatment in countries where financial compensation is allowed due to a shortage in their home countries.

Selection

Success of a donor egg bank is dependent on selection of suitable donors who will produce a large enough number of good quality eggs. Not only should the specific demands of recipients be met, but also rigorous screening of the candidates is performed. Some of the criteria are requirements by governing bodies, such as the Food and Drug Administration (FDA), United States Center for Disease Control (CDC), National Institute of Health (NIH), American Association of Tissue Banks (AATB), the American Association for Reproductive Medicine (ASRM), and the Society for Assisted Reproductive Technology (SART), while others are custom standards of each individual program. These guidelines are summarized by the ASRM Practice Committee Report [44]. The FDA, which determines the minimum requirements by the federal government, mandates testing of egg and embryo donors for an array of communicable diseases under the Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) rules, although there are unique exceptions specifically added for embryo donation (www.fda.gov).

The ASRM and SART have additional guidelines for determining donor eligibility, which includes general health, psychological assessment, age restrictions, genetic disorders, sexual history, and overall family health. Individual centers may have even more rigorous evaluations, such as enhanced genetic and psychological testing [45], as well as physical attributes based on recipient demands, such as race, education level, and appearance. Also, the basal antral follicle count (AFC) of potential donors is typically taken into consideration to determine if the person would be an effective donor. For instance, at Reproductive Biology Associates (RBA) in Atlanta, an AFC of at least 18 is required for consideration.

Management

Once a candidate is verified as donor eligible, a contract is prepared and signed by both parties. A detailed profile is compiled with information to help recipients choose an appropriate donor. Information needed for the profile is determined by the clinic and may include physical attributes, such as eye, hair and skin color, body type, education, occupation, talents, and hobbies. A recipient can then browse through these profiles to select the best fit for her needs.

Donors are responsible for self-administering the ovarian stimulation drugs on the precise schedule depicted by their treatment protocol. Stimulation protocols are commonly determined by AFC count and donor age, as well as previous stimulation history, if available. The contract should describe what happens should a donor fail to take the stimulation drugs correctly. Typically, the clinic may cancel the cycle at any point, for the above reason or if the donor is responding

poorly, and there is indication that there may not be enough developing follicles to justify retrieval. In this case, donors are typically compensated only partially, and they may or may not return for a subsequent stimulation, depending on the doctor's decision.

The specific donor simulation protocol is determined by the physician. It was recently reported that, although the number of mature oocytes and embryos obtained from administration of gonadotropin-releasing hormone agonist for final oocyte maturation was significantly higher than those obtained from human chorionic gonadotropin, fertilization, implantation, and clinical pregnancy rates were not different between the two treatments [46]. Thus, it does not appear that overall oocyte quality is affected by which drug is used to trigger maturation.

Single Versus Multiple Donations

Multiple donations by a single donor can be advantageous for all three parties that are involved. First, where donor compensation is allowed, the donor may benefit financially from multiple donations, which is often the main incentive for young donors to participate. Second, the recipient may have added confidence in a specific donor whose eggs have previously been used to obtain healthy pregnancies. For the clinic, sequential donor cycles provide valuable information about the performance of the donor's eggs. If they survived cryopreservation well, followed by good fertilization and embryo development and resulted in healthy pregnancy, the clinic may start with thawing fewer eggs for subsequent cycles, thereby maximizing efficiency from the donation.

Despite concerns about donor health and inadvertent consanguinity [44], there are no known disadvantages of multiple egg retrievals on subsequent oocyte quality. In fact, Opsahl et al. (2001) reported no adverse effect or decline in oocyte competence in up to six sequential donations. Furthermore, the interval between donation cycles did not correlate with success rates [47]. More recently, Nel-Themaat et al. (2011) [48, 49] did an in-depth comparison of donor-oocyte performance from first, second, and third donations from a vitrified egg bank. Again, no difference between sequential cohorts was observed [48, 49]. These reports suggest that oocyte banks can encourage donors with good performing first cohorts to return for subsequent donations without fear of decline in fertility due to multiple donations.

Successful donors may also opt to return for additional donations with less aggressive ovarian stimulation in subsequent cycles, as they do not need to produce such large numbers of oocytes to procure live births. In addition, because of their high oocyte-to-baby rate, the best prognosis donors are ideal candidates for egg splitting between multiple recipients.

Recipient Selection and Management

Donor-oocyte recipients are individuals who are clinically or socially unable to produce competent, genetically sound oocytes. These include women who are infertile due to ovarian failure, advanced reproductive age, women with a critical genetic defect, patients that lost their fertility due to cancer or other disease treatment, and homosexual, male couples. Recruitment of recipients is mostly performed by the clinicians, as a large percentage of recipients are patients that have attempted previous (non-donor) IVF cycles unsuccessfully and are using oocyte donation as a last resort in an attempt to have a baby that is at least genetically related to the male partner. Thus, the doctor may suggest donor oocytes as a more realistic approach, especially in women of advanced reproductive age.

Potential recipients are subjected to the same medical tests that apply to regular IVF patients, with the addition of more rigorous psychological counseling as depicted in the ASRM guidelines [44]. Uterine receptivity is of utmost importance to establish a pregnancy, and for patients that are utilizing surrogates to carry the pregnancy, the surrogate also has to be evaluated.

Recipients usually have an idea of what phenotype they desire in an oocyte donor and are

presented with the donor profiles of available oocytes. At RBA where the egg bank and treatment center are the same entity, the clinic helps narrow the potential donors down to only a handful from which the recipient must choose. Recipients are also required to select a backup donor if the first selected donor has fewer than six eggs banked. Oocytes are allotted on a first come, first serve basis, and if there are extra oocytes available, the patient may purchase additional ones. Reproductive Biology Associates guarantees two good quality blastocysts for transfer from a donor-oocyte cycle. This can normally be accomplished by warming about six vitrified oocytes. Naturally, these numbers will be unique to each program and depends on the efficiency of the vitrification and ICSI procedures used, as well as the "quality" of the oocytes prior to freezing. Should the clinic fail to meet this agreement, the recipient will be offered a free cycle at RBA. In cases where more than the desired number of embryos for transfer is obtained, the leftover embryos remain the property of the recipient, who may opt for cryopreservation. It is critical that the contract between the clinic and the oocyte recipient clearly states the expectations and responsibility of the recipient and the clinic.

For programs that do not have their own egg banks, the agreement might be very different in that the patient purchases a specific number of oocytes from a third-party egg bank, so that the clinic does not carry the responsibility for the quality of the eggs. It is thus expected that each program deals with recipient management uniquely.

Recipient hormonal preparation should be synchronized with the timing of oocyte warming to ensure the uterus is receptive at the time of embryo transfer. Protocols are based on individual patient indications, which is beyond the scope of this chapter.

Oocyte Quality

Noninvasive Oocyte Evaluation

Noninvasive oocyte quality evaluation may be the most important task in egg-banking donation programs for optimum management of resources, in order to reduce the risk of ovarian hyperstimulation syndrome and minimize multiple pregnancies. The ability to identify the most competent oocytes would be of great benefit to the general practice of in vitro fertilization (IVF) and especially in egg donation treatments, allowing oocytes with the highest developmental potential from a cohort to be prioritized and equally distributed among multiple recipients.

The steep decline in both natural fertility and success after assisted reproduction treatment with increasing maternal age is universally recognized, and at present, female age still represents the most predictive variable of oocyte competence [50]. The high success rates reported in recipients of donor oocytes, irrespective of their age, are comparable to those of young women undergoing autologous-assisted cycles, leading to the conclusion that age of the oocyte donor is the single most important factor predicting reproductive success [51, 52]. For example, studies of egg donation have indicated that reproductive age of donors plays a much larger role in fecundity decline than uterine deterioration [53]. The consequent pregnancy loss related to maternal age cannot be inferred from age-specific pregnancy rates in natural fertility populations [54] or from patients undergoing assisted conception technology [55]. This recognition of the maternal age factor has influenced egg donor recruitment immensely so that at present, healthy donors <30 years old are usually selected.

Apart from the general effect of age, specific recipient or cycle-related variables do not seem to predict success or failure with high probability. Variations in oocyte quality within a cohort from a given woman and between women of the same age make investigating the influence of those variables challenging, as indicated by discordant outcomes in recipients sharing eggs from the same donor [56, 57] and in a study of egg donation to two or three recipients [58]. In the latter study, 85–90 % of the variation in pregnancy and live birth outcomes could not be explained by specific donation characteristics, such as age and number of oocytes harvested. Donor heterogeneity in terms of the oocyte quality (the "donor effect") remains unexplained and under-investigated, yet is responsible for the

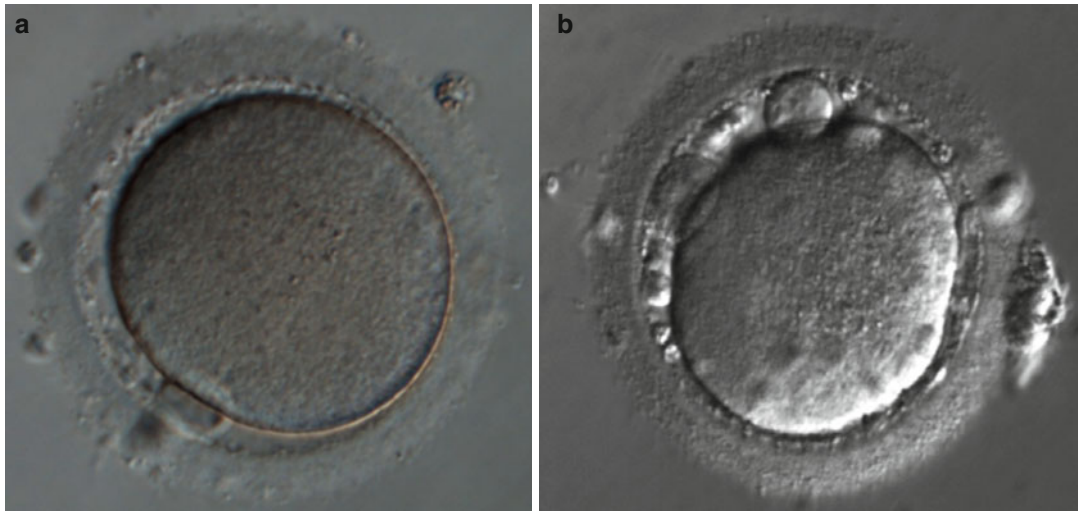

Fig. 20.2 (**a**) Good quality oocyte; photo taken at RBA, ZP Nagy, T. Elliott. (**b**) Poor quality oocyte image courtesy of Dr. Thomas Ebner

failure of most oocyte donation treatment cycles. Further improvements in clinical success will require identification and selection of favorable donor characteristics, as well as avoidance of factors that compromise either ovarian function (e.g., a history of disease or chemotherapy) or signs of imminent ovarian failure (e.g., increased serum FSH concentrations). Most importantly, if oocyte competence could be evaluated through a better understanding of the biological characteristics of this donor effect, the benefits for reproductive care would be enormous.

There exists general opinion that oocyte morphology, as determined by conventional microscopy, is a poor representation of its developmental competence [59]. The relationship between MII oocyte morphology and ICSI outcome is controversial. The use of different criteria for oocyte evaluation may be partly responsible for the discrepancies between different studies. It is generally recognized that a "normal" human MII oocyte should have a round clear zona pellucida, a small perivitelline space containing a single unfragmented first polar body (1PB), and a pale moderately granular cytoplasm that does not contain inclusions when observed under light microscopy (Fig. 20.2a) [60–63]. However, the majority of the oocytes retrieved after ovarian hyperstimulation exhibit one or more variations of the described "ideal" morphological criteria [59, 64]. This is true also for oocytes obtained from proven fertile donors [65]. Abnormal zona pellucida, large perivitelline space, vacuoles, refractile bodies, increased cytoplasmic granularity, smooth endoplasmic reticulum clusters, and abnormal, fragmented, or degenerated polar bodies can all be observed after oocytes are denuded (Fig. 20.2b). However, the correlation between these "abnormal" oocyte morphotypes, fertilization rates, and embryo development is still unclear. Furthermore, embryo quality has been found to be unrelated to oocyte appearance, and similar clinical pregnancy and implantation rates have been reported after transferring embryos derived from "abnormal-" or "normal"-appearing oocytes [62, 66]. Therefore, it has been suggested that all oocytes can be fertilized by ICSI, independent of their morphologic appearance under light microscopy [62, 66].

In contrast, other studies have reported a correlation between oocyte morphology and embryo developmental potential [67, 68]. A recent systematic review investigating if any single or group of noninvasive morphological features of MII phase human oocytes have a predictive value for further development did not support the general opinion about the features of "good-" and "bad"-quality oocytes or respective developmental competence [69]. Features evaluated in the above-mentioned study were the following: meiotic spindle by polarized light microscopy, zona

pellucida, vacuoles or refractile bodies, polar body shape, oocyte shape, dark cytoplasm or diffuse granulation, perivitelline space, central cytoplasmic granulation, cumulus–oocyte complex and cytoplasm viscosity, and membrane resistance characteristics. According to the authors, none of these features had prognostic value for further developmental competence of oocytes. Furthermore, it is clear that only a minority of morphologically normal oocytes produce pregnancies, suggesting that most of the problems leading to poor embryonic development and implantation failure cannot be detected using standard microscopic evaluation [70, 71].

In the end, beginning with the first microscopic evaluation of denuded oocytes, only a few extremely abnormal-appearing features are particularly important for selecting oocytes that should *not* be used. These include giant oocytes and those with large polar bodies. Although the occurrence of these morphotypes is relatively rare after ovarian hyperstimulation, the use of these cells for IVF is potentially dangerous. It has been shown that all embryos generated from giant oocytes are chromosomally abnormal due to hyperploidy. What is especially worrisome is that they may cleave normally and develop to the blastocyst stage [72]. Naturally, transfer of these embryos could increase the risk of miscarriage. However, in clinical practice, oocytes are obtained from a young, homogeneous population of donors and thus typically exhibit a relatively uniform quality. Of course, not all of them result in live births, further suggesting that morphological evaluation is not a dependable approach for oocyte quality determination. At present, routine oocyte analysis is therefore mostly restricted to a simple assessment of nuclear maturity (i.e., presence of the 1PB is indicative of a mature MII oocyte).

Genomic and Post-genomic Evaluation of Oocyte Quality

As described above, the current morphological criteria used to select and classify oocytes are not sufficient for choosing the ideal oocyte for fertilization or the resulting embryo for transfer. Research into new molecular and cytogenetic methods for the identification of competent oocytes is yielding promising results [73].

Aneuploidy is remarkably common in human oocytes and is a major cause of spontaneous abortion, embryonic arrest, implantation failure, as well as failed IVF cycles [74–76]. Therefore, a recipient can desire to have donated oocytes genetically screened to lessen the risk of a trisomy conception and potentially improve her clinical outcomes.

Data obtained from the cytogenetic analysis of human oocytes in an IVF setting have clearly shown a direct relationship between advanced maternal age and increasing aneuploidy rates [77–80]. Specifically, such studies suggest that the expected aneuploidy rate in the oocytes of women under 25 years of age is 5 %, increasing to 10–25 % in the early 30s and typically exceeding 50 % in women over 40. However, cytogenetic studies in donation cycles have been surprisingly contradictory. The scantly published PGS data on embryos derived from oocyte donors indicate unexpectedly high rates of chromosome anomalies (56–57 %) [81, 82]. According to Reis Soares et al. (2003), the reason for the observed abnormalities could be that donors are frequently subjected to more aggressive stimulation protocols, compared to other women of similar age, in order to guarantee the production of a large cohort of oocytes. A better approach for examining the incidence of aneuploidy in young fertile women would be to analyze oocytes directly, thereby removing male-derived confounding factors as well as postzygotic errors.

In a recent study by Fragouli et al. (2009), a total of 121 metaphase II oocytes and their corresponding first 1PB were analyzed with the use of a comprehensive cytogenetic method, comparative genomic hybridization (CGH). The oocytes were obtained from 13 young donors (average age 22 years) without any known fertility problems. All oocytes were mature at the time of retrieval and were unexposed to spermatozoa. A low aneuploidy rate (3 %) was detected [83]. These results clearly indicate that meiosis I segregation errors are not frequent in oocytes of young fertile women. However, the low aneuploidy rate detected in donor oocytes in this study

is in sharp contrast to the 65 % abnormalities reported by Sher et al. (2007) in their attempt to examine donor oocytes and PB via CGH [84]. This extreme difference in oocyte abnormality rates could be attributed to various technical/methodological issues or patient-specific factors, and has been discussed in detail previously [80]. It is important to note that previous data, obtained using a wide variety of cytogenetic techniques, including CGH, spectral karyotyping, and conventional chromosome banding studies, are all indicative of a low aneuploidy rate for donor oocytes. The incidence of chromosome imbalance in these studies varies from 4.5 to 23 %, with most finding <12 % aneuploidy for oocytes of women under 30 years of age [77–80].

Overall, the data reported so far clearly indicates that young oocyte donors without any known fertility problems have an extremely low rate of aneuploidy in their oocytes after the completion of meiosis I. Therefore, genetic testing of donor oocytes in a clinical setting cannot be justified. On the other hand, it is plausible that some donors fall in a category more susceptible to meiotic aneuploidy. Advanced age, aggressive hormonal stimulation, or other still unrecognized patient-specific factors can predispose some donors to increased incidence of meiotic aneuploidy, suggesting a positive effect of PB genetic screening. However, 1PB analysis presents significant methodological and conceptual problems that markedly hamper its efficiency, especially in IVF clinics. Prima facie, about half of female meiotic aneuploidy occur during the second meiosis after fertilization [85]. Consequently, considering also male factors (about 5 %) and postzygotic (about 25 %)-derived errors, the test of only the 1PB is poorly indicative of the genetic constitution of the resulting embryos. Second, it was recently reported that chromatid errors greatly outnumber whole chromosome aneuploidy during the first meiosis [86], since chromatid errors could be rescued during the second meiotic division, as the case of balanced PD. Therefore, testing only the first PB eliminates the chance of rescue during the second meiotic division. Finally, the detection of extra or missing chromosomes in a polar body is supposed to be indicative of a reciprocal loss or gain of chromosomes in the corresponding oocyte. However, noncomplementary aneuploidy, such as meiotic anaphase lag and germ line mitotic errors, can lead to a meiotic segregation characterized by aneuploid daughter cells, while the other cells are euploid for that chromosome, leading to misdiagnosis [87, 88]. In conclusion, lack of clinical indication and inefficiency of 1PB genetic approach definitively do not support its application in oocyte donation programs.

It seems likely that the greatest advances will originate from the evolution of molecular genetic technologies. The application of microarray to analyze individual oocytes and their associated cumulus cells (CCs) provides a simultaneous assessment of activity for thousands of genes and reveals potential viability markers [89–91].

Fragouli et al. (2010) combined a comprehensive cytogenetic investigation of oocytes with a detailed assessment of their transcriptome and showed that aneuploidy is associated with altered transcript levels, affecting a subset of genes [92]. Some of the highlighted genes produce proteins involved in spindle assembly and chromosome alignment. Additionally, several differentially expressed genes produce cell surface or excretory molecules, suggesting that noninvasive methods of assessing oocyte aneuploidy could be developed in the future.

The investigation of gene expression in cumulus cells is also of great interest for both research and clinical applications. It is widely recognized that bidirectional communication exists between the human oocyte and CCs, which is essential for the production of competent oocytes. Cumulus cells share the same follicular environment as the oocyte with which they are associated and therefore may be indicative of its quality. Analysis of gene expression in these cells may provide an indication of the microenvironment in which the oocyte matured. The fact that cumulus cells can be collected and analyzed without manipulating or compromising the oocyte makes them attractive as targets for oocyte competence assays. Several studies have already linked differential gene expression in granulosa cells, with subsequent embryonic

developmental capacity [93, 94]. Recently, Adriaenssens (2010) and others have shown that the expression of ovulation-related genes in CCs is associated with patient and treatment characteristics and oocyte developmental potential and differs with the type of gonadotropin used, and it also showed strong correlation with subsequent embryo development and quality [89–91]. Moreover, microarray analysis has permitted the cataloguing of virtually all of the genes expressed in cumulus cells, a first step toward identifying genes influencing or associated with oocyte competence [95]. However, gene expression is highly dependent on cell cycle phase and on experimental conditions, such as culture medium and air composition. Therefore, before translating this information into clinical applications, all of these factors should be addressed and standardized. Moreover, although data concerning gene expression provide useful information regarding the gene activity of oocytes and cumulus cells, a change in the number of mRNA transcripts derived from a given gene does not necessarily indicate altered utilization of the pathway in which it functions. Most genes are under some degree of regulation at the posttranslational level, through protein modification, degradation, or sequestration. Consequently, there may be occasions when a change in the concentration of active protein is not mirrored by an alteration in gene activity. An additional consideration is that many genes produce more than one type of protein, accomplished by utilizing mechanisms such as alternative splicing and posttranslational modification. Investigation of gene expression provides no information concerning posttranslational events. Therefore, noninvasive analysis of cellular-secreted molecules and metabolites approaches are emerging.

Recently, improved equipment and optimized methods of mass spectrometry have provided sufficient sensitivity to allow proteomic profiles to be generated from single oocytes and embryos, while metabolomic investigations have searched for indicators of oocyte/embryo quality in spent culture medium [49, 96]. Techniques such as these may ultimately lead to noninvasive tests for oocyte quality, revealing previously hidden information concerning both oocyte and embryo developmental competence.

Despite the intensive research and some promising results [73, 96, 97], the application of microarray and mass spectrometry techniques for proteomic and metabolomic characterization of single oocytes is still in the early stages. Once fully validated, these new approaches are expected to revolutionize oocyte and embryo selection, and may lead to improved implantation rates and higher probabilities of success using elective single embryo transfer (eSET). However, presently none of these methods are ready to be used in clinical practice.

Clinical Strategies and Efficiency of Donor-Oocyte Banking

Oocyte donation using cryotop-vitrified/warmed oocytes has been recently evaluated to provide evidence that oocyte banking is technically feasible and yields ongoing pregnancy rates (OPRs) similar to those obtained with fresh embryos. Nagy et al. (2009) reported high fertilization rates and similar embryo development when comparing the use of vitrified and fresh oocytes in their ovum donation program, with both methods leading to high cumulative clinical pregnancy rates (85 and 78 %, respectively). When the authors compared these results with those from the donor's previous fresh cycles, they observed a very similar outcome [98].

In 2008, Cobo and colleagues compared the in vitro development of donor-vitrified/warmed oocytes with those of sibling oocytes of the same stimulation cohort [99]. After denuding, mature oocytes were randomly assigned either to fresh or cryopreserved group. This model is extremely valuable to assess the possible effects of the vitrification procedure on oocyte developmental potential, since embryos could be simultaneously generated from vitrified and fresh oocytes from the same cohort using the same semen sample. A survival rate of 96.7 % was achieved, and no significant difference in embryo preimplantation development was detected between vitrified and fresh oocytes. Moreover, pregnancy,

implantation, miscarriage, and OPR per transfer (65.2, 40.8, 20, and 47.8 %, respectively) were comparable to results obtained from fresh oocyte donations in the same program [100]. In a subsequent publication [101], the potential benefits of oocyte banking for cancer patients were highlighted by the survival and clinical results obtained from this donation program.

Very recently a randomized, triple-blind, single-center, parallel-group controlled-clinical trial, including 600 recipients selected among 1,032 eligible patients, compared the outcome of vitrified-banked oocytes with the gold standard procedure of employing fresh oocytes. There were no differences in donor ovarian stimulation parameters, demographic baseline characteristics for donors and recipients, ovum donation indications, or male factor distribution between groups [102]. The resultant OPR per intention-to-treat was 43.7 and 41.7 % in the vitrification and fresh groups, respectively. This high evidence-level clinical trial confirmed the effectiveness of oocyte cryo-storage in an ovum donation program and failed to demonstrate the superiority of using fresh oocytes instead of vitrified-banked ones in terms of OPR [10, 103]. These remarkable findings underline the clinical efficiency of oocyte vitrification and demonstrate that the use of stored vitrified oocytes is currently feasible and yields good clinical outcomes that are comparable to fresh oocyte donation cycles.

The overall donation efficiency seems to be elevated when vitrified oocytes are used instead of fresh donations. In the previously mentioned study by Nagy et al. (2009), when fresh and frozen oocyte donation cycles were compared, one of the most striking differences was the number of oocytes allocated per recipient: on average about five times higher in fresh cycles (7.7 vs. 35.8, $p < 0.05$) [98]. It was possible to keep the number of warmed oocytes relatively low in the study group due to the extremely high survival rates of vitrified oocytes. As a consequence, a total of 17 patients achieved ongoing clinical pregnancies from ten cryopreserved oocyte donation cycles versus seven patients from nine fresh oocyte donation cycles using the same donors. This outcome suggests that the general efficiency of oocyte donation can be significantly improved using cryobanking. Moreover, recipients end up having a higher number of extra embryos in a fresh donation cycle, adding to the ever-increasing problem of surplus cryo-stored embryos. In contrast, there were very few supernumerary embryos cryopreserved in the cryo-egg group. Nonetheless, re-vitrification of leftover embryos occurred in 66.7 % of patients, in conjunction with an OPR of 49.1 %, which reflected the excellent yields obtained from the cryobanking strategy. Revitrified embryos, which are embryos derived from fertilizing vitrified and warmed oocytes, were also shown to result in live births when transferred, reinforcing this concept [104].

Multiple pregnancies should be avoided, particularly in donation programs, since recipients have an increased risk of obstetric complications when carrying more than one fetus, especially since most recipients are of advanced maternal age, exposing them to an even higher risk than the typical IVF patient. The developmental competence of embryos obtained from vitrified oocytes was apparently not affected by the vitrification procedure, since they maintained the potential to be fertilized and develop into high-quality blastocysts. Furthermore, it was shown that by increasing the proportion of eSETs, it is possible to reduce the number of twins without affecting delivery rates of oocyte recipients in cryobanking programs [105, 106]. In the study of Garcia et al. (2011) blastocyst formation rates were 41.3 and 45.3 % for the study and control groups, respectively. Pregnancy rates (PRs), implantation rates (IRs), and miscarriages rates (MRs) were similar for study and control groups (PR: 61.8 vs. 60.0 %; IR: 43.9 vs. 42.9 %; MR: 9.5 vs. 5.9 %). The delivery rate was similar after eSET and double embryo transfer (32.6 and 32.1 %, respectively). Overall, IR calculated from the number of oocytes warmed in this study reached 19 %; in other words, approximately five warmed oocytes resulted in one implantation [105]. These data support the use of eSET in cryo-oocyte banking programs with the aim to minimize multiple pregnancies.

Finally, one of the most relevant aspects related to the use of cryo-stored oocytes is the

availability of these gametes once the endometrial preparation for the recipient is finished. In the study by Cobo and Diez. (2011), the mean number of days of endometrial preparation was 15.5 ± 4.6 and 22.4 ± 5.4 for recipients receiving vitrified and fresh oocytes, respectively (not significantly different). Moreover, 11 patient cycles were cancelled because of endometrial bleeding or estrogen replacement for longer than 50 days in recipients of fresh oocytes. No patients were cancelled in the vitrification group due to such causes [10]. These findings demonstrated one of the most relevant advantages of oocyte cryobanking. With the establishment of more egg-banking programs, there should be a significant drop in the cycle cancellation rate of oocyte recipients.

Overall, the mentioned publications represent a justifiable change in the current practice of oocyte donation, as they highlight the feasibility of a safer and more efficient approach to oocyte donation via vitrification.

Embryo Banking

Donor and Recipient Selection

Considering the recent progress in oocyte cryopreservation and clinical outcomes reported with egg-cryobanking, the application of donor embryo banking is steadily becoming less frequent. Indeed, providing that male fertility is preserved, there may be no benefit in offering embryo versus oocyte donation cycles. In the case of a female with severe infertility, oocyte donation allows the possibility to generate embryos at least genetically related to the father, a common wish among recipient couples. Moreover, donated oocytes come preferentially from young fertile donors, which increases a recipient's chance of pregnancy compared to using "spare" embryos obtained from infertile couples. This is not surprising considering that couples will first have their seemingly best embryos transferred, consequently leaving those of lesser quality for donation. Furthermore, couples that carry a genetic defect may undergo PGD with high efficiency, circumventing the need for embryo donation in most cases.

Cryopreservation of oocytes instead of embryos in assisted reproduction programs has been outlined earlier [107], and the recent increase of efficiency reported by various groups has made it a realistic possibility that embryo cryobanking may become less common. However, in some cases, embryo donation is still a viable option, and cryobanked embryos could be considered a backup for particular situations in which both partners are unable to produce viable or genetically normal gametes. Moreover, with the liberalization of societal norms, there may be single women or lesbian couples that may choose to have families of their own. Embryo donation would be an option for them instead of going through an ovarian stimulation coupled with sperm donation. Finally, embryo donation is generally a significantly more affordable way of obtaining a pregnancy, which may be the primary factor of consideration for many couples. The spare embryos that commonly result from in vitro fertilization cycles are usually kept for this purpose.

Many couples, after attaining their desired family size or giving up any further pursuit of having children, may never use their surplus embryos. Since lower quality embryos typically remain, particular attention should be paid to selection of those most suitable for donation purposes, based not only on the recipient's criteria but also on available embryo quality.

Embryo Quality

There currently is not one ideal criterion for embryo evaluation, but many studies have suggested that a combination of several different morphologic criteria, each of which has been individually shown to be predictive for embryo competence, leads to a more accurate embryo selection for transfer. Observation of embryos from pronuclear to blastocyst stage yields information on morphology at different developmental stages. Combining data from these observations allows prediction of later embryo developmental

potential and would be particularly useful if individual embryo culture systems are adopted [108, 109].

During embryonic genome activation at the pre-morula stage, a large percentage of embryos undergo developmental arrest. Therefore, culture to the blastocyst stage currently represents the most significant and most widely used embryo selection criterion for optimizing clinical outcomes. Recently, the improvement of culture systems has allowed blastocyst development with extremely high efficiency in most IVF laboratories. Consequently, embryos for banking can be selected according to their ability to develop to the blastocyst stage, as well as their morphological grade. Avoiding multiple pregnancies is extremely important, especially in older recipient. Accordingly, the banking of good quality blastocysts for embryo donation will allow more eSETs, drastically reducing the risk of twins and higher-order pregnancies while maintaining acceptable chance of pregnancy. However, during the past three decades, there have not been any radical improvements in regard to how embryologists evaluate embryos. Even though large amounts of valuable morphological data and experience have been accumulated, they all rely on the same equipment and visual observation of embryos.

The application of preimplantation genetic screening (PGS) is currently the most widely used but also the most debated [110]. A recent report stated that day 3 blastomere biopsy coupled with FISH analysis does not improve efficiency of PGS cycles [111]. Trophectoderm biopsy coupled with comprehensive chromosome screening does, however, hold great promise. Providing that indications for testing were already present for donors, PGS of blastocysts before cryopreservation could potentially increase the implantation rate of donated embryos. Moreover, PGS can minimize a recipient's risk of a trisomy conception.

As described for oocytes, noninvasive evaluation tools other than morphologic observation hold great promise for the future, but at present, these technologies have not yet been validated on human embryos. Among these are continuous time-lapse observation of embryo development [112, 113], as well as metabolic assessment of spent culture media [96]. These techniques, however, have only recently been introduced to IVF laboratories, and variables that could predict implantation potential and embryo viability are still under examination.

Clinical Efficiency of Cryo-embryo Banking

Few studies have published success rates after embryo donation. Some have reported very good pregnancy rates after embryo donation, and in one study, PRs of 77 % per patient were obtained with IRs of 30.9 %, based on 13 pregnancies in 17 embryo recipients [114]. Most studies, however, show slightly more conservative results with pregnancy rates between 19.1 and 52.4 % [115–118]. One study that evaluated a large series of frozen-embryo donation cycles reported a pregnancy rate of only 17 % per transfer cycle [119].

The reason for this difference in PRs may be because the spare embryos donated anonymously from couples after IVF are often of lesser quality, as the better ones are usually transferred in the earlier cycles [120]. Indeed, the embryos created from oocyte and sperm donations were found to be associated with higher IRs (41.7 %) than those donated by infertile couples that have undergone IVF (13.2 %) [121]. Accordingly, high variability in success rates from donor embryo cycles is present between IVF centers. Since the oocyte is the major contributor to embryo viability, the efficiency of an embryo-banking program depends on the same prognostic criteria described for female gamete quality evaluation.

Cryopreservation Strategies for Embryo Banking

So far, there is no single embryonic stage that is definitely superior in terms of outcome for frozen-embryo transfer (ET) cycles [122], and successful cryopreservation of human embryos has been achieved with both strategies at the zygote

(day 1), cleavage (day 2/3), and blastocyst (day 5) stages. Introduction of vitrification has allowed successful cryopreservation of embryos at all stages of development (for review, see [19]). Since there is apparently no superior embryonic stage for freezing tolerance, the decision of which freezing stage cryopreservation should be performed primarily depends on the IVF program's management and individual patient cycle parameters.

It has been documented that slow freezing can be damaging to several cellular components. Ahn et al. (2002), using the mouse model, provided evidence that freezing and thawing can affect the integrity of the cell membrane, actin fibers, and mitochondria while increasing the production of reactive oxygen species [123]. Other evidence suggests that ice crystal formation is mainly responsible for damage, since it may cause protein modification within the embryo and lead to blastomere necrosis [124]. Degenerated or necrotic cells can disrupt cell signaling and release necrotic cytoplasmic material, thereby impairing blastocyst development. Transfer of partially damaged cleavage-stage embryos is associated with decreased implantation rates, as well as lower PRs when compared to the transfer of fully intact embryos [125]. Therefore, assisted hatching with lysed cell removal (LCR) has been proposed to improve implantation potential of cryopreserved embryos. Indeed, microsurgical correction of partially degenerated embryos promotes hatching and restores viability in the mouse model [126, 127]. Although the developmental potential of partially damaged human embryos (one or two lysed cells) seems to be preserved when a limited number of necrotic blastomeres are removed, the loss of three or four blastomeres significantly impairs the embryo's viability and cleavage potential [128, 129]. A recent retrospective report by Cobo and colleagues, using the cryotop vitrification method, demonstrated embryo survival rates with a significantly higher proportion of intact embryos than slow freezing (496/513 [96.7 %] vs. 375/1,046 [35.9 %], respectively). Similarly, Rezazadeh Valojerdi (2009) also found that the percentage of the embryos with excellent morphology and 100 % intact blastomeres was significantly higher in the vitrification group (642/699, 91.8 %) when compared with conventional slow freezing (438/779, 56.2 %). Patients with vitrified/warmed embryos had a greater chance to receive all post-warmed embryos compared to those with slow frozen-thawed embryos. This may be due to the higher survival rates observed in the vitrification versus slow-freezing group (96.9 % vs. 82.8 %). Additionally, no cancelled embryo transfer cycles were observed due to the degeneration of all post-warmed embryos observed after vitrification (0 % vs. 4.60 %) [130].

In a prospective randomized study, Balaban and colleagues showed that vitrification (with EG and 1,2-propanediol [PROH] as CPAs) has less impact on the embryo metabolism when compared to slow freezing, resulting in higher survival rates and, subsequently, better in vitro development [131]. Since the early embryo mainly uses pyruvate as an energy source [132], the amount consumed by the embryo may provide an indication of embryonic health.

These data provide evidence that vitrification induces less trauma to cells and is therefore a more effective cryopreservation technique for human embryos than conventional slow freezing. Therefore, embryos displaying a high degree of fragmentation and slow cleavage rates that normally are advised to be discarded from storage procedures due to low cryopreservation survival rates may be reevaluated for storage by using the vitrification method.

Conclusion

Benjamin Franklin once said: "Lost time is never found again." This was the reality for thousands of women struggling with infertility—until recently. Cryobanking not only pauses time for oocytes and embryos, but it gives back some lost time in the reproductive life of a patient.

Although donor eggs and embryos can never result in a women's biological child, it provides a very fulfilling alternative, namely, giving birth or raising from birth, a baby that will be legally hers and often the biologic/genetic offspring of her male partner.

It furthermore enables same-sex male couples the opportunity to have children of their own.

Because of the high quality of oocytes donated by young healthy women, donation strategies have consistently produced the highest pregnancy rates reported for any in vitro fertilization (IVF) technique. Although fresh oocyte donation is a proven IVF procedure, the possibility of banking the donated oocytes and embryos can dramatically improve the general efficiency of the procedure and overcome traditional drawbacks associated with the use of fresh oocytes or embryos in donation cycles [98]. It is realistic to expect that using cryopreserved eggs and embryos is slightly less effective than when using fresh material, but the impact of the technique, as discussed above, clearly justifies its application in routine clinical work, and as the technology of vitrification is further improved, we expect that there soon will be no detectable difference in outcomes from fresh and cryopreserved eggs and embryos.

As was outlined in the previous sections, there are many factors that contribute to the success of cryobanking. The challenge is to find the most appropriate combination of factors in order to guarantee the highest survival and subsequent embryo implantation rates, followed by healthy live births, while keeping the method practical and cost-effective for the laboratory and clinical practice.

With continuous improvement in cryopreservation strategies, we anticipate oocyte and embryo donation for infertility treatment should and will be performed only through cryobanking, as it provides a more efficient, safer, and more affordable alternative to fresh donation.

Franklin also said: "An investment in knowledge pays the best interest." Through rigorous research and acquiring of knowledge, dedicated scientists were able to develop the technologies that enable effective cryobanking, which is now paying out interest in an opportunity for many infertile people to have children of their own.

Editor's Commentary

I believe the era of egg banking has begun, and it is very likely that it will forever change the way in which we practice egg donation. In my 25 years of practice, I have seen few advancements as significant as oocyte vitrification, and its impact promises to be profound. As Peter Nagy details in his exhaustive chapter describing the development and use of vitrification for preserving and banking oocytes, benefits *will* be realized in both the clinical and laboratory theater.

So many times over the years patients would muse, "Wouldn't it be great if there were egg banks just like there are sperm banks?" I always believed that someday this would occur; I am just pleased that it all seems to be happening right now. Theoretically, and at least preliminarily, freezing eggs solves many problems. The urgency of matching donors to recipients disappears; the disparity of good and bad donor stimulations can be mended; eggs can be quarantined; harvesting large numbers of eggs for one recipient, numbers beyond which any one patient can reasonably use herself, will not occur, and diagnostic testing on the cohort of eggs will ultimately improve selection for use and improve efficacy. These are just a few of the promised benefits.

A few words of caution, however, are in order. The technique is still considered to be experimental by ASRM, and yet, we are seeing it used clinically as if it is standard of care, so much for following practice guidelines. Despite the encouraging early results, obviously there has been no long-term follow-up of the children conceived through this method. Perhaps more concerning would be the normal development of those children conceived following egg vitrification, followed by a refreeze as a blastocyst, and followed by a second thaw and embryo transfer.

Finally, I suspect not every program has the clinical or scientific ability to perform these techniques, or at least perform them well. Yet, everyone who presently offers egg donation is probably going to want to perform freezing as well. Perhaps vitrification and egg banking should be delegated to regional centers of excellence where patients are referred rather than trying to recreate this method in the 400+ IVF centers in the USA. That idea probably will not go over well with practitioners, but as an Internet-savvy public migrates to the busy clinical programs who have demonstrated success, these centers may come to exist de facto.

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Gestational Carriers and Surrogacy

21

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Key Points

- The most common form of surrogacy involves a gestational carrier, a clinical arrangement in which the woman carrying the fetus is not genetically related to the baby.
- Difficulty in relinquishing the baby has led to a discontinuance of the practice of traditional surrogacy where the birthmother is also the genetic parent.
- The first case of a gestational carrier surrogate occurred in 1985. Today more than 2,500 cycles occur annually in the USA alone.
- Surrogates and intended parents need to have personalities that can deal with ambiguity and stress, as well as be empathic, adaptive, and resilient.

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Surrogacy is likely the earliest treatment for impaired fertility dating back to the beginning of reported history. The term is derived from the Latin word *surrogatus,* meaning "substitute" or "appointed to act in place of." Historically, from Babylon to the Bible, there have been laws and customs allowing a substitute woman, or surrogate, to act in the place of a barren wife, thus avoiding the inevitability of divorce in a childless marriage [1].

Today, "traditional surrogacy" occurs when a woman carrying a pregnancy is genetically related to the baby by providing her own eggs. In this instance, the pregnancy can be established medically by intrauterine inseminations or through in vitro fertilization (IVF). However, the most common form of surrogacy, accounting for approximately 95 % of all surrogate pregnancies in the USA, is "gestational surrogacy" or "gestational carrier." In this arrangement, the woman carrying the pregnancy is not genetically related to the baby, and the egg(s) is from the intended biological mother, who generally for medical reasons cannot carry a pregnancy herself, or is from an egg donor. Women acting as surrogates may be commercially recruited and paid for their service (the most common) or may be altruistic as when a family member or friend volunteers pro bono.

The Bible tells the story of Abraham and Sarah who, when unable to conceive, asked Sarah's handmaiden Hagar to carry a child for them. Abraham had intercourse with Hagar and she subsequently gave birth to a boy, Ishmael, who

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she then gave to Sarah to raise. Fourteen years later, when Sarah was 90 years old and Abraham 100, she miraculously became pregnant and gave birth to a son, Isaac. This story, also, describes the emotional consequences of years of infertility and the problems surrounding the arrangement: Hagar was E slave and thus had no rights or choice; Sarah became extremely angry and resentful of Hagar after she was impregnated, causing great tension in the household, and Sarah never accepted Ishmael as her son, in fact insisting that Abraham cast him and his mother out of the tribe after Isaac was born. Abraham was greatly distressed as he loved Ishmael but did as he was told.

While traditional surrogacy no doubt continued to be practiced over the centuries, it was only within the last 35 years that surrogacy came into the mainstream of reproductive options when other treatments failed. In 1976, the first legal agreement in the United States between a traditional surrogate and intended parents was brokered by lawyer Noel Kean, who later was connected with the infamous Baby M case. No compensation was paid to the surrogate in this first arrangement. Four years later, the first documented case of a surrogate being paid occurred when Elizabeth Kane gave birth to a son for the compensation of $10,000. She was considered a good candidate to be a surrogate as she was married, had children, and had also given up a child for adoption prior to marriage. However, after relinquishing the child and giving up parental rights, she spoke out against the practice of surrogacy as she and her family later felt completely unprepared for the feelings and distress surrounding the arrangement. Other legal cases, including Baby M in 1986, illustrated the difficulty in relinquishment that may occur in traditional surrogacy and have led to the general denunciation of this practice.

The advent of in vitro fertilization, and later oocyte donation, created the possibility that a surrogate could become pregnant and carry a child that was not genetically related to her. The first successful case of a gestational carrier giving birth occurred in 1985, after the biological mother had undergone a hysterectomy. These technological advances have allowed for gestational possibilities that not many people would have imagined a few years ago: grandmothers giving birth to their own grandchildren, the oldest occurring in 2008 when a 61-year-old Japanese woman whose daughter had no uterus gave birth; gay male couples having babies; surrogate arrangements that cross borders, cultures, and socioeconomic strata; and the creation of an industry that some critics refer to as “rent-a-womb” [2].

While no data is available on traditional surrogate births, statistics on the number of gestational carrier cycles and births in the USA have been compiled by the ASRM-SART Registry Reports since the 1980s. Between 2004 and 2009, the number of initiated gestational cycles grew by almost 70 % (1,508–2,566), while the number of births more than doubled (530–1,013) with almost 6,600 live-born babies during this period [3]. See Fig. 21.1. However, since surrogacy is highly regulated or banned in many countries, the majority of these arrangements occur in the USA, and it is likely that these numbers are much higher than those currently available.

Indications

The first pregnancy following IVF and the use of surrogacy was reported in 1985 [4], and since then this form of assisted reproduction has become, not without controversy, an integral part of IVF and the only option to parent their own biological (genetic) child for many couples [5].

Candidates for gestational surrogacy include:

1. Women born without a functional uterus, for example, patients with Rokitansky-Kuster syndrome, a condition characterized by the congenital absence of the uterus and the upper third of the vagina; patients with uterine malformations not amenable to surgical corrections (e.g., small unicornuate uterus); patients with extensive uterine scarring like in the Asherman’s syndrome; or patients treated with endometrial ablation for severe menometrorrhagia
2. Women post-hysterectomy (for intractable postpartum hemorrhage, for abnormal placentation like the placenta percreta or accreta, for endometrial cancer, or for menorrhagia

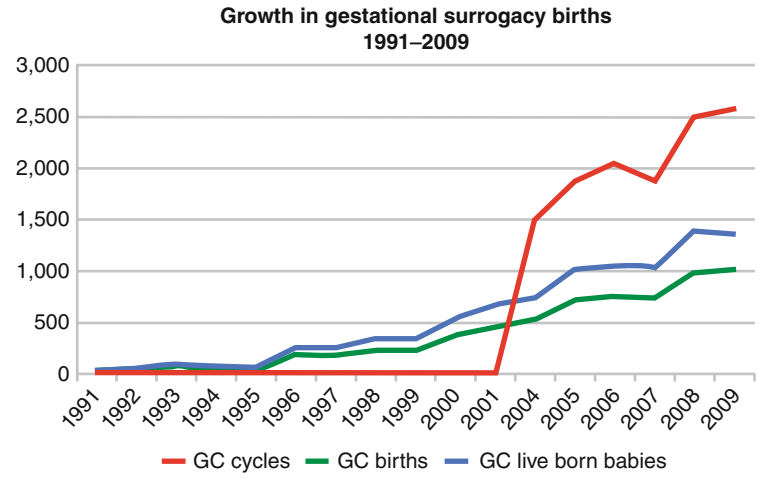

Fig. 21.1 Growth in gestational surrogacy births

due to diffuse and large fibroids or severe adenomyosis)

3. Any woman with severe medical conditions incompatible with pregnancy (e.g., severe heart disease, severe pulmonary hypertension, kidney failure requiring dialysis, status post organ (liver, pancreas, lungs, heart) transplant, severe clotting disorders)
4. Patients with recurrent pregnancy loss strongly suspected due to a uterine factor or patients with multiple and unexplained implantation failures
5. Male same-sex couples

Medical Assessment and Preparation

Medical Evaluation of the Gestational Carrier

Gestational carriers should be healthy women of reproductive age who have previously carried a pregnancy to term without complications. Generally, gestational carriers are recruited through agencies and matched with commissioning parents (intended or biological). Once a potential carrier has been identified, the physician treating the commissioning parents should establish the suitability of the carrier for pregnancy. A thorough medical evaluation, including a review of the past medical and surgical history and family and social history together with a complete physical exam, is carried out. At the time of the visit, the carrier is also informed of the various treatment protocols, the possible side effects, and the potential for medical complications. A specific set of laboratory screening tests for the gestational carrier is listed in Table 21.1.

Table 21.1 Laboratory testing for the gestational carrier and her partner

CBC, blood type and Rh, TSH, PRL
HIV 1 and 2; hepatitis B (HbsAg, anti-HBc); hepatitis C (anti-HCV); RPR; CMV (IgG and IgM)
Rubella, varicella
Urine drug screen
PAP smear, cervical culture screening for gonorrhea and chlamydia

Does not need to be performed in an FDA-approved laboratory

The uterine cavity is assessed with a saline sonohysterogram. Some programs, perhaps in an excess of prudence, perform a "mock cycle" prior to the real transfer to establish whether the endometrial response of the surrogate uterus to the standard dosages of hormones is appropriate. Rarely, the results of the endometrial biopsy performed during the "mock cycle" indicate a need to adjust the dosages of estradiol and/or progesterone.

Finally, if the gestational carrier is 40 years or older, a mammogram and a maternal-fetal consultation are typically ordered. The male partner of the gestational carrier is also tested for hepatitis B (anti-HbsAg and anti-HBc) and hepatitis C (anti-HCV), RPR, and HIV.

Table 21.2 Laboratory testing for the intended parents

(a) CBC, blood type and Rh, TSH, PRL, AMH; day 3 FSH and E2
(b) HIV 1 and 2; hepatitis B (HbsAg, anti-HBc); hepatitis C (anti-HCV); RPR*
(c) Rubella and varicella
(d) PAP smear
(e) Cervical culture screening for gonorrhea and chlamydia*
For the male partner:
(a) Blood type and Rh, semen analysis
(b) HIV 1 and 2; hepatitis B (HbsAg, anti-HBc); hepatitis C (anti-HCV); RPR and CMV (IgG and IgM)*
(c) Urine culture for gonorrhea and chlamydia*

Note that those indicated by the *asterisk* need to be performed in an FDA-approved laboratory

Laboratory Testing for the Intended Parents Requiring Gestational Surrogacy

The intended genetic mother is screened and tested like an oocyte donor, thus requiring the following exams performed in FDA-approved laboratories (*summarized in* Table 21.2): HIV 1 and 2, hepatitis B (anti-HbsAg and anti-HBc) and hepatitis C (anti-HCV), RPR, and cervical culture screening for chlamydia and gonorrhea. To be FDA-compliant, the testing needs to be done twice, the first time before the intended genetic mother is accepted into the program or prior to the carrier beginning her medical evaluation; the second set of the same tests must be obtained no more than *30 days* before the oocyte retrieval (in practicality, this second set of testing can be drawn at the baseline ultrasound appointment).

The intended genetic father is considered like a sperm donor, and also for him, there are FDA-required tests (Table 21.2): HIV 1 and 2, hepatitis B (anti-HbsAg and anti-HBc) and hepatitis C (anti-HCV), CMV (IgG and IgM), RPR, and urine culture for chlamydia and gonorrhea. Also for the intended genetic father, the FDA requires two complete sets of laboratory tests, the second being no more than *7 days* prior to the egg retrieval.

If the intended parents (mother or father) are not providing the gametes (i.e., are using donor oocytes or donor sperm), then the FDA-required set of laboratory screening applies to both providers of gametes (as for oocyte and sperm donors).

Choice of a Protocol for Ovarian Stimulation for the Intended Genetic Mother and Preparation of the Gestational Carrier

The choice of a protocol for ovarian stimulation protocol varies according to the age of the patient, her body mass index (BMI), the ovarian reserve, and the ovarian response to previous cycles. In general, the ovarian stimulation protocols can be divided into two groups: (1) long or luteal phase protocols using a GnRH agonist (the most commonly used) and (2) short or follicular phase protocols using GnRh antagonists (ganirelix or Cetrotide).

In the long protocol, a GnRH agonist (commonly leuprolide acetate) is started in the midluteal phase of the previous cycle, with 0.5 mg subcutaneous daily until the onset of menses. At the same time, the menstrual cycle of the gestational carrier is also synchronized with the use of leuprolide acetate started in the midluteal phase of the previous menstrual cycle. Generally the menses of the surrogate are manipulated so to start in advance (about 5–7 days) of the menses of the intended mother. Two days prior to starting the ovarian stimulation of the intended mother, the gestational surrogate in addition to leuprolide acetate begins the assumption of estradiol tablets at fixed incremental doses (2 mg per 5 days, followed by 4 mg for 4 days, and then 6 mg from cycle day 10), while the intended parent starts the gonadotropin stimulation (rFSH and/or hMG). The ovarian response is monitored by ultrasound and serum estradiol level and dosage adjustments are implemented if necessary. The hCG is administered when an appropriate number of follicles have reached a mean diameter between 18 and 20 mm.

On the day that the intended parent receives hCG, the gestational carrier stops taking leuprolide acetate and decreases Estrace to 4 mg daily

instead of 6 mg daily. The day before oocyte retrieval, the gestational carrier is instructed to commence the evening use of progesterone (vaginal preparations). The day of egg harvesting, the gestational carrier increases the vaginal progesterone to twice daily. Some still prefer the use of daily intramuscular progesterone injections (50 mg), and few others add intramuscular progesterone to the vaginal preparations. This protocol is generally continued with progressive decrements in estradiol from gestational week 6–7, until the completion of the tenth gestational week of pregnancy is achieved. Embryo transfer occurs 3–5 days after the retrieval. The day of the transfer is determined based on the number and morphology of available embryos.

Psychological Assessment and Preparation

The story of Abraham and Sarah gives credibility to the importance of psychological preparation, education, and assessment of all parties involved in gestational carrier and surrogacy arrangements. Like Abraham and Sarah, couples who pursue gestational surrogacy often do so after years of infertility and failed treatment. For others, such as women without a uterus or gay male couples, gestational surrogacy offers the only option for having a child that is at least partially genetically connected to them. Whatever the path that has brought patients to pursue using a gestational carrier, it has taken an emotional toll on them and the stakes are high for all involved. The gestational carrier or surrogate, like Hagar, also has a history that has shaped her decision to enter into this agreement and, most likely, a family that will be impacted by the experience. Lastly, a child, like Ishmael, who is created and born from the arrangement, will always carry a reflection of the legacy of his/her birth within the family, possibly affecting psychosocial development. Hence, appropriate psychological assessment and preparation of surrogates/gestational carriers (GCs), her partner if in a relationship, and the intended parents (IPs) is crucial.

Only recently has the American Society for Reproductive Medicine (ASRM) published practice guidelines on the medical and/or psychological evaluation of gestational carrier/surrogacy participants [6]. With the legal risk that exists with these arrangements and the ability to be sure all participants are in a good place to move forward with treatment, withstanding the uncertainties ahead, counseling becomes an important part of medical care and should occur before treatment begins. Standard of care with the psychological evaluation involves a three-pronged process with separate counseling sessions of the GC (with partner, if applicable) and IPs, culminating with a group meeting of all parties.

Oftentimes IPs and GCs come in for the psychological assessment having met, talked, and established that they want to work together. However, they may have little concept of what is entailed in a successful surrogacy relationship: They present like couples who just met, fell in love, and want to get married but have no idea who they are marrying, how hard marriage is, and what happens to the relationship after the honeymoon ends. The following sections will outline issues that should be considered and discussed during the counseling to help assess and prepare for a successful surrogacy relationship.

Gestational Carrier/Surrogate Interview

Whether traditional or gestational, minimal research is available on the experience of surrogate mothers. Common motivations for becoming a surrogate include financial gain, enjoyment of pregnancy, self-fulfillment, value and worth, and wanting to help others [7]. It takes a special woman to be a surrogate: She must be able to work with the IPs before, during, and after the pregnancy; she will need to relinquish the baby she has carried after giving birth; and she will have to handle these relationships and experiences while caring for her own family, dealing with her own feelings as well as the reactions of others in regard to her decision to be a surrogate. Although research indicates that overall women

do not experience psychological problems as a result of being a surrogate [7, 8], the challenges are significant and the potential for problems exists at every turn.

Hanafin [9], who has been working with surrogacy arrangements for over 25 years, identifies personality, characteristics, and qualities, which are positive indicators of a woman's appropriateness as a surrogate. To begin, a woman needs to have given birth so that she has experienced pregnancy, birth, and postpartum adjustment to be able to provide full informed consent about what she is undertaking. Having given birth previously will also provide important information on both her psychological adjustment and medical condition. A potential GC should be in a stable home and life situation, and not in the middle of transition or personal crisis. GCs who are dealing with job loss or stress, health and family problems, and marital difficulties may be at risk for emotional complications. Besides emotional stability, it is important that a GC be financially stable and not receiving forms of welfare or public assistance, so that acute financial need is not her primary motivation, effecting decision-making and consent. She should also have no history of problems with authority or the legal system that could indicate the potential for difficulties within the contractual relationship. Consequently, it is recommended that IPs see that a criminal and financial background check has been conducted prior to working with a GC.

Another consideration is the GC's husband's job situation as an increasing number of military wives are applying to be surrogates. These women are often sought out as they are seen as being accustomed to adapting to change, following direction, working with structure, and having strong values. At times, military wives will consider becoming a GC while their husbands are deployed overseas as a way to earn money and focus their energies. However, with many of our troops being deployed to combat areas with the risk of injury or death, it is time of anxiety, transition, and unknowns, and thus, it is recommended that surrogacy not be undertaken until her partner has returned safely home.

A surrogate needs to have a personality that can deal with ambiguity and stress as well as being empathic, adaptive, and resilient [9]. To be able to identify these qualities and psychological characteristics, it is recommended that all potential GCs be given standard psychological testing which will provide important information about her personality. The analogy can be drawn between standard medical tests, such as blood checks for FSH levels that are given to ovum donors to determine acceptability, and standard psychological testing: a woman can seem great to the eye and ear, but the blood test tells something that cannot be identified in an interview. Mental health professionals consider personality testing with the Minnesota Multiphasic Personality Test-2 (MMPI-2), which has been used in psychiatric, employment, and forensic settings for over 70 years, or the Personality Assessment Inventory (PAI) to be good choices in third-party assessments and standard of care (detailed in *Infertility Counseling*, GC Task Force, [10]). These tests will indicate not only the presence of psychopathology or difficult personality characteristics but also whether the GC is being open, honest, and forthright in her test-taking attitude and approach to the assessment. Recent research on the use of MMPI-2 with GCs has found that majority of applicants are within normal clinical limits yet score higher on validity scales that indicate, not surprising, a positive presentation of high personal standards and values [11, 12].

The clinical interview involves assessment and psychosocial preparation of the GC and, if applicable, her husband/partner, as his support, involvement, and understanding are crucial. Often it begins with a discussion of motivations for becoming a GC; the decision-making process; description of the contact and quality of the interactions thus far with the IPs; and sense of the GC's general support system (partner, family, community, etc.). History taking is an important part of the assessment and should include: family and marital history; psychiatric history; reproductive history, including fertility, pregnancy, and postpartum; history of previous loss or trauma including abortions, adoptions, perinatal death, and physical/sexual abuse; and history of

interaction with the legal system. A discussion of expectations and fantasies/wishes about the relationship during pregnancy and after birth should be addressed: How does the GC feel about abortion, multiple pregnancy, and fetal reduction, and who should be making these decisions? What contact does she desire and imagine will occur while pregnant, during birth, and after relinquishing the baby? How does she see her relationship and contact changing with the IPs and child after birth and in the future? What issues does she see occurring within her own family during this time, and how will she deal with it? These questions and discussion will help in preparing the couple for what is ahead. (A list of positive and negative indications for being a gestational carrier can be found on Table 21.3).

Table 21.3 Psychological indications of surrogate/gestational carrier appropriateness

Positive indicators
History of healthy full-term pregnancy
Experience and competence with motherhood
Motivations that reveal obtainable goals
Motivations that reflect empathy
Spousal support if applicable
Stable lifestyle
No major conflicts or transitions in the next 2 years
Cognitive ability to provide informed consent and conceptualize risks
Absence of psychopathology
History of making successful decisions for herself
Financial stability
Demonstrates tolerance for ambiguous and unclear situations
Able to express and articulate concerns and questions
Negative indicators
Poor pregnancy, postpartum, and/or medical history
Lack of martial/social support
Acute financial need or coercion
Psychopathology and/or history of poor psychological functioning
Defensive psychological testing
Elevations on the psychological test scales that are more than two standard deviations above the mean
Unrealistic expectations regarding time involved
Significant current stressors or life transitions
Chaotic lifestyle
Impulsivity or high anxiety
Limited cognitive ability
History of antiauthority behavior and rigidity in thinking
Unresolved or untreated history of child or sexual abuse
History of drug/alcohol addiction/abuse
Unresolved issue concerning prior abortion or reproductive loss issues
Lack of empathy
Inability to communicate in her native language with medical professionals

Ref. [8], adapted with permission

Intended Parents Interview

Intended parents, whether heterosexual, gay, or single, need similar personality qualities as surrogates. They need to be empathic, adaptive, trusting, and resilient as well as have the ability to tolerate lack of control. For patients that have struggled with years of infertility and treatment failure, it is important that they have had the opportunity to emotionally work through associated losses and hurts. Sometimes having spent years of dealing with the loss of control during treatment, IPs will approach using a GC as means of regaining control. This behavior may also be experienced in interactions with the treatment team. Hanafin notes "observing how (*IPs*) treat the professionals and other team members can be revealing and predictive of future behavior" with the surrogate and her family [9].

The clinical interview will follow a similar course as the GCs, with history taking, a discussion of decision-making, and relationship expectations. It is necessary to obtain a full medical, psychological, marital, and family history from the IPs to understand the process that has brought them to gestational surrogacy. How they have coped with losses, disappointments, and failures in the past should be discussed as well as how these issues have impacted their marriage. Expectations regarding contact with the GC and her family during the pregnancy and after birth should be reviewed. If they will be using an egg and/or sperm donor, the issues related to raising a nongenetically related child will need to be addressed. In addition, it is important to discuss

and confirm that legal consultation and contracts for both the IP and surrogate have been obtained prior to treatment.

Time should also be allocated to talking about the future, not only in regard to the relationship and contact with the GC but also to what they will be disclosing to their child about the origins of his or her birth. It is comforting to note to IPs that despite the difficult road to become a parent, ongoing research is indicating that families conceived via surrogacy are doing well and adapting normally [13].

Group Interview

Once both individual interviews of the GCs and IPs have been held, a final meeting is needed whereby all parties involved are brought together to review what was learned in the sessions and discuss how the relationships will work moving forward. At times, logistical issues may occur when the IP and the GC live many miles apart and will necessitate a coordination of the evaluations by different mental health professions. The GC may have already been psychologically screened by an agency before matching as well as the IPs having received prior counseling, particularly if coming from another country for treatment. The group interview at the clinic may be the first time the GC and IP have met in person. Thus, it is important that the clinic counselor has all supporting documentation and reports prior to facilitating the group session. An official translator may be required for patients traveling from abroad and not fluent with the English language.

The mental health professional will need to address any current or potential problem areas that were identified during the separate meetings and help the parties come to an understanding of how these issues will be dealt with. It is helpful to review the salient points from each session regarding their motivations toward surrogacy and expectations of each other regarding contact during and after the pregnancy. This should include their expectations about degree of openness and future relationships with the child, each other, and their families. It is also necessary to discuss how decision-making regarding embryo transfer, medical care, multiple pregnancy, multi-fetal reduction, fetal anomaly, termination, etc., will be handled. IPs and GCs having similar approaches to decision-making are extremely helpful. Finally, discussion of the future should include a plan for support and assistance when differences or difficulties arise. Counseling and support resources need to be identified, and legal contacts should be confirmed.

Both the IP and GC must understand that empathy will be the glue that makes this relationship work and hold it together to a successful outcome. There may be notable differences between the two couples (or individuals), such as culture, religion, race, and backgrounds, yet they must find common ground and the ability to empathize with each other and adapt to the unexpected will help greatly. All parties should leave counseling with a clear understanding of expectations, communication, and how needs and differences will be handled when they inevitably occur in this and all relationships.

Surrogacy Agencies

With the growth of technology allowing for gestational surrogacy, a whole industry has developed that identifies and brings together potential surrogates and intended parents. The Internet has created a means for people to meet and pursue these arrangements with numerous websites devoted to surrogacy: a recent search on Google brought up over 500,000 hits regarding agencies, agents, and resources on the topic. What to do and how to do it can be overwhelming.

The decision to use a gestational surrogate often occurs for a couple or individual after years of treatment failure and disappointments, which may make them financially and emotionally vulnerable in their decision-making. At times, IPs may try to find a GC on their own, through the Internet or word of mouth, sometimes because of financial concerns or wanting to regain a sense of control lost during infertility. However, as in private adoptions, this may open patients up to

exploitation, and working with a reputable surrogacy agency or agent can alleviate many potential problems. On the other hand, the motivation to become a surrogate, also, may involve vulnerabilities and risks to the woman and her family pursuing this arrangement. Thus, how these arrangements and relationships are facilitated becomes crucial in their success.

There is wide variation in screening and services offered by surrogacy agencies and lawyer/agents. Some act as a "matchmaking" service, while others provide full legal and psychological services throughout the process. Matchmaking agencies/agents will search and find women interested in being a GC but often do only minimal prescreening, usually outsourced to independent practitioners, before matching the IPs and GC. If the IP and GC decide to move forward, the IP incurs the cost of medical and psychological screening, which ultimately may find the GC unsuitable. While the financial loss is difficult, what is often more distressing is that the IP and GC have formed a relationship and are upset that it cannot proceed forward. Without adequate agency prescreening prior to matching, IPs are more vulnerable to continued loss, disappointment, and sadness. If they move forward and become pregnant, the GC and IPs are pretty much on their own to navigate the relationship, pregnancy, and birth. Furthermore, if there are problems or differences between the IP and GC during this period, there is no infrastructure of professionals or counseling in place to help navigate the difficulties.

Surrogacy agencies providing full service to IPs and GCs have legal, psychological, and medical staff in-house to assess, facilitate, and support both parties before treatment, during a pregnancy, at birth, and after relinquishment to ensure the best interests of everyone involved. These agencies will have the IPs and GCs fill out an in-depth application that identifies background, history, and desires regarding the arrangement. Potential GCs will have medical screening; criminal, credit, legal, and driving background checks; psychological testing and clinical interviews of the GC and her husband/partner; home visits; and legal consultation. Only after both the IPs and GCs have been fully screened and accepted by the agency will a match take place. At this time, some agencies will have the GC select the IP, while others do it the opposite way. The GC will be provided support throughout a pregnancy and after birth by participating in monthly support groups with other GCs and counseling. The IPs will be supported similarly and have the agency staff available for assistance in understanding how to work best with their surrogate, manage their own anxieties, and be available if difficulties or problems occur.

While each clinic will have their own requirements for medical and psychological screening, many issues should be addressed before IPs contract with an agency or GC. Table 21.4 provides a list of questions patients should consider when choosing a surrogacy agency or agent/lawyer to work with.

Cross-Border Surrogacy

International travels have proliferated for intended parents requiring the service of gestational surrogacy. The growing interest in "reproductive tourism" and "reproductive outsourcing," including a dramatic rise in Indian gestational surrogacy, has generated both legal and ethical concerns [14].

There are a number of factors that may promote cross-border surrogacy: (1) individual countries may prohibit the service for religious, ethical, or legal reasons; (2) the specific service may be unavailable because of lack of expertise or lack of affordability and supply of donor gametes and surrogates; (3) the service may be unavailable because it is not considered sufficiently safe; (4) certain categories of individuals may not receive a service in their countries, especially at public expense, on the basis of age, marital status, or sexual orientation; (5) individual patients may fear lack of medical privacy and confidentiality and thus travel abroad; and finally, (6) services may simply be cheaper in other countries [15, 16].

Particularly for gestational surrogacy, the economic motivation is the most cited reason for Americans traveling abroad (mainly to India).

Table 21.4 Questions to consider when choosing a surrogacy agency

1. What criterion is utilized by the agency or agent/lawyer when recruiting and screening a potential gestational carrier (GC)? Is the medical and psychological screening done before or after the matching and introduction meeting with intended parents (IPs)?
2. Does the agency/agent meet in person with the GC before matching? Do they meet in the office? Is there a home visit?
3. Has a criminal background check been completed on the GC and her husband/partner by the agency/agent? Does the agency/agent check whether the GC and her husband/partner have been involved in any other legal cases or lawsuits?
4. Does the agency/agent complete a credit check? Does the agency/agent check if the GC or her family is receiving any public assistance (i.e., food stamps, Medicaid)?
5. Has the agency/agent obtained a driving record on the GC and her husband/partner?
6. Has the potential GC ever been a surrogate before? What was this experience like for her and the IPs? Has a reference been obtained from the previous IPs?
7. Has GC ever applied and been turned down by another agency/agent/clinic before? Has she ever applied and been turned down as an egg donor before?
8. Has a psychological evaluation on the GC and her husband/partner been completed by a licensed mental health professional trained in third-party assessment? Did it include standardized psychological testing and clinical interview with both?
9. Was the psychological evaluation completed in person or over the telephone or the Internet/Skype?
10. Has the GC obtained clearance from her obstetrician? Have her medical records been reviewed?
11. What services do agency staff members provide and what is outsourced?
12. How long has the agency been in business? What legal problems, if any, have the agency incurred any legal with their arrangements?
13. Does the agency/agent utilize an independent escrow agency? What access does the client have to the distributions?
14. Is the entire agency fee due if a pregnancy does not occur or is it broken into installments?
15. What are the legalities of the states in which GCs are recruited? Is her state surrogacy friendly or will the GC have to travel to give birth?
16. Does the GC already have health insurance or will the agency be obtaining it for her? If she has health insurance, has it been checked to see if it excludes surrogacy pregnancy care?
17. Will the IP and GC each have their own legal representation?

The entire process can cost $25,000 (inclusive of airfare, accommodations, and the surrogate's fee), which is significantly lower (about one-third) than the total medical costs for the same service in the USA. Surrogacy is legal in India, and the carrier's name does not appear on the birth certificate. However, it has been already reported that for reproductive travelers to India using gestational carriers, after birth determining parentage for children born in India may become a legal and quite distressing quagmire.

In India, many of the women live together in a group setting, physically attached to the IVF clinic and stay there for the duration of the pregnancy. Some programs also offer egg donors. One recent profile of Rotunda – the Center for Human Reproduction in Mumbai – which offers both surrogacy and egg donation, does not allow any of the parties to meet (the gestational carriers are in confined "gestational wards" until the delivery). Recently this clinic coordinated a process with a gay male Israeli couple, an Indian egg donor, and an Indian gestational surrogate. The gestational surrogate was not told she was carrying a child either for a same-sex couple or foreigners. The article profiling the arrangement noted that "on some contracts, the thumbprint of an illiterate surrogate stands out against the clients' signatures." Other concerns have been raised about the carriers' level of understanding, including whether their lack of knowledge regarding with whom they are contracting undercuts any agreement, whether donor egg information is adequate for recipients, and whether immigration and citizenship issues are clearly and reliably established [17].

Conclusion

Surrogacy has been practiced throughout the ages and now, with the help of assisted reproductive technology, may involve up to five adults (gestational carrier, intended mother, intended father, sperm donor, egg donor) in the creation of a child. While the medical treatment involved in gestational surrogacy is fairly straightforward, the emotional, legal, and social issues of this complex relationship are significant. However, with appropriate preparation and support, this arrangement can be a positive, life-giving experience for all involved. The growth of cross-border surrogacy raises ethical concerns, and further research is needed on the impact on children created across continents and cultures as well as on the GC, her family, and intended parents.

Editor's Commentary

The practice of surrogacy in the United States has experienced its own evolution over the past several decades. Similar to egg and embryo donation, surrogacy has engendered much controversy and criticism, and yet it endures. Even the nomenclature has changed and can lead to much confusion and misunderstanding. The terms "surrogate," "gestational surrogate," "gestational carrier," and "intended parent(s)" are often used quite generally when discussed publically or in the lay press. Yet, medically and legally all of the above parties must be very specifically defined and consented.

Covington and Patrizio clearly elaborate the importance of the multidisciplinary approach to the modern practice of gestational surrogacy. Perhaps more than any other form of assisted reproduction, a thorough understanding of the medicine, the psychology, and the law that relates to this important clinical activity is absolutely requisite to the successful practice of the method. Close collaboration of the professional entities and the careful integration of the necessary component parts require a great deal of time and skill as well.

The public often views surrogacy askance. The commercial nature of the arrangements and commodification of eggs, uterus, and sperm makes it an easy target for more traditional-minded individuals who would prefer reproduction to occur "naturally." However, there is really nothing "natural" about our field of medicine, and gestational carrier surrogates are a rather "natural" extension of egg and embryo donation services. Certainly for women unable to carry a baby, for a variety of reasons, this gestational surrogacy provides them with an alternative that is both efficacious and relatively safe. However, it remains important that the profession carefully monitors the practice and develops published professional and ethical guidelines, in order to avoid unwanted controversy, particularly as it relates to cross-border arrangements that might be exploitive or illegal. This is an important clinical service that should be nurtured which will allow it to continue to grow in popularity for years to come.

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Assisted Reproduction in Same Sex Couples

22

Dorothy A. Greenfeld and Emre Seli

Key Points

- Evolution of gay rights has led to a general social acceptance of homosexuality, and an increasing number of individuals from same sex unions openly express a desire to become parents and seek reproductive care.
- Lesbians often achieve parenthood through intrauterine insemination or IVF, sometimes with donor egg as well as donor sperm ("donor embryo"), and through "reciprocal IVF" a process where one partner donates eggs to the other.
- Increasing numbers of gay men seek fatherhood through IVF using an egg donor and a gestational carrier surrogate.
- There is no persuasive evidence to suggest that children raised by gay parents are harmed or disadvantaged and by that fact alone ART programs should treat all requests equally without regard to marital status or sexual orientation.

In recent years a growing recognition of same sex unions as culturally and socially acceptable has led inevitably to a parallel acceptance of such unions as a foundation for family. Advances in gay rights, the liberalization of legal restraints, and the increasing availability of assisted reproduction have led to more men and women being open about their homosexuality, open about their relationships, and open about their desire to become parents within the context of a same sex relationship [1, 2]. As a result, fertility programs have experienced a growing demand for service from same sex couples seeking parenthood through alternative reproductive techniques. This movement has culminated in a phenomenon commonly referred to as the "gay baby boom" [3].

Conception for same sex couples requires assisted reproduction by definition. As such, gay men and women considering parenthood through these means face a decision-making process not common to heterosexual couples. For example, lesbian couples entering fertility treatment need to give consideration as to who will carry the pregnancy and how to choose a sperm donor. Gay

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male couples need to give consideration as to who will provide the sperm as well as how to choose an egg donor and a surrogate.

This chapter will address the increasing numbers of planned lesbian and gay families resulting from assisted reproductive technology (ART) and the decision-making process unique to gay couples when planning such families. A discussion of the historical significance of the contribution that the gay civil rights movement has made toward this new openness, a review of the literature on same sex parents and their children, and medical, social, and psychological issues unique to this population will be included. Clinical considerations in treating gay men and women and recommendations for inclusion of same sex couples in the fertility setting also will be described.

Historical Overview of Same Sex Reproduction in the USA

It is currently estimated that in the USA there are between 6 and 14 million children with at least one gay parent [1]. According to the US Census report of 2010, same sex couples live in every state in the union, and one in five same sex couples is raising children [4]. Many of these children were adopted (4 % of all adopted children in the USA live with a gay parent) [5]. Others were conceived in a heterosexual relationship that resulted in divorce when one parent came out as gay. Increasingly, however, children are born to gay parents and conceived through assisted reproduction. As noted above, this ongoing phenomenon is due in part to a new openness and a growing determination among same sex couples to marry and have children. Currently, same sex marriage is legal in eight countries around the world: Argentina, Belgium, Canada, Iceland, the Netherlands, Norway, Portugal, South Africa, Spain, and Sweden. In the USA, same sex marriage is legal in six states: Connecticut, Iowa, Massachusetts, New Hampshire, New York, and Vermont. It is also legal in the District of Columbia [6].

Of course, the growing numbers of gay couples choosing to become parents together didn't happen overnight or in a vacuum. In fact, the movement toward social acceptance and the openness exhibited by gay men and women have evolved considerably in the past 40 years with a somewhat tumultuous history.

In the 1950s in the USA it was dangerous to be admittedly gay or "out." At the time homosexuality was viewed as criminally deviant as well as medically psychopathological. For example, in 1953 President Eisenhower issued executive order 10,405 which banned gays from being employed by the federal government [7]. Others were threatened and afraid of losing their jobs as well. Gay men and women could be legally prosecuted and, on occasion, end up in jail or a mental institution. In the psychiatric community it was believed that both gay men and lesbians were "curable," but lesbians were regarded as more likely to respond to "treatment." Lesbianism was described as a form of neurosis that involved narcissistic gratification and sexual immaturity, while gay males were generally depicted as predatory hypersexual loners [8].

Events occurred in the following decades that served as a catalyst to the gay civil rights movement toward greater equality. The first, the so-called Stonewall Rebellion is usually cited as the event which triggered the start of the gay rights movement in America. The Stonewall Inn, a gay bar in the Greenwich Village neighborhood of Manhattan, was the site of a routine police raid on June 28, 1969. Such raids were common at the time, an expression of society's intolerance and prejudice toward gays, but on that particular night the patrons fought back, leading to a riot, which continued for several days. Over the next weeks and months gays and lesbians formed activist groups to mount what became the beginning of a national campaign for gay rights [7, 8].

Another significant source of gay pride happened in 1973 when the American Psychiatric Association, in what was described as a contentious meeting, voted to remove homosexuality as a psychopathological syndrome from its Diagnostic and Statistical Manual (DSM), the official list of psychiatric disorders [9]. To appreciate the significance of such an event, it is important to remember that this represented a dramatic conceptual shift by the most important national organization of the American psychiatric profession [7]. Similarly, the American Psychological Association,

the national organ of American psychologists, voted to eliminate homosexuality as a psychiatric diagnosis in 1975, and since then several organizations have called for nondiscrimination for gay men and women and their children. These organizations include the American Academy of Family Physicians, the American Academy of Pediatrics, the American Bar Association, the Child Welfare League, and the National Association of Social Workers [10].

The Emergence of Assisted Reproduction for Lesbians and Gay Men

As gay men and women became more confident and candid about being gay and about their same sex relationships, they grew in determination and confidence about planning families and becoming parents within the context of their same sex relationships. The movement toward gay men and women seeking parenthood through reproductive assistance began in the lesbian community and had its inception in California. In 1979, health activists seeking to provide medical care to lesbian and single heterosexual women opened the Lyon-Martin Health Center in San Francisco. One of the founders, Sherron Mills, wanted to start an insemination service for lesbian and single heterosexual women who wanted to start a family, but the Board of Directors balked at such an idea. In 1983, Mills left the Lyon-Martin clinic and opened the first lesbian-owned sperm bank offering insemination services to lesbians [11].

At that time the initial ethical arguments against such treatment were that it was a waste of medical resources because the patients were not technically infertile and that such treatment was not in the best interest of the children who would be stigmatized and needed both a mother and a father [12, 13]. Interestingly, these concerns applied not only to women who were gay but to all women who were single (gay or heterosexual). Dunstan, for example, stated, "If, as we must assume, the dominant inescapable interest must be of the child and his enjoying a normal upbringing … then deliberately to contrive its birth into a lesbian union or to a single woman would be to deny it justice" [12].

In recent years the inclusion of same sex female couples seeking parenthood together has become quite common in fertility treatment centers. Lesbians seek parenthood through intrauterine insemination (IUI) or in vitro fertilization (IVF), sometimes with donor egg as well as donor sperm, and, increasingly, through a process referred to as "reciprocal IVF" where one partner provides the eggs and the other partner carries the pregnancy, in effect one is the biological mother and one is the birth mother [14].

In the late 1970s a few agencies in the USA began to offer surrogacy as an option for parenthood to infertile couples, but gay men were not part of that first wave of intended parents. At that time the commonly used treatment was "traditional surrogacy," which meant that the woman legally contracted to carry the pregnancy was artificially inseminated by the intended father. She relinquished the baby to the intended parents when it was born, and the intended mother adopted the baby. By the 1980s gay male couples began to actively pursue this form of parenthood [15].

Gestational surrogacy is where the woman carrying the pregnancy goes through IVF and embryo(s) implanted which are not genetically related to her. In 1984, the first birth through "gestational surrogacy" was achieved in the USA [16]. Since that time increasing numbers of gay men seek fatherhood through IVF using an egg donor and a gestational surrogate. Typically, one partner provides the sperm but in some cases, the eggs are divided and each partner's sperm fertilizes half of the oocytes retrieved. Many times the couples choose to transfer an embryo from each partner, often resulting in twins who are in fact half siblings [17].

Barriers to Assisted Reproduction for Gay Couples

ART is not for everyone, and barriers to treatment are a very real factor to many couples, gay or straight. For example, the financial costs associated with treatment often running to thousands of dollars are prohibitive to many. Another

prohibitive factor for many is their geographical location, where information about how to proceed with such a parental quest may be lacking and, worse yet, access to treatment and treatment centers may not exist, especially in some very rural parts of the country [18].

Perhaps the most egregious barrier for gay couples seeking ART is when there is access to treatment, but it is not available to gay couples. For example, while lesbians commonly are welcomed by fertility treatment centers, the issue is often quite different for gay men. Gay men seeking parenthood through ART using an egg donor and a gestational surrogate [15, 19] are not always welcomed by fertility treatment centers. For example, a survey of 369 fertility centers in 2005 revealed that most programs (79 %) routinely accept lesbians for treatment but are less likely to accept gay men [20]. In 2006, the Ethics Committee of the American Society for Reproductive Medicine (ASRM) issued a statement with the following recommendation: "Unmarried persons, gays and lesbians have interests in having and rearing children. There is not persuasive evidence that children raised by single parents and or by gays and lesbians are harmed or disadvantaged, and by that fact alone programs should treat all requests for assisted reproduction equally and without regard to marital status or sexual orientation" [21].

Despite the obstacles, gay men and women remain determined to move forward and choose to have families. A study in 2006 of 133 lesbian and gay youth between 15 and 22 years of age determined that the majority expected to be partnered and married and to be raising children as adults [22].

Key Issues Regarding Same Sex Reproduction: Review of the Literature

Historically, gay men and women have been denied custody or visitation with their children following divorce because of "judicial and legislative assumptions about adverse effects of parental homosexuality on children" [23]. Research on gay men and lesbians and their children began to appear in the literature in the 1980s, initiated by researchers looking at whether there was sufficient data to support some of the assumptions about children of gay parents. These assumptions included the expectation that such children would experience stigmatization, poor peer relationships, emotional problems, and/or abnormal psychosexual development [23, 24]. Since then the body of literature has grown substantially and has focused on the attitudes and behavior of gay and lesbian parents and the psychosexual development, social experience, and emotional status of their children [25].

Motivations for Parenthood

In a study of the association between motivation for parenthood and its impact on the parent child relationship, Bos et al. compared 100 lesbian two-mother families planning parenthood through insemination with 100 heterosexual families with no history of infertility treatment. Both groups were in the process of making the transition to parenthood. Investigators compared parenthood motives, reflection (how often subjects thought about the reasons for having children), and strength of the desire to have children. Results were that while both groups rank their parenthood similarly, lesbian mothers had spent more time thinking about having children and their desire to have a child was stronger compared to heterosexual mothers [27]. A study looking at parental motivations among gay and heterosexual fathers found that fathers from both groups were motivated by the same thing: the desire to nurture children, to have the constancy of children in their lives, to achieve a sense of family that children provide, and to have a sense of immortality through having children [28].

Family Relationships, Attitudes, and Behaviors

In the 1980s several studies compared parenting behaviors of divorced lesbian mothers to divorced heterosexual mothers. In both groups mothers had

custody of the children [29–31]. The studies were in agreement that there were no significant differences in the quality of family relationships between groups. More recently, studies have looked at planned lesbian families—where children were conceived through donor insemination and compared them to heterosexual-led families and found that measures of self-esteem, psychological adjustment, parental stress, anxiety, depression, and attitudes toward child-rearing revealed no significant differences between groups [30, 32, 33].

Several studies also compared divorced gay fathers with divorced heterosexual fathers (neither group had custody of the children); no differences were found in terms of nurturance and parental roles. Fathers in both groups were involved with their children and were equally nurturing, although gay fathers were found to adhere to stricter disciplinary guidelines, to place greater emphasis on guidance and cognitive skills, and to be more involved in children's activities [28, 34, 35]. Gay fathers were more cautious about displaying physical affection toward their partners in front of the children than were their heterosexual counterparts [35].

Other studies considered the partnership status of divorced gay fathers and its effect on the quality of parenting. Crosbie-Burnett et al. reported that family satisfaction was reported to be highest by gay fathers, their partners, and the children when the partner was well integrated into the family [36, 37]. Another study found that gay fathers who had a partner and especially those who lived with a partner gave themselves higher marks for managing parental challenges than did single gay fathers [38].

Gender Identity and Sexual Orientation of Children of Gay Parents

A long held myth about gay parenting is that children of gay parents would likely be confused about their gender identity and would more likely be gay. This assumption has been explored in several studies. Studies of young children of lesbian mothers reveal no differences in their choices of toys, dress, activity, or choice of friends from those children raised by heterosexual mothers [25]. Studies of adolescents revealed no differences as well. Huggins looked at 36 adolescents between the ages of 13 and 19 half of whom had divorced heterosexual mothers and half of whom had divorced lesbian mothers. Only one subject, a son of a heterosexual mother, identified himself as gay [39]. Three studies examined the sexual preferences of children of gay fathers. Bailey et al. queried 43 men between the ages of 17 and 43 who were conceived in a heterosexual relationship, but whose fathers divorced or separated and became openly gay. Thirty-seven subjects were heterosexual [40]. Another study described 19 sons and daughters of gay men who were between the ages of 14 and 35 years of age. Sixteen reported a heterosexual preference [41]. Miller studied 14 sons and daughters of gay fathers. Of that group of children, who were between the ages of 14 and 33 years of age, two described themselves as lesbian or gay [42].

The sexual orientation of adults raised by gay parents has also been studied. Tasker and Golombok compared young adults raised by lesbian mothers to young adults raised by single heterosexual mothers and found no differences between groups in rates of reported same sex attraction [43]. In general, studies suggest that children raised by gay parents do not identify as gay in significantly higher rates than do children raised by heterosexual parents [18].

The Social and Psychological Adjustment of Children of Gay Parents

The social and psychological well-being of children of gay and lesbian parents has long been an area of consideration by researchers based on the following concerns: that children in gay households may be at risk for psychopathology because they lack a live-in male or female role model; that such children may be exposed to a higher level of stress by virtue of the fact that they are growing up in a gay household; and that children with gay parents will likely suffer stigmatization and peer victimization leading to lower self-esteem [17].

Studies looking at young children of lesbian two-mother families found that they were no more likely to be rated as having psychological difficulties than children raised in two parent heterosexual households [3, 31]. In studies of older children Gartrell et al. found that 10-year-olds with lesbian mothers did not differ from population-based norms in rates of emotional and behavioral problems [44]. Another study compared 12–16-year-olds from lesbian-led and heterosexual-led families and found no differences in rates of depression, anxiety, and overall psychological functioning [45].

Wainwright et al. examined the psychosocial adjustment of adolescents living with female same sex parents and compared them to adolescents living in opposite-sex parents and found that in terms of self-esteem, psychological adjustment, academic achievement, and parental warmth, there were no significant differences between groups. What the authors determined was that the teenagers' adjustment was not based on their parents' sexual orientation but rather on their relationship with their parents. Those who had closer relationships with their parents did better overall regardless of sexual orientation [46].

A study addressing stigma and peer relationships looked at 8–12-year-olds in planned lesbian mother households and found that though reports of stigmatization by peers was low overall, those children who did perceive higher levels of stigma experienced lower levels of psychological well-being [47]. Gartrell et al. reported similar results when interviewing 10-year-olds raised in lesbian-led households. Though few reported experiencing homophobia, those who did experience homophobia suffered more emotional and behavioral problems [44].

Gay Fatherhood Through Assisted Reproduction

As gay men increasingly choose fatherhood through surrogacy and egg donation, there are as yet no studies on the well-being of children resulting from these procedures. However, two recent studies have begun to explore the demographic, medical, and psychological aspects of gay men seeking fatherhood through ART. Greenfeld and Seli medically and psychologically assessed the first 30 gay men seeking ART in their program (15 couples) and reported their findings. All subjects met medical and psychological criteria for acceptance into the program. All of the couples were in a committed relationship and had been together for at least 6 years. Subjects had given the decision as to who would provide the sperm a great deal of careful thought. Most of the subjects (80 %) chose one partner to be the sperm donor. He was the elder, the one with "better genes," or the one who cared most about being biologically related to the resulting offspring. Three couples chose to transfer an embryo from each partner [17].

Bergman et al. looked at the transition to parenthood for gay fathers whose children were conceived through surrogacy. Through structured interviews with one of the partners of 40 gay male couples, the authors described demographic and psychological changes in the lives of gay males as a result of parenthood. Fathers were predominantly Caucasian and socioeconomically well-off (mean income was $270,000). Subjects reported changes in lifestyle with friends more likely to be other parents, changes in job with one partner often opting to be the stay-at-home father, greater closeness with families of origin, and increased self-esteem as a result of becoming fathers [48].

Medical Aspects of Reproduction for Same Sex Couples

Medical screening of same sex couples follows ASRM guidelines for medical screening of heterosexual couples entering ART programs with the obvious qualification that, in the case of lesbian couples, two women are involved in the screening and, in the case of gay males, it is two men. While both partners are part of the initial screening, typically, the partner providing the gametes ultimately becomes the identified patient.

Lesbian Couples

Medical screening for lesbian couples entering an ART program includes a meeting with the primary physician who takes a careful medical history of both partners and discusses the options for treatment. These include intrauterine insemination with donor sperm, IVF with donor sperm, and so-called reciprocal IVF where one partner provides the oocytes and the other carries the pregnancy. This medical consultation includes the couple's plans for proceeding. Who, for example, will carry the pregnancy? Who will provide the sperm?

Gay Male Couples

Medical screening of gay male couples entering an ART program includes a meeting with the primary physician who takes a careful medical history of both partners and provides an explanation of the procedures involved in ART using oocyte donation and gestational surrogacy. The partner providing the sperm also undergoes a semen analysis and communicable disease testing mandated by the US Food and Drug Administration (FDA).

Social and Psychological Aspects of Same Sex Reproduction

The transition to parenthood for most couples, heterosexual or gay, involves decision-making and thoughtfulness and raises a number of concerns. Is this the right time to have a child? Will we be good parents? Can we afford to have children? Is this a world we want to bring a child into? For the gay couple, however, the process can be much more complicated [49]. Gay men and women choosing parenthood through assisted reproduction often struggle with homophobic attitudes in society, questionable family and social support, legal issues, and the decisions they must make in order to achieve conception. Who will provide the sperm and the egg? Who will carry the pregnancy?

Homophobia

Homophobia is described as negative feelings toward homosexuals and those thought to be homosexual. These feelings include antipathy, contempt, prejudice, aversion, and irrational fear. Homophobia can lead to discrimination and in the worst cases is state sponsored and can lead to criminalization and prosecution of homosexual behaviors. Eighty countries around the world consider homosexuality illegal, and five countries carry out the death penalty for homosexual behavior (Iran, Mauritania, Saudi Arabia, Sudan, and Yemen) [18].

Internalized homophobia refers to negative feelings toward oneself because of one's homosexuality. Those who experience internalized homophobia display lower levels of self-esteem, lower levels of disclosure about being gay, decreased family and social support, and greater psychological distress [49].

Gay couples contemplating parenthood, especially those who have themselves been the victims of discrimination and homophobia, may be concerned that their offspring may be discriminated against for having gay parents. Those who experience internalized homophobia may struggle with their own beliefs that homosexuality is wrong and/or that gay persons are indeed less fit to be parents than heterosexual persons. They may subscribe to the belief that every child needs both a mother and a father and that growing up in a gay household is therefore harmful to children.

Family and Social Support

When contemplating parenthood, heterosexual couples may take for granted social and family support for their decision to have a child, but such is often not the case for same sex couples. Gay men and women often face family dissolution, social isolation, and even violence as a result of coming out. Even family and friends who have shown support for their gay friend or family member may recoil at the idea of gay parenthood. Thus, same sex couples may face nonsupport and even moral condemnation from family and friends

when announcing their intention to become parents at the very time they could use that support the most [18]. The act of parenting may raise hostility and the old mythology that children may be stigmatized or that gay men and women are psychologically unfit to parent.

On the other hand, studies report that the very act of having children brings some gay couples closer to their families. Bergman et al. found that the gay men in their study reported feeling closer to family once they had children [49] Gartrell et al. in a longitudinal study of the transition to parenthood among lesbian couples found that post childbirth 69 % of the 84 lesbian mothers reported that having a child did indeed enhance the quality of their relationship with their family [44]. Gay couples who become parents often find great changes in their social life. They may shift from having gay friends who are childless and have no desire to have children to spending more time with other parents, gay or heterosexual.

Legal Issues

Despite the fact that same sex marriage is legal in some parts of the USA (and some other parts of the world), same sex couples continue to be denied the same legal protections that are provided to heterosexual couples [18]. For the most part, heterosexuals who are planning to become parents do not start the process with a legal consultation as is so often the case for same sex couples. Typically, when same sex couples become parents together, even though they share an equal commitment to parenting, the partner who is biologically related to the offspring is generally regarded as the "legal parent." In some cases the nonbiological parent gains legal parenthood through a process known as second-parent adoption. Unfortunately, fewer than half the states allow second-parent adoption leaving couples to seek legal rights through wills or powers of attorney. Many states solve such issues through the courts on a "case by case basis."

In an article promoting the importance of second-parent adoption for gay families, the American Academy of Pediatrics argues that denying legal parent status through adoption for second (nonbiological) parents prevents "these children from enjoying the psychological and legal security that comes from having two willing, capable, and loving parents" [50]. The legal sanction provided by second-parent adoption accomplishes the following: second-parent custody rights are protected should the legal parent die; protects second-parent rights to custody should the couple separate; establishes the requirement for child support from both if couple separates, ensures child's eligibility for health benefits from both parents; gives both parents the legal right to make medical decisions for their children; and creates the basis for financial security in the case of the death of either parent [50].

Also legally complex is the subject of surrogacy. A legal contract between surrogate and the intended parents is required in all cases, but when the intended parents are of the same sex, the issues may be more difficult. For example, Wald presents the scenario of a gay male couple who live in New York and contract with a gestational surrogate who lives in Ohio. Because the birth certificate is based on where the surrogate delivers, and in this case it would be Ohio, second-parent adoption does not apply in Ohio for same sex couples, so only one of the fathers would legally be the parent [51].

Decision-Making for Prospective Gay Parents

Same sex couples planning parenthood often give consideration to the question of whether to adopt or to choose assisted reproduction. Lesbians who choose the latter often do so for one or more of the following reasons: because of one partner's desire to experience pregnancy and childbirth, because they wish to raise a child from birth, and/or because they believe that the biological connection is more likely to elicit family support [18]. Gay men choosing surrogacy over adoption do so because they may want the biological connection to the child, they desire to raise the child from birth, and/or because they believe the surrogacy process may be easier and will allow them more control over the intrauterine life of their future children. In addition, some gay men are

concerned about the possible emotional difficulties a child may experience later in life when they learn they were relinquished by birth parents [52].

Lesbians: Who Will Carry the Pregnancy?

Lesbians choosing assisted reproduction need to give consideration as to who will carry the pregnancy, whether to use a known or unknown sperm donor, and what donor characteristics they regard as most important. For some, the issue of who will carry the pregnancy is an easy decision if one partner very much wants to be pregnant and the other does not. Among lesbian couples who both want to carry a pregnancy, they typically decide that each should have the opportunity to do so, and hence the decision becomes about who will go first. That decision usually is based on the age of the intended mothers, their work schedules, and sometimes about which partner has the greater sense of urgency [2]. Goldberg looked at the transition to parenthood in 29 lesbian couples and how they made the decision about the carrying the pregnancy. In 41 % of the couples the birth mother was the one who had the greatest desire to experience pregnancy and birth. For 14 % the reason was primarily determined by difficulties in fertility, where the partner who had initially opted to carry the pregnancy had not gotten pregnant and the other partner subsequently became the birth mother. Forty-five percent made the decision based on practicality—who had the better job? The better insurance? Who was more able to take maternity leave? While most couples in the study found that the decisions they made really worked for them, those who chose for fertility reasons often had significant difficulty with the decision, especially when it involved choosing the partner who had least wanted to carry [53].

Lesbians: Decisions About the Donor

Once couples have made a decision about who will carry the pregnancy, they need to think about the sperm donor. Part of the decision-making process is whether to use an anonymous donor or one who is known to them (such as a friend). Previous studies of heterosexual couples who need a donor sperm found that they overwhelmingly choose anonymous donors [54], but for lesbians who weigh the pros and the cons of known versus anonymous carefully, the decision is mixed. Goldberg studied pregnant lesbians and their partners and found that 59 % chose an anonymous donor, 31 % chose a known donor, and 10 % chose an "identity release" donor who is willing to be contacted when the offspring reach 18 (increasingly, sperm banks are offering a category of sperm donors who are willing to have their identity released to offspring) [53].

Some women choose anonymous donors because they do not know anyone who would be willing to donate or anyone they would be willing to ask to donate, but others are very clear about why they want to choose an anonymous donor. Some cite legal concerns about the possibility that a biological father might want to claim custody and, in any case, that they want to raise a child together without interference from another person. Sometimes it is the nonbiological mother who feels most strongly about using an anonymous donor because of concern that using someone known would complicate and potentially interfere with the security of a two-mother family and that a third party could even potentially threaten her position as a co-parent [18].

Lesbian couples who choose a known donor want their children to have information about who their biological father is, though they typically do not want him to serve in the role of father. These couples often make the decision out of concern for the offspring, feeling that they may want information about their biological and genetic history. Finally, some lesbian couples use known donors because they desire to complete the insemination process in private (either with home insemination or through sexual intercourse with the donor) without interference from the medical establishment. Another issue for lesbian couples when considering using a donor is to determine the characteristics they consider most important about the donor. Just as heterosexual couples seeking donor sperm often select a donor who physically resembles the intended father, so

too do lesbians often choose physical characteristics such as eye color, hair color, height, and race which are physically comparable to the nonbiological mother. These commonalities may include interests, hobbies, talents, education, and occupation. Couples often feel that this matching is important to help create a more cohesive family link based on shared traits common to both mothers [18].

Gay Male Couples: Who Will Provide the Sperm?

In their study of gay male couples seeking fatherhood through ART, Greenfeld and Seli found that participants typically had given the question of who would provide the sperm a great deal of thought and were very clear about their decision. Most chose only one of the partners to donate, but their reasons for choosing him were varied. Sometimes it was because he was the one who cared more about the biological connection or because he had "better genes." In other instances one partner was chosen because he was older and both agreed that he should "go first," or in some cases, one partner had children from a previous heterosexual relationship and the other partner wanted a chance to be biologically related to a child. The few couples that had equal desire for biological fatherhood chose to inseminate equal numbers of oocytes to transfer one embryo from each partner to the carrier [17]. Because there are so few studies on gay men and ART, we do not know whether the nonbiological father feels in any way left out of the process or less connected to the offspring than the biological father.

Gay Male Couples: Decisions About Donors and Surrogates

Gay men also face the decision of whether to use a known egg donor or an anonymous donor. Those who seek a known donor or an agency "identity release" donor often have in mind the idea that they want to provide offspring information about their genetic heritage. One study found that gay males who used anonymous donors looked for these characteristics: the donor should be tall, attractive, educated, and bearing a resemblance to the non-inseminating partner [17].

Typically, gay couples do not choose donors with whom they and their offspring will have ongoing relationships with, but the same is not always true for the surrogates. Couples usually contract with a surrogate who is recruited through an agency. During the treatment process and subsequent pregnancy, gay men often have a close relationship with the surrogate and appreciate her input, defer to her on aspects of the pregnancy, and value her female presence [17]. In fact gay men often form ongoing relationships with the surrogate because "she is necessarily part of the pregnancy for the duration" [54]. Another issue of importance for gay men when choosing a surrogate is to determine that she resides and will deliver in a state where surrogacy is legal and where both fathers can be on the birth certificate.

Psychological Evaluation of Same Sex Couples Entering ART

The psychological consultation with same sex couples entering ART programs is both informational and evaluative. Pretreatment preparation and information provides couples with a clear understanding of the physical, financial, legal, and emotional demands of the treatment. Gay men and women do not typically enter these ART after a history of infertility and thus are not familiar with the medical treatment and the emotional ups and downs that can accompany it. The consultation is evaluative in that is important to determine that couples are psychologically prepared for this treatment. Specifically, it is important to determine that they share a close and supportive relationship and are equally committed to the process, and that they do not have complicated social and psychiatric problems that could interfere with the treatment or their ability to become or function as parents. The consultation follows the recommended guidelines of the American Society for Reproductive Medicine as well as the guidelines

of the American Psychological Association for counseling same sex couples [55, 56].

Summary and Conclusions

Gay men and women increasingly seek assistance from fertility programs in order to achieve parenthood. Because same sex couples do not get pregnant accidentally, they enter these programs after careful consideration and thought [52]. Fertility programs offering ART to same sex couples need to be respectful of couples' relationships and demonstrate an appreciation of the challenges unique to same sex couples participating in their programs. Clinicians and staff members need to work toward providing a "gay-friendly" environment that is gender neutral and sensitive to all matters homophobic.

The literature on gay men and women and their children conceived through assisted reproduction has some limitations. Most of the studies have small sample size and their subjects are predominantly white, urban, well educated, middle to upper class, and lesbian. In fact, in a review of 23 studies published between 1978 and 2003, only three addressed gay fathers [26]. Despite these limitations the consensus is that these families are doing well and that there are no significant differences in the psychological development in children raised by gay families compared to children raised by heterosexual parents [23, 25, 26].

Editor's Commentary

Egg and embryo donation is well suited to fit the needs of many gay and lesbian couples wishing to have children. Increasing social tolerance of the gay community and the general acceptance of all individuals desire to reproduce have fostered a dramatic increase in the number of openly homosexual couples seeking fertility treatment. However, all offered treatments require careful planning and attention to the many details that may be outside the bounds of standard ART practice. This would include collaboration with attorneys to address the legal issues inherent to surrogacy contracts and discuss the rights and duties of parenting under local state law. It is in the best interest of patients to be evaluated by a mental health-care professional as well, not to document their sanity or psychiatric status, but rather to establish the normalcy of their intent to parent and discuss contingencies in the case of illness or separation.

Only a few states formally recognize marriage of same sex couples, and individuals who are legally married in one jurisdiction may later move to less favorable locales. Therefore, documenting the intent of all involved parties and the stated lifelong desire to co-parent can only strengthen the claims of individuals should a challenge occur later. Advanced directives should be executed as well regarding the disposition of cryopreserved sperm, eggs, or embryos to assist in their use should an individual die or become incapacitated.

ASRM, ACOG, and most other medical professional societies have taken a strong and unambiguous stand on endorsing the treatment of gay and lesbian patients, without restriction and without prejudice. I believe a sustained increase in usage of assisted reproductive services will occur and that clinical services for gay community will soon become a routine part of every ART practice.

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Immunologic and Clinical Consequences of Oocyte Donation Pregnancies

23

Marie-Louise P. van der Hoorn, Sicco A. Scherjon, and Frans H.J. Claas

Key Points

- Genetic dissimilarity reflected by the number of human leukocyte antigen (HLA) mismatches results in an altered immunological reaction in oocyte donation pregnancies compared to naturally conceived pregnancies.
- Pregnancy-induced hypertension, seen in a large number of recipients of donated oocytes, is more frequent with immunologically unrelated donors.
- Placental damage and basal plate abnormalities may be the consequence of a graft-versus-host phenomenon or organ rejection type of reaction.
- HLA mismatches are inherent to oocyte donation pregnancies and lead to more vascular complications, and it may be worthwhile to consider HLA typing of participants in order to select compatible haploidentical combinations.

Oocyte donation pregnancies are a result of in vitro fertilization of a donated oocyte by either a relative or more commonly an unrelated donor. In contrast to normal pregnancy, where the fetus is a semi-allograft expressing both maternal (self) and paternal (nonself) genes, in oocyte donation both fetal haplotypes are foreign to the gestational carrier. The placenta and fetal membranes are directly exposed to maternal tissue. Therefore, during an uncomplicated pregnancy, specific local immune adaptations are necessary at the fetal–maternal interface. It is possible that the genetic dissimilarity reflected by the number of human leukocyte antigen (HLA) mismatches results in an altered immunological reaction in oocyte donation pregnancies compared to naturally conceived pregnancies.

This chapter, based on two publications by the authors [1, 2], discusses the maternal and fetal complications of oocyte donation pregnancies. Furthermore, the immunogenetic and immunological similarities between oocyte donation pregnancies and transplantation are discussed. Pregnancy conceived after oocyte donation

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reflects an interesting model to study immunological reactions.

Clinical Aspects of Oocyte Donation Pregnancies

Many studies of oocyte donation pregnancies have focused on perinatal complications, such as preeclampsia, the mode of delivery, and immediate neonatal problems, such as prematurity. With regard to the recipient, most of the emphasis has been on short-term complications of pregnancy, because of the higher incidence of both early and late obstetrical problems. The maternal, fetal, and placental complications are discussed below.

Maternal Complications

Advanced maternal age leads to potential medical and obstetric complications. Pregnant recipients above the age of 40 are at an increased risk for gestational diabetes, preeclampsia, and thrombophlebitis [3]; above the age of 45, they are at an increased risk of hypertension, proteinuria, premature rupture of membranes, second and third trimester hemorrhage, preterm delivery, and lower mean infant birth weights [4, 5]. One study that corrected for maternal age and multiple gestation concluded that women who conceived with donor oocytes remain at high risk for preterm labor, preeclampsia, and protracted labor, requiring caesarean section delivery [6]. The rate of caesarean section deliveries in oocyte donation pregnancies is increased compared to spontaneous conceptions and is reported to range from 40 to 76 % of cases [7–14].

Pregnancy-Induced Hypertension

Oocyte donation pregnancies are associated with a higher than expected incidence of pregnancy-induced hypertension (PIH), ranging from 16 to 40 % of cases [7, 8, 10, 12, 13, 15–18]. This is most likely due to a higher incidence of placental pathology [19]. It has been suggested that the increased rate of hypertension in oocyte donation pregnancies is related to advanced maternal age, nulliparity, and ovarian failure [19], since these factors are associated with multiple obstetric complications [20]. However, a study by Sheffer-Mimouni et al. found that these factors were not independent risk factors for PIH [12]. They concluded that the higher incidence of PIH in oocyte donation pregnancies is due to an altered immune response. In another report, an increased risk for PIH was observed in women with oocyte donation pregnancies in women <35 years or >40 years of age [21].

In the studies above the control groups were spontaneously conceived pregnancies. Since IVF pregnancies are associated with more obstetric complications than naturally conceived pregnancies [22], they represent a more appropriate control group to examine the consequences of oocyte donation. Wiggins and Main found a threefold increased incidence of hypertensive complications in oocyte donation compared to standard IVF pregnancies (26 % vs. 8 %, respectively, $p=0.02$) [18]. For nulliparous women this difference was even more significant, with 37 % of the oocyte donation group and 8 % of the standard IVF group affected by hypertension ($p<0.003$). Multiple logistic regression analysis in nulliparous patients showed an odds ratio of 7.1 ($p=0.019$). In singleton and twin pregnancies, the same effect was found (OR: 4.9, $p=0.017$). Maternal age was not an added risk factor for the development of PIH (OR: 1.0) [18]. Interestingly, the incidence of PIH appears to be significantly higher if the oocyte donor is unrelated to the recipient (20 % vs. 3.7 % for standard IVF, $p=0.03$), versus a related, sibling donor (8 % vs. 3.7 % for standard IVF, $p=0.31$) [23]. This study retrospectively analyzed 61 oocyte donation pregnancies that were classified into two subgroups according to the relationship between the oocyte donation and recipient, and 127 non-donor IVF pregnancies. The groups were matched for age, parity, and number of fetuses. This study is the only one that has specifically examined the immunogenetic origin of the oocyte and its relationship to complications of pregnancy. These data suggest that PIH is more frequent with an immunologically unrelated donor.

Bleeding

A possible result of the unique, nonphysiological immunologic relationship between the fertilized oocyte and the maternal decidua is shallower placental invasion [24, 25]. The higher incidence of bleeding complications in the first trimester could be related to this insufficient placentation. On the other hand, excessive invasion might result in more postpartum hemorrhage in oocyte donation pregnancies as a result of placenta previa or abnormal placentation [12].

The incidence of first trimester vaginal bleeding is increased in oocyte donation pregnancies, ranging from 12 to 53 % of cases [7, 13, 19]. Significant blood loss is estimated to occur in 43–53 % of first trimester cases [12, 13] and 6 % of second trimester cases [12, 19]. The incidence of first trimester bleeding is substantially higher if compared to standard IVF pregnancies [13], and second trimester bleeding is higher if compared to the spontaneously conceived population (<1 %) [26]. It has been assumed that more bleeding complications are associated with multiple implantation sites and early fetal loss [27]. However, in oocyte donation cases in which only two embryos per cycle are transferred, the frequency of bleeding still remains high [13]. Other explanations, such as endometrial preparation therapy, have been suggested, but a possible relationship between various steroid replacement regimens and first trimester bleeding is difficult to assess.

Long-Term Consequences

The study of the trafficking of intact fetal cells into the maternal circulation (fetal cell microchimerism) is relevant to oocyte donation pregnancies, because it is not yet known if these circulating fetal cells play a role in establishing or maintaining tolerance to the conceptus. This merits further investigation. Furthermore, the consequences of the persistence of foreign circulating fetal cells for the mother's long-term health are currently unknown. In one study, however, allogeneic male fetal cells were shown to persist for up to 9 years in the circulation of healthy postpartum women who conceived using oocyte donors and delivered male infants [28]. The implications of becoming microchimeric with an unmatched population of fetal progenitor cells are an area for future research.

Oocyte donation conception is often hidden from the mother's and the baby's medical records, so correlations between oocyte donation and specific adverse outcomes are difficult to make. In approximately 40–50 % of the cases, the fact that it was an oocyte donation pregnancy is never disclosed to the child or other family members [29]. The literature search revealed no studies evaluating long-term effects of oocyte donation for the mother. Long-term outcome studies are therefore warranted [30].

Fetal and Neonatal Complications

In most studies that assessed the obstetrical outcome after oocyte donation, relatively little has been reported on fetal and/or neonatal complications. Elevated risks (relative to the general population) are primarily related to the higher incidence of multiple gestation [19, 31]. The incidence of intrauterine growth restriction is also not increased compared to the general population [13]. The incidence of preterm deliveries in oocyte donation singleton pregnancies (10.6 %) is not increased if compared to the general population [13, 14]. Significantly, there appears to be no effect of oocyte donation pregnancy (with or without PIH) on neonatal birth weight [11, 32]. The general health status of children under 5 years old who were conceived using oocyte donation is at least as good as that of children conceived using standard IVF procedures [13]. There is also no increase in the incidence of congenital malformations in infants resulting from oocyte donation pregnancies [12, 14].

Placental Pathology

At the fetal–maternal interface, significant histological and immunohistochemical differences are present when comparing oocyte donation and non-donor IVF pregnancies. Characteristic pathologic findings in oocyte donation cases include a higher incidence of villitis of unknown etiology,

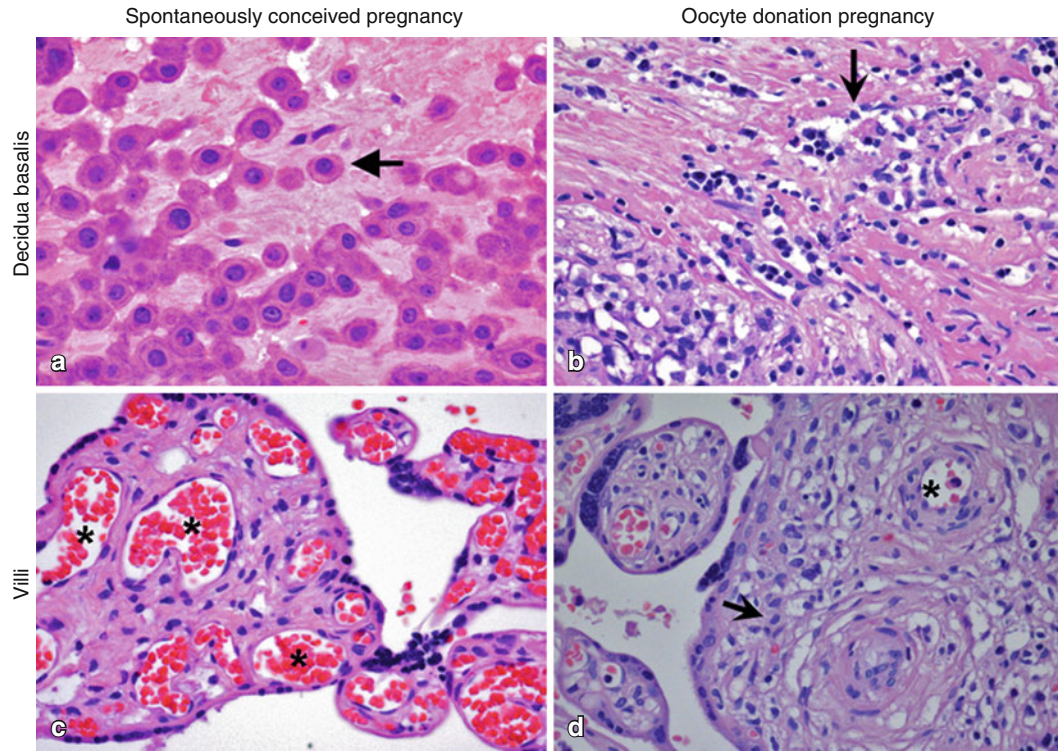

Fig. 23.1 Photomicroscopic images from oocyte donation and spontaneously conceived pregnancies placentas. (H&E stained sections, original magnification 400×). (**a**) Normal decidua basalis from a spontaneously conceived pregnancy with normal decidual cells (*arrow*). (**b**) Decidua basalis of OD pregnancy placenta with deciduitis illustrated by the infiltration of mononuclear cells (*arrow*). (**c**) Villi of a spontaneously conceived pregnancy placenta. (**d**) Villi from an OD pregnancy placenta. The stromal cellularity is increased by an infiltrate of mononuclear cells (*arrow*). Fetal capillaries are shown by the (*asterisks*)

chronic deciduitis, massive chronic intervillositis, maternal floor infarction, and ischemic changes, as seen with preeclampsia [33–35] (Fig. 23.1). The chronic deciduitis observed in oocyte donation placentas is characterized by its severity and the presence of a dense, fibrinoid deposition in the basal plate. Furthermore, an increased infiltration of CD4+ T helper cells and CD56+ NK cells is present in the basal plate of oocyte donation placentas [35]. It is in the basal plate where extravillous trophoblast (of fetal origin) interfaces with and invades the maternal tissue. The extravillous trophoblast cells do not express classical HLA-A and HLA-B molecules, thereby preventing interaction with cytotoxic T cells. However, they do express a unique combination of HLA antigens (HLA-C and the nonclassical HLA-E and HLA-G) that interact with KIR receptors on uterine natural killer cells [36–38], although HLA-C can also serve as a target molecule for CD8+ T cells [39]. The striking findings of a dense fibroid deposition and mononuclear cell infiltration in the basal plate suggest that the placental abnormalities are related to an immune-mediated response that is more pronounced in oocyte donation pregnancies. The placental damage may be the consequence of a type of graft-versus-host disease and/or organ rejection type of reaction [35].

Immunologic Aspects of Oocyte Donation Pregnancies

Compared to the knowledge on maternal complications, relatively little is known about the underlying immunology in oocyte donation pregnancies.

However, understanding the role of the immune system in oocyte donation pregnancies might have a broader biological significance in that it may give insight into immune mechanisms leading to immunologic tolerance for HLA-mismatched solid organ transplantations. The normal fetal–maternal immunology is discussed below, followed by immunological consequences in oocyte donation pregnancies.

Normal Fetal–Maternal Immunology

A successful pregnancy is an interesting immunologic paradox. The fetus carries paternal and maternal genes but is not rejected by the maternal immune system, over a period of 9 months. In spontaneously conceived gestations, several specific protective mechanisms have been postulated to explain the maternal tolerance of the fetus. Since the fetal tissue is directly exposed to the maternal blood, it is at risk of being attacked by components of both the innate and acquired immune system, with the potential risk of death. Therefore, to develop tolerance to the fetus, humans need an immune privileged site at the fetal–maternal interface in order to reproduce [40]. In spontaneously conceived pregnancies, immune recognition of the semi-allogeneic fetus takes place, but the soluble and cellular components of the maternal immune system are kept under control (or are locally downregulated), leading to a maternal immune system that favors implantation of the embryo [41]. The currently accepted view is that a successful pregnancy depends on an appropriate balance of the different components of the maternal immune system, with predominance of T helper 2 immunity [42–44]. At the human fetal–maternal interface, maternal recognition of fetal antigens presented by trophoblast cells or by fetal cells trafficking into the maternal circulation is essential for the induction of immunoregulatory mechanisms [45]. It is apparent that activated T cells at the maternal interface include regulatory T cells [45, 46]. These regulatory T cells have an important role in the local downregulation of human fetal-specific allogeneic T cell responses [47]. In studies of peripheral blood, only minor differences in systemic immunoregulation were found between pregnant women and nonpregnant female controls [48]. All of these protective mechanisms maintain the immunosuppressive environment in the pregnant uterus, and in this way the semi-allogeneic fetus is capable of surviving in the uterus.

Oocyte Donation Failure

The European Society of Human Reproduction and Embryology (ESRHE) publishes data annually on assisted reproductive technology. Following oocyte donation, 5,516 clinical pregnancies were reported from 12,685 embryo transfers, giving a clinical pregnancy rate of 43.5 %. The mean delivery rate of these embryo transfers was 27.2 % (n = 3,448) [49]. This means that a total of 71.8 % of all embryo transfers after oocyte donation are not continuing. For IVF the pregnancy rate was 32.4 % (31,665 pregnancies from 96,572 embryo transfers). The pregnancy rate in oocyte donation pregnancies is higher compared to IVF pregnancies (43.5 % vs. 32.4 %, respectively), which at a first glance seems to be surprising. However, the reason to perform oocyte donation is ovarian failure, and as there are rarely uterine abnormalities, oocyte donation might therefore be more successful compared to IVF pregnancies, in which there may be an underlying and unknown mechanism responsible for implantation failure. Unsuccessful embryo transfers in oocyte donation procedures resulting in miscarriage may be related to a non-optimal HLA match between the oocyte donor, sperm, and gestational carrier. Surprisingly, nearly 30 % of all embryo transfers in oocyte donation pregnancies result in a continuing pregnancy, resulting in a mother who carries a completely allogeneic fetal allograft. A number of complications have been described, of which some might be due to the allogeneic nature of the fetus. Taking the more vigorous immune response in oocyte donation into account, theoretically it might be valuable to perform HLA typing of the oocyte donor and recipient in order to select haploidentical combinations that would be more similar to spontaneously conceived pregnancies.

Preeclampsia and Oocyte Donation Pregnancies

Preeclampsia is a syndrome characterized by new onset hypertension and proteinuria after 20 weeks of gestation. Immunologic abnormalities, similar to those observed in allograft rejection, have been observed in preeclamptic women [50]. Furthermore, women with preeclampsia have an increased level of circulating fetal DNA in comparison to controls [51]. The host-versus-graft immune response is stopped by removal of the transplanted organ; preeclampsia is more rapidly recovered by removal of the fetal products after delivery [52].

The control of placentation has an immunological basis, with interaction between maternal and fetal genes. Preeclampsia might be the consequence of an unsuccessful attack of the maternal nonspecific host defense on the implanting blastocyst and eventually results in defective implantation which may lead to stimulation of the maternal inflammatory response [15]. Changing partner, artificial donor insemination, and oocyte donation all increase the risk of hypertensive disorders in pregnancy, while there is a protective effect of prolonged period of semen exposure [53]. Because in pregnant recipients there is a short duration of exposure to non-maternal antigens, this could contribute to an altered or inadequate immunoprotection of placentation, eventually resulting in preeclampsia. Preeclampsia is thought to have an underlying immunological mechanism demonstrated by uterine NK cells and their relation with implantation. NK cells express KIR receptors to which HLA is able to bind. The combination of maternal KIR AA genotype and fetal HLA-C2 is associated with an increased risk of preeclampsia [37]. In this interaction, HLA-C2 will only bind with an inhibitory KIR receptor, possibly resulting in too much inhibition of uterine NK cells. It is thought that the inhibition of uterine NK cells results in inadequate trophoblast invasion into the spiral arteries, which will eventually lead to preeclampsia. Since this combination has a deleterious effect in evolution, the frequencies of these genotypes have been tested. Indeed, populations with a high frequency of KIR AA have a low frequency of C2 and vice versa [37].

In the Netherlands, the law forbids commercial and anonymous oocyte donation. Oocyte donation based on noncommercial purposes is allowed, but infertile women must find their oocyte donor by themselves. Therefore, many women who require oocyte donation to become pregnant go abroad for treatment. It is possible that hereby, the protective effect of the incidence of KIR AA and HLA-C2 in a population is not present, and this might partly contribute to the increased incidence of preeclampsia in oocyte donation pregnancies. The sperm of donors with a C1/C1 genotype is predicted to be safer than C2/C2 males, since this results in a fetus expressing C2 [54]. If the day comes that HLA typing is performed before fertilization of the donated oocyte, the combination of maternal KIR AA, fetal C2, and sperm donors with the C2/C2 genotype should be avoided in order to decrease the incidence of preeclampsia. If the fetus has more C2 genes than the mother, the risk of getting preeclampsia is two times higher (OR 2.09, 95 % CI: 1.24–3.58, $p = 0.007$) [54]. Of course, preeclampsia not based on the combination KIR AA-HLA-C should not be excluded as undoubtedly other mechanisms as well play a role in the pathogenesis of preeclampsia.

Immune Studies in Oocyte Donation

Although other mechanisms may be involved, it is likely that downregulation of the maternal alloimmune response to the fetus in an oocyte donation pregnancy is far more difficult than in spontaneously conceived pregnancies with semiallogeneic fetuses. Compared with spontaneously conceived pregnancies, there is a higher degree of antigenic dissimilarity in oocyte donation cases. If the five most immunogenic HLA antigens (HLA-A, HLA-B, HLA-C, HLA-DR, and HLA-DQ) are taken into consideration, the maximal number of mismatches in spontaneous conceived pregnancies would be five (Fig. 23.2). In oocyte donation pregnancies, this could reach a maximum of ten mismatches. Since oocyte donation pregnancies are characterized by more HLA mismatches, it is to be expected that a possible relationship between aspects of immune

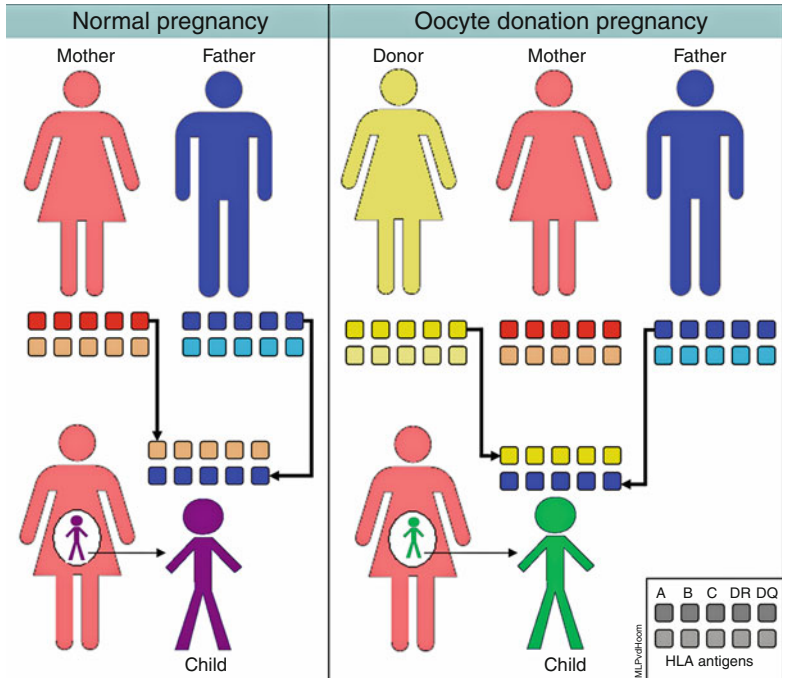

Fig. 23.2 Schematic drawing of the inheritance of the most immunogenic HLA antigens in a spontaneously conceived and an oocyte donation pregnancy. In a spontaneously conceived (or non-donor IVF) pregnancy, the child inherits antigens of the father and antigens of the mother. The five most immunogenic HLA antigens (HLA-A, HLA-B, HLA-C, HLA-DR, and HLA-DQ) are depicted in *red* for the mother and in *blue* for the father. The child inherits one set from the mother and one set from the father. Comparing the antigens of the child with the mother, a maximum of five mismatches is possible. In an unrelated oocyte donation pregnancy, no antigens from the mother are present in the fetus. The antigens of the donor are depicted in *yellow* and the antigens from the father in *blue*. The set of genes inherited by the child contains no antigens of the mother; therefore, a maximum of ten mismatches is possible between the mother and the child in an oocyte donation pregnancy

regulation and the number of HLA mismatches will become more apparent in oocyte donation pregnancies. In pregnant women who conceived by oocyte donation, an increased percentage of intracellular IFN-γ (Th1)- and IL-4 (Th2)-positive CD4+ T lymphocytes was found in peripheral blood compared with pregnant women after spontaneous conception [55]. This hyperactivation of Th1 and Th2 cells, induced by the allogeneic fetus, is specific for oocyte donation pregnancies. IFN-γ is also involved in spiral artery formation. Furthermore, the Th2 effect was more pronounced in oocyte donation pregnancies than in spontaneously conceived pregnancies [55]. This suggests that the additional mechanism of Th2 immunity in oocyte donation pregnancies leads to a successful pregnancy, even with a completely allogeneic fetus. Although this study investigated immune cells in the peripheral blood, the widely accepted view is that the active immune mechanisms take place at the fetal–maternal interface; therefore, it is possible that an effect will be even more prominent at this location. Recently, a statistically significant correlation between the extent of HLA mismatches and the percentage of CD4+CD25dim activated T cells in the decidua parietalis of uncomplicated pregnancies was described [39].

In spontaneously conceived pregnancies, the correlation between the number of amino acid triplet sequence (HLA epitope) mismatches between pregnant women and their children, and antibody production in the pregnant woman against the paternal antigens inherited by the child has been studied [56]. A positive correlation was found between the number of triplet mismatches (0–22) and the percentage of women producing HLA antibodies ($p < 0.0001$). If 0 triplet mismatches

were present, no antibodies were formed, even in the case of 1 or 2 classical HLA antigen mismatches. It remains to be established whether the actual number of HLA mismatches or epitope mismatches is more important in establishing tolerance to the fetus. However, it is likely that in oocyte donation pregnancies, the number of both HLA antigen and epitope mismatches will be even higher than in spontaneously conceived pregnancies. Therefore, the percentage of women producing antibodies will be higher, and this may have clinical implications. Although the clinical relevance of specific anti-fetal HLA antibodies is controversial, a recent study clearly showed that the presence of these antibodies in early pregnancy is associated with a reduced chance of a live birth [57].

The immune system clearly plays an important role in oocyte donation pregnancies. Unfortunately, there is a lack of information from the mother's perspective about the long-term effects of exposure to foreign cells and antigens in the recipient, since the usual clinical endpoint is the chance of having a take-home baby. From the literature, it is unknown at present whether, later in life, the consequences of having conceived using oocyte donation may be harmful or not. In addition, when investigating immunologic aspects of oocyte donation pregnancies, it is important to analyze the underlying reason why oocyte donation was necessary. For example, it is accepted that premature ovarian failure is a heterogeneous disorder in which some of the idiopathic forms are based on abnormal self-recognition by the immune system [58]. It is possible that the preexisting immunologic mechanisms involved in premature ovarian failure may contribute to the immunologic differences between oocyte donation and spontaneously conceived pregnancies.

Oocyte Donation and Transplantation

In oocyte donation pregnancy, the mother is exposed to foreign cells and antigens, a situation that has some resemblance to blood transfusions and organ transplantation. It is to be conceived that the downregulation of the maternal alloimmune response to the fetus during oocyte donation pregnancies needs more adaptation compared to a spontaneously conceived pregnancy. The degree of antigenic dissimilarity (reflected by the number of HLA mismatches) is in general higher in oocyte donation pregnancies compared to spontaneously conceived pregnancies. In the transplantation setting, the degree of HLA compatibility between the donor and recipient is relevant for graft survival. More mismatches will lead to poorer graft survival [59]. Enhanced graft survival has been observed in kidney transplant recipients who prior to transplantation received a blood transfusion [60]. However, as discussed later, pre-transplant blood transfusion can have different immunomodulatory effects as they either activate or suppress the immune system of the recipient.

The underlying immunogenetic differences between solid organ transplantation and oocyte donation pregnancies are similar; the medical complications such as graft rejection and preeclampsia might be similar. However, the medical consequences for pregnant women by oocyte donation or for transplantation patients are totally different (Fig. 23.3). For solid organ transplantation, the donor requires an extensively screening and the patient receives immunosuppressive therapy and has a comprehensive medical follow-up. In contrast, an oocyte donation pregnancy most commonly consists of an unknown donor and the pregnant women do not receive extra medical care and do not use any additional medication. Oocyte donation pregnancies result in an immunologically unique situation, and until now it remains unclear how the mother is able to accept the fully allogeneic allograft. The immunological principles present in spontaneously conceived pregnancies are most likely as well present in oocyte donation pregnancies.

Downregulation of the Immune System by HLA-DR-Matched Blood Transfusions

Pre-transplant allogeneic blood transfusion has a positive effect on kidney graft survival [60]: patients transfused with one HLA-DR-matched

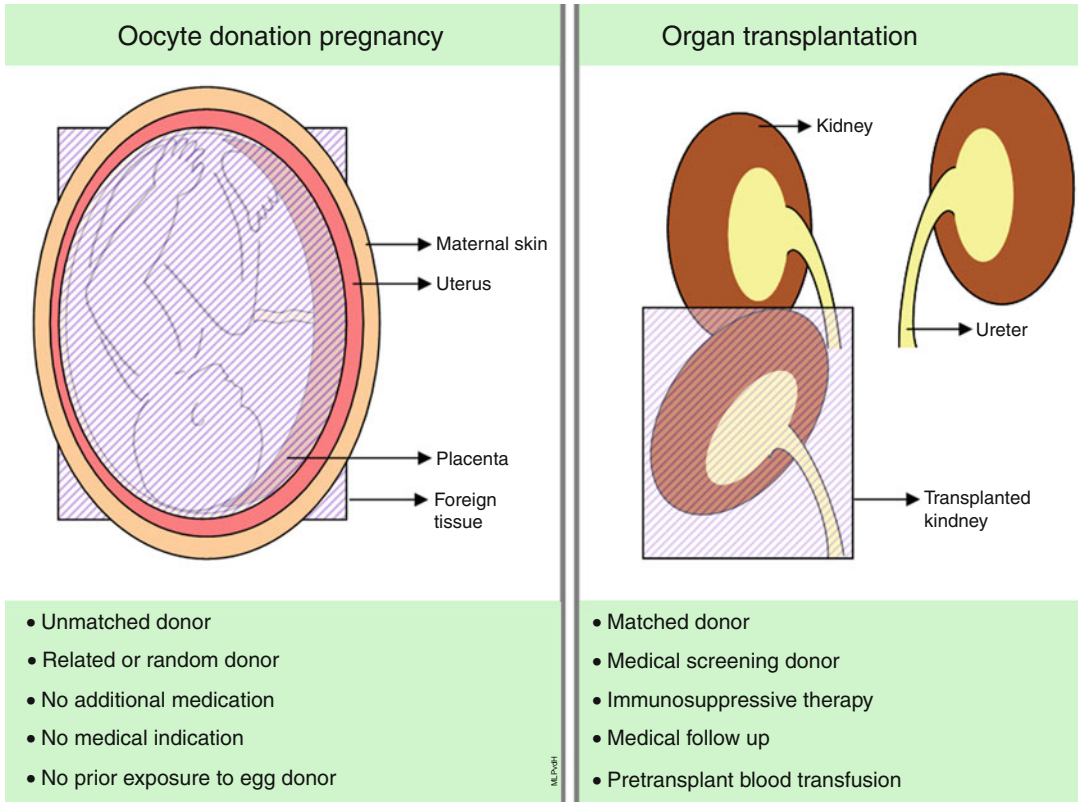

Fig. 23.3 Oocyte donation versus organ transplantation. A schematic overview of the differences in the medical consequences between oocyte donation and solid organ transplantation, while in both situations antigenic dissimilarity is present

transfusions (semi-allogeneic, a situation similar to a normal pregnancy) showed an enhanced kidney [61] and heart [62] transplant survival. No beneficial effect was seen for pre-transplant blood transfusion with fully HLA-DR-mismatched blood transfusions (a situation similar to oocyte donation pregnancies). In addition, HLA alloantibody formation was significantly higher after fully HLA-mismatched transfusions compared to one HLA-DR-matched transfusions [63]. The immune mechanism suggested to be involved in modulation of alloreactivity by blood transfusion might as well occur during conception and prior exposure to semen [64]. The shared HLA-DR allele is supposed to play a pivotal role in the downregulation of the immune response [65, 66] as CD4+ regulatory T cells may recognize an allopeptide in the context of this self HLA-DR on the transfused blood cells. When this allopeptide is shared between the blood donor and organ donor, CD4+ T cells are capable to downregulate all activated T cells involved in graft rejection, leading to an enhanced graft survival. A similar mechanism may play a role during a normal pregnancy or during an oocyte donation pregnancy where the fetus shares the HLA class II allele with the mother. However, the situation is different in fully allogeneic oocyte donation pregnancies, where the fetus is completely HLA mismatched. It is to be expected that a stronger or different immune regulation is necessary to prevent rejection of the fully allogeneic fetus. Studies in mice demonstrate that the maternal T cell repertoire is aware of paternal antigens during pregnancy, but in healthy pregnancy reactive T cells do not mediate a detrimental anti-fetal immunity [67]. In human, it has been shown that a distinct subset of HLA-DR + regulatory T cells is involved

in the induction of preterm labor and in the induction of organ rejection after transplantation [68]. All these studies suggest that a HLA-DR match play an important role in the induction of immunological tolerance. Since more HLA mismatches are inherent to oocyte donation pregnancies, one can imagine that the higher number of HLA-DR mismatches in oocyte donation pregnancies lead to more complications. As the allogeneic fetus is able to survive 9 months in the uterus, without any additional immunosuppressive medication as is needed in solid organ transplantation, it is likely that a very efficient local and peripheral immune regulation is responsible for such a successful oocyte donation pregnancy.

Overview

Although oocyte donation gives infertile women the opportunity to conceive, it may lead to harmful consequences during pregnancy if compared with spontaneously conceived pregnancies. This chapter gave an overview of the consequences of oocyte donation pregnancies with respect to their atypical fetal–maternal immunologic relationships. All of these complications can be the consequence of oocyte donation pregnancies; however, other factors that correlate with infertility and age could also be an underlying cause. For example, women conceiving through oocyte donation are more often primigravidas and more frequently have ovarian failure compared with women who conceive spontaneously. These factors are all associated with obstetrical complications [20]. More studies that correct for these confounding variables (e.g., maternal age, nulliparity, and ovarian failure) are needed to determine the specific role that oocyte donation plays in these important obstetrical complications. The higher risk of maternal morbidity in women who conceived through oocyte donation is a limitation of this form of treatment for infertility. For the benefits to outweigh the risks, it might be important to select low-risk donor–recipient combinations. Considering the immunologic mechanisms in oocyte donation, it might be worthwhile to perform HLA typing of donor and recipient in order to select haploidentical combinations that would be more comparable to spontaneously conceived pregnancies than fully HLA-mismatched combinations.

Although the literature conclusively demonstrates an increased risk of oocyte donation-related pregnancy complications for the mother, it does not show an increased complication rate for the fetus or newborn [11–14]. Since there is a general lack of studies on the long-term outcome of oocyte donation pregnancies, it is currently unknown whether the child or mother experiences any consequences later in life. In oocyte donation pregnancy, the mother is exposed to foreign cells and antigens, a situation that is comparable to blood transfusions and organ transplantation. Oocyte donation pregnancy leads to a hyperactivation of Th1 and Th2 cells compared to spontaneously conceived pregnancies [55]. This suggests that the allogeneic fetus induces an additional mechanism that leads to a successful pregnancy.

Conclusions

In oocyte donation pregnancies, the fetus is allogeneic to the gestational carrier. This creates an interesting immunological paradox. The fetus is accepted by the mother although being immunogenetically completely unrelated to the mother (unless the egg is donated by a relative). The increased rate of maternal complications in oocyte donation pregnancies may be related to the allogeneic nature of the fetus. Understanding the role of the immune system in successful oocyte donation pregnancies also has broader biomedical significance in that it may also give insight into immune mechanisms leading to immunologic tolerance for HLA-mismatched solid organ transplants. In solid organ transplantation, the same immunogenetic dissimilarity is present; however, immunosuppressive drugs are unavoidable to maintain the graft. Resemblances between graft rejection and pregnancy complicated by preeclampsia are clearly present. Multiple immunomodulatory strategies are used by trophoblast cells in the placenta to avoid rejection, including altered HLA expression, synthesis of immunosuppressive molecules, and expression of high levels of complement

regulatory proteins. It is possible that in oocyte donation pregnancies, immunomodulatory strategies lead to an active downregulation of the alloimmune response and as a consequence to acceptance of the fetal allograft.

Editor's Commentary

Placental vascular abnormalities, pregnancy-induced hypertension and preeclampsia, intrauterine growth retardation, and stillbirth have been consistent and troubling observations that have plagued the pregnancies of many patients throughout the history of egg and embryo donation. These serious complications occur at a higher incidence than seen in the general population of spontaneous pregnancies and higher than what is noted in women going through ART using their own oocytes. Furthermore, these events occur in young and old recipients alike, yet the etiology for the findings has never been fully explained.

Van der Hoorn and colleagues present a fascinating model based on accepted traditional schemes of allogenic transplantation to explain how host incompatibility with the embryo may at least partially explain many of the observed obstetrical abnormalities. This model would suggest that HLA genotyping and matching should be performed routinely and allogenic dislikeness minimized. This would also be true for cases involving gestational carriers providing surrogate services.

To my knowledge few if any practices presently advocate this policy of screening and matching, but in many ways it makes sense, and I find the concept fascinating. In essence, donors and recipients would be matched on HLA compatibility no different than what is routinely done for organ transplantation patients and for similar reasons. Finally, long-term health consequences due to mismatched and circulating fetal stem cells may also impact on the health of mothers and will be important to monitor in the years ahead.

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Part V

Legal and Regulatory Issues

FDA Regulatory Approach to Reproductive Tissues

24

Karoll J. Cortez, Ellen Lazarus,
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Key Points

- FDA regulations related to reproductive tissue donation are designed to reduce the risk of communicable disease transmission and protect the public health.
- Infectious disease transmission has been documented for most substances of human origin, including the presence of infectious agents in reproductive tissues.
- Reproductive tissue establishments are subject to FDA inspection and enforcement, at which time a FDA inspector may take samples, question personnel, review SOPs and medical records, and observe personnel at work during the manufacturing process.
- Donor specimens must be tested using FDA-licensed, approved, or cleared donor screening assays, and the FDA has determined that more than one assay may be necessary to adequately evaluate a donor for a particular communicable disease (e.g., for HIV, both anti-HIV-1/2 and HIV-1 nucleic acid amplification [NAT] testing).

FDA Regulatory Approach to Tissues

FDA regulations related to reproductive tissue donation are designed to reduce the risk of communicable disease transmission. The goal of this chapter is to provide a broad overview of how FDA regulates donated reproductive tissues used for assisted reproductive technologies (ART) that will be useful for clinicians and laboratories providing these medical services and treatments. This chapter relies on FDA regulations and FDA guidance documents. It is recommended to refer to the regulations themselves, and the guidance

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The findings and conclusions in this chapter have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any agency determination or policy.

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Table 24.1 Part 1271 of the 21 Code of Federal Regulations (CFR) applicable to cells and tissues recovered on or after May 25, 2005

Rule	Subparts	Scope
1. Establishment registration and listing[a]	Subpart A	(A) General provisions pertaining to the scope and purpose of Part 1271, as well asdefinitions
	Subpart B	(B) Procedures for establishment registration and product listing
2. Donor eligibility (DE)[a]	Subpart C	(C) Provisions for the screening and testing of donors to determine their eligibility
3. Current good tissue practice (CGTP)[b]	Subpart D	(D) Current good tissue practice (CGTP) requirements
	Subpart E	(E) Certain labeling and reporting requirements
	Subpart F	(F) Inspection and enforcement provisions

[a]Applicable to all HCT/P manufacturers, including reproductive tissue establishments
[b]The regulations in Subpart D that are applicable to reproductive tissue establishments manufacturing HCT/Ps regulated solely under Section 361 are 21 CFR 1271.150(c)—manufacturing arrangements, and 1271.155—exemptions and alternatives. Subpart F is applicable to reproductive tissue establishments

Table 24.2 Examples of HCT/Ps

From living donors	From post-asystole (cadaveric) donors
Reproductive cells and tissues (e.g., oocytes, semen, embryos)	Musculoskeletal tissues
Embryonic pluripotent cells derived from embryos	Bone
Hematopoietic stem/progenitor cells from peripheral blood and cord blood	Cartilage
	Fascia
Other cell therapy products (e.g., pancreatic islet cells, mesenchymal stem/stromal cells, fibroblasts)	Tendon
	ligament
Manipulated autologous chondrocytes	Skin
	Epithelial cells on a synthetic matrix
Amniotic membrane	Dura mater
	Cardiovascular tissues (e.g., heart valves, pericardium)
	Ocular tissues (e.g., cornea, sclera)
	Tissue/device and other combined products

21 CFR 1271.3(d). This list is non-inclusive. Some of the products may be obtained from either living or nonliving donors

documents and other references, for complete information about the regulatory requirements.

Infectious disease transmission has been documented for most substances of human origin [1–6], and the presence of infectious agents in reproductive tissues has been reported, indicating the potential for transmissibility through transfer of reproductive tissues [7–24]. Oocytes, semen, and embryos are regulated by the FDA as human cells, tissues, and cellular- and tissue-based products (HCT/Ps). The HCT/P regulations were put in place based in part on reports of distribution of imported human tissue without adequate screening and testing for HIV and hepatitis and a report by CDC from the early 1990s that HIV had been transmitted through transplantation of human tissue [25]. Three "tissue rules" constitute the basis of FDA's comprehensive regulatory approach[1] for HCT/Ps (Table 24.1). The tissue rules apply to a broad range of human cells and tissues that undergo varying types and extent of processing. Examples of HCT/Ps, including reproductive tissues, are provided in Table 24.2, and products not considered HCT/Ps are listed in Table 24.3.

[1]In February 1997, FDA proposed a tiered, risk-based approach to the regulation of cellular- and tissue-based products (62 FR 9721, March 4, 1997). Since 1997, FDA published three proposed tissue rules that were finalized as Title 21 of the Code of Federal Regulations (CFR) Part 1271.

Under the tiered, risk-based regulatory approach, some HCT/Ps (herein referred to as "tissues") are regulated solely under the legal authority of Section 361 of the Public Health Service Act (PHS Act) and the regulations in 21 CFR Part 1271 (the "tissue rules"). Other more complex cell- and tissue-based products are also regulated as drugs, devices, and/or biological products under section 351 of the PHS Act and/or the Federal Food, Drug, and Cosmetic Act (FDCA). Oocytes and embryos intended for reproductive use are generally regulated solely under Section 361 of the PHS Act and the tissue rules and do not require premarket review. Nonreproductive uses of reproductive tissues generally require premarket review.

Table 24.3 Examples of products not considered HCT/Ps

Vascularized human organs for transplantation
Whole Blood or blood components
Secreted or extracted products, for example, human milk, collagen, cell factors
Certain types of minimally manipulated bone marrow
Ancillary products used in the manufacture of HCT/Ps
Cells, tissues, and organs derived from animals other than humans
In vitro diagnostic products
Blood vessels recovered with an organ for use in organ transplantation

21 CFR 1271.3(d)

Regulatory Requirements Applicable to Reproductive Tissue Establishments

Clinical practices and laboratories engaged in certain aspects of reproductive tissue donation and handling are subject to the applicable provisions in the tissue rules. If you engage in these activities, your practice is considered a reproductive tissue establishment that must register and provide a list of products with FDA (21 CFR Part 1271 Subparts A and B), unless an exception applies (see Table 24.4). You must also perform a donor eligibility determination for most donors (described in 21 CFR Part 1271 Subpart C). In general, only certain provisions of the current good tissue practice (described in Subpart D) are applicable to reproductive tissue establishments, as detailed later in this chapter. Reproductive tissue establishments are subject to inspection and enforcement (Subpart F). The following overview highlights aspects of the tissue rules generally applicable to reproductive tissues and reproductive tissue establishments.

Table 24.4 Exceptions from the tissue rules

Exception	Example
(a) Tissues are used solely for nonclinical scientific or educational purposes	Use of sperm cells for nonclinical academic research purposes
(b) Tissues are removed from and implanted in the same individual during the same surgical procedure	Removal of skin from a body site to cover a defect in another site in an individual during a plastic surgery procedure
(c) A carrier that during usual course of business accepts, receives, carries, or delivers tissues	UPS, FedEx, DHL
(d) Establishments that do not recover, screen, test, process, label, package, or distribute, but only receive or store tissues only for implantation, transplantation, infusion, or transfer within their facilities	Hospital blood bank/tissue service that receives and maintains inventory of musculoskeletal tissues for use in the OR
(e) Establishment that only recovers reproductive tissues from a donor and immediately transfers them into a sexually intimate partner of the donor	Ob/Gyn practice performing artificial insemination of a woman with her partner's semen
(f) Individuals under contract, agreement, or other arrangement with a registered establishment that only recover tissues and send them to the registered establishment. This exception applies only to registration and listing requirements. Individuals in this category must comply with all other applicable requirements	Obstetric practitioner contracted to perform cord blood collection

21 CFR 1271.15

General Provisions of the Tissue Rules

Subpart A of the tissue rules sets out the purpose and scope of the tissue rules. It also lists pertinent definitions of terms (examples are provided in Table 24.5). The criteria for regulation solely under the tissue rules, as opposed to regulation both under these rules and additional statutory authority, are described, as well as specific circumstances whereby an individual or establishment would not be required to comply with some or all of the rules (Table 24.4).

Table 24.5 FDA definition of terms in the regulations that are particularly relevant to tissues for reproductive use

Definition	Meaning	Reference
Autologous use	Implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered	1271.3(a)
Establishment	Place of business under one management, at one general physical location, that engages in the manufacture of human cells, tissues, and cellular- and tissue-based products. "Establishment" includes: 1. Any individual, partnership, corporation, association, or other legal entity engaged in the manufacture of human cells, tissues, and cellular- and tissue-based products; and 2. Facilities that engage in contract manufacturing services for a manufacturer of human cells, tissues, and cellular- and tissue-based products	1271.3(b)
HCT/Ps	Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient, including oocytes, semen, and other reproductive tissue	1271.3(d)
Manufacture	Means, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue and the screening or testing of the cell or tissue donor	1271.3(e)
Transfer	The placement of human reproductive cells or tissues into a human recipient	1271.3(g)
Biohazard legend	Appears on the label and is used to mark HCT/Ps that present a known or suspected relevant communicable disease risk	1271.3(h)
Directed reproductive donor	A donor of reproductive cells or tissue (including semen, oocytes, and embryos to which the donor contributed the spermatozoa or oocyte) to a specific recipient and who knows and is known by the recipient before donation. The term directed reproductive donor does not include a sexually intimate partner under 1271.90	1271.3(l)
Donor	A person, living or dead, who is the source of cells or tissue for an HCT/P	1271.3(m)
Donor medical history interview	A documented dialogue about the donor's medical history and relevant social behavior, including activities, behaviors, and descriptions considered to increase the donor's relevant communicable disease risk	1271.3(n)
Quarantine	The storage or identification of an HCT/P, to prevent improper release, in a physically separate area clearly identified for such use or through use of other procedures such as automated designation	1271.3(q)
RCDAD	Relevant communicable disease agent or disease 1. (i) For all human cells and tissues: human immunodeficiency virus, types 1 and 2; hepatitis B virus; hepatitis C virus; human transmissible spongiform encephalopathy; and *Treponema pallidum* (ii) For viable, leukocyte-rich cells and tissues: human T-lymphotropic virus, types I and II (iii) For reproductive cells or tissues: *Chlamydia trachomatis* and *Neisseria gonorrhoeae* 2. A communicable disease agent or disease meeting the criteria described in § 1271.3(r)(2), but not specifically listed in § 1271.3(r)(1), is relevant if it is one: (a) For which there may be a risk of transmission by an HCT/P, either to the recipient of the HCT/P or to those people who may handle or otherwise come in contact with the HCT/P, such as medical personnel, because the disease agent or disease: (i). Is potentially transmissible by an HCT/P; and	1271.3(r)

(continued)

Table 24.5 (continued)

Definition	Meaning	Reference
	(ii). Either (1) has sufficient incidence and/or prevalence to affect the potential donor population (§ 1271.3(r)(2)(i)(B)(1)) or (2) may have been released accidentally or intentionally in a manner that could place potential donors at risk of infection (§ 1271.3(r)(2)(i)(B)(2)) (b) That could be fatal or life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure (§ 1271.3(r)(2)(ii)); and (c) For which appropriate screening measures have been developed and/or an appropriate screening test for donor specimens has been licensed, approved, or cleared for such use by FDA and is available (§ 1271.3(r)(2)(iii))	
Relevant medical records	A collection of documents that includes a current donor medical history interview; a current report of the physical assessment of a cadaveric donor or the physical examination of a living donor; and, if available, the following: 1. Laboratory test results (other than results of testing for relevant communicable disease agents required under Subpart A); 2. Medical records; 3. Coroner and autopsy reports; and 4. Records or other information received from any source pertaining to risk factors for relevant communicable disease (e.g., social behavior, clinical signs and symptoms of relevant communicable disease, and treatments related to medical conditions suggestive of risk for relevant communicable disease)	1271.3(s)
Responsible person	A person who is authorized to perform designated functions for which he or she is trained and qualified	1271.3(t)
FDA	The Food and Drug Administration	1271.3(x)
Available for distribution	The HCT/P has been determined to meet all release criteria	1271.3(z)
Distribution	Any conveyance or shipment (including importation and exportation) of an HCT/P that has been determined to meet all release criteria	1271.3(bb)
Establish and maintain	Define, document (in writing or electronically), and implement; then follow, review, and, as needed, revise on an ongoing basis	1271.3(cc)
Quality audit	A documented, independent inspection and review of an establishment's activities related to core CGTP requirements. The purpose of a quality audit is to verify, by examination and evaluation of objective evidence, the degree of compliance with those aspects of the quality program under review	1271.3(gg)
Quality program	An organization's comprehensive system for manufacturing and tracking HCT/Ps in accordance with Subpart A. A quality program is designed to prevent, detect, and correct deficiencies that may lead to circumstances that increase the risk of introduction, transmission, or spread of communicable diseases	1271.3(hh)
Recovery	Obtaining from a human donor cells or tissues that are intended for use in human implantation, transplantation, infusion, or transfer	1271.3(ii)
Storage	Holding HCT/Ps for future processing and/or distribution	1271.3(jj)

Registration with FDA and Listing of Products

Subpart B of the tissue rules requires all establishments that manufacture tissues[2] to register with FDA and list all the products they manufacture, within 5 days of beginning operations. This requirement allows FDA to obtain accurate information about the cell and tissue establishments, facilitating inspections and timely communications of safety-related information.

FDA determines regulatory compliance through periodic inspections. HCT/P establishments may begin to manufacture, market, and distribute

[2]Refer to Table 24.3 for the definition and list of activities that are considered to be manufacturing steps under the tissue rules.

certain products once they have registered with FDA; however, registration does not indicate that an establishment has been inspected or that it is in compliance with the regulations. Registration and listing must be updated annually,[3] even if none of the information has changed.

Donor Eligibility (DE) Determination

Subpart C of the tissue rules requires all establishments that manufacture tissues to evaluate all potential donors by performing a donor eligibility determination, along with related requirements, unless an exception applies. Table 24.6 provides a summary of those exceptions. One example is that the regulations do not require a donor eligibility determination when a reproductive tissue, such as semen, is transferred to a recipient who is a sexually intimate partner of the donor. If a reproductive establishment has any tissues from donors whose donor eligibility determination has not been completed yet, those tissues are considered to be under quarantine, and there are requirements associated with tissues under quarantine (Table 24.7).

The donor eligibility determination is a conclusion that a donor is either eligible or ineligible to donate cells or tissues, based on the results of

Table 24.6 Exceptions to the requirements for a donor eligibility (DE) determination

Exception	Example	Explanation[a]
1. Tissues for autologous use	An oocyte is recovered from a woman and the embryo formed is later transferred to her	The oocyte donor in this case is an autologous donor and she is not required to have a donor eligibility determination
2. Reproductive tissues donated by a sexually intimate partner of the recipient	An oocyte is recovered from a woman and the semen donor is the woman's sexually intimate partner	The semen donor in this case is a sexually intimate partner, and he is not required to have a donor eligibility determination[b]
3. Cryopreserved cells or tissue for reproductive use, other than embryos, originally excepted under (1) or (2) of this section at the time of donation, that are subsequently intended for directed donation, provided that: (i) Additional donations are unavailable, for example, due to the infertility or health of a donor of the cryopreserved reproductive cells or tissue (ii) Appropriate measures are taken to screen and test the donor(s) before transfer to the recipient	A man who is diagnosed with testicular cancer has a sexually intimate partner; for subsequent family building, he cryopreserves his semen prior to his cancer treatment Later, he is not with his initial sexually intimate partner and now intends to make a directed donation to a gestational carrier	At the time of semen recovery, eligibility determination for this donor was excepted in accordance with 1271.90(a)(3). There is no available tissue and appropriate measures are taken to screen and test the donor(s) before donation to the gestational carrier occurs
4. A cryopreserved embryo originally intended for use by a sexually intimate couple that is subsequently intended for directed or anonymous donation. When possible, appropriate measures should be taken to screen and test the semen and oocyte donors before transfer of the embryo to the recipient	A sexually intimate couple forms embryos for their own reproductive use. They have excess cryopreserved embryos they decide to donate	A donor eligibility determination was not initially required of either partner at the time of embryo cryopreservation. The subsequent directed or anonymous donation may proceed under this exception

21 CFR 1271.90(a)

[a]Additional labeling will apply under 21 CFR 1271.90(b)—see Table 24.11 for additional information

[b]If excess embryos formed from gametes from intimate partners may be later transferred to a gestational carrier or donated, it may be prudent to consider performing donor testing at the time of collection so that the results are subsequently available

[3]21 CFR 1271.21(b)

Table 24.7 Quarantine of tissues

Requirement	Description
Quarantine[a]	Tissues must be kept in quarantine until completion of the donor eligibility determination unless an exception applies. Semen from anonymous donors must be quarantined until the retesting required under 1271.85(d) is complete
Identification of tissues in quarantine	A tissue that is in quarantine pending completion of a donor eligibility determination must be clearly identified as quarantined. The quarantined tissue must be easily distinguishable from other tissues that are available for release and distribution
Shipping of tissues in quarantine	If a tissue in quarantine is shipped prior to completion of DE determination, it must be kept in quarantine during shipment. The tissue must be accompanied by records that: Identify the donor (e.g., by a distinct identification code) State that the DE determination has not been completed State that the product must not be implanted, infused, transplanted, or transferred until completion of the DE determination unless an exception applies

21 CFR 1271.60(a–c)
[a]See Table 24.5 for definition of quarantine

Table 24.8 Current relevant communicable disease agents or diseases (RCDADs) for which HCT/P donors undergo screening and/or testing

Agent	Type of donated cells and tissues	Screening	Testing
Chlamydia trachomatis	Reproductive	X	X
Neisseria gonorrhea	Reproductive	X	X
HIV-1 and HIV-2	All	X	X
Hepatitis B	All	X	X
Hepatitis C	All	X	X
Syphilis	All	X	X
TSE	All	X	
WNV	All	X	
Sepsis	All	X	
Vaccinia (recent smallpox vaccination)	All	X	X
HTLV-I and HTLV-II	Viable and leukocyte-rich[a]	X	X
CMV	Viable and leukocyte-rich[a]	X	X

RCDADs are communicable diseases that meet the regulatory definition (1271.3(r)) as being relevant and for which donors must be evaluated, depending on the type of donated HCT/P. Donors who are found to have risk factors or positive test results for RCDADs must be determined ineligible. Depending on available information, the list of RCDADs that FDA has determined to meet the definition is subject to change. The most current list can be found on the FDA website http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/TissueSafety/ucm151757.htm
[a]Examples of viable, leukocyte-rich cells or tissue include, but are not limited to, hematopoietic stem/progenitor cells and semen. Cells and tissues are considered to be viable and leukocyte-rich based on their status at the time of recovery, even if later processing might remove leukocytes

all required donor screening and testing for relevant communicable disease agents or diseases (RCDAD), as defined in the regulations. See Table 24.8 for a list, current as of the time this text is published, of the diseases and disease agents for which HCT/Ps undergo testing and/or screening. Figure 24.1 provides an overview of the donor eligibility determination process, with accompanying citations within Subpart C. A flow diagram illustrating the steps of the donor eligibility determination process is provided in Fig. 24.2.

The tissue regulations require that standard operating procedures (SOPs) must be established and maintained[4] to assure that the review of the records used to make the donor eligibility determination (referred to as "relevant medical

[4]21 CFR 1271.47(a)

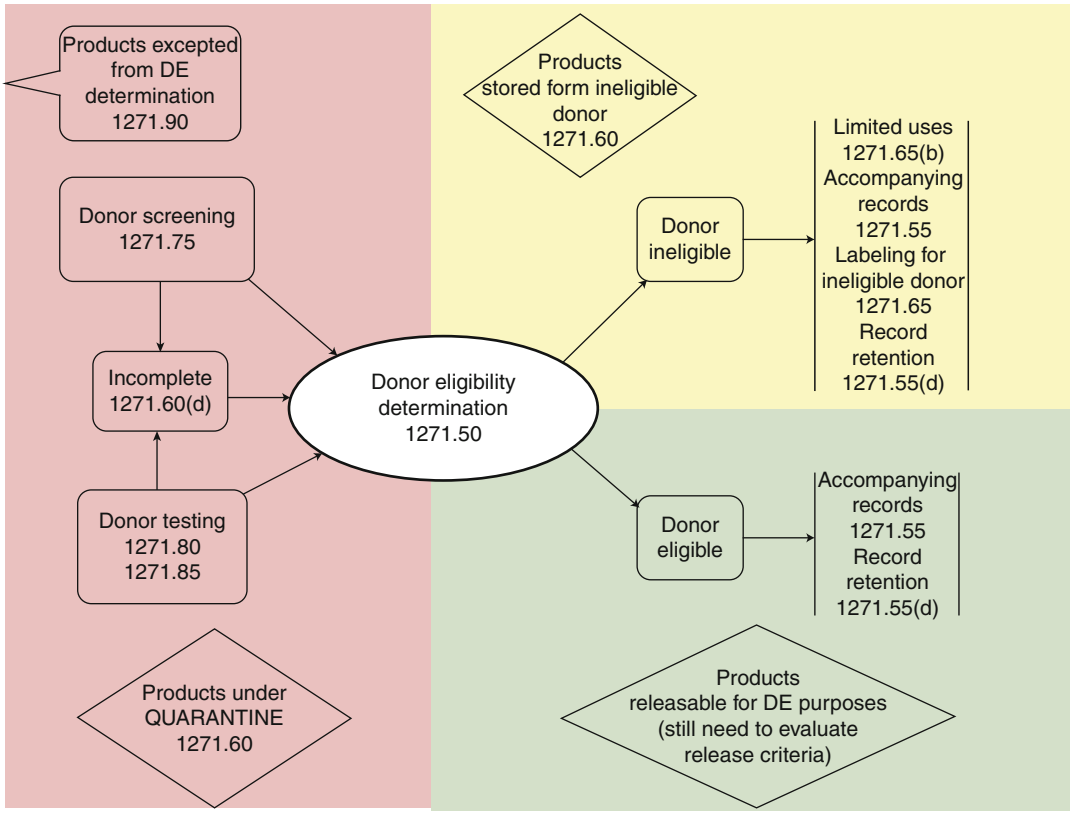

Fig. 24.1 Overview of the donor eligibility determination process. All of the major requirements that apply to reproductive establishments in making a donor eligibility determination are mapped in this figure. The areas in *red* represent regulations applicable prior to the donor eligibility determination (tissues may not be distributed), the *green* represents regulations applicable for donors found to be eligible (may be distributed), and the *yellow* represents products from donors found to be ineligible (may be distributed only under certain circumstances). Standard operating procedures are required under 1271.47

records" and defined in the regulation) is properly conducted. In addition, for medical records created for the purpose of assisting in determining donor eligibility, such as records of the donor medical history interview, SOPs must be established and maintained to assure that such records are current, complete, and reliable [26].

Assessing Whether a Donor Eligibility Determination Is Required for a Particular Donor

A donor eligibility determination is generally required for all tissue donors, including all anonymous and directed donors of reproductive tissues.[5] However, as described above and listed in Table 24.6, there are some exceptions to the requirement for a donor eligibility determination for other reproductive tissue donors. In the case of an embryo or of cells derived from an embryo, a donor eligibility determination is required for both the oocyte donor and the semen donor.[6] Determining whether or not a donor eligibility determination is required for a particular donor

[5]21 CFR 1271.45(b)

[6]Gestational carriers are recipients of reproductive tissues. FDA regulations do not require recipients to have a donor eligibility determination. Evaluation of gestational carriers is performed according to clinical practices and professional organization standards.

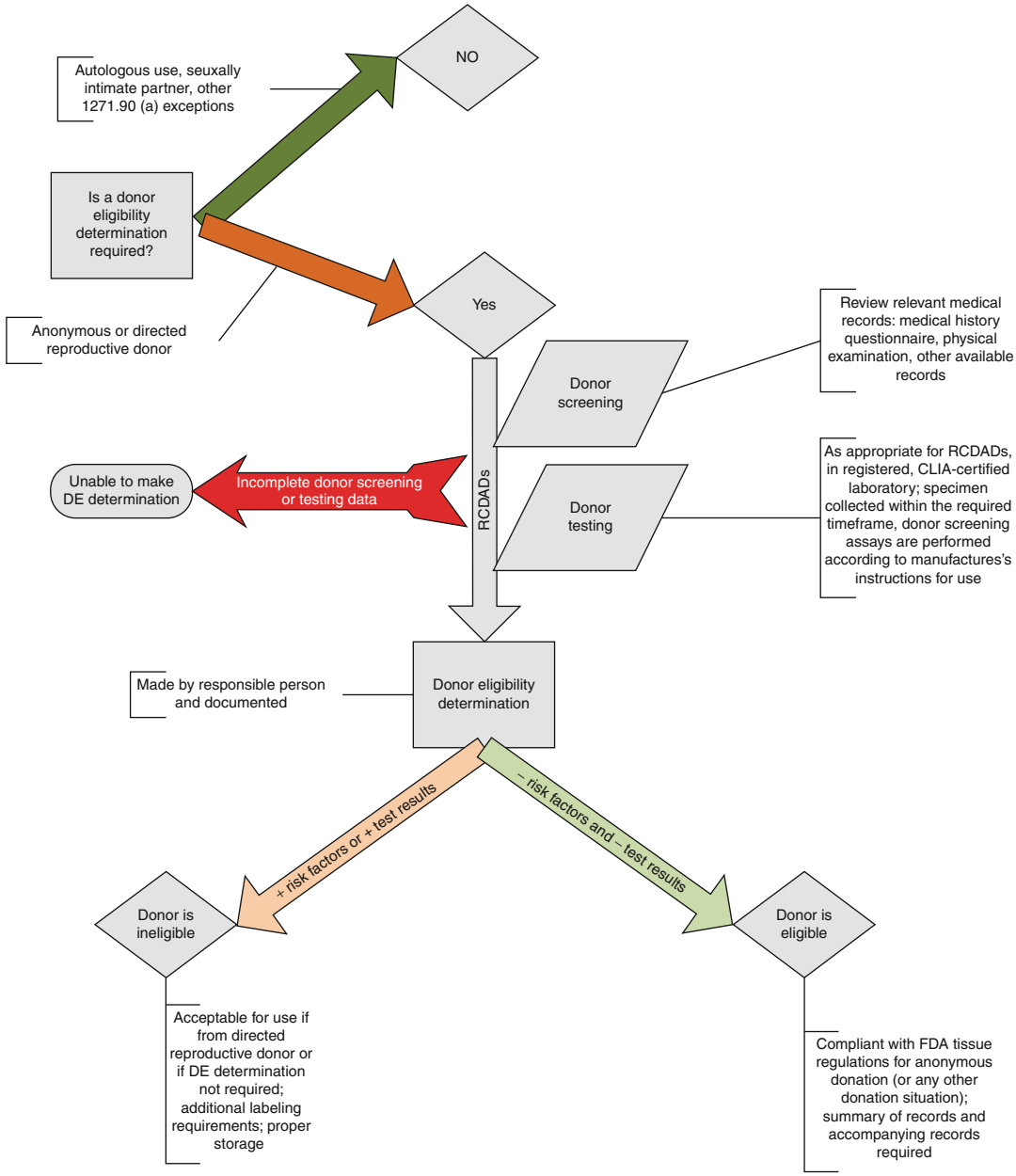

Fig. 24.2 Flow diagram of donor eligibility (DE) determination. Standard operating procedures are required. Records must be retained for 10 years

can be quite complex for embryo transfer because there is more than one gamete involved. In this setting, it is helpful to systematically and separately consider each gamete donor (the individual from whom the gametes are being retrieved) and his or her relationship to the recipient (the individual to whom the embryo will be transferred),[7] in order to assess whether a donor eligibility determination is required.

[7]The reproductive tissue donor may be the recipient herself (autologous oocyte donor), a sexually intimate partner (semen donor), an individual who knows and is known to the recipient before donation (referred to as a directed reproductive donor in the regulations), or anonymous.

The following information on donor evaluation outlines the donor eligibility determination process that would pertain to anonymous and directed donors of reproductive tissues and to other situations where the donor eligibility determination is required.

Communicable Disease Agents for Which Donors Must Be Evaluated

The tissue rules require that the donor eligibility determination be performed to evaluate donors for presence of, or risk factors for, RCDADs (Table 24.8). Establishments may perform donor screening and testing for agents in addition to those identified as RCDADs by FDA.

Donor Screening

Donors must be screened by reviewing "relevant medical records"[8] for risk factors for RCDADs.[9]

Screening a reproductive tissue donor involves several steps to gather and review pertinent medical information. These include a donor medical history interview for risk factors or conditions. The medical history interview may take place in person or by telephone. Because a donor medical history interview must be a documented dialogue, if a donor medical history questionnaire is self-administered, the interviewer should review and verify the answers with the individual who has filled out the questionnaire form [26]. A physical examination of the donor is also performed to evaluate for physical evidence of communicable disease. For reproductive donors, it is acceptable to choose to examine only those parts of the body that are necessary to evaluate for RCDADs based upon relevant donor history that has been obtained during the interview and review of available records. It is also acceptable to rely on records of a recent report of a physical examination by other health-care professionals [26]. For example, it is advisable to perform a genitourinary examination to assess for the risk of RCDADs related to the genitourinary tract. A review of other available records for any clinical evidence of RCDADs is also part one of the screening steps. Available records can include laboratory results, medical records from sources other than those generated by the reproductive establishment, and records or other information received from any source pertaining to risk factors for relevant communicable disease.

The detailed lists of current risk factors or conditions, as well as clinical evidence and physical evidence of RCDADs identified by FDA as pertinent in screening a tissue donor can be found in Guidance for Industry: Eligibility Determination of Donors of HCT/Ps (the Donor Eligibility Guidance, August 2007) [26].

The donor screening information (i.e., relevant medical records) must be obtained in order to make the donor eligibility determination,[10] prior to transferring embryos.[11] It may be preferable to perform the donor screening step at a time that would allow the results to be available and able to be assessed prior to recovering the donated tissue. Current donor screening information facilitates the evaluation of communicable disease risk. If a complete donor screening procedure has been performed on a living donor within the previous 6 months, an abbreviated donor screening procedure may be used for repeat donations. The abbreviated procedure must determine and document any changes in the donor's medical history since the previous donation that would make the donor ineligible, including relevant social behavior.[12] Each reproductive establishment should determine, for purposes of their standard operating procedures (SOPs),[13] what is a reasonable time frame within which to collect donor screening information.

[8] As defined in the regulations (21 CFR 1271.3(s))

[9] 21 CFR 1271.75(a)

[10] 21 CFR 1271.75(a)

[11] 21 CFR 1271.45(c)

[12] 21 CFR 1271.75(e)

[13] 21 CFR 1271.47(a)

Table 24.9 Timing of specimen collection for reproductive tissue donor testing: number of days before tissue recovery

Donor	Timing	Description
Oocyte	30 days	Allows for logistical time necessary for donors receiving hormonal stimulation
Anonymous semen donor (cryopreserved)	7 days[a]; collect a new specimen and retest at least 6 months after date of donation[b]	Provides flexibility for the testing of anonymous repeat semen donors
Semen donor (not cryopreserved)	7 days	Collecting specimens as close to the time of donation as possible decreases the risk that donors become infected between the time of specimen collection and recovery of the tissues

Specimens may be collected up to 7 days before or after recovery for most donors (see 21 CFR 1271.80(b))
[a]Repeat semen donors are not required to be retested at the time of each donation, as long as a specimen has already been collected and tested according to 21 CFR 1271.85(d). The semen is quarantined pending completion of the required retesting
[b]Except as provided under 21 CFR 1271.90 and except for directed reproductive donors

Donor Testing

Testing for RCDADs is required to adequately and appropriately reduce the risk of transmission of relevant communicable disease. When testing donors, there are three main areas to consider.

Timing of Collection of Specimens for Use in Testing

Table 24.9 summarizes the required regulatory time frames for reproductive tissue donor specimen collection. Coordinating the collection of donor specimens within the required time frame and obtaining subsequent test results involve careful planning in the ART setting, particularly when there is more than one donor to test. It is also important to consider the possibility that positive assay results may be obtained, and it may be helpful to plan in advance how to proceed when a donor is found to be ineligible. For example, it may be preferable to collect the test samples and perform the testing sufficiently early, within the specified time frame, so that the results are available and can be assessed prior to recovering the donated tissue.

Using the Correct Assay

Donor specimens must be tested using FDA-licensed, approved, or cleared donor screening assays[14] in accordance with the manufacturer's instructions for use.[15] A current list of tests recommended in order to adequately and appropriately reduce the risk of communicable disease transmission of RCDADs can be found on the FDA website and in the Donor Eligibility Guidance [26]. FDA has determined that more than one assay may be necessary to adequately evaluate a donor for a particular communicable disease (e.g., for HIV, use of both anti-HIV-1/2 and HIV-1 nucleic acid amplification [NAT] testing).

Performing the Assay Correctly

Performing the assay correctly (i.e., in accordance with the manufacturer's instructions for use) begins when specimens are collected from the donor. Each assay has particular requirements for specimen collection (e.g., which collection tubes may be used), storage (e.g., what temperature ranges specimens may be stored and for how long), and handling (e.g., how soon a specimen

[14]A current list of the licensed, approved, or cleared donor screening tests is available on the FDA website http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/TissueSafety/ucm095440.htm
[15]21 CFR 1271.80(c)

must be tested after collection). The specimen collection, storage, and handling requirements in the manufacturer's instructions for use are not the same for all assays; those handling requirements are optimized for the performance of the individual assay. It is important to be familiar with the requirements for the donor screening assays used, and the standard operating procedures should be written in a way that ensures the manufacturer's instructions are met to avoid errors that prevent the ability to make a complete donor eligibility determination.

Laboratories Performing Donor Testing

Laboratories performing donor testing are considered manufacturers[16] under the tissue rules and must therefore adhere to regulatory requirements.[17] Reproductive tissue establishments are required to ensure that any establishments with whom there are manufacturing arrangements or agreements to perform any step in manufacturing (e.g., donor testing) are in compliance with the tissue rules (further discussed in Subpart D, below).[18]

Some issues that are particularly relevant with respect to evaluating a contract donor testing laboratory for compliance with the tissue rules include the requirements to:

- Register with FDA
- Use appropriate FDA-licensed, approved, or cleared donor screening tests, in accordance with the manufacturer's instructions for use
- Retain records related to donor testing for 10 years
- Be certified to test human specimens under the Clinical Laboratory Improvement Amendments (CLIA) or meet equivalent requirements as determined by the Centers for Medicare & Medicaid Services (CMS)[19]

[16]21 CFR 1271.3(e)

[17]21 CFR 1271.10(b)

[18]21 CFR 1271.150(c)

Incomplete Information for Making a Donor Eligibility Determination

For all tissue donors where a donor eligibility determination is required (e.g., anonymous and directed reproductive donors), all of the required information must be obtained in order to make the donor eligibility determination.

Review of Relevant Medical Records and Making the Donor Eligibility Determination

The establishment must make a donor eligibility determination,[20] which is a determination of whether the donor is eligible based on the results of all required donor screening and testing. The donor eligibility determination must be performed by a responsible person[21] (defined in the regulations as a person who is authorized to perform designated functions for which he or she is trained and qualified). The donor eligibility step must be documented, dated, and signed by the responsible person.[22]

After the donor eligibility determination has been completed, establishments must also consider the requirements for record retention, the summary of records, accompanying records[23] (Table 24.10), and any additional labeling that is required when gametes from ineligible donors are used (Table 24.11).

[19]Examples of the latter include laboratories that have been accredited by accrediting organizations approved by CMS. Certain states are exempt under CLIA because CMS has found their state programs to be in compliance with CLIA standards. Information about the CLIA program is available at the website. http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/CLIA/.

[20]21 CFR 1271.45(b)

[21]21 CFR 1271.50(a)

[22]21 CFR 1271.55(d)

[23]21 CFR 1271.55

Table 24.10 Record requirements after the donor eligibility (DE) determination is completed

Records	Content	Function
(a) Accompanying records	1. Distinct identification code, for example, alphanumeric, affixed to the tissue container[a] 2. A statement that DE determination has been made and the donor is eligible or ineligible 3. A summary of the records used to make the DE determination (as described in (b))	Relates the tissue to the donor and to all records pertaining to the tissue
(b) Summary of records (as referenced above in (a)(3))	1. A statement that the communicable disease testing was performed by a laboratory that is CLIA[b] certified or that meets equivalent requirements as determined by CMS[c] 2. A listing and interpretation of the results of all communicable disease tests performed 3. The name and address of the establishment that made the DE determination 4. In cases of tissues from ineligible donors under 1271.65(b), a statement noting the reason(s) of ineligibility	Provides information to the end user about the evaluation of the donor
(c) Deletion of personal information	The accompanying records must not contain the donor's name or other information that could identify the donor	Maintain donor privacy
(d) Record retention	1. Records must contain documentation of: Results and interpretation of all testing for relevant communicable disease agents and name and address of testing laboratory Results and interpretation of all donor screening for communicable diseases DE determination, including name of responsible person 2. All records must be accurate, indelible, and legible, in English, or retained and translated to English and accompanied by a statement of translator authenticity 3. Records must be made available for authorized inspection by or upon request by FDA. Records that can be readily retrieved from another location by electronic means are considered "retained" 4. Retain records for at least 10 years after the date of the tissue distribution, disposition, or expiration, whichever is latest	Records must be retained for documentation purposes, allow for review in the event of an adverse event, and allow for inspectional evaluation and quality assurance review

21 CFR 1271.55

[a]Exceptions are stated in 1271.55(a)(1), including directed reproductive donors

[b]Clinical Laboratory Improvement Amendments (http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/CLIA/)

[c]Centers for Medicare & Medicaid Services

Ineligible Donors

Donors who are found to have either risk factors or positive test results for RCDADs must be determined to be ineligible.[24] In general, reproductive tissues must not be implanted or transferred unless and until the donor has been determined to be eligible.[25] However, in certain circumstances, cells and tissues from a donor found to be ineligible may be donated. For gamete donors, donation from an ineligible donor is permitted when a gamete donor knows and is known by a specific

[24]21 CFR 1271.75(d), 1271.80(d)

[25]21 CFR 1271.45 (c)

Table 24.11 Examples of required labeling[a] for reproductive tissues that are excepted from the donor eligibility determination under 1271.90(a)

Situation where label must be applied	Label required[b]
1. For HCT/Ps excepted under § 1271.90(a)(1), if the HCT/Ps are stored for autologous use	"FOR AUTOLOGOUS USE ONLY"
2. All required screening and testing has not been performed. For example, if the manufacturer performed some but not all of the required testing and screening or did not use a registered, CLIA-certified laboratory or FDA-licensed, cleared, or approved donor screening tests[c]	"NOT EVALUATED FOR INFECTIOUS SUBSTANCES"
3. Unless for autologous use only, when (1) the donor eligibility determination is not performed or is not completed or (2) the results of any screening or testing performed indicate the presence of RCDADs or risk factors for or clinical evidence of RCDADs	"WARNING: Advise recipient of communication of communicable disease risks"
4. If the results of any screening or testing performed indicate the presence of RCDADs or risk factors for or clinical evidence of RCDADs	
5. When a donor's test results are positive or reactive for any relevant communicable disease agent or disease	"WARNING: Reactive test results for (name disease agent or disease)"
6. When reproductive tissue will be donated to a directed recipient under 1271.90(a)(3) or to a directed or anonymous recipient under 1271.90(a)(4), and the screening and testing is performed before transfer to the recipient rather than at the time of recovery	"Advise recipient that screening and testing of the donors were not performed at the time of cryopreservation of the reproductive tissue, but have been performed subsequently"

[a]21 CFR 1271.90(b). See also the Donor Eligibility Guidance [24] for examples for these labeling requirements
[b]More than one of the required labels may apply to a particular gamete or embryo
[c]This label would not apply to reproductive cells and tissue labeled in accordance with item six in this table

recipient before donation (i.e., directed reproductive donor[26]) or for sexually intimate partners when a donor eligibility determination is performed although it is not required under the tissue regulations.

Tissues from an ineligible donor must be stored or identified in such a way as to prevent improper release of the tissues[27] (e.g., to a recipient other than the intended recipient from the directed reproductive donor or sexually intimate partner).

Current Good Tissue Practice

Current good tissue practice (CGTP) in Subpart D of the tissue rules requires establishments to recover, process, store, label, package, and distribute tissues and screen and test donors in a way that prevents the introduction, transmission, or spread of communicable disease. The communicable diseases covered under CGTP include (but are not limited to) viruses, bacteria, fungi, parasites, and transmissible spongiform encephalopathy agents. Given the wide range of tissues covered, the aims are broad and they are designed to allow the establishment's flexibility to determine how to meet the goals through established procedures.

The CGTP provisions applicable to tissues for reproductive use are limited to requirements for manufacturing agreements (21 CFR Part 1271.150(c)) and for requesting exemptions and alternatives (21 CFR Part 1271.155).

With respect to manufacturing agreements,[28] if another establishment is engaged to perform any

[26]As defined in the regulation (21 CFR 1271.3(l))
[27]21 CFR 1271.60
[28]21 CFR 1271.150(c)

step in manufacturing, that establishment must comply with requirements applicable to the manufacturing step or steps they perform. Under this requirement, before an establishment enters into a contract, agreement, or other arrangement with another establishment to perform any step in manufacture (e.g., donor testing, cryopreservation), it is necessary to ensure that the contracted establishment is in compliance with applicable CGTP requirements. If, during the course of this contract, agreement, or other arrangement, information becomes available suggesting that the establishment performing the contract manufacturing may no longer be in compliance with the regulatory requirements, reasonable steps must be taken to ensure they comply. If it is determined that the contract manufacturing establishment is not in compliance with those requirements, the contract, agreement, or other arrangement with the establishment must be terminated. Additional information about how to comply with this requirement can be found in the FDA guidance document "Guidance for Industry: Compliance with 21 CFR Part 1271.150(c)(1) – Manufacturing Arrangements" [27].

In the limited situations in which there is a desire to use a tissue/tissue product despite the regulatory requirements not being met, an exemption or alternative may be requested. A detailed discussion of exemptions and alternatives is beyond the scope of this chapter. However, for the FDA to be able to grant an exemption or alternative, the FDA must find that such action is consistent with the goals of protecting the public health and/or preventing the introduction, transmission, or spread of communicable disease and that the information provided justifies the exemption or that the proposed alternative satisfies the purpose of the requirement.[29] The FDA website contains useful information on this topic [28].

Inspection of Establishments and Enforcement

Reproductive tissue establishments are subject to FDA inspection. The rules in this subpart (Subpart F) apply to establishments manufacturing tissues that are regulated solely under Section 361 of the PHS Act and the tissue rules. This subpart describes the inspection process, which can occur with or without prior notification and at a frequency determined at FDA's discretion. During an inspection, FDA may take samples, question personnel, review SOPs, and observe personnel at work during the manufacturing process. FDA may also review and copy records, although donor and recipient confidentiality is observed [29]. If there are observations that require attention by the manufacturer, these will be presented to the reproductive tissue establishment in writing at the close of the inspection. Note that foreign establishments that distribute tissues in the USA are subject to inspection by FDA.

Summary

Reproductive tissues are subject to the FDA tissue rules with the goal of minimizing the risk of communicable disease transmission. The tissue rules applicable to reproductive tissues include requirements for registration and listing with FDA, making a donor eligibility determination, and some other aspects of GTP, including manufacturing arrangements. The overview of the tissue rules provided in this chapter may be useful to reproductive tissue establishments in their operations and in maintaining regulatory compliance.

Editor's Commentary

The governmental oversight of gamete donation mandated by the law in August 2007 and stewarded by the FDA has brought about dramatic changes in the way in which egg and embryo donation is practiced in the USA. At the time, many practitioners, including myself, viewed the entry of a federal agency into our medical practices as an unnecessary and uninvited encumbrance. Evidence-based results gathered for more than 10 years of international practice, representing in excess of 100,000 cases, failed to define an appreciable risk of disease

[29] 21 CFR 1271.155(c)

transmission. Colleagues performing the same techniques in areas outside the USA were not subject to the strict testing schedules and use of NAT testing now required by the FDA of each nonexempted case. The cost of the extra testing, as well as the need for hiring well-trained personnel to maintain the SOP and assure compliance, added additional cost to an already expensive procedure. And lastly, everyone worried about the dreaded FDA unannounced inspection of their practice.

Yet, I have grown accustomed to the regulations, and I have also successfully undergone 3 FDA audits in the past 5 years. More importantly, I have come to better appreciate the position of the FDA and the need for governmental oversight of egg donation. First, we must not forget the fact that the transmission of HIV through donor sperm insemination did occur and it spawned the concern that ignited the public interest in safety and regulation. As Drs. Cortez, Lazarus, and Greenwald clearly state, it is the goal of the FDA to *protect* the public health and *prevent* the introduction, transmission, and spread of communicable disease. If the potential is there, and the potential *is* there, then it is reasonable that the FDA be involved in the oversight and regulation of gamete donation, and that includes both egg and sperm. This is particularly true as it relates to reproductive tissue and cells that might be frozen abroad and shipped into centers for use in the USA. These FDA "encumbrances" are in place to protect our patients, which, in the case of egg donation, include both the donor and the recipient. Ultimately, it is all about preserving and protecting the safety and health of women and children.

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Essential Elements of Informed Consent in Egg Donation and Surrogacy

25

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Key Points

The doctrine of informed consent reflects a commitment to respect the autonomy and self-determination of every individual.

The essential components of informed consent include voluntariness, understanding, disclosure, competence, and consent.

Informed consent is lacking if patients were not informed of the material risk, or unwilling to consent to treatment had they been informed of the material risk.

It is essential that an interdisciplinary team be assembled with competent professionals to aid egg donors and surrogates in the process of true informed consent regarding the medical process and procedures.

Assisted reproductive technology encompasses a myriad of medical, ethical, moral, emotional, psychological, and religious issues. This is especially true when considering the variety of complex concerns that arise when a patient wishes to be a surrogate or donate her eggs. Informed consent represents a particularly important consideration in the field of assisted reproductive technology. The purpose of this chapter is to identify the most significant ethical and legal issues confronting egg donors and gestational surrogates and offer guidance to medical professionals in a position to communicate relevant information to their patients in order to obtain their informed consent.

Infertility currently affects 7.3 million people in the USA [1]. Of those struggling with infertility, 40 % of cases are attributed to male infertility, 35 % to female tubal factors, and 25 % attribute infertility to problems with female ovulation [2]. At least 25 % of infertile couples have more than one factor causing infertility [2]. Approximately 5–10 % of infertile couples will have no readily apparent cause for their infertility [2]. With the help of assisted reproductive technology, millions of people have been able to have children and create families that they otherwise would not have conceived. With new scientific breakthroughs, however, medical professionals are now forced to reassess practice areas that have been set in stone for decades [3]. This is why informed consent is so important to protect physicians from liability.

An analysis of legal and ethical issues involving egg donation and surrogacy necessarily begins with an introduction to each topic. This chapter will discuss (1) essential elements of informed consent, (2) egg donation, and (3) surrogacy, and finally, this chapter will conclude

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with recommendations to medical professionals concerning how to obtain informed consent when addressing a patient who wishes to donate her eggs or becomes a gestational surrogate. The information provided in this chapter is garnered from a variety of sources including the latest case law and guidelines in the USA. Nonetheless, medical professionals should consult with an attorney and their applicable state laws to ensure that they are practicing in accordance with the state's guidelines for medical professionals on how to obtain informed consent.

Informed Consent

The doctrine of informed consent reflects a commitment to respect the autonomy and self-determination of every individual. In the field of egg donation and surrogacy, informed consent will often include additional information not usually discussed in other contexts. It recognizes the inherent right of every woman to determine what will happen with her own body [4]. States generally have informed consent laws not specifically directed toward gestational surrogate or egg donation contexts but nonetheless are indicative of how courts and state legislatures view informed consent. New York, for example, defines lack of informed consent as "the failure of the person providing the professional treatment … to disclose to the patient such alternatives thereto and the reasonably foreseeable risks and benefits involved as reasonable medical … practitioner under similar circumstances would have disclosed, in a manner permitting the patient to make a knowledgeable evaluation." *McKinney's Public Health Law § 2805-d(1)*. New York, like most states, focuses on what reasonable physicians in similar situations should divulge to their patients.

The components of informed consent include (1) voluntariness, (2) understanding, (3) disclosure, (4) competence, and (5) consent [5]. This chapter will discuss each component as it relates to egg donors and gestational surrogates. Physicians should ensure that each element of informed consent has received adequate attention. Addressing each component individually will enable a physician to adequately meet the needs of patients while also ensuring that a physician's work has been both thorough and thoughtful. The components of informed consent offer physicians a general roadmap to follow in the process of gaining informed consent while protecting them from liability. While helpful, these guidelines do not supplant state laws, and a medical professional should always be informed of the laws of the state in which they practice.

First, when a patient consents to a medical procedure, it must be an informed act that is voluntary. Voluntariness only exists when a patient is free from substantial control, persuasion, or manipulation exerted by others [5]. In the surrogacy context especially, physicians should be aware of whether a surrogate is voluntarily committing herself. Physicians should pay special attention to these considerations when a surrogate or egg donor is performing the task for a family member, as persuasion is more likely to be present in these situations. To satisfy this first component, it is crucial that physicians ensure that a patient has freely and voluntarily consented to any medical procedure [4].

Second, a patient must possess extensive understanding of the procedure along with its risks and foreseeable consequences. Understanding flows from having enough information to make a reasonable decision [6]. Thus, physicians should ensure that a patient's decisions are made with full knowledge of the medical issues that may arise. Physicians will have to educate a patient to be fully aware of the entire procedure, its risks, complications, and important considerations that must be made. One useful way to convey some of the information that donors and surrogates need to know is to prepare an informational brochure to be used along with the consent forms and discussions between physician and patient [7]. Making sure that a patient possesses the requisite understanding to offer her informed consent mandates that physicians give specialized attention and care to every single donor or surrogate.

Third, to facilitate the first two components of informed consent – voluntariness and understanding – it is a physician's duty to disclose all relevant information. Full understanding flows from a

physician's ability to provide patients with full disclosure. For this reason, disclosure is a vital component in obtaining informed consent. A physician violates his/her duty to disclose when he/she fails to provide a patient with any facts that are necessary to facilitate an intelligent and voluntary consent. Necessary facts include facts that a reasonable person would want to know, without which would alter a patient's decision to undergo a certain procedure. There must be a showing that a reasonable person in the position of the patient would still have accepted the treatment had the material risks and dangers been disclosed. See *Bedel v. University OB/GYN Assoc. Inc.*, 603 N.E.2d 342 (Ohio Ct. App.,1991).

Fourth, a patient's ability to give informed consent turns on her competence. Competency describes the legal fitness of an individual and whether or not she is able to make the decision to donate ova or become a surrogate. The fundamental issue here is whether the patient is competent enough to be held accountable for the consequences of his/her decisions and actions [8]. The state of New Hampshire, for example, states that "informed consent occurs when a competent person, while exercising care for his or her own welfare, makes a voluntary decision about whether or not to participate in a proposed medical procedure of contractual arrangement that is based on full awareness of the relevant facts." *N.H. Rev. Stat. § 168-B:1(VI)*. Similarly, the state of New York states that "a competent adult has a common-law civil right to decline or accept medical treatments, a violation of which right results in civil liability for those who administer medical treatment without consent…" *McKinney's Public Health Law § 2805-d*. The competency component thus requires that a physician determine whether a patient possesses the psychological and physical wherewithal to make a competent decision to be an egg donor or surrogate [5].

The fifth and final element of informed consent is consent itself. This component encompasses the discussions that occur between a physician and patient as well as the consent forms that donors and surrogates must sign. Open and honest communication between physician and patient has significance especially in the context of egg donation or surrogacy. This chapter will advise physicians on what information is pertinent to share in the donor and surrogate context as well as how this information should be discussed with patients. What information to disclose is likely to be influenced by standards promulgated from professional societies, such as the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology.

A doctor's failure to obtain the informed consent from his or her patient can subject the doctor to liability. If a patient claims that informed consent was lacking, she must show that she (1) was not informed of the material risks, (2) was injured, (3) and would not have consented to the treatment had she been informed of the material risks [9]. The tort of informed consent requires a showing that the physician failed to disclose alternatives and failed to inform the patient of reasonably foreseeable risks associated with the treatment. See *Gross v. Saint Peter's Hosp. of City of Albany*, 873 N.Y.S.2d 882 (N.Y. Sup. Ct. 2009). Additionally, an individual must prove that lack of informed consent was the proximate cause of the resulting injury or condition. See *Trabel v. Queens Surgi Center*, 8 A.D.3d 555, 557 (N.Y. App. Div. 2d Dep't 2004) and *Mondo v. Ellsyain*, 302 A.D.2d 437, 438 (N.Y. App. Div. 2d Dep't 2003). Thus, it is crucial that a physician educate a patient so that any decision she makes is an informed one. To disclose information to a patient and ensure that she understands all material information will enable the patient to possess all the relevant information to form the basis of an intelligent and voluntary consent [10].

Moreover, physicians should acknowledge that it is often difficult for a patient to absorb fully all the information provided to her in an initial discussion. Similarly, it is difficult for patients to be fully aware of the meaning, much less the ramifications, of signing a physician's consent forms. Consent forms cannot possibly address all of the specific details and variations encompassed in an egg donation or surrogacy agreement [4]. For these reasons, physicians must be open to answering follow-up questions that a patient has after having the time to absorb the information and think about the consequences of her decision.

Informed consent is a process of ongoing dialogue that occurs between physician and patient.

Physicians should address each of the following concerns with a patient who is interested in becoming an egg donor or surrogate. While not exhaustive, giving adequate and thorough answers to the issues provided in this "checklist" will facilitate a physician's ability to obtain a patient's informed consent. Additionally, a physician should consult state laws and seek legal guidance while being open to answering any additional questions a patient may have. Important topics to discuss include, but are not limited to:

1. The screening tests that will be performed on the patient
2. The procedures that will be performed on the patient
3. The medications prescribed to the patient and any potential side effects
4. The risks and side effects of any drugs, procedures, and anesthesia
5. Every currently known way that eggs or resulting embryos might be used
6. The cost of treatment and the costs of treatment for any complications
7. The information that will be kept on file and shared with potential recipients and/or intended parents
8. The point at which a donor or surrogate can no longer change her mind about the donation or commitment to gestate a child
9. A consideration of the medical, psychological, emotional, ethical, and social implications
10. Whether a donor or surrogate fully understands and agrees with all the conditions
11. The risks of child birth and multiple gestations for a surrogate and the health effects [11]

While being attentive to each of these considerations will pave the way for a physician to begin educating a patient and obtaining her informed consent, a physician cannot do it alone. A team of professionals is necessary, and although it is not a physician's role to inform patients of the legal or psychological consequences of being an egg donor or surrogate, physicians should encourage patients to obtain independent legal counsel as well as undergo a psychological evaluation. Doing so enables patients to be informed of the psychological and emotional risks [11]. While this chapter focuses primarily on the role of physicians, it will touch upon the roles of lawyers and psychologists in order to provide a solid foundation upon which physicians can inform their patients of the process of donating eggs or becoming a gestational surrogate.

It is absolutely *essential* that an interdisciplinary team be assembled with competent professionals to aid egg donors and surrogates in the medical process and procedures. An interdisciplinary team of professionals should include infertility physicians to assess and manage the IVF process, obstetricians and gynecologists to manage the pregnancy, lawyers to prepare an egg donation agreement or a surrogacy contract and manage the insurance coverage, and psychologists, psychiatrists, and counselors to ensure that the intended parents are comfortable and trusting of another woman carrying their child and a donor or surrogate is comfortable and prepared to part with either their eggs or a child [12].

Egg Donation

The first child conceived through in vitro fertilization ("IVF") was born in 1978 [13]. Since then, the prevalence of IVF has grown significantly, and the use of egg donors to create families is now well established. In 2009, the Society for Assisted Reproductive Technology's IVF Success Rate National Summary reported that 367 clinics reported data on 142,241 treatment cycles resulting in the birth of 56,778 babies [14]. As the prevalence of IVF continues to grow, the physician's role in obtaining informed consent for this procedure is only becoming more imperative. This section focuses on the interests of donors themselves and the role that a physician plays in informing egg donors of the risks involved in this procedure.

The egg donation process is a complex one. The disclosure and consent components of informed consent require that physicians inform patients of the medical process of donating eggs. A physician should be familiar with each medical step of the process in order to fully disclose and

inform patients of the risks, side effects, and overall process of egg donation so as to ensure that informed consent has been given. As with any procedure involving sedation, egg donation involves risks of complications stemming from the use of anesthesia. Furthermore, egg retrieval leads to the possibility that blood vessels and organs near the ovaries can be damaged resulting in infection or infertility [15]. These are just some of several considerations that physicians should discuss with their patients.

The American Society for Reproductive Medicine provides guidelines for physicians to help identify potential donors. These guidelines help a physician ensure that a potential donor is competent to donate eggs – the fourth essential element of informed consent. It is recommended that donors be between the ages of 21 and 34. The guidelines state: "The rationale for the younger limit is to ensure that the donor is mature enough to provide true informed consent" [16]. Furthermore, the lower limit of 21 ensures that a potential donor can legally enter into a contract [11]. The rationale for donors to be under the age of 34 is that "younger women typically respond favorably to ovulation induction, produce more eggs and high-quality embryos with high implantation, and have subsequent high pregnancy rates" [16]. Some programs prefer to use egg donors who have already given birth or successfully donated eggs because it is believed that they are more likely to be fertile. It is also beneficial because it is easier to anticipate their feelings about having genetic offspring born to someone else [17]. The American Society for Reproductive Medicine further suggests that a woman should not donate eggs if she has a serious psychological disorder, abuses drugs or alcohol or has several relatives that do, currently uses psychoactive medications, has significant stress in her life, is in an unstable marriage or relationship, has been physically or sexually abused and not received professional treatment, or is not mentally capable of understanding or participating in the process [11]. A physician should make sure that an egg donor minimally meets these requirements prior to moving on to the next step – medical and psychological screening.

A potential donor will have to partake in general medical screening, infectious disease screening, and screening for inheritable diseases [17]. General medical screening will include a physical examination, an ultrasound, a drug test, and a detailed medical history report of the donor and close blood relatives. The infectious disease screening tests involves taking blood samples from a potential donor to test for a variety of infections and medical problems. When blood or tissue is transferred from one person to another, it can carry with it viruses or bacteria. For this reason, the infectious disease screening is a critical component of the process to minimize the risk that a donor egg could cause illness in the recipient [17]. The screening for inheritable diseases aims at learning about a donor's genetic makeup in order to minimize the chance that a baby will have certain genetic disorders, inheritable diseases, any major medical problems, mental retardations, or psychiatric problems [17]. These screenings are crucial before a woman can donate her eggs. In addition, physicians should inform patients that they may or may not have access to the results of these screenings. Physicians should consult their state laws to know who may have access to these results.

In addition to providing an understanding of the medical process of egg retrieval, a physician should also be aware of the underlying reasons why a woman has chosen to donate her eggs. This will facilitate a physician's ability to assess the voluntariness, understanding, and competence of a potential donor. A woman may choose to donate her eggs and be compensated for providing them to another woman or couple. Alternatively, a woman may choose to donate her eggs to be compensated for providing them to a laboratory for use in embryonic stem cell research, for development of stem cell lines, or for somatic cell nuclear transfer [18]. Having experienced infertility herself, or knowing someone who has, women often feel the altruistic need to give back to society through this life giving act. The information that a medical professional will have to disclose to a patient in order to obtain informed consent entirely depends upon the purpose for which a woman chooses to donate her eggs [19].

Egg Donation and Informed Consent

There is an ethical obligation on the part of physicians to ensure that a donor is fully aware of the medical risks and ramifications of her decision to donate her eggs. Most complicated for physicians is the difficulty in informing donors of actual risks involved given the lack of knowledge about long-term effects of the hormone therapy and egg retrieval procedure [20]. Although the long-term effects of an egg retrieval procedure are uncertain, it has been linked to a risk of ovarian cancer [19]. The Practice Committee of the American Society for Reproductive Medicine concluded that "currently, there are no clearly documented long-term risks associated with oocyte donation, and as such, no definitive data upon which to base absolute recommendations" [19]. Thus, it is apparent that comprehensive studies are needed to identify the short- and long-term effects of the hormones used by assisted reproductive technology. Nonetheless, to date, studies have been unable to clearly determine whether the hormones used in donors to increase the production of eggs increase the risk of various cancers. In order to obtain informed consent, physicians must inform donors that concrete scientific data as to the actual risks and side effects associated with reproductive technology is largely unknown.

Knowledge that data is lacking about the long-term effects of egg donation is one among many pieces of information a physician must share with a potential donor in order to obtain her fully informed consent. As previously discussed, physicians must inform donors as to whether genetic tests will be carried out and, further, whether the results of those tests will be disseminated to potential recipients. Physicians should also inform patients that donating eggs is likely to result in the birth of a child. Importantly, donors must be aware of the ongoing ethical obligation to provide medical updates if they learn about genetic or other conditions that are pertinent to the offspring's health [21]. Donors should also contemplate the possibility that an offspring, unaware of their genetic heritage, may marry and procreate with a potential half-sibling. These are just some of the considerations that physicians ought to include in their discussions with a potential donor.

Physicians in the donor context should also be aware that oftentimes women choose to donate their eggs on more than one occasion. The egg donation process has potential risks which are exacerbated by multiple donations. For this reason, it is important that physicians are attentive to concerns for the safety of donors [19]. The Practice Committee of the American Society for Reproductive Medicine recommends that a prudent physician would be wise to consider limiting the number of cycles for a single egg donor to approximately six [19]. With a concern for the safety and well-being of a donor, physicians can make certain that she is not being taken advantage of, that she is informed of the risks inherent in the egg donation process, and that she is aware of the fact that increased risks are involved when a donor chooses to donate her eggs on multiple occasions.

Just as important as the physician's role to inform patients of the medical concerns associated with egg donation, physicians should also encourage donors to obtain counseling to address any psychological or emotional feelings that may arise [22]. The 2008 Guidelines for Gamete and Embryo Donation by the American Society for Reproductive Medicine aver that egg donors and their partners would benefit from psychological counseling to aid in the decision of whether to donate eggs. They further suggest that a physician should facilitate a donor's access to psychological counseling by a qualified mental health professional if needed [22]. Donating eggs requires a donor to confront complex ethical, emotional, and social issues. A psychological screening will help potential donors evaluate their desire to donate eggs and to think through these concerns [17]. This in turn will aid in a physician's ability to address the essential elements of informed consent.

Physicians should also encourage donors to consult with independent legal counsel. Often, physicians are not adequately equipped to inform donors of their legal rights and responsibilities. Consequently, the American Society for Reproductive Medicine encourages donors to consult with a lawyer in order that their consent

is fully informed [22]. Given the fact that explicit laws concerning egg donation are unclear, donors benefit immensely from having legal representation to help navigate the uncharted territory of assisted reproduction. Lawyers will likely assist donors in obtaining a pre-donation agreement and seek a judicial determination or recognition of parentage, if necessary [16]. Lawyers will also inform donors of their legal rights to stop the process at any time prior to egg retrieval and any consequences of exercising that right. A donor or surrogate must be informed that she cannot be forced to undergo medical procedures against her will and that she may withdraw her consent at any time prior to retrieval of eggs as a donor. In conjunction, it is critical that a donor be informed of the program's policy on withdrawing consent [17] and the financial implications, if any, to the donor. This is crucial for obtaining informed consent given the voluntariness component.

In addition, lawyers will inform donors that all legal rights and duties pertaining to any resulting child are severed once the eggs are donated. While lawyers will also inform donors that they may not be notified of the results of any medical or psychological tests, lawyers will also point out the possibility that a donor can later be contacted for medical information in the event of a problem with the child's health. Depending on governing state and federal rules, donors should be informed of the fact that they may not have contact with the child(ren) or even know if they exist. On the other hand, lawyers will address the possibility that children born as a result of an egg donation may be able to contact them in the future despite their desire for anonymity. While it may be assumed that a donor's anonymity can be achieved, it is quite possible that future courts and legislatures may give more weight to an offspring's interest in knowing his or her genetic origins rather than to the donor's interest in privacy [21]. Given the fact that Web sites now exist that enable individuals conceived through assisted reproductive technology to easily access information regarding donor identification, physicians should prepare donors for this possibility. Thus, donors will have to consider the impact that an egg donation will have on themselves as well as their own family or future family [21].

Once a physician has informed a donor of the medical risks involved in the process of egg retrieval and has advised the donor to seek independent counseling and legal advice, the next step in obtaining informed consent is to have an egg donor sign a donor medical consent form. To protect themselves from liability, physicians should make certain that a donor consent form highlights several pieces of crucial information. While not an exhaustive list, donor consent forms should clearly and succinctly state applicable state laws and the following information: donors should be informed that the law in the area of assisted reproductive technology is uncertain, and therefore, donors are advised to seek legal counsel regarding their rights and responsibilities; donors should be required to undergo medical and psychological screenings to determine whether the individual is an appropriate donor; donors must provide a detailed history, including a comprehensive medical and social history of themselves and their partners as well as a sexual history; donors must undergo screening for inheritable diseases; donors should understand that the information gathered during the screening process will be shared with staff members as well as potential recipients; and donors should be informed that they may not have access to certain test results and psychological screening results; subsequently, donors will be required to take a variety of medication to stimulate the production of eggs; donors will then have to agree to undergo a procedure under anesthesia to retrieve eggs; donors must understand that they relinquish control of any resulting embryos created from an egg retrieval procedure; donors must be aware that a donation is likely to result in the birth of a child, and furthermore, donors have no legal claims, rights, or obligations to any resulting children; regarding anonymity, donors should be informed that anonymity will be maintained to the best of involved parties' abilities, unless a court of law or state law requires disclosure; finally, donors should understand that because the procedures are relatively new, it cannot be guaranteed what the court system will do in response to any questions, requests, or even the enforceability of the consent or agreement given [23]. Donor consent forms are an important component

of the physician's duty to obtain informed consent. Physicians themselves should consult legal counsel to draft these forms in accordance with their state laws and professional guidelines.

Surrogacy

Like egg donation, the use of gestational surrogates to create families has become a common way to create families. By 2008, there have been approximately 28,000 births via surrogates [24]. There are several types of surrogacy. Traditional surrogacy involves an agreement whereby a fertile man and an infertile woman contract with a surrogate who supplies the ovum which is artificially inseminated with the sperm from the fertile man. The surrogate, who is biologically related to the child, carries the child to term for the intended couple. Gestational surrogacy is an alternative type of surrogacy that involves a fertile man and a fertile woman – who, while capable of producing ova, cannot carry a child. In this case, the woman's ovum is fertilized with the man's sperm in vitro, and the resulting embryo(s) is implanted into the surrogate who then carries the child to term. While a gestational surrogate is the birth mother, she is not biologically related to the child in any way. Gestational surrogacy may also consist of a surrogate who is gestating an embryo composed of the intended father's sperm and a third-party woman's ova or even a surrogate who is gestating an embryo composed of two gamete donors for another couple who are the intended parents – bringing the number of parties involved to five (gamete donors, a surrogate, and a couple) [25]. Traditional surrogacy is often perceived as more legally and psychologically complicated given that there is a biological and genetic link between the carrier and the child. Thus, the use of a gestational surrogate is the more common approach in the USA because it is less likely to result in legal complications given that the gestational surrogate has no genetic link to the child she is carrying [26]. For this reason, this chapter will solely address the implications of informed consent in the context of the gestational surrogate.

A gestational surrogate's experience, while unique, is similar to the experience of any pregnant woman. An understanding of a surrogate's experience is crucial to enable medical professionals to obtain informed consent. After signing a contract with the intended parents, surrogates often undergo a physical examination and psychological testing. Next, a surrogate will have a procedure whereby embryo(s) are transferred into her uterus. The remainder of the process is quite normal: she must modify her behavior and refrain from smoking, drinking, using drugs, or prescription medicine. She must go through 9 months of pregnancy and all of its attendant risks and side effects. She may need to take sick leave from work due to doctors' appointments or complications. Finally, she must endure the pains of childbirth. Certain aspects of a gestational surrogate's experience are unique, however. For example, a surrogate may be asked to abort an abnormal fetus or to selectively reduce multiple fetuses [27]. Furthermore, upon giving birth, a surrogate will have to give the child to another person(s). Often sensitive situations such as these arise, and a physician must be attentive to the interests of the surrogate as well as the intended parents.

Informed Consent and Surrogacy

According to scholars, the doctrine of informed consent raises two primary issues in the context of gestational surrogacy. The first issue is whether consent can justifiably be sought; the second is whether it is possible for a gestational surrogate to understand, prior to conception, the psychological risks she is taking on [9]. This section will address these concerns while providing advice and guidance to physicians caring for potential surrogates in order to ensure that physicians obtain a potential gestational surrogate's informed consent. A gestational surrogate should consult with a medical professional, an attorney, and a psychologist. This section will educate a physician as to the information that is provided to patients by each professional in the process.

While it is undoubtedly crucial for physicians to obtain informed consent from a surrogate given

the sensitive nature of the experience, it is debatable whether a woman can fully comprehend the process she is about to undertake if she has never carried a child before [5]. A woman should be informed that even if she has been through a prior pregnancy, carrying a child whom she knows is not hers to keep will likely be a different experience entirely [28]. Nonetheless, a physician who follows guidelines similar to those outlined in the donor checklist should be able to obtain an informed consent from a gestational surrogate.

In order to ensure that a gestational surrogate is capable of giving her informed consent, it is advised that she be at least 21 years old and has already borne a child [5]. This ensures that the gestational surrogate is more aware of the sacrifice she is making, and she understands the bonding that occurs between a woman and the child during a pregnancy [24]. In addition, it is beneficial if a surrogate is married with children and/or in a stable relationship. This ensures that she is less likely to experience feelings of loss resulting from relinquishing a child. This will also reduces the risk that she will revoke her consent to relinquish the baby. Finally, selecting a surrogate who has financial support or employment ensures that she is less likely to be vulnerable to financial coercion [24]. Concerns such as these enable physicians to determine the competency, understanding, and voluntariness of a gestational surrogate and facilitate a physicians' ability to help his patient give fully informed consent.

To obtain informed consent, it is a physician's responsibility to educate a potential gestational carrier on the medical risks inherent in the process. This necessarily involves a discussion concerning the implications of multiple pregnancies and selective abortion and the risks of having a miscarriage, stillbirth, or a child with physical or mental defects or disabilities. Multiple gestations cause an increased risk in complications in both the fetuses and the mothers. Based on the American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART) data from 2007, the guidelines for the number of embryos to be transferred in in vitro fertilization cycles were revised in an effort to reduce the number of higher order multiple pregnancies which occur when three or more implanted embryos implant and develop [29]. To address this concern for the safety and well-being of the gestational surrogate and child(ren) she is carrying, the number of embryos transferred should be agreed upon by the physician and patient prior to transfer [29].

It is crucial for a physician to convey important information to a gestational carrier through a gestational carrier consent form. This form should include, inter alia, the following information: a general description of the procedure including a physical examination and a detailed social history of the gestational carrier and her partner; a screening of inheritable diseases; a psychological screening; information concerning the fact that results from medical examinations and psychological screenings will be shared with members of the gestational carrier program and intended parent(s) and that such results may or may not be shared with the carrier or her partner; a description of the hormones, medications, and implantation procedure; an explicit non-guarantee as to the results of implantation, the normalcy of any resulting pregnancy, or the development of the embryo(s); further, the forms should state that there are unknown side effects from the medications used and that such risks may include an abnormal pregnancy or abnormal fetal development; and finally, the forms should outline the psychological consequences of becoming a gestational surrogate and the legal consequences – which should be noted as often uncertain and varying according to time, place, and parties. The outline of legal consequences should also address the relinquishment by the gestational carrier of any rights, duties, or claims to the resulting child born through the agreement while making it clear that the physician is not a psychologist or a lawyer. As such, individual psychologists and lawyers should be obtained prior to the end of the process. Physicians themselves should consult state laws and guidelines and inform their patients to do the same. Finally, the gestational surrogate consent form should outline the essential elements of informed consent so as to ensure that the surrogate's decision was voluntary, knowledgeable, competent, and based upon full disclosure by a physician.

The complexities of third-party reproduction require considerations of medical, psychological, and legal issues. Just as in the context of egg donation, a physician's ability to obtain informed consent requires that physicians inform gestational surrogates of the benefits of obtaining psychological and legal counseling. Physicians ought to be sensitive to the complex issues of pregnancy and childbirth experienced by the gestational surrogate – feelings and experiences often not anticipated at the time consent is given and often not experienced outside the pregnancy context. Physicians should encourage patients to contact psychologists to deal with any feelings they may experience as a result of being a gestational surrogate. The Practice Committee for the American Society for Reproductive Medicine and the Practice Committee of the Society for Assisted Reproductive Technology state that physicians should inform gestational surrogates that a psychological assessment by a qualified mental health professional is recommended for all gestational carriers [22]. In fact, some states require surrogates to undergo a psychological evaluation before being permitted to become a gestational surrogate and some authorities even recommend counseling for all intended parties prior to signing a contract and even up to 1 full year after delivery.

A psychological evaluation should include family history, educational background, assessment of stability, motivation to donate, reproductive history, interpersonal relationships, sexual history, history of major psychiatric and personality disorders, substance abuse in donor or first-degree relatives, legal history, and history of abuse or neglect [22]. Psychological counseling should cover, among other things, the costs of surrogacy; the psychological and emotional risks involved; the degree of involvement the surrogate may wish to have with the child; the social stigma attached to being or using a surrogate; and finally, how to inform the child of his or her origin [24]. As long as physicians have sensitive, thoughtful, and informative discussions with their patients prior to becoming a surrogate, physicians should have no problem enabling their patients to give fully informed consent.

Psychological counseling will provide gestational surrogates with the support and counseling needed to think through the complex ethical, emotional, and social issues that a surrogate will confront throughout her experience. Counseling through the decision-making process will be helpful to better equip a surrogate with the information and support she needs in order to make a fully informed decision. The voluntariness component is implicated immensely in this process. Counseling will better allow a surrogate to decide, based on her own free will, whether she would like to commit herself to carrying a child for another individual or couple. In addition, psychological counseling will make sure that a potential surrogate is able to fulfill the complex requirements of gestational surrogacy. This goal implicates the competency component of informed consent. The goal is to ensure that a potential surrogate is able to follow instructions, be held accountable, and be reliable and responsible throughout this process. In the surrogate context, these characteristics are crucial given that the health and welfare of the child are at stake. Furthermore, to obtain informed consent, it is important that a surrogate understand the process and be given support and guidance throughout. Talking through issues with a counselor will minimize the chance that a surrogate will have regrets or psychological problems following the experience [17].

In addition to counseling, physicians should encourage gestational surrogates to retain independent legal counsel. Given the fact that there is legal uncertainty inherent in the field of reproductive assistance, legal counsel is extremely important to enable a potential gestational surrogate to become aware of information (and lack thereof) in areas in which a qualified attorney can better equip a gestational surrogate than a physician. Among other relevant information, a lawyer will likely inform a gestational surrogate of the following information: a surrogate's legal rights and responsibilities as they relate to the child; how to ensure that a surrogate will not be liable for any child or child support in the future; the legal uncertainties in the field of assisted reproductive technology, and the legal risks of

revocation of consent. Additionally, lawyers should further inform surrogates of the implications of signing a contract with a surrogacy agency and/or the intended parents. These contracts often detail a surrogate's responsibilities. Importantly, contracts are different from consent forms in their legal consequences [11]. Lawyers should advise clients to refrain from signing any consent forms or contracts until the informed consent process is completed. Furthermore, surrogates should refrain from signing anything until they have had the opportunity to meet with a lawyer to discuss the provisions of the contract and consent forms. A lawyer will undoubtedly inform surrogates that most state laws do not address gestational surrogacy specifically and thus cannot guarantee that their legal understanding will be enforced by a court if a dispute arises [11]. As long as a physician ensures that a patient's legal rights are being adequately addressed by an attorney, a physician can more fully focus on the medical aspects of the procedure.

Case Law

Currently, there is no existing US case law specifically dealing with lack of informed consent in the surrogate context. However, the topic is touched upon in arguably the most famous traditional surrogacy case to date. *In re Baby M*, 537 A.2d 1227, 109 N.J. 396 (N.J. 1988). Among other issues, the intended parents argued that their informed consent was lacking because they were not provided with enough information about the results of the surrogate's psychiatric evaluation, her past occupation as a go-go dancer, the domestic abuse that tainted her marriage, or the surrogate's husband's history of alcoholism and drunk driving [24]. On the other hand, the surrogate argued that her informed consent was lacking as she did not fully comprehend the strength of the bond she would have with the child. The New Jersey Supreme Court ultimately held that the surrogate contract between the parties was void as against public policy. However, the court did not specifically rule on the informed consent issue. Nonetheless, this case highlights just a few of the considerations that should be addressed in the discussion between a physician and patient concerning informed consent.

An examination of cases dealing with informed consent outside the egg donation or surrogate context elucidates how courts would likely deal with allegations of lack of informed consent against physicians in the surrogacy context. The facts and legal arguments vary from case to case, but the practical result of each court decision is to apply the "prudent patient" standard. Under this standard, a doctor must disclose to a patient all material facts, risks, and alternatives which a reasonable person would deem to be significant in making the choice of whether to undergo a procedure. *Howard v. University of Medicine and Dentistry of New Jersey*, 172 N.J. 537, 547 (N.J. 2002). Patients "must prove by expert testimony that the medical condition complained of is a risk inherent in the medical procedure performed" and that the "risk is material in the sense that it could influence a reasonable person's decision to consent to the procedure." *Baylor University Medical Center v. Biggs*, 237 S.W.3d 909, 914 (Tex. App. Dallas 2007), citing *Barclay v. Campbell*, 704 S.W.2d 8, 9–10 (Tex. 1986). Under the informed consent doctrine, courts routinely hold that the information provided by a physician must give the patient a "true understanding" of the nature of the procedure. See, *Valles v. Albert Einstein Medical Center*, 569 Pa. 542, 551 (2002); *Vasa v. Compass Medical P.C.*, 456 Mass. 175 at 178 (2010).

To establish a sound cause of action for lack of informed consent, an individual must establish that a "reasonably prudent person in patient's position would not have undergone the treatment if he or she has not been fully informed and that lack of informed consent was a proximate cause of injury or condition for which recovery is sought." *Johnson v. Staten Island Medical Group*, 82 A.D.3d 708 at 709 (App. Div. N.Y. 2011), citing *McKinney's Public Health Law § 2805-d(3)*. Despite the fact that assisted reproductive technology has been around for quite some time, the laws of most states have struggled to keep up with the complex legal issues that continue to arise as a result of the technology. Thus, whether

or not an egg donor or gestational surrogate can successfully maintain a cause of action against a physician for lack of informed consent will inevitably turn on the facts and circumstances of the individual case.

The legal enforceability of gestational surrogate contracts, on the other hand, is more developed. Significant case law has advanced demonstrating that many states are beginning to find gestational surrogate contracts enforceable. *Raftopol v. Ramey*, 299 Conn. 681 (Sup. Ct. Conn. 2011), for example, is indicative of most state courts' position on the topic. In this case, the Supreme Court of Connecticut held that (1) a contract between a gestational surrogate carrier and intended parents is valid; (2) the gestational surrogate has no parental rights with respect to the children to whom she lacks any biological relationship; (3) the domestic partners who are the intended parents are the legal parents of the children; and (4) an intended parent who is a party to a valid gestational surrogate agreement may become a parent without first adopting the children.

While *Raftopol v. Ramey* is exemplary of the direction in which most state courts are heading, it should be noted that the fourth holding is currently an issue that is less developed and has been met with inconsistent decisions among states. As a result, different state courts have reached conflicting results with regard to the issue of whether an intended parent of a child born through a gestational surrogate can obtain a pre-birth order or whether the child must be adopted after birth. As courts wrestle with these complex legal issues, physicians will have to deal with more practical questions of potential legal and ethical dilemmas that often arise in the field of assisted reproductive technology.

Conclusion

In order to ensure informed consent has been given, a physician should enable a potential egg donor or gestational surrogate to be fully aware of the implications of her decision. The components of informed consent include (1) voluntariness, (2) understanding, (3) disclosure, (4) competence, and (5) consent [5]. Physicians should require that each element of informed consent has received adequate attention. It is of the utmost importance that physicians contemplate the vast array of foreseeable consequences and convey this information to patients.

Physicians should discuss with a potential egg donor the implications of her decision. An egg donor must consider the risks and side effects she will face in the short term and the long-term consequences of her decision. She should address any emotional feelings that may arise from donating eggs, having genetic offspring, potentially having her autonomy compromised in the future, and possibly never knowing the resulting child(ren) or even if any exist. Physicians must discuss these implications with a potential egg donor prior to an egg retrieval procedure.

Physicians should discuss with potential gestational surrogates the procedure, the risks, and possible complications. A gestational surrogate must carefully consider the possibility of miscarriage, multiples, and abortion. She must carefully address any emotional responses she may have. All of these considerations must be fully addressed before moving forward with an agreement to become a gestational surrogate.

Egg donors and gestational surrogates must understand the legal uncertainty that they face given the fact that the laws of most states have struggled to keep up with the complex legal issues that continue to arise in the area of assisted reproductive technology. Physicians should consult local state laws and guidelines to protect themselves from liability that could arise due to lack of informed consent. To facilitate understanding of these complex issues, an interdisciplinary team of competent professionals including lawyers, psychologists, and social workers should be assembled to aid egg donors and gestational surrogates in their decision-making process. Ultimately, physicians should address the medical aspects of egg donation and surrogacy – while facilitating patients' exposure to the ethical, emotional, social, and legal aspects of egg donation

and gestational surrogacy. At the end of the day, a physician's best protection is the adequacy of the information provided. An interdisciplinary team is essential in providing this information and addressing the voluntariness of the consent.

Editor's Commentary

Today, more than ever, obtaining informed consent from our patients and donors is critically important. Unfortunately, it is often looked upon as a "necessary chore," and forms are merely handed out for signature, often by staff members that are not physicians, often without review and certainly without adequate discussion. As the procedures evolve and become increasingly complicated, the need for constant revision of our consents is also warranted.

As Melissa Brisman points out, the process of informed consent is an "ongoing dialogue" between the doctor and the patient. Attorneys tend to focus on published policies, guidelines, and statements from professional societies. Therefore, physicians need to be familiar and keep abreast of statements made by organizations such as the ASRM, ACOG, New York State Department of Health, or the NIH involving informed consent and assisted reproduction and adhere closely to their recommendations.

Must donors and recipients of donor eggs see an attorney? Melissa gives a compelling argument for this additional step, yet it is certainly not a standard recommendation made by our professional societies or, for that matter, by myself. It does add cost and complexity to an already taxing activity. However, I would argue that there is rarely harm in having "too much information" (TMI for the younger audience), and therefore, if couples or donors wish to seek additional counsel prior to participating, I would not dissuade them. I do strongly believe that all gestational carrier surrogacy cases must involve attorneys (actually multiple ones since multiple parties are inherently involved and should be independently represented), and in my opinion, to perform surrogacy without involving lawyers constitutes malpractice.

Acknowledgment Danielle M. Austin is a law student at Fordham University School of Law. She is a summer clerk at the firm, Melissa B. Brisman, Esq., LLC, where she assists Ms. Brisman in the legal aspects involved in helping her clients start or expand their families.

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Statutory and Case Law Governing the Practice of Third-Party Reproduction

26

Susan L. Crockin and Amy B. Altman

Key Points

- The legal status, rights, and responsibilities of all participants and offspring need to be clarified, as do the legal duties and obligations of the medical, legal, and other professionals who assist in third-party reproduction arrangements.
- Given the increasingly frequent interstate nature of many arrangements, participants may benefit from experienced legal counsel to carefully analyze choice and conflicts of law issues to protect themselves and any potential offspring.
- A clearly drafted and negotiated legal agreement addressing potentially divisive issues such as parentage status, future contact, financial terms, disposition of genetic material, and future change of circumstances can clarify intentions, rights, and obligations and add a layer of protection to participants, both known and unknown to one another, as well as to the medical programs that assist them.
- Contract, tort, malpractice, and other legal theories, as well as potential criminal prosecutions may be involved in actions brought against professionals involved in assisted reproduction.

Louise Brown's birth in 1978 ushered in a new era in both reproductive medicine and law. Before then, reproductive law focused largely on contraception and abortion-related concerns, and parentage legislation focused on parent–child status and ensuring child support obligations for parents regardless of whether children were born in or out of wedlock. IVF was virtually unheard of and technologies that now make frozen embryos, donor eggs, gestational surrogacy, and preimplantation genetic diagnosis possible were not yet developed.

As assisted reproductive technologies (ARTs) continue to radically alter the ways in which our society creates families, the legal frameworks that regulate them and attempt to secure the families they help create are being challenged. This chapter provides an overview of the statutory and case law that has both developed around and impacts on third-party reproduction in ART.

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Statutory ART Law

This section provides an overview of the limited statutory law addressing ARTs in the USA. Table 26.1 offers a snapshot of current state laws and provides a reference for this discussion. Given the variability, nuances, and changeability of ARTs law, however, any statutory information must be continually updated and verified.

Model Acts

"Model acts"—as the term suggests—are models, not actual laws, drafted and proposed in the hope they will serve as a deliberative example for states considering enacting actual legislation. All or any part of a model act can be enacted in a given state, or can serve as general guidance for states that choose to draft their own language. In 2002, the National Conference of Commissioners of Uniform State Laws (NCCUSL), a long-recognized national authority on family law and whose model acts have been adopted by many states in establishing their statutes, enacted the model Uniform Parentage Act [1]. Originally divided over whether surrogacy agreements should be prohibited, in 1988 the Commissioners had offered two alternative surrogacy provisions in an earlier model act [2]. One provided for judicially regulated surrogacy; the other voided any agreements. Only two states adopted either provision. In 2002, according to the preface to the UPA, "NCCUSL once again ventured into this controversial subject." It withdrew the earlier act and substituted Article 8, which allows for validation and enforcement of gestational agreements. Article 8 was "bracketed" from the remainder of the model act in recognition that some states might want to omit this controversial topic. The Article allows for judicially approved gestational surrogacy agreements while nonvalidated agreements are unenforceable—but not void, providing an incentive for judicial oversight. The Act removes the requirement that one of the intended parents be genetically related to the child and includes potential child support liability for failing to comply with the outlined procedures.

A number of states have adopted many of the 2002 UPA provisions, as noted throughout this chapter. Other model acts have been proposed, but not adopted by any state, including one by the American Bar Association Family Law Section's ART Committee, which, after decades of work, and revisions is currently under further review for updates and amendments. It's history and purpose to "... provide[s] a flexible framework ... to resolve contemporary controversies, to adapt to the need for resolution of controversies ... that may have not yet occurred ...", [3], serve as a strong reminder of the challenges in crafting legal guidance for rapidly evolving technologies and families.

Donor Insemination Laws

Laws related to sperm are a major exception to the limited number of ART statutes. Over 35 states have some form of statutory law on artificial insemination. Many derive from the 2002 Uniform Parentage Act (UPA), which both defines donors and clearly distinguishes between donor and parentage status based on intent. "A donor is not a parent of a child conceived by means of assisted reproduction" [4]; whereas, "a man who provides sperm for, or consents to, assisted reproduction by a woman…with the intent to be the parent of her child, is a parent of the resulting child" [5]. The UPA requires a written record signed by both intended parents, but also states that "[f]ailure of a man to sign a [required] consent, before or after birth of the child, does not preclude a finding of paternity if the woman and the man, during the first 2 years of the child's life resided together in the same household with the child and openly held out the child as their own" [6]. A number of sperm donor laws also predate the ARTs and the UPA and have no additional requirements.

Thirty of these laws apply only to married couples. Some are limited to defining donor status, while others are more expansive, also defining parental status or required procedures, such as written consent by the husband or physician. Still others, such as Florida and Virginia, are found within more recent and comprehensive ARTs statutes.

Artificial or donor insemination, long predating the ARTs, has never been considered an assisted reproductive technology from a medical perspective. It should be noted, however, that some recent and model legislation has nonetheless included it within statutory definitions. This discrepancy points up an important role for medical professionals: educating lawmakers to ensure enacted ARTs laws accurately reflect what may be unfamiliar medical technologies to those outside the medical field. In the absence of a full understanding of the medical definitions and technologies, lawmakers may otherwise create incompatible definitions and laws. Both the UPA and the ABA's Model Act conflate artificial insemination with intrauterine insemination and consider both an assisted reproductive technology.

Donor Egg and Donor Embryo Laws

Only 13 states have some statutory guidance on egg donation, and almost all also address embryo donation. Nine are based on the UPA language, which defines a "donor" as "an individual who produces eggs or sperm used for assisted reproduction, whether or not for consideration" [7]. The remaining laws are drafted in a variety of terms. Interestingly, three additional states address embryo donation but not egg donation (Georgia, Louisiana and Ohio). Louisiana, the only state to define an embryo as a "juridical person," [8] provides for its "adoptive implantation" while prohibiting sale of an embryo. Florida, in contrast, allows reasonable compensation for embryo donation [9]. While not all of the statutes require written consent to gamete or embryo donation by participants and/or physician, in the authors' views, it is prudent practice regardless of whether or not statutorily addressed.

Surrogacy-Related Statutes

While most surrogacy law has evolved through court cases as discussed in the following section, a small but growing number of states have enacted statutory schemes that address traditional and/or gestational surrogacy. Among those, some prohibit surrogacy, others allow it with compensation or other restrictions, and still others outline procedures to recognize legal parentage for intended parents involved in these arrangements.

Twenty-one states have some form of surrogacy legislation. Eight jurisdictions prohibit surrogacy altogether. Some, such as the District of Columbia and Michigan, criminalize entering into or drafting such a contract. At least 11 states statutorily address and recognize some form of surrogacy. Statutes that permit compensation generally limit such payments to medical and necessary living expenses. Some states, such as New Hampshire, expressly extend coverage to any lost wages, health insurance, disability insurance, life insurance during the pregnancy, reasonable attorney's fees, court costs, and counseling fees [10]. (In states without surrogacy statutes, compensation may be less restrictive.) Seven of those statutes outline procedures for either entering into agreements, obtaining pre- or post-birth orders recognizing parental rights for intended parents, or both.

Other ART-Related Statutes

There are also a variety of miscellaneous ART-related statutes passed in a number of states. Fifteen address insurance coverage and, to varying degrees, mandate coverage or mandate offering coverage for a variety of infertility-related treatments. Updated information on state-specific insurance coverage can be obtained from websites maintained by both RESOLVE (www.resolve.org) and the National Conference of State Legislatures (www.ncsl.org). Other state statutes apply to safety; some were passed in reaction to highly publicized lawsuits involving serious medical mishaps, such as embryo mix-ups or physician malfeasance. At least six state statutes require testing in addition to FDA and professional guidelines that may address the same issues. New Hampshire requires both donor medical evaluation and recipient counseling and evaluation; Louisiana prohibits use of fresh semen; Michigan and California require HIV testing; and

New York and Rhode Island have both sperm testing and evaluation guidelines. In South Dakota, an HIV-positive sperm donor could face felony charges. Under California's Penal Code, use or implantation of any gametes or embryos other than as consented to in writing is unlawful. These are but a few examples of the variations among state statutes, a full discussion of which falls outside the scope of this chapter.

Case Law

A Legal Primer on Establishing Parentage

Establishing parent–child status of children born via ARTs should be at the center of any legal discussion on this topic and resolved before entering into any third-party family building arrangement. With ART advances and increasingly common third-party arrangements, including interstate and international ones, the legal status, rights, and responsibilities of all participants and offspring need to be clarified, as do the legal duties and obligations of the medical, legal, and other professionals who assist them.

The law has struggled to balance new technologies, new ARTs statutes, older parentage laws, evolving public policies, and concerns over the financial and legal needs and welfare of children. Under common law principles, a man who fathers a child is typically recognized as having both legal and financial responsibilities to that child regardless of whether he is married to the child's mother. Most states also rely on common law principles dating back to colonial America, which follows English law, which presumes a child born within a marriage is the child of both husband and wife. Often referred to as "Lord Mansfield's Rule," in many states the presumption of paternity was deemed irrebuttable, meaning no legal challenge would be allowed. The underlying rationale was to avoid bastardizing children. In modern times, the rule has been eroded, and in many states the presumption can be, and has been, successfully challenged. This can become a legal starting point for establishing both paternity and maternity of children born through the ARTs.

Family law (including parentage status, rights, and obligations) is a matter of state, not federal law. As such, no statute or court decision from one state is "precedent" for another. Given the relative novelty and limited number of decisions on these issues, however, many courts look beyond their state borders for guidance on how other courts have responded to similar disputes.

State adoption laws may also apply, particularly if a state has not enacted ART legislation. Although state adoption laws vary widely, certain basic principles are common: buying and selling babies is strictly prohibited (although "birth parent expenses" are frequently permitted); consents to adoption are not allowed before birth (with some exceptions); legally recognized birth fathers must consent or have their rights terminated; and any promises to place a baby for adoption prior to birth or for financial consideration are unenforceable at best.

Legal actions may be necessary to clarify legal status for children born through third-party arrangements. For example, consensual actions to obtain court orders are often needed to establish intended parents' parentage over that of the gestational carrier and her spouse. Contested cases can also arise if participants dispute who is, or who should be, the legal parents of the child.

In interstate cases, one state or federal court may be required to interpret and apply the laws of another state under a "conflicts of law" analysis. Finally, the "Full Faith and Credit" clause is a federal constitutional requirement that one state must recognize and uphold valid court orders from another state. One relevant exception in this field is the federal "Defense of Marriage Act" (DOMA) [11], which allows any state to disregard marriages from another state that violate its public policy. As same-sex marriage becomes more widely accepted and recognized in a growing number of states, DOMA has come under increasing judicial scrutiny, with the United States Supreme Court agreeing to near challenges to the law as this book went to press.

Status of Embryos and Gametes

Significant legal implications flow from how embryos and the consent forms and agreements crafted to clarify their use and disposition are

characterized. Starting in 1992, a growing list of divorce cases has addressed the legal nature of IVF frozen embryos and helped define ARTs and third-party reproduction.

The first and still seminal case involved "custody" of seven frozen embryos created by a divorcing couple who had not made an advance directive, *Davis v. Davis* [12]. Tennessee's highest court characterized IVF "pre-embryos" as falling into a unique category—"neither property nor persons"— and entitled to "special respect" because of their potential for life, relying in part on ASRM (formerly AFS) guidelines, *Ethical Considerations of the New Reproductive Technologies,* ASRM 1990 [13]. The court concluded that absent an advance directive, the husband's constitutional right *not* to procreate essentially trumped his wife's right to procreate, at least where she had other means to parent. In 2000, Massachusetts became the first state high court to review a couple's prior agreement that would have *allowed* procreation over a concurrent objection and rejected that agreement on public policy grounds, *AZ v. BZ* [14]. It ruled that "forced procreation is not an area amenable to judicial enforcement" [15]. A subsequent New Jersey court voided a couple's agreement to *donate* their embryos for procreation after the wife's change of mind and objection, *J.B. v. M.B* [16]. That court found forced procreation equally repugnant regardless of whether the ex-wife would be deemed the legal mother of any resulting child. The principle that no one should be forced to become a biological parent prior to implantation may have potentially far-reaching future implications for gamete donation, especially as egg freezing becomes more widely utilized.

Parentage Involving Sperm, Egg, and Embryo Donation

While the majority of states have sperm donor statutes (see Table 26.1), there have been a number of reported cases—with mixed results—involving known sperm donors seeking to establish or acknowledge their paternity of children born to lesbian couples and single women. More recent cases seem to reflect an increasing sensitivity to, and recognition of, alternative families. In a 1995 case in New York, *Thomas S. v. Robin Y*, a known sperm donor was able to establish his legal paternity to a child born to a lesbian couple [17]. More recently, in 2007 and 2009, appellate courts in Pennsylvania, Kansas, and Massachusetts, *Ferguson v. McKiernan;* [18] *In the Interest of K.M.H.* [19] *and Jane Doe v. XYZ Co. Inc.* [20], all rejected the concept that known donation and single motherhood were against the public policy of those states. The Kansas Supreme Court ruled that a donor sperm statute that applied to single women did not unconstitutionally deprive a known donor of his paternity rights. It also rejected the application of Missouri law, where the insemination occurred and whose law would have likely recognized paternity. These cases illustrate the value of a written agreement prior to the donation to clarify and memorialize the respective participants' parent-donor status. Given the increasingly frequent interstate nature of many such arrangements, participants will also want experienced legal counsel to carefully analyze choice and conflicts of law issues to protect themselves and any potential offspring.

With many fewer egg donor statutes and cases, two divorce decisions involving custody of children born from donor egg may be illustrative. Courts in both New York and Ohio summarily rejected husbands' efforts to gain custody based on being the only genetic parent, *McDonald v. McDonald* [21] *and Ezzone v. Ezzone* [22]. Courts may apply the underlying rationale of any relevant donor sperm laws under an equal protection analysis to uphold the original intentions of parties using donor eggs or donor embryos.

Ideally, donor sperm or egg arrangements will involve both appropriate consent forms and a written agreement between the donors and intended parents. For married, heterosexual intended parents, court involvement should not be necessary. For same-sex couples and single parents, additional legal steps such as a post-birth adoption may be available and are strongly recommended to solidify their legal parent–child status within and outside of the home state.

Table 26.1 State laws regulating gamete donation, embryo donation and surrogacy

State	Egg	Embryo	Sperm	Surrogacy	Insurance	Judicial involvement – file consent	Other (non-third party)
Alabama	Yes	Yes	Yes	No	No	No	
Alaska	No	No	Yes	No	No	No	
Arizona	No	No	Yes[a]	Yes[b]	No	No	
Arkansas	No	No	Yes	Yes[c]	Yes	No	
California	No	Yes[d]	Yes	No	Yes	No	Penal code liability; testing requirements; advertising must have written warning; Dr. full disclosure regarding disposal; no purchase for research can donate
Colorado	Yes	No	Yes	No	No	No	
Connecticut	Yes	No	Yes	Yes[c]	Yes	Yes	IPs with approved gestational agreement may request a replacement birth certificate with IPs names (Effective 1 Oct 2011)
Delaware	Yes	Yes	Yes	No	No	No	
District of Columbia	No	No	Yes	Yes[b]	No	No	
Florida	Yes	Yes	Yes	Yes[c]	No	No	Compensation must be reasonable
Georgia	No	No	Yes	No	No	No	
Hawaii	No	No	No	No	Yes	No	
Idaho	No	No	Yes	No	No	No	
Illinois	No	No	Yes	Yes[c]	Yes	No	Qualifications for surrogate, IPs, and contract
Indiana	No	No	No	Yes[b]	No	No	
Iowa	No	No	No	No	No	No	
Kansas	No	No	Yes	No	No	Yes	
Kentucky	No	No	No	Yes[b]	No	No	
Louisiana	No	Yes[d]	No	Yes[b]	Yes	No	Embryo destruction prohibited; sperm donations must be tested for HIV, except when the sperm is donated by a husband to his wife
Maine	No	No	No	No	No	No	Sperm testing
Maryland	No	Yes[d]	Yes	No	Yes	No	Physicians duty to disclose re: embryo disposition
Massachusetts	No	Yes[d]	Yes	No	Yes	No	Insurance coverage from infertility
Michigan	No	No	No	Yes[b]	No	No	Test sperm for HIV
Minnesota	No	No	Yes	No	No	No	
Mississippi	No	No	No	No	No	No	
Missouri	No	No	Yes	No	No	No	
Montana	No	No	Yes	No	Yes	No	
Nebraska	No	No	Yes[a]	Yes[b]	No	No	
Nevada	No	No	Yes	Yes[c]	No	Yes[e]	
New Hampshire	No	No	Yes[a]	Yes[c]	No	Yes[e]	Testing requirements; donor and recipient qualifications

Table 26.1 (continued)

State	Egg	Embryo	Sperm	Surrogacy	Insurance	Judicial involvement – file consent	Other (non-third party)
New Jersey	No	Yes[d]	Yes	No	Yes	No	
New Mexico	Yes	Yes	Yes	Yes[b]	No	No	
New York	No	No	Yes	Yes[b]	Yes	No	Violation of surrogacy limitations—first face a civil penalty; professionals involved in the arrangement "shall be guilty of a felony" if fee exceeds adoption expenses
North Carolina	No	No	Yes	No	No	No	
North Dakota	Yes	Yes	Yes	Yes[c]	No	No	
Ohio	No	Yes	Yes	No	Yes	No	
Oklahoma	No	Yes	Yes	No[b]	No	Yes[e]	
Oregon	No	No	Yes	No	No	No	
Pennsylvania	No	No	No	No	No	No	Testing required: within 30 days of sperm or egg
Rhode Island	No	No	No	No	Yes	No	Testing: control by Department of Health
South Carolina	No	No	No	No	No	No	
South Dakota	No	No	No	No	No	No	Felony to donate sperm if have HIV
Tennessee	No	No	Yes	Yes	No	No	
Texas	Yes	Yes	Yes	Yes[c]	Yes	Yes[e]	
Utah	Yes	Yes	Yes	Yes	No	Yes[e]	
Vermont	No	No	No	No	No	No	
Virginia	Yes	Yes	Yes	Yes[c]	No	No	
Washington	Yes	Yes	Yes	Yes[c]	No	No	Disclosure of donor info: once 18 child may request and fertility clinic must provide donor's identifying and medical information: donor may opt out of providing ID information only
West Virginia	No	No	No	No	Yes	No	
Wisconsin	No	No	Yes	No	No	Yes[e]	
Wyoming	Yes	Yes	Yes	No	No	No	

Key: [a]Sperm: AZ = only discusses support, not parentage; NE: father cannot deny parentage if knew of AI; NH: donor is father by agreement only

[b,c]Surrogacy: AZ = prohibits contracts, but PBOs done frequently; CA: defines agreement and parentage orders can be brought at any time; DC: prohibits contracts; FL and IL = only discuss gestational carriers; IA: only that contracts are allowed; MI: surrogacy arrangements are not enforceable; NE, NM, and WA: permit uncompensated surrogacy agreements only; ND: prohibits traditional surrogacy, only permits gestational carrier agreements; NY: restrictions; OK: 1983 AG opinion: paid surrogacy prohibited per child trafficking laws; VA: permits uncompensated surrogacy agreements for married couples only—[b] = prohibits; [c] = allows; KY, LA, NE: Trad. surrogacy void, does not address gestational carrier; ND: prohibits trad. surrogacy, permits gestational surrogacy.

[d]Embryo: CA, MA, MD, NJ: require MD to provide information regarding embryo donation for procreation; LA: embryo as "juridical persons" available for "adoption implantation"

[e]Judicial involvement: NV and WI: file consent with Department of Health; NH, TX, and UT: file surrogacy contracts with court; OK: consent for embryo donation

Egg freezing is too recent a development to have fostered litigation in the USA to date, but will inevitably present new legal challenges. Professional guidelines, until 2011 considered egg freezing to preserve a woman's own reproductive potential experimental, *Ovarian Tissue and Oocyte Cryopreservation,* ASRM 2006 [23]. Whether frozen donor eggs must be quarantined; how compensation to donors and payments by intended parents or programs will be structured consistent with applicable law and professional guidelines; how donors, intended parents, and future children may access information about one another; and whether donors may change their mind as to eggs that have been donated and frozen but not yet thawed or fertilized under theories applied to frozen embryo disputes discussed above are among the many likely future legal issues.

Embryo donation, except in those relatively few states with legislation, adds another layer of uncertainty to the legal status of resulting children. Adoption and any donor gamete laws may be relevant, but neither is precisely applicable. At a minimum, genetic parents must expressly consent to the donation, ideally enter into a written legal agreement which both clarifies their intent to relinquish (and the recipients' intent to accept) any legal claims they may have to the embryos and all parental rights, responsibilities, or obligations to any resulting children. Mental health counseling, agreements as to any future contact, and representation by experienced legal counsel to determine if a post-birth adoption is available-and advisable are all recommended steps to avoid future uncertainties.

Other Parentage Issues

Parentage, Embryo Mix-Ups, and Third Parties

Embryo mix-ups, despite professional precautions, have occurred with understandably serious consequences. These cases raise both novel questions of legal parentage and, as discussed more fully in the following section, significant issues of provider liability. If an intentional or inadvertent mix-up of gametes or embryos results in a live birth, potentially explosive custody battles may arise and their resolution difficult to predict. Outcomes may turn on a number of factors, including when the discovery is made, whether the mix-up involved donor gametes or embryos (as opposed to the intended parents' genetic material), state law, and both the original intentions and subsequent responses of the multiple, impacted patients. As discussed below, such litigation has been brought in at least a few states, including California, New York, and Michigan. No statute specifically addresses parentage of children inadvertently born to unintended recipients. Individual state parentage, ART and adoption laws, as well as constitutional law principles, will guide the resolution of any such parentage dispute.

Both New York and California courts refused to rule that intended parents in embryo mix-ups should be considered donors. See *Robert v. Susan B* [24]. (husband not a donor of child born from donor egg/husband sperm and mistakenly implanted in single woman; wife's maternity rejected without genetic or gestational connection) and *Perry-Rogers v. Fasano* [25] (New Jersey couple whose embryo was mistakenly transferred to another patient deemed legal parents despite New York's irrebuttable presumption of maternity for woman who gives birth). In a third widely publicized case, a woman who was mistakenly implanted with another couple's embryos voluntarily completed the pregnancy and relinquished the child to the genetic parents, *Morells v. Savage* [26].

Patients and programs may also have conflicting interests, with the recipients desiring to keep any mix-up from any genetic parents while the genetic parent(s) will likely want to assert custody rights over the resulting child. Intention, genetics, and gestation will all play a role in determining parentage and custody in any resulting lawsuits. The 2006 ASRM Ethics Committee Report on disclosure of medical errors involving gametes and embryos provides clear guidance: "[I]t is obligatory to disclose immediately errors in which the wrong sperm are used for insemination or gam-

etes or embryos are mistakenly switched and the result is embryo transfer, conception, or the birth of a child with different genetic parentage than intended" [27]. These situations typically give rise to claims for both parentage and professional liability against those whose mistakes led to the mix-up. Anecdotally, there have been multiple such scenarios either settled outside of the glare of unwanted publicity and litigation—including cases where the parties agreed to allow the child to remain with the unintended recipients, or not disclosed to the patients.

Posthumous Parentage Using Stored Genetic Material

Frozen embryos and gametes also create significant legal issues, including whether surviving spouses, family, friends, or others may use genetic material stored by a now-deceased patient and the legal status—including inheritance rights—of any resulting child. There is little law, and no consensus, on this issue in the absence of explicit directions by the deceased as to the posthumous use of their genetic material. There have also been rare cases involving whether genetic material can be *extracted* from a deceased individual for use. These cases present both novel legal issues and competing public policies. Inconsistent court decisions on whether any biological offspring are entitled to Social Security survivorship benefits led to a 2012 United States Supreme Court decision on an appeal from a New Jersey case raising these issues, *Astrue v. Capato* [28]. In a unanimous decision, the Supreme Court confirmed multiple state courts' rulings that state law—not the federal Social Security law itself—determines whether biological offspring are legally deemed a "child" of the deceased who are thus entitled to federal benefits. That ruling means that eligibility will continue to be a state-by-state determination with variable outcomes. While these situations may involve parentage and donor determinations, the core legal issues involving surviving spouses and offspring are outside the scope of this chapter.

Surrogacy

Surrogacy arrangements usually involve both a legal agreement and the courts, the latter if only to consensually obtain a birth order to ensure the intended parents' legal parentage. As these issues are addressed in other chapters, this discussion is limited to case law. Potential participants should be thoroughly advised as to any legal vulnerabilities of particular states, interstate, or international arrangements before deciding to go forward. In parentage disputes, courts will likely look to any agreements and the parties' intentions, as well as applicable laws.

In the majority of states, a "traditional" surrogate who carries a pregnancy resulting from her own eggs, usually fertilized through artificial insemination, is considered a birth mother and fully subject to the protections and restrictions of traditional adoption laws. As such, advance decisions as to parentage and custody may be voidable and payments prohibited as against public policy. Few medical or legal professionals recommend this form of surrogacy.

A 1993 highly publicized and much cited case from California involving gestational surrogacy, *Johnson v. Calvert* [29], is instructive. The gestational carrier sought to be recognized as the child's mother despite her prior agreement with a married couple to the contrary. An intermediate court found that maternity, like paternity, should be determined by genetics, and ruled the gestational carrier could not be the mother because the egg was not hers. Such reasoning, however, would have also made egg donors mothers.

On appeal, the California Supreme Court looked to its state UPA law, which had provisions for determining maternity, based on both delivering a child and proof of genetic parentage. Finding that both "mothers" had presented legally acceptable methods of proving their maternity, the court ruled that the parties' *intent* should control and was clear: to create a child of and for the genetic parents. The court found no intent to create a child for the gestational carrier and thus ruled that her constitutional right to procreate was not implicated. It also held that the surrogacy arrangements did not violate the state's public policy. Over a

decade later, similar reasoning led the Kansas Supreme Court to deny constitutional claims and paternity to a known sperm donor, as previously discussed (*In the Interest of K.M.H)* [30].

The California Supreme Court also distinguished a gestational carrier arrangement from a "true 'egg donation' situation," in which if "a woman gestates and gives birth to a child formed from the egg of another woman with the intent to raise the child as her own, the birth mother is the natural mother under California law." It likened the gestational carrier to a very important, in utero, baby sitter.

Just as *In re Baby M* [31], one of the first (1988) and most widely publicized surrogacy cases which deemed a traditional surrogate a birth mother and voided the surrogacy agreement, is cited by almost every state court confronted with a traditional surrogacy dispute*, Johnson* is widely cited by courts around the country involved in ART disputes to clarify maternity and paternity and the varying roles of genetics, gestation, and intention:

> Society has not traditionally protected the right of a woman who gestates and delivers a baby pursuant to an agreement with a couple who supply the zygote from which the baby develops and who intend to raise the child as their own; such arrangements are of too recent an origin to claim the protection of tradition. To the extent that tradition has a bearing on the present case, we believe it supports the claim of the couple who exercise their right to procreate in order to form a family of their own, albeit through novel medical procedures [32].

States have strongly trended toward distinguishing gestational surrogacy/carrier arrangements from traditional surrogacy, recognizing legal parentage for intended parents (at least where one if not both are also the genetic parents) and not considering gestational carriers to be birth mothers. Procedures to establish parentage vary from state to state (and sometimes court to court). Some courts [33] refuse to consider the contractual arrangement, while others have endorsed these agreements. See, e.g. *Raftopol v. Ramey* [34] (Connecticut recognizing contract and two men as legal parents of child born to gestational carrier). Procedures, venues, and timing (pre- or post-birth) are both state (statute and case law) and fact specific and can be dramatically impacted by both choice and conflict of law issues, an especially critical issue to resolve in multistate arrangements, discussed in the following section. All parties should have an interest in clarifying legal parentage to the fullest extent and at the earliest time possible.

When intended parents and carriers live in different states or countries, what law will be applicable both to any contract and to a determination of parentage are critical issues to resolve thoroughly prior to any final decision to go forward. While parties can choose the applicable law to a contract (subject to certain rules of reasonableness), there remains the possibility of a "conflicts of law" issue, where a court must determine which law applies in either a dispute or judicial parentage action. In some cases, the possible applicability of a state's unfavorable surrogacy laws will be sufficient reason not to enter into an arrangement with a particular potential gestational surrogate/carrier.

While typically one or more parties must reside in the state whose laws are being relied upon, in at least one case, a court found sufficient contacts to proceed without any party residing in that state, *Hodas v. Morin* [35]. The *Hodas* court ruled that Massachusetts both had jurisdiction and was a proper choice of law to grant a pre-birth parentage order to intended parents who were Connecticut residents and whose gestational carrier was a New York resident. Those two states have conflicting laws so the parties had contractually agreed to use Massachusetts law and to have prenatal care and birth take place in a hospital in Massachusetts, a state where pre-birth parentage orders can be obtained. Given the opposing laws and finding Massachusetts had a "substantial relationship" to the transaction because of the prenatal care and intent for the birth to occur at a Massachusetts hospital, the court concluded Massachusetts had authority to recognize parentage and create a birth certificate. Such an outcome cannot be assumed, however, and other state courts might come out quite differently.

These issues take on even greater importance where intended parents are not US residents. Immigration, contract enforceability, and

financial issues all become critical issues that require expert and independent legal advice prior to entering into any surrogacy arrangement. With respect to parentage, there have been multiple instances of international parents being unable to return to their home countries with their children or without having their parent–child status recognized despite obtaining US court orders of parentage [36]. Expert immigration legal counsel is necessary in such cases. Gestational surrogate carriers may need additional legal protections and representation as to both parentage and financial risks and obligations. There have been anecdotally reported instances in which gestational carriers have been held financially responsible for maternity and newborn coverage when international parents have either not secured an insurance policy or failed to pay out of pocket, as agreed, for expensive neonatal costs. In particularly tragic scenarios, some international parents have refused to return to the US for their children born with anomalies and high hospital bills, leaving gestational carriers with parental obligations as well as financial vulnerability [37].

Same-Sex Couples and Single Parents

Same-sex couples and single intended parents present unique issues and vulnerabilities, especially given the dramatic differences in relevant state laws. Some states now recognize same-sex marriage, while others refuse to do so, and federal law (the so-called Defense of Marriage Act or DOMA [38]) currently permits the latter to disregard marriages from other states. Although within their home states legally married, same-sex couples need no additional legal steps to both be fully recognized as parents of a child born to one of them, when out of state one member of the couple may have virtually no legal rights to their child. As a result, the majority of same-sex married couples are advised to adopt their child after birth to ensure legal recognition of their joint parent–child relationship in any state.

Female same-sex couples are at risk of being mischaracterized. A nonbiological partner may not be recognized if artificial insemination was used. Alternatively, the partners may be seen as an egg donor and/or a gestational carrier, especially if consent forms and other written documentation are not accurately tailored to reflect their actual intentions. A number of such cases have been heard around the country, with varying results. Although ultimately reversed, two lower California courts initially ruled against the genetic mother of twins born to her former same-sex partner, largely based on the gestational mother's contention that her former partner had been simply an egg donor as the boilerplate medical consent forms reflected, *K.M. v. E.G* [39].

An almost decade long custody dispute between a former Vermont same-sex couple (who had entered into a civil union under that state's laws) illustrates the vulnerability different state laws can create, *Miller-Jenkins v. Miller-Jenkins* [40]. In that case, the biological mother relocated to Virginia with the child and refused to recognize court orders from Vermont granting her former partner visitation as the child's second parent. Notwithstanding principles of "full faith and credit," lower courts in Virginia refused to uphold the Vermont court orders. The Virginia Supreme Court ultimately acknowledged the validity of those orders, but the biological mother, now married to a man, has successfully flouted numerous court orders, including an order reversing the original custody order and granting custody to the nonbiological mother as the court's last resort effort to allow her to see the child, and in January 2010 reportedly fled the country with the child [41].

Male same-sex couples face similar and more complex legal issues since they cannot physically produce eggs, or carry and deliver their own child. In 2009, a case highlighting the vulnerability of male couples and choice of states in which to safely pursue parenthood was highlighted in *A.G.R. v. D.R.H. and S.H.* [42] when the sister of one of the men who had agreed to be a gestational carrier for them, and who had no genetic connection to the twins she carried, was nonetheless awarded joint legal custody of the twins she carried and delivered in New Jersey. Despite the couple's legal marriage under California law, being registered as domestic partners under New Jersey law, and entering into a contract with the

sister of one of the men to carry a pregnancy created from anonymous donor eggs and the sperm of the other man, the carrier was awarded maternity and custody rights. "[T]he court holds that [the sister] possesses parental rights under New Jersey law with respect to the twins and that the gestational carrier agreement…is void and serves as no basis for termination of parental rights of the plaintiff and the consent to judgment of adoption is void and that the parental rights of [the sister] remain in effect and have not been terminated" [43]. The intended father who provided sperm was the legal father, while the second intended father, the carrier's brother, was left with no parental rights. After joint custody arrangements failed, in 2011, the same judge gave full legal and physical custody to the legal father [44].

Preventative Role of Legal Agreements

Given the typical time lag between law and medical advances, legal agreements between intended parents and any third-party donor or surrogate can at least partially address and reduce these vulnerabilities. Agreements are essential in any surrogacy arrangement and highly recommended in any donor gamete (egg or sperm) arrangement. Where available, co-parent adoptions for nontraditional intended parents such as same-sex couples and single parents are also advisable. While a discussion of the contents of such agreements is beyond the scope of this chapter, a clearly drafted and negotiated legal agreement addressing potentially divisive issues such as parentage status, future contact, financial terms, disposition of genetic material, and future change of circumstances can clarify intentions, rights, and obligations and should add a layer of protection to participants, both known and unknown to one another, as well as to the medical programs that assist them.

Any agreement should be drafted in conformity with applicable state laws, with *separate* legal counsel for the respective parties. Even with little law as to the enforceability of such agreements, at a minimum a written record of the parties' intentions will likely help both avoid and resolve disagreements. Additionally, because they are directly between the participants, they may provide a separate, contractual basis for any disputes that do arise, as opposed to solely relying on consent forms, and thus may remove the medical program from being at the center of any dispute.

Anonymous frozen sperm donation may not lend itself to this added layer of protection, and given the majority of states with donor insemination laws, agreements may be less important, at least for sperm bank donors and married recipients. Once egg freezing becomes standard practice, direct agreements may be less accessible as well, but these arrangements will lack the protection of an explicitly applicable law as in sperm donation.

Provider Issues

Third-party ART law can also involve allegations of civil or criminal wrongdoing against professionals. This section provides an overview of the types of litigation brought against ART professionals. For a more complete discussion of the law and cases in this area, readers are referred to *Legal Conceptions*. The evolving law & policy of assisted reproductive technologies [45].

Cases have been brought against physicians, embryologists, IVF programs, embryology labs, genetic testing facilities, donor banks, facilitators or matching programs, escrow agents, lawyers, and miscellaneous supporting individuals. Civil claims and licensing investigations are more common; the relatively rare criminal prosecutions have focused on substantial misdeeds by medical, legal, and other professionals involved in the ARTs. Incarceration, probation, monetary fines, and loss of license are all possible consequences for professionals or practices.

To understand the potential types of claims requires an understanding of both the variety of legal theories that can be used and the respective roles, responsibilities, and standards of care applied to various professionals. Contract law governs breaches of an agreement and liability may turn not only on whether there was a breach but also whether the original contract was consis-

tent with public policy. Under tort law, claims are typically brought for negligent or intentional acts (including "gross" or extreme negligence) or professional malpractice, essentially alleging a failure to adhere to an applicable standard of care. All are based on state law, which can vary considerably. Criminal law usually requires a specific intent or mens rea and a statutory violation.

There is very little law defining the applicable standards of care involved in ART practice. For medical professionals, it may derive from both state-specific medical-malpractice law and professional guidelines such as those promulgated by ASRM and other organizations. For lawyers, state malpractice law and ethical and professional rules will all be relevant. The few, mostly older, cases regarding standard of care for ART professionals offer helpful guidance. In a 1992 case, *Stiver v. Parker* [46], a traditional surrogate sued the surrogacy program that recruited her, as well as its director, four doctors, and a lawyer who were all affiliated with the program for negligence after she gave birth to a child with cytomegalovirus (CMV). She alleged none of the defendants fully informed her of the associated risks of surrogacy and failed to perform any medical screening of the intended father whose semen allegedly transmitted CMV to her. The trial court dismissed her claims, noting CMV was one of the risks listed in her signed consent form. The federal appeals court reversed. It found that the surrogacy "broker," as well as the doctors who performed the artificial insemination and the lawyer who participated in the arrangement were all "engaged in the surrogacy business and expected to profit thereby" and as such should each be held to a new, higher standard of care and not simple negligence. By recruiting a healthy woman into the surrogacy program, that court ruled that each defendant owed her an "affirmative duty of protection" to keep her from harm. The court noted the program design included only a single brief consultation with a lawyer, provided by the program shortly before the insemination, at which time the surrogate was expected to review and shortly thereafter sign the contract and was only provided with a copy after the insemination. The case was remanded to the lower court for a factual determination of whether failure to screen the intended father breached that higher standard of care.

A second lawsuit filed in 1997 by a Pennsylvania traditional surrogate after the death of the infant she gave birth to for a single father is also instructive. In *Huddleston v. Infertility Ctr. of Am* [47], Phyliss Huddleston brought a wrongful death lawsuit against the attorney (the same one sued in *Stiver*), whom the court referred to as a "broker," and his new surrogacy program after the 6-week-old baby was shaken and killed by his father. Huddleston argued that the defendants breached their duty to her to investigate or counsel the intended parent to ensure his parental fitness and the child's well-being. As did the *Stiver* trial court, the lower court rejected her claim and dismissed the lawsuit, finding the intended parent, not the surrogate, was the broker's and Center's client and to whom a duty was owed. It ruled that the defendants acted only as intermediaries between the surrogate and their client, and therefore owed her no legal duty.

The appellate court reversed, citing *Stiver*, and ruled that the defendants had a higher duty of care to avoid foreseeable harm, including injury and death of the child. It found the defendants were involved in "a business operating for the sole purpose of organizing and supervising the very delicate process of creating a child, which reaps handsome profits from such endeavor, and must be held accountable for these foreseeable risks of the surrogacy undertaking because a 'special relationship' exists between the surrogacy business, its client-participants, and, most especially, the child which the surrogacy undertaking creates…thus ICA owed them [the appellant and child] an affirmative duty of protection" [48]. While the court dismissed most of the claims, it sent the case back to the lower court for a factual determination of whether that higher duty of care had been breached. The father was also convicted of manslaughter and sentenced to 12–25 years in jail [49].

There are additional possible claims that may be brought against medical and other professionals by donors and surrogates. Although ultimately unsuccessful in her attempt to be declared the

mother of a child she carried for a couple she knew, Anna Johnson, a California gestational carrier, alleged that the medical defendants failed to inform her of the physical and emotional risks of IVF, acted in excess of her consent, and "knew or should have known" she was "susceptible to mental distress because of her prior history of miscarriages and stillbirths" (facts that she had not disclosed), *Johnson v. Calvert* [50]. At least a few similar unreported cases have been brought by gestational carriers against the professionals who screened them or coordinated their arrangements, which have been settled privately, and therefore the terms of which are not publicly available [51].

At least one surrogacy program has been sued over failure to properly retain and manage funds that its intended parent clients believed had been escrowed for payments to their gestational carriers. In 2009, dozens of clients of SurroGenesis whose gestational carriers had not been paid filed a class-action lawsuit against both the California program and its escrow company, alleging fraud and breach of contract after it abruptly closed. At the time of its closing, millions of dollars of client funds were unaccounted for, *Madrones v. SurroGenesis, et al.* [52].

A donor or spouse has also sued medical professionals in sperm donation cases where they failed to follow state law requirements such as confirming or obtaining written consents or agreements. There have been suits against physicians to financially support the child if their failure to follow legal requirements allowed intended fathers to avoid parentage status and obligations [53]. Regardless of individual outcomes, these cases strongly suggest that physicians and their medical programs should be aware of the applicable law to medical procedures they perform.

Another arena in which medical professionals have been sued and found liable for monetary damages have been in cases involving embryos that have been lost, discarded, or—relevant to this chapter—implanted in another patient. The parentage and custody consequences were discussed earlier in this chapter.

Most lawsuits brought against providers have been against physicians or medical practices, although a smaller number have also been brought against embryologists, attorneys, and others. Liability may attach to the medical director on down to laboratory or clinic personnel, or other employees or affiliated professionals who may have been involved in, and had some responsibility for, an alleged incident or situation, which allowed it to occur. Whether embryologists are considered medical professionals and therefore subject to malpractice claims are unsettled questions. In at least one case involving embryo labeling and administrative errors, the Louisiana Supreme Court has refused to recognize embryologists as subject to that state's medical malpractice law [54]. In some states, medical professionals have the preliminary protections of medical malpractice tribunals, which screen claims for questionable merit. That characterization may also determine applicable theories of liability, from medical malpractice to negligence, as well as the applicability of malpractice or "errors and omissions" insurance coverage.

Contract, tort, malpractice, and other legal theories, as well as potentially criminal prosecutions will be involved in actions brought against the professionals involved. A 2006 ASRM Ethics Committee Report, "Disclosure of Medical Errors Involving Gametes and Embryos," makes it clear that "clinics have an ethical obligation to disclose errors out of respect for patient autonomy and in fairness to patients" [28]. On such occasions, medical professionals have been sued civilly and also in some instances faced license revocation. Thus, in *Susan v. Robert B, discussed earlier,* the doctor who mistakenly implanted another couple's embryo in a single woman and then reportedly both attempted to end her pregnancy and, after failing to do so, attempted to prevent the discovery of the mix-up until long after the birth had his license revoked [55].

Over a decade ago, a notorious situation triggered both civil cases and criminal prosecutions involving three ART physicians at UC-Irvine after their unauthorized dispositions of hundreds of gametes and embryos were discovered. Dr. Ricardo Asch and two other physicians in the practice were

later charged with mail fraud relating to fraudulent billing practices. Dr. Stone was ultimately convicted. Dr. Balmaceda was arrested in Argentina but posted bail and fled the country. Dr. Asch fled to Mexico, where he was apprehended in 2010 but never prosecuted as Mexican authorities refused to extradite him and released him from custody [56]. UCI patients claiming their eggs were taken without their consent, inseminated with either sperm from their husbands or other male patients, and transferred to other, unwitting patients or used for unauthorized research also brought over one hundred civil lawsuits. At least twelve children were born into and raised by other families. Settlements were reached in most of the cases, totaling over $23 million dollars [57].

In another extreme case of mismanagement of an ART program, in 1992 Dr. Cecil Jacobson was convicted of using his own sperm, instead of that of donors, for several years as well as knowingly lying to patients that they were pregnant. Jacobson was ultimately found guilty of over 50 counts of a criminal indictment and had his medical license revoked, *US v. Jacobson* [58].

In 2011, two attorneys and their nonlawyer accomplice pled guilty in federal court to criminal conspiracy to commit wire fraud for transmitting and filing fake documents in connection with an international surrogacy scheme they had devised [59]. The three women recruited American gestational surrogate carriers, sent them to the Ukraine to be implanted with embryos created from unrelated donor sperm and eggs, and, after their return to the US, matched them with American couples under the false pretense that the surrogates had been abandoned by their original (nonexistent) intended parents. The lawyers misrepresented to the court that the arrangements had been made prior to implantation. Court orders of parentage were obtained in California, a state that recognizes legal parentage based on intention at the outset of a pregnancy regardless of genetics. As with many schemes, without a specific law that has been violated, charges were brought under mail or wire fraud statutes since the fraudulent scheme involved money and correspondence crossing state lines.

The scheme, considered by many to be baby manufacturing or baby buying and selling, reportedly involved at least 40 families and possibly many more. The intended parents and gestational carriers were found to have been largely unaware of the illegal activities and thus none were prosecuted. The families have been advised to undergo an adoption to ensure the child they are parenting will be considered legally theirs.

Attorney Hillary Neiman was sentenced to 5 months in jail and 7 months home confinement; Attorney Theresa Erickson was sentenced to 5 months in jail and 9 months of home confinement.

Testing and screening practices raise additional legal issues in ART treatment, largely beyond the scope of this chapter except when performed on donors, on preimplantation IVF embryos using donor gametes or embryos, or during a third-party pregnancy. These cases can involve a variety of professionals, entities, and laws from different fields and jurisdictions.

Cases involving children born with genetic disorders traced to sperm and egg donors have challenged existing tort theories of "wrongful life," "wrongful birth," and "wrongful conception." Many states disallow "wrongful life" claims (brought by or on behalf of a child) on the theory that impaired life cannot or should not be subject to valuation. Some states also reject "wrongful birth" claims (brought by a parent), which if allowed typically depend on direct causation such as a botched abortion or tubal ligation. Parents in states that disallow such theories have sought to distinguish donor screening failures under novel legal theories, including "negligent preconception" wrongs, arguing that the professionals who *selected* donors "caused" the children's births. Those theories were rejected in two cases, *Johnson v. Superior Court* (sperm) [60] and *Paretta v. Medical Offices for Human Reproduction* (eggs) [61], but liability was found on other grounds. Another such case, *Donavan v. Idant Laboratories* [62], ultimately failed under a choice of law theory after the court applied New York law, where the sperm bank was located and which does not allow wrongful life claims, to bar

a New Jersey mother and her 13 year old child's claims. The mother's claims were barred under the applicable statute of limitations. This is yet another example of the critical role choice and conflicts of law play.

As the field of genetics continues to offer newer and earlier information to would-be parents and families through PGD and otherwise, courts may be forced to revisit and redefine "reproductive wrongs." Along with substantive legal principles and choice and conflict of law issues, new testing options will likely continue to push the envelope of defining the legal rights and responsibilities of those who order, administer and receive genetic testing.

Conclusion

In the past 30 years, there has been exponential growth in both reproductive treatment options and those who seek to use them. This overview of the evolving statutory and case law surrounding third-party ART arrangements should provide practitioners with a better understanding of the current state of the law and areas where patients and clients remain vulnerable to legal uncertainties.

Multiparty and multi-jurisdictional family building, including cross-border reproductive arrangements, is on the rise and demands legal clarity for all involved. Applicable professional standards of care will continue to be tested and defined. Choice and conflicts of law will remain critical concepts. Legal theories of law that impact ART arrangements and outcomes will become more established, reducing the current legal uncertainties and variability in this still emerging field of law.

Extraordinary advances in reproductive medicine will continue to require a rethinking of the very concepts of family as well as DOMA's viability may soon be resolved by the US Supreme Court reproductive law and policy. As statutory and case law continue to develop and address the legal status of intended parents, donors, gestational surrogates, and the children they all create, these medical advances will be accompanied by more legal certainty for all. There is no question that the ARTs and the families they make possible are here to stay. The challenge for the law is to continue to develop in ways that will both recognize these families and protect all involved in helping make them possible.

Editor's Commentary

Susan Crockin, JD and Amy Altman, JD, have carefully elucidated the critical role of the law as it impacts ART patients and providers, and the families we all strive to create. As one example, they outline the emerging legal standards for pre-birth court proceedings to establish the status of the parent-child relationships before the event. We, as practitioners, have the great advantage of intentionally creating new life; after all these are not the unexpected pregnancies that many laws were created to define and address. Although we expect to confront the medical, reproductive and psychosocial issues surrounding fertility, we often fail to consider the obvious, but equally important legal discussion that needs to occur prior to executing informed consent and prior to initiating therapy. Today this may necessitate familiarity with local, state, federal and even international law and I think it is fair to say that physicians would be ill advised to lead such a discussion.

So called "alternative" parenting has become commonplace events in the practice of assisted reproduction, but law often lags behind evolving clinical practice, leaving both the patients and the professionals involved with their care, in the lurch. In many Third-party ART cases attorneys are as necessary to the delivery of care to our patients as the conventional healthcare associates (i.e. nurses, psychologists and social workers) that we normally depend upon.

The model acts noted in this chapter, as well as efforts by some states and other legal professional groups, can provide thoughtful and proactive efforts at creating a logical framework for developing a stan-

dard operating procedure for modern practice. They can be quite helpful in understanding the complex social and legal needs of our increasingly diverse and challenging patients, and medical practitioners should welcome and acquaint themselves with such efforts.

Our practices will evolve with the technology and so will the law. In the field of assisted reproduction, we need to get used to the idea that attorneys are not adversaries, but rather, our partners and an important asset to our practices.

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Part VI

Culture, Religion, and Ethics

Health Equity and Access to Oocyte Donation

27

Mavis Jones and Jeff Nisker

Key Points

- Regulatory systems and agencies have the potential to correct inequities in the delivery of fertility care services, but jurisdictions differ on the issue of access to oocytes and embryos.
- In most societies, motherhood plays a central role in women's lives, and access to embryos and oocytes for medical treatment of intractable infertility is a growing health equity issue.
- Women with ovarian failure represent a specific population affected by inequitable access to oocytes and embryos, and they face a potentially remediable situation if one considers that changes in policy and funding could address their need.
- If a culture of true altruism existed, it is likely that cryopreserved embryos, no longer required by women who have successfully completed IVF, would be donated to others who do not have the financial means to afford assisted reproduction.

In many countries women are delaying having children for reasons such as educational pursuits, career goals, or establishing relationships with partners prior to starting a family [1–4]. As human reproductive physiology does not accommodate the social norms of late reproduction, many women will need medical assistance in order to conceive, including strategies for oocyte preservation [5–7] and donation [8–13]. Although innovations in medical technologies now make it much more likely that some women will be able to have children, these new medical possibilities may also lead to inequities in access to care.

Oocyte depletion may be the result of cancer treatment [8, 14–19], advanced reproductive age [8, 20], or other etiologies [8, 21–23]. Because little or no *public* funding exists in many countries for the medical treatment of oocyte depletion [8, 10], in these contexts the latest techniques are only available to those who can afford it. This creates great discrepancies among different women in their ability to have children. Table 27.1 shows six examples of national funding and

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Table 27.1 Regulation of oocyte donation in six countries

Country	Assisted reproduction funding	Regulation of donation/payment
Australia	Determined state by state, from full coverage for over six cycles to more limited public funding [10]	No payment for donation allowed [24]
Canada	Funding for IVF in two provinces: Quebec, up to three cycles; Ontario, for bilateral tubal occlusion only, up to three cycles [11]	Egg donation or egg sharing and payment for same are prohibited with criminal penalties, but enforcement of prohibition has not occurred [25]
France	IVF cycles funded for heterosexual couples with proof of 2 years cohabitation [26]	French bioethics guidelines prevent payment for oocytes, but there are programs for altruistic donation
Israel [27]	IVF funded for an unlimited number of cycles, up to two live births. Fertility services available to women until age 45 with own ova	Women between 45 and 51 can access donated ova for fertility services. Recent initiatives include funding for imported ova and cryopreservation for single women up to age 33
United Kingdom	NHS subsidizes infertility treatment for couples meeting specific eligibility criteria; the amount of subsidy varies by region [12]	No payment for donation allowed, but gamete donors can be compensated £55.19 for each day of missed work, capped at £250 [28]
United States	14 states mandate that insurers provide some coverage for infertility diagnosis and treatment, but not all of these cover IVF; no state requires coverage of fertility preservation methods for newly diagnosed cancer patients [9]	Overall, practices are governed by self-regulation. Louisiana banned the sale of oocytes in 2010; Indiana limited compensation to oocyte donors at $3,000 plus expenses in 2008; Virginia excluded oocytes from restrictions on the sale or purchase of body parts in 2008 [25]

regulation disparities: Australia, Canada, France, Israel, the UK, and the USA.

For women seeking infertility treatment because of oocyte depletion, the ability to become pregnant depends on their access to at least one of the following: (1) their own vitrified oocytes [16], (2) their own previously cryopreserved ovarian tissue [16], (3) other women's oocytes through clinics that facilitate their procurement [8–13], (4) oocytes procured previously from commercial oocyte banks, (5) oocytes from women who are advertised on the Internet or newspapers they are willing to sell their services or donate oocytes [29, 30], (6) oocytes from women who respond to patients' advertisements on such sites [31], and (7) oocytes altruistically "donated" by family members or friends.

Ethical problems exist regarding altruistic donation of oocytes [32–35] as they do for altruistic donation of other tissues [36–38]. In most countries where legislation regulates assisted reproduction [33, 39–47], it is legal (and thus in some circles considered ethical) for women who have completed their families to undergo an IVF cycle to provide oocytes for women with oocyte depletion, as long as they are not being paid to do so. The legislation in these countries [33, 40–44, 46, 47] requires comprehensive counseling before a woman can choose to accept the physical [48–54] and psychological [55–57] risks of the infertility drugs and surgery inherent in making such a donation, and the psychological risks of donation itself [32, 58–62]. The risks to oocyte donors undergoing treatment with ovarian stimulating drugs and the retrieval include severe ovarian hyperstimulation syndrome (OHSS) [63–69], or even death on rare occasions [70], but also the physical pain of the oocyte aspiration as well as infection or blood loss resulting from the surgery [71]. Apart from the physical risks there may also be emotional and social ones. There is a possibility that egg donation may decrease a donor's own chances to later conceive [13] and women who donate for financial reasons may later come to regret that decision if they in turn experience infertility [72]. One retrospective study of oocyte donors in the USA suggests that women do not recall being aware of all the physical and psychological risks, or the severity of these risks, when they first donated [13]. A quarter of the women in this study reported either long-term negative, or ambivalent, feelings about the process [13].

In this chapter we examine access to oocytes as an issue of health equity. We explore the complexity of the issue by raising questions about other actors involved in the assisted reproduction. We do not propose easy answers or firm recommendations; rather, our intent is to open a conversation about an area of health equity that is too often oversimplified. We hope to raise issues for discussion among health professionals and scientists, who, by the nature of their practice and research, are in a position to advocate for equitable health care.

Health Equity and Assisted Human Reproduction Policy

According to the International Society for Equity in Health (ISEqH), health equity is "the absence of potentially remediable, systematic differences on one of more aspects of health across socially, economically, demographically, or geographically defined population groups or subgroups" [73, 74]. A key concept in that definition is "potentially remediable," as health inequities are seen to be conditions that can be improved with appropriate reforms. While there are *inequalities* in how health care is accessed among individuals, *inequity* has to do with access to resources across population groups (rather than individuals) [75]. Once an inequitable aspect of a system is corrected, it opens up the system to meet the health needs of a large number of people whose needs were previously unmet.

Because the desire to become a mother can be motivated by both biology and social norms, stress and anxiety may arise from the inability to fulfill the social roles of parenting. This is of course experienced differently by different women; but the inability to become pregnant may impact significantly on a woman's mental and emotional well-being [76]. Some studies point out that the depression and anxiety experienced

by women who are infertile may even make it harder for them to conceive [3, 11, 77].

Regulatory systems have the potential to remediate inequities, but many jurisdictions differ on the question of oocyte/embryo access. In Canada, for example, the federal government's Canada Health Act [78] and anti-discrimination Charter [79] as well as Assisted Human Reproduction Act [45] and other policies and regulatory oversights in assisted reproduction have not translated into equitable access to reproductive health care [10]. In vitro fertilization (IVF) remains unfunded in Canada except in the province of Quebec [72, 80] and for bilateral tubal occlusion (approximately 20 % of women seeking IVF) [8] in the province of Ontario. A single cycle of IVF costing $10,000 including medications would represent in Ontario 14 % of the median family income [80]. Considering that a woman may go through several IVF cycles before having a baby, these costs are prohibitive for the majority of prospective parents.

Given that motherhood takes such a central role in the majority of women's lives in many societies and the population of women who cannot conceive is growing (more girls and young women surviving cancer to childbearing age, more women delaying parenthood), access to embryos and oocytes for medical treatment of infertility is a health equity issue. While there are now many innovative configurations in parenting relationships, some involving specific population groups and requiring various techniques of assisted human reproduction, *women affected by oocyte depletion* is a specific population group affected by inequitable access to oocytes and embryos. This group is the focus of our chapter. They face a potentially remediable inequity if one considers that changes in policy and funding could address the inequity.

Women Affected by Inequitable Access to Embryos and Oocytes

There are many contextual nuances of donor-assisted conception as it happens in practice. Even where social policy initiatives and general societal change have ameliorated, to an extent, discrimination connected to heteronormativity – the paradigm where family = female mom + male dad + biologically related kids (and ≠ anything else) – nontraditional families still may face subtle discrimination and related barriers in their quest to build a family. In Australia, for example, government statements in the last few years have recommended that funded assisted reproduction not be accessible to single women or same-sex couples unless they can prove infertility [79]. Such "nontraditional" families may be engaged in serious battles against discrimination – a discussion outside the scope of this chapter – however, when it comes to the technicalities of reproduction, for many of the women involved, a low-tech solution could help them achieve pregnancy without medical intervention. For women with oocyte depletion, access to embryos and oocytes is the *only* means by which they can achieve pregnancy. The following sections describe two particular circumstances that may affect a woman's fertility in this way: low income and cancer survivorship.

Women with Low Socioeconomic Status

Infertility may have its most burdensome effect on women of low socioeconomic status (SES). As established, altruistic surrendering of oocytes by a family member or friend is "oocyte donation" in the true sense. However, it may be argued that the vast majority of "donated" oocytes are in fact purchased from clinics, having been provided to the clinics for a fee by a socioeconomically disadvantaged woman [8–13]. Those most able to afford fertility treatment tend to be women who have delayed childbearing in order to build a professional career and stable income or women with financially better-off partners, parents, or other supports. Women in this situation are also able to advertise for paid oocyte "donors," for example, in the publications of prestigious universities [29–31], for which they will pay several thousand dollars per cycle of participation. Although oocyte purchasing is problematic ethically and clinically [10, 81–83], now many women with the financial resources purchase oocytes on the "black market" in Canada [84] or

in the USA [85, 86] or in Eastern European countries [87], where women have no regulatory protection from the potential physical harms of IVF medications and surgery [48–54] or the psychological harms of IVF [55, 57] and oocyte donation [32, 58–62]. As well, financially less well-off women are often in no position to afford fertility treatment much less advertise for a paid donor. Women living with low SES who suffer from infertility have limitations that may not be immediately apparent to planners and providers of treatment services (not to mention people of higher SES) [88]. Lower-paying jobs are often the most tenuous, as employers may view these employees who are frequently absent for doctor's appointments as easily "replaceable." Even with a sympathetic employer, a woman in this situation may be unwilling to sacrifice a few hours' income to look after her health needs. A woman in this situation may feel forced to make difficult choices in order to access infertility treatments. In fact, she may be placed in the position of being an oocyte donor to another wealthier woman in exchange for a subsidized IVF cycle [10, 12, 13] and a lower chance of pregnancy after the IVF medications and surgery [3, 10]. Similarly, women who cannot afford to cryopreserve all embryos not transferred "fresh" in their treatment cycle may, in exchange for a second IVF cycle, give up these embryos to patients in the clinic who are financially in a position to purchase them, or may similarly sell them for research purposes [39]. These practices are inequitable and potentially coercive [10, 89] and add medical risks to the women not using all her oocytes for her own reproductive purposes [10, 63–71].

Socioeconomically disadvantaged women may also be at higher risk of developing health problems that lead to infertility. Women still tend to be the primary caregivers in their families and communities, and low SES women bear the additional stressors of employment insecurity and limited resources which can lead them to de-prioritize their own health needs [90]. So, for instance, given two women with a sexually transmitted disease which could lead to infertility [91], the woman with a more stable and/or higher income is more likely to receive the appropriate treatment – not to mention her likelihood of having regular pelvic exams to detect more serious illnesses. Socioeconomic status, rather than the specific health problem, often determines the type of reproductive care women receive [10].

Women and Girls Diagnosed with or Having Survived Cancer

Another group of women who may need access to donor oocytes are cancer survivors. As advances in cancer treatment have occurred, girls and adolescent women have between 70 and 90 % rate of cure [92–94]. Many of these women will require assisted reproduction in order to have children later in their lives as their chemotherapy and other cancer treatment strategies immediately or in the long term render them oocyte depleted [16]. Further, many women with breast cancer and other malignancies may want the opportunity to preserve their fertility potential (through cryopreservation of oocytes or ovarian tissue) prior to chemotherapy [5–7, 14, 17–19, 95–100], or will later want access to donated oocytes. However, oocyte and ovarian tissue cryopreservation strategies are extremely expensive processes. Although female cancer patients may qualify for fertility preservation in the USA, Canada, and other countries, they may be denied the choice to have a child because they, their partners, or their parents did not have the financial qualifications to access fertility preservation strategies or to purchase oocytes. In most countries, only young women who, by virtue of membership in a financially secure family, have accessed fertility preservation strategies will later be able to undergo assisted reproduction to have a child. Even then, the woman in this situation will only be able to access IVF if she has been able to accrue the financial means to pay for it, or if sufficient subsidy is available.

Thinking Forward: A Note on Children

While this chapter has taken a reproductive rights approach to health equity issues, we recognize that practitioners must also be aware of the long-term consequences of the decisions they make

with their patients. Women with oocyte depletion who seek to expand their family through donated oocytes or embryos will, if successful, give birth to children who may be raised without knowing at least one genetic parent, if not both (in the case of embryo donation). There is a growing awareness of the implications of their birth circumstances for donor-conceived children, and some aspect of clinical practice may need to make women aware of potential future issues. First, donor-conceived children may benefit from knowing about heritable health conditions in their genetic family tree. Practices differ across jurisdictions in terms of information collected on donors and the provision of information to children [101]; and in some jurisdictions minimal information is obtained. Second, the increasing number of children born from donor gametes (both sperm and eggs) has drawn attention to the emotional, psychological, and ontological consequences of being the product of genetic material with limited access to family information or history [102]. Many infertility programs provide counseling to families on how to tell a child about his/her origins; however, as there is no standard, consistent approach across clinics [103].

Many analysts point to the parallels between adoption and donor conception, noting that public adoptions have evolved to make birth family information available to the child in recognition that lack of such information can have a significant, negative impact on an individual's identity and mental health [104, 105]. On that note, adoption is a too often neglected as an option for prospective parents seeking to build a family, yet there are significant numbers of children who are seeking to complete their family as well. For instance, a recent report on adoption and infertility in Ontario, Canada, noted that of the 9,401 children available for adoption in 2007–2008 through the provincial Children's Aid Societies (CAS), only 822 – or 9 % – were adopted in that period [80]. Unlike infertility treatment, public adoptions tend to cost the parents very little financially [80], although the legal and social policy requirements make it unlikely an infant could be adopted. For prospective parents who wish to form the parental bond with an infant, private domestic or foreign adoptions (which should be pursued with legal counsel and through accredited agencies) are an option – and may not be that different in expense or waiting period, to medical assisted reproduction, considering the cost and number of cycles often required. In any case, the outcome for the parents is family completion; and no matter how supportive the foster home, the outcomes for children dramatically improve once they are placed in a permanent family [106]. Although these issues may not be at the forefront of a woman's mind who is experiencing the pain of infertility, it is important to consider the long-term consequences of current practice decisions. For some women with oocyte depletion, their infertility is the long-term result of decisions made in the past. Even if cancer treatment saved their life, they are now dealing with infertility; even if delaying childbearing to focus on work led to professional fulfillment, they are now dealing with infertility. Recognizing and understanding that the method of family expansion has implications for a woman's life, and that of her child, down the road, is an important responsibility assumed by the practitioner providing services today.

Altruistic Donation: A Potential but Not Simple Solution

One option to address the costs and equity issues of access to oocytes and embryos is, of course, the idea of altruistic donation [107–112]. Yee et al. [61] from their research and that of others [113–115] on altruistic oocyte donation from known donors, and the research of European investigators on anonymous oocyte donation [116, 117], point out that although "altruistic donation is in general, a more morally and ethically acceptable form of donation than paid donation, donor recruitment continues to be a major challenge" [61]. They believe that "legislation alone is unlikely to achieve societal attitudinal changes without

complementary measures to raise the public awareness of the need for, and the value of, gamete donation" [61]. However, in many jurisdictions including the USA and Canada, rather than "rais[ing] the public awareness" of this "need" and "value," their lack of public funding of IVF may impart the opposite [61].

If a culture of altruism could be created, it is possible that more cryopreserved embryos, no longer required by women who have undergone IVF, could be donated to women who do not have the financial means to access IVF. Only 20 % of cryopreserved embryos are currently donated to other patients [8, 118–122], with the main reasons cited being avoidance of genetic relationships, particularly consanguinity in their children [8, 123, 124]. On one level, altruism could promote more equitable access (especially to those who cannot afford treatment) through increasing the donation of vitrified or cryopreserved oocytes, as well as cryopreserved embryos no longer required for reproductive purposes [8]. In countries where equitable access to having a child is facilitated by public funding of clinically appropriate infertility treatment [33, 40–44, 46, 47, 112], more oocytes and embryos are available through altruistic donation.

However, altruism, although generally considered "good" [111], cannot be prescribed by health policy-makers nor expected from individual citizens [8]. Discussions of assisted reproduction must also take into account that in every case, reproduction cannot happen without a woman's body [125] and women are the ones assuming the health risks associated with egg donation. While informed consent is a complex issue on its own, it must be said that a woman seeking to donate her oocytes to a friend or family member must be encouraged to fully understand the physical, emotional, and psychological risks attendant to the process. Even in cases where a woman (and in the case of embryos, her reproductive partner) has personally undergone these procedures and chooses to altruistically donate the remaining oocytes or embryos, there may later be emotional or psychological consequences to this action.

Conclusions

Ginsburg and Rapp wrote: "if we only focus on the immediate world surrounding assistive reproductive technologies, we are at risk of missing some of the fundamental ways in which issues of reproductive justice reverberate over the life course and through family systems, communities, and broader policies" [126]. Equitable access to reproductive medicine has been inhibited from occurring in some countries that provide public funding for other areas of medicine because of disagreement as to whether IVF and related technologies are *necessary* medical services. Although reproductive medicine does not cure life-threatening conditions, it is far from being merely a cosmetic discipline. Issues in reproductive health equity, such as access to oocytes and embryos, may not be of high importance to the majority of people who do not suffer fertility problems or have yet to consider building a family. But for individuals dealing with infertility and limited resources, reproductive health equity becomes a matter of vital importance. In a paradigm where equitable access to good reproductive health care is given, practitioners on the frontlines may have opportunities to improve not just equitable access, but quality of care.

Editor's Commentary

Jones and Nisker present a fascinating view of assisted reproduction and oocyte donation in the context of affordable access to care. In the USA and Canada, where such services are typically not a covered benefit by a second party payer, whether private insurance or governmental subsidy, patients are often shut out of the health care system for financial reasons. Having worked my entire professional life juggling both "county" and "private" practices, the disparity is quite obvious.

It is true that the expense of a typical egg donation cycle is beyond the means of a patient with middle level or lower income. As a result, critics have viewed assisted reproduction askance as an *elitist* medical practice, catering to a privileged class of patient. This is particularly true of egg and embryo donation, where average expenses per treatment may top $30,000 and success is not guaranteed. And some criticism is probably justified, as most private offices now resemble that of the boutique plastic surgeon, who also only takes cash, rather than the university based clinic, from which it all began.

Often times the discussion about fair and equitable access to fertility care breaks down along "class lines", the stereotypic *have versus have nots*, which I find unfortunate. Egg donation is portrayed in this light precisely because of its expense. However, I do not agree that a "black market" exists for donor egg services; notice I said services as opposed to "purchased eggs." The high price is not all profit; the overhead expense of running a 7-days-a-week practice and lab, increasing malpractice premiums, and rising cost of donor screens and reimbursement account for the majority of the fees charged. Furthermore, despite Internet blogs to the contrary, I have seen little if any objective evidence over the years to substantiate the claim that indigent women are "selling their eggs" in order to either get by or to obtain health care for themselves. I think it is an urban myth that suggests greedy doctors are exploiting poor young women who sell their eggs to rich old women only later to regret having participated. Plainly speaking, that just has not been my experience.

In a perfect world all infertile patients would donate their supernumerary gametes and embryos to less fortunate individuals to adopt; fertility care would be universally covered; and women not seeking compensation for their services would altruistically donate eggs. However, we obviously live in a less than perfect world, and in fact in countries that ban the free-market payment of egg donors, the practice has largely dried up. Yet, the problems pointed out by Jones and Nisker are very important ones and very real ones, and we do need to pay better attention to the breach in health care delivery presented by socioeconomics. There truly is an inequity in assisted reproduction and we would be hypocritical not to at least recognize it. The gulf that divides the patients that can afford our professional services from those who cannot must be bridged by legislation that either mandates second payer coverage by private insurance or by the government. If and when this ever happens, I can only hope that egg donation is somehow included in the benefits, for as the authors point out, patients needing these services represent a large and growing number of the population.

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28 Religious Views: The Impact of Traditional Theological Opinion on the Practice of Third-Party Reproduction

Joshua U. Klein

Key Points

- Providers of assisted reproductive technology (ART) should familiarize themselves with the major religious issues that arise from providing patients' therapy for infertility and appreciate that conflicts may be irreconcilable.
- Physicians may discourage patients from using ART due to their own religious beliefs, as approximately 5 % of surveyed doctors object to the use of donor gametes and up to 3 % stated they would not assist patients in obtaining treatment involving their use.
- Donor eggs and embryos may be the treatment modality most vulnerable to religious criticism and objection of all the therapies used in ART.
- Theological concerns generally focus on perceived potential damage to relationships between husbands and wives, parents and children, and ultimately family and society.

> And the Lord remembered Rachel, and the Lord listened to her [prayers], and He opened her womb.
> Genesis 30:22

> Rabbi Tanchuma in the name of Rav Bibi said, "There are three Keys in the hand of the Holy One [and no other]: the Key to resurrection, the Key to rain, and the Key to the womb."
> Genesis Rabbah 73:4 (commenting on the above)

> [God] creates what he pleases, He grants to whom He pleases females, and He grants to whom He pleases males… and He makes whom He pleases barren; verily He is knowing, powerful!
> Sûrah 42:49–50

Religion and Assisted Reproduction

Throughout the millennia of human civilization, until quite recently, the science underlying human biology, physiology, and pathophysiology had been enshrouded in a seemingly impenetrable veil of mystery, a garment comfortably inhabited by religious beliefs. The more modern science has threatened to disrobe human function and dysfunction of its arguably supernatural vestments, the more tightly wound and securely fastened these layers of complexity seemingly have become. Almost nowhere has this tension been more dramatically illustrated than in the still-unfolding history of religious attitudes to assisted reproductive technology (ART).

Most basic theology outlines religion in terms of a divine, spiritual, or supernatural counterpart to the contrastingly physical, mundane, or natural world more familiar to most human beings. When viewed through this dichotomous (and oversimplified) lens of theology, human reproduction may represent the ultimate paradox: It is a

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Table 28.1 How infertility may be experienced by participants in religion

	Judaism	Christianity	Islam	Hinduism	Buddhism
Procreation a religious duty	√			√	√
Infertility imposed by God	√	√	√		
Infertility caused by karma				√	√
Infertility a punishment for wrongdoing	√	√	√	√	√
Infertility points to a "higher calling"		√		√	√

Adapted from Dutney [15]

process both wholly and undeniably physical – in fact, one might argue it is the *quintessential* physical function of the natural world, and yet religious traditions spanning almost the entire spectrum of human history, geography, and culture have been unanimous in recognizing an important role for a "divine partner" in procreation and ascribing corresponding religious significance, in the form of various rules and rituals, to the acts and experiences inherent to human reproduction [1].

Assisted reproductive technology, itself a triumphant offspring of the light shed by modern science on the biology of conception and establishment of pregnancy, has been greeted with ambivalence and, to some extent, apprehension by the religious community from its very outset. While most organized religion places a significant emphasis on the importance and centrality of family building in society, the generally "unnatural" qualities of assisted reproduction have challenged traditional notions of spousal intimacy and sexual relations and threatened to devalue familiar and cherished bonds of parenthood and familial lineage [4]. More broadly, but also often more implicitly, there is sometimes a fundamental sense of unease in religious circles about proceeding with unnatural "means" (ART and IVF) despite near-unanimous agreement on the justified value of the "end" (childbearing). Frequently this is experienced in terms of "overreaching" too far into God's domain [5]. While each of the major organized religions has taken its own unique stance on various treatments and circumstances, the misgivings with which religious infertility patients often struggle generally demonstrate some universal themes, particularly the balancing of the religious pursuit of procreation and family building with the sense of infertility having been "ordained" by God and/or a deserved "punishment" for some spiritual misstep. Efforts to circumvent the "natural" with the "unnatural," and the attendant appropriateness of such efforts, lie at the very core of religious unease with assisted reproduction (Table 28.1).

As with many other major technological innovations that challenge cultural and societal norms but hold enormous potential for improving people's quality of life, widespread acceptance of assisted reproduction, while not immediate, was not long in coming. Within the 1st one to two decades of its introduction, the basic premise of ART came to be accepted and practiced (if not quite embraced) in societies worldwide. In the USA, for instance, the first IVF baby was conceived in 1981; just 15 years later, almost 1 in 100 of all babies born in the USA were the products of IVF (by 2009, that figure had risen by 50 % to about 1.5 in 100) [6].

Religion and the ART Provider

In 2008, the European Society of Human Reproduction and Embryology Task Force on Law and Ethics published a statement on "Equity of access to assisted reproductive technology" [11]. The Task Force declares that "equity in access to infertility treatment not only means that people are not excluded for discriminatory reasons but also that they should have access without excessive burdens." In the same paragraph,

Table 28.2 Guidelines for the care of patients for whom religion has become an important part of the way they experience infertility

Be prepared for patients' concerns to take an unexpectedly religious turn from time to time and for the likelihood that their religious orientation will be expressed in clumsy, unsophisticated ways
Be aware of the major religious traditions represented in the community and how those traditions have responded to developments in ART
Do not assume that a particular couple will have an attitude that mirrors the official view of the religion with which they identify
Do not try to "correct" apparent wrongheadedness ("This is God's judgment on us because of the termination I had when I was nineteen") but be supportive of the patient's gradual "reframing" of faith in the light of the experience of infertility ("God has also given us access to ART and the wonderful people in this [clinic] and is with us as we work through this IVF cycle together")
Identify people in the community to whom patients could be referred for spiritual support or counsel, for example, ministers or priests who have personal knowledge of the experience of infertility

Adapted from Dutney [15]

however, they also specify that if "a particular group does not want to use ART for cultural or religious reasons, this inequality does not show inequity." When taken to task for this seeming inconsistency in a letter to the editor [12], Dr. Pennings replies by addressing the issue head on: "To what extent do practitioners have a duty to look for treatment adapted to the religious and ethical values of the patients?" He formulates the following approach [13]:

> If alternative methods are available that do not violate a person's religious beliefs, it is the duty of the clinician to inform the patient of the existence of such methods… Nevertheless, the patients' religious convictions do not oblige the physician to act against his or her own view of appropriate treatment and good clinical practice. The patient-friendly approach makes the wishes of the patient one of the criteria, not the supreme or absolute criterion… The lack of effort by fertility specialists to look for 'religious' treatments does not lead to unjustified discrimination of these groups.

While some religious authorities might perceive Dr. Pennings's view as insensitive to the needs of religious patients, even more extreme positions certainly do exist; for example, a symposium on religion in assisted reproduction published in a peer-reviewed journal included a contribution from an Italian bioethicist entitled "A secular perspective on twenty-first century ethics in human reproduction: why religious views and attitudes are becoming obsolete and possibly dangerous" [14]. The author declares that "religious solutions to reproductive problems… no longer adequately fulfill the needs of humanity in our modern era."

A more receptive approach, which likely more closely resembles that taken by most clinicians, is offered by Andrew Dutney [15]. While he concedes that "it is a matter of irritation to some people in the Reproductive Medicine Units and the community that religion presents itself so forcefully as a stakeholder in ART," he maintains that a clinician's "capacity to offer appropriate care will be enhanced by developing a greater awareness not only of the nature of spirituality and religion and its relation to family formation and infertility but also, quite concretely, the incidence of religious identification in their community and the various forms that that identification may take." Dutney outlines general principles for the care of patients for whom religion has become an important part of the way they experience infertility (Table 28.2). When it comes to DIVF, where religious issues are at their most complex and controversial (see below), even the most religiously savvy clinician would be wise to lean heavily on the support and guidance of clergy and other members of the patients' spiritual community in order to navigate the sensitive but oftentimes grave nature of the questions and difficulties that are inevitably confronted. Nevertheless, even with regard to DIVF, the general principles of awareness and sensitivity are undoubtedly of value.

In addition to the appropriate role of the ART provider in recognizing and incorporating patients' religious beliefs, the question of how clinicians' beliefs themselves may influence ART care has been studied. In a recent survey of over 1,100 practicing OB/GYNs in the USA, physicians who

considered religion "very important" or "the most important" part of their lives were significantly more likely to discourage pursuit of ART and even decline to help patients obtain ART services if the patient is unmarried, plans to be a single parent, has a female sexual partner, or has HIV [16]. When further analyzed by religious affiliation, Evangelical Protestants and Muslims were the denominations that retained statistical significance after stratification. Furthermore, while only 1–2 % of all physicians surveyed had a moral or ethical objection to artificial insemination or IVF with patient/partner gametes, 4–5 % of physicians expressed such an objection to using donor gametes, and 2–3 % stated they would not help the patient obtain such treatment [16]. These results overall stand in contrast to findings reported in an earlier study, in which religious affiliation and level of observance were completely unrelated to opinions about access to ART services [17]; importantly, however, this earlier study surveyed US ART clinic directors, rather than generalist OB/GYNs, which may account for the discrepancy. Ultimately, with increasing acceptance of ART and third-party reproduction in societies worldwide, the personal moral/religious objections of women's health providers will likely continue to diminish.

Religion and Oocyte Donation

It is worth noting that the announcement of pregnancies from IVF using donor oocytes (DIVF) followed very soon after the successful introduction of non-donor IVF in the USA [7, 8]. Nevertheless, robust growth in DIVF did not occur immediately but rather accelerated mainly in its second and third decades of existence, lagging behind the explosive growth that non-donor IVF experienced. From 1995 to 2006, for instance, while all ART volume in the USA increased by 130 %, DIVF volume increased by 224 % (CDC). In the absence of specific medical or scientific innovation to explain this "deferred" growth, we have postulated previously that ethical and religious concerns unique to DIVF may have limited early acceptance of this approach; by the late 1990s, many of these hesitations had been addressed and/or dismissed [9].

Before delving more deeply into some of the particular concerns and approaches that specific religious groups maintain with regard to DIVF, it is instructive to consider the broad perspective Baruch Brody [10] provides on the major categories of discomfort religious authorities routinely express when considering ART:

1. The new reproductive techniques disrupt the connection between unitive conjugal intimacy and procreative potential that is required by morality.
2. The new reproductive techniques often introduce third parties into the process of reproduction, and this is morally illicit.
3. The new reproductive techniques often result in a morally illicit confusion of lineage, since children are often unaware of their biological parents.
4. Some new reproductive techniques (IVF) often involve a failure to implant fertilized eggs. This is a form of early abortion and is therefore morally illicit.
5. The new reproductive technologies often involve a dehumanization of the reproductive process and are therefore morally illicit.
6. Some new reproductive techniques (especially surrogacy) involve commercialization and exploitation that makes them morally illicit.

As Brody points out, most of the difficulties that religious authorities have with ART fall into one of these six categories, as opposed to the archetypal groupings of harms, rights, and justice that more typically represent the lines of analysis in bioethics.

Table 28.3 presents the degree to which each of these six categories is relevant to each of the four major treatment scenarios in ART: non-donor artificial insemination (AI), artificial insemination with donor sperm (AID), non-donor (oocyte) in vitro fertilization (IVF), and donor oocyte IVF (DIVF). DIVF is clearly the treatment modality most vulnerable to religious criticism/objection. While some data suggest that religious identification and/or observance has only a minor effect on patients' general attitude toward the

Table 28.3 Potential religious objections to various fertility treatments

	AI	AID	IVF	DIVF
Disruption of unity of conjugal intimacy and procreative potential	+/–	+	++	++
Introduction of third party	–	++	–	++
Confusion of lineage	–	++	–	++
Potential destruction of embryos	–	–	+	+
Dehumanization of reproduction	+/–	+/–	+	++
Potential for commercialization or exploitation	–	+	–	++

Table 28.4 Concerns of some major religions regarding use of oocyte donation

	Catholicism	Islam	Judaism
Disruption of unity of conjugal intimacy and procreative potential	++	–	–
Introduction of third party	++	++	++
Confusion of lineage	+	++	++
Potential destruction of embryos	+	+/–	–
Dehumanization of reproduction	++	+/–	–
Potential for commercialization or exploitation	+	+/–	+/–

use of donor gametes (Eisenberg) [18], there is a general consensus that the alignment of patients' reproductive goals with their religious and spiritual priorities will significantly ease the burden of infertility and its treatment, along with their associated physical, psychological, and emotional hardship. To this end, as highlighted above, efforts by the clinician to broaden and/or deepen his/her familiarity with and understanding of the positions' various established religions vis-à-vis oocyte donation will improve and enrich the care he/she is able to provide.

Table 28.4 highlights the concerns raised by some of the major religions with regard to oocyte donation, based on Brody's work mentioned earlier [10]. A more exhaustive review of the basic theology of several major established religions and their general positions on infertility treatment can be found elsewhere [19–21]. The remainder of this chapter will highlight in more detail several of these specific objections and how individual religious traditions tackle these issues.

Case Study: DIVF and Catholicism

The position of the Catholic Church with regard to oocyte donation is grounded in and reflects its overall position on assisted reproduction. The Vatican maintains that "reproductive capacity should be exercised only through a sexual act in the context of a loving marriage," a belief arising from the "indissolvable unity of sex, love and procreation" [22]. The Church is therefore opposed to any reproductive techniques, such as IVF, that violate this unity. The moral underpinnings of this position stem primarily from a concern for the dignity of the child: "The more human procreation diverges from the Creator's design for the transmission of human life imprinted in the nature of the human person as a truly human expression of married love, the more human embryos are at risk of being viewed as impersonal objects, not equal to their parents in dignity and worth" [23].

While the objections outlined above would apply equally to both "non-donor IVF" and oocyte

donation, the use of third-party gametes for IVF magnifies and exacerbates the moral and religious objections on several additional levels, including marital fidelity, normative parenting, and familial relationships [9]. The Vatican explicitly outlines these concerns in its landmark statement on assisted reproduction "Congregation for the Doctrine of the Faith: Instruction on respect for human life in its origin and on the dignity of procreation," published in 1987. Regarding the use of IVF with donor gametes, the Vatican writes:

> Heterologous artificial fertilization [using donor gametes] is contrary to the unity of marriage, to the dignity of the spouses, to the vocation proper to parents, and to the child's right to be conceived and brought into the world in marriage and from marriage. Respect for the unity of marriage and for conjugal fidelity demands that the child be conceived in marriage; the bond existing between husband and wife accords the spouses, in an objective and inalienable manner, the exclusive right to become father and mother solely through each other. Recourse to the gametes of a third person, to have sperm or ovum available, constitutes a violation of the reciprocal commitment of the spouses and a grave lack in regard to that essential property of marriage which is its unity. Heterologous artificial fertilization violates the rights of the child; it deprives him of his filial relationship with his parental origins and can hinder the maturing of his personal identity. Furthermore, it offends the common vocation of the spouses who are called to fatherhood and motherhood: it objectively deprives conjugal fruitfulness of its unity and integrity; it brings about and manifests a rupture between genetic parenthood, gestational parenthood and responsibility for upbringing. Such damage to the personal relationships within the family has repercussions on civil society: what threatens the unity and stability of the family is a source of dissension, disorder and injustice in the whole of social life.

Hence, it is clear that while the foundation for the Church's opposition to oocyte donation rests within the general objection to disrupting the "natural" framework of procreation within a conjugal relationship between a married couple by having the act of conception occur in vitro, the full force of the Church's position derives from concerns about damage to relationships: between husband and wife, between parents and children, and ultimately between family and society. It would be inaccurate to summarize the opposition of the Catholic Church to oocyte donation as a mere "offshoot" or "extension" of its general opposition to IVF; rather, the concept of oocyte donation represents a culmination of sorts of its discomfort with all assisted reproductive technology: In the view of the Church, DIVF not only removes human reproduction from its proper spiritual home and reduces procreation to an unnatural laboratory technique, it also spoils the very concepts of marriage and family by damaging those same relationships family building is intended to cultivate.

The robustness of the Vatican's opposition to IVF in general, and particularly to third-party reproduction, was reflected in the Medically Assisted Reproduction Law, also known as Law 40/2004, which was supported by the Church and despite vigorous opposition, was signed into law in Italy in 2004. Among the tight restrictions imposed on all assisted reproduction techniques (including a ban on treatment for patients who are not part of a heterosexual couple, prohibiting the fertilization of more than three oocytes at one time, and a requirement to transfer all available embryos, in conjunction with a ban on embryo cryopreservation) was a blanket prohibition on the use of third-party gametes. Supporters of the legislation viewed third-party reproduction as representing an "emotional and spiritual wedge between husband and wife both symbolized by and enacted in sexual infidelity" [4]. The specific harms this "wedge" might cause included [24]:

a) The risk of future incestuous relationships among children of anonymous donors
b) Damage to the personal identity of the child, because of lack of knowledge about biological origins
c) Parental rejection of the donor child, especially among infertile men who cannot claim biological paternity
d) The risk of positive eugenics – i.e., creating a child with sought-after characteristics of a donor

In 2009, the Italian Supreme Court deemed parts of Law 40/2004 unconstitutional, including the regulations regarding number of embryos to be transferred and the ban on embryo cryopreservation. But the prohibition on third-party reproduction was upheld, reflecting the force of the Church's opposition to the practice.

Case Study: DIVF and Islam

While adhering firmly to its ancient principles, Islam was actually among the first of the major organized religions to stake out a formal and explicit position on assisted reproduction in general and third-party reproduction in specific. This is undoubtedly a reflection of the overarching Islamic concept of *Shari'aa* law as not merely a set of rules that regulates overtly religious and ritual activities but rather a framework of instructions intended to guide all observant Muslims in the entirety of their everyday activities, including social, political, economic, and even medical pursuits [25]. While all *Shari'aas* are thought to reflect God's will, specific laws are derived from "primary sources" when available; these sources include the Qur'an (word of God as delivered to the prophet Muhammed), *sunna* and *hadith* ("customs" and "traditions" of Muhammed as authenticated by Islamic jurists), *ijma* ("consensus" of the community of believers), and *qias* ("analogy," application of past decisions/principles to new questions). When no reference can be found in the primary sources, Islamic clergy and scholars rely on "secondary sources," the most prominent of which is the process of interpretation, analogy, and personal reasoning known as *itjihad*. Contemporary Islamic authorities use this tool to produce a *fatwa*, or nonbinding religious judgment [26].

The first, and in some ways still most influential, *fatwa* on the subject of assisted reproduction was issued in 1980, just 2 years after Louise Brown's birth in Britain, by the Grand Shaykh of Al-Azhar University in Egypt. Al-Azhar was founded in 970 AD and is considered by most Muslims to be the center of religious thought and education in the Sunni Islamic world (approximately 80–90 % of the world's Muslim populations are Sunni).

The *fatwa* begins by emphasizing the priority placed in Islam on marriage and procreation: "Lineage and relationships of marriage are graces of Allah to mankind, highly appreciated, and they are the basis of judgment… Therefore, origin preservation is a most essential objective of Islamic law" [26]. It is no accident, however, that the importance of family building is framed in terms of "origin preservation"; this reflects the equally high priority being placed on the clarity and purity of "lineage and relationships," a concept broadly encompassed under the rubric of *qarabah* – literally "closeness" but perhaps best translated as "kinship" [27, 29]. Consistent with the principle of pronatalism but ever mindful of preserving lineage, the fatwa ultimately deems assisted reproduction permissible (even obligatory, when appropriate) when using the gametes of husband and wife, but third-party reproduction is strictly *haram* (forbidden). The *fatwa* states:

> If pregnancy cannot occur through normal body contact (intercourse) due to some illness, it is then permissible to impregnate a woman by her husband's sperm through medical assistance… If a trustworthy physician recommends in vitro fertilization and shall be responsible for its appropriateness, then it is permissible and obligatory as a treatment for a woman who has pregnancy impediments…
>
> If the husband is impotent, it is unlawful to have a stranger donate sperm. This consequently will confuse origins; furthermore, the method implies adultery… If an ovum is to be fertilized by a sperm from a man who is not her husband [i.e. donor oocyte], and the man's wife acts as surrogate, it is then considered adultery and confuses origins, and is unlawful [26].

This ban on third-party reproduction is predicated, therefore, on three major concerns [28]:

a) Reproduction outside of marriage is considered analogous to adultery (zina), with the resultant offspring considered laqith (illegitimate).
b) There is potential for future incestuous relationships among the offspring of anonymous donors.
c) More broadly, third-party reproduction destroys a child's lineage (nasab) and leads to a "mixture of relations," thereby hopelessly confusing issues of kinship, descent, and inheritance.

While many more minor *fatwas* addressing issues related to assisted reproduction have been issued subsequently, the general guidelines regarding the use of IVF and the prohibition of donor gametes outlined in this initial (and quite prescient, for its time) *fatwa* of the Grand Shaykh of Al-Azhar have essentially remained in force throughout the Sunni world to this day.

In stark contrast, however, the story has evolved quite differently in the Shia Muslim world, which includes much of Iran and Lebanon. Inhorn recounts the unfolding of this narrative quite dramatically [24]:

> The year 2000, however, was a watershed in Lebanon. At a Middle East Fertility Society meeting held in Beirut in late 1999, the audience of Middle Eastern practitioners was stunned when a group of Iranian female physicians, dressed in black chadors, described in great scientific detail the clinical outcomes of their egg donor programme. When questioned by the incredulous audience, these Iranian physicians explained that the Supreme Leader of the Islamic Republic of Iran, Ayatollah-al-Khamene'i, the hand-picked successor to Iran's Ayatollah Khomeini, had in 1999 issued a fatwa effectively permitting both egg and sperm donor technologies to be used…
> This millennial moment in Iran had an almost immediate impact… Starting with entrepreneurial Shia IVF physicians who cited the new Iranian guidelines, the local Lebanese clergy soon followed, issuing formal fatwas… about the permissibility of third-party reproductive assistance, especially egg donation, which most agreed was now halal, or religiously permitted.

As a consequence of these events, Shia Iran and multi-sectarian Lebanon are currently the only two Muslim countries where egg donation is permitted. It is also instructive to note that the text of Ayatollah-al-Khamene'i's groundbreaking *fatwa* explicitly states his justification for allowing the practice: preventing the "marital and psychological disputes" that would inevitably arise from the lack of treatment options for the couple's infertility. At the time, and to some extent still today, the idea that preservation of marriage is prioritized over preservation of lineage was as unprecedented and shocking to traditional Sunni clergy as it was a welcome relief to many infertile Shia Muslims [24].

It should be noted that even in Iran, third-party reproduction remains controversial and the religious (and therefore legal) climates are only relatively "permissive." The issue of sperm donation is particularly complicated. While Ayatollah-al-Khamene'i's *fatwa* did explicitly permit the use of both donor eggs and donor sperm, in order to distance the arrangement from any semblance of *zina* (adultery), many Shia clergy mandated the use of the mechanism known as *mut'a* – temporary marriage – between the donor and the infertile spouse. In the case of egg donation, the husband therefore becomes temporarily married to the (presumably single) egg donor; this relationship is permissible as a man is technically allowed to marry more than one woman. With regard to an infertile husband, however, the wife is not allowed to marry another man (even temporarily), and the sperm donation is thus excluded by way of technicality. This restriction was actually codified in Iranian legislation in 2003 [26]. Quite interestingly, however, embryo donation (i.e., donation of an embryo created by gametes from an infertile married couple) is indeed allowed, given the married status of the respective "sources" of the gametes. Therefore, while a man with an infertile wife may have the option of reproduction via egg donation with *mut'a* marriage (and thus can retain his biological connection to his offspring), a woman with an infertile husband has no such avenue available to her; her only option becomes embryo donation, thus requiring her to surrender a biological connection to the offspring despite (theoretically at least) her being completely "fertile" [30].

In sum, egg donation is largely prohibited in most of the Islamic world, which comprises populations with allegiance to Sunni traditions. The reasons for this prohibition include concerns regarding adultery, future unknowing incest among offspring, and general problems arising from the blurring of lineage. Followers of Shia Islam represent the major exception to this prohibition, as egg and embryo donation (but not sperm donation) are considered permissible. The complex interplay among multiple legitimate but competing priorities will no doubt continue to produce discussion and a continuing evolution in Islamic religious thought on this issue.

Case Study: DIVF and Judaism

In the biblical account of creation, the very first words God speaks to Adam and Eve convey the imperative to reproduce: "And the Lord blessed them, and the Lord said to them: Be fruitful and

multiply" [3]. Indeed, conversely, the Talmud dramatically illustrates the tragedy of infertility: "Any person who has no children is considered dead" [2, 33]. Consistent with the primacy of the mandate on procreation and continuity in the Jewish tradition, reproduction and family building have been prioritized for thousands of years. While faith in divine intervention is emphasized in traditional Jewish thought, seeking and obtaining high-quality medical care and/or necessary interventions is recognized as the "vehicle" through which divine assistance may be delivered, and observant Jews who struggle with infertility are generally strongly encouraged to seek treatment [31].

In light of the above, it may come as no surprise that among the earliest reports of pregnancies following ovum donation was a series reported by a group from Israel [34]; several of the patients described were apparently religiously observant, and the procedures were carried out with the permission of the Chief Rabbi of Israel [32]. Nevertheless, most of the traditional (i.e., orthodox) Jewish rabbinic authorities have been quite hesitant to endorse the legitimacy of the practice.

The main challenge in *halacha* (Jewish law, analogous to *Shari'aa*) with regard to egg donation is the question of maternal identity, that is, who is recognized as the mother of the offspring resulting from DIVF treatment? If available, a satisfying answer to this question would in turn help resolve the myriad related issues that DIVF raises for observant Jews, such as the following: Should the egg donor be Jewish in order for the child to be considered Jewish? Should the donor be single (i.e., unmarried) in order to avoid concerns for an adulterous reproductive relationship? Who are considered the offspring's relatives (this question has multiple implications, including prevention of future incest, adherence to laws of inheritance, and many other laws and rituals pertaining to familial relationships)? Perhaps more fundamentally, is the recipient actually fulfilling the *mitzvah* (divine commandment) to "be fruitful" altogether if procreation is achieved via another woman's gametes [31, 32]?

The primary difficulty in resolving the question of maternal identity in DIVF stems from the novelty of the concept in the Jewish tradition. Whereas the concept of artificial insemination is referenced, albeit tangentially, in multiple Talmudic sources, the very existence of a female gamete, let alone conception via a third-party oocyte, was generally not familiar to ancient rabbinic authorities [35]. Some commentators cite a Biblical interpretation [3] describing Dinah, daughter of Jacob, being conceived by Rachel but subsequently divinely "transferred" to the womb of her birth mother – Leah – as proof that the birth mother is the "true" mother; however, many rabbis deem this interpretation merely metaphorical (*midrash*) and therefore invalid as a *halachic* precedent [36].

Many prominent contemporary rabbis have formally considered the question of maternal identity, but little consensus can be found. The spectrum of legitimate expert rabbinic opinions on "who is the mother" ranges from the birth (gestational) mother to the genetic mother (i.e., the oocyte donor), to both mothers "sharing" the motherhood, and to the potentially disturbing opinion that a child born of DIVF, *halachically* speaking, has no mother at all [37]. While historically the preponderance of evidence and opinions have slightly favored the gestational mother as the *halachic* mother, more recently, for unclear reasons, the trend in rabbinic opinion now seems to be heading in the direction of the genetic mother as the "real" mother [37]. The depth of these differences of opinion, combined with the severity of the repercussions of an error in judgment, has actually led many leading contemporary rabbis, including Rabbi Mordechai Eliyahu, Rabbi Yosef Shalom Elyashiv, and Rabbi Shlomo Zalman Auerbach, to forbid the practice of DIVF altogether. Ultimately, there is no "bottom-line" Jewish position on DIVF; even from a purely *halachic* perspective, the particulars of any individual patient's situation may merit differential consideration. Couples are therefore encouraged to seek guidance from a trusted rabbinic authority before proceeding with treatment. Several Jewish community organizations, such as *ATIME*, *Puah*, and *Bonei Olam*, have been created in order to help facilitate this process with regard to DIVF and fertility treatment in general.

Conclusion

While it may fairly be observed that in many ways religion and assisted reproductive technology make strange bedfellows, there is no escaping the reality that they are bedfellows nonetheless. Indeed, the pursuit of family building and procreation in actuality makes allies out of modern science and ancient theology; as one commentator wrote: "Counterintuitive as it may be, a Gideon's Bible would not be out of place among the pornographic magazines in the Reproductive Medicine Unit men's room" [15]. In many ways, from the perspective of traditional religion, third-party reproduction represents the ultimate clash between the "natural" and the "unnatural," and specific views on any particular treatment will hinge on the priorities and weight assigned to the various considerations that are many times aligned as much as they are at odds with each other. Regardless, it seems reasonable to recommend that in order to provide high-quality care, ART providers, while relying on the support and guidance of appropriate religious leaders, should attempt to become familiar with and/or at least sensitive to the major religious issues that may arise in the course of their patients' treatment.

In this chapter, we have reviewed in some detail the views of three major religions on DIVF and touched briefly on how some of these positions have affected the political and legislative climate surrounding ART. The Catholic Church adamantly condemns DIVF not only as an extension of its general disapproval on in vitro human reproduction; rather, it views DIVF as a uniquely problematic entity representing an attack on the familial bonds of love and intimacy that drive most patients to seek fertility treatment in the first place. Islam's perspective on DIVF reflects a world divided: Sunni Muslims reject the practice with concerns for adultery, future incest, and a general confusion of kinship and lineage, whereas Shia Muslims, supported by their religious leadership, have come to embrace the practice (with quite a few caveats, limitations, and exceptions). Traditional Judaism, while overall among the most outspoken advocates for most fertility treatment, has wrestled for decades with the question of maternal identity in DIVF; the inability to reach consensus on the answer to this question has led many leading authorities to ban its practice altogether, even if in theory it involves no outright transgressions.

While the depth and breadth of religious scholarship addressing the relationship between traditional theology and assisted reproduction is quite impressive, even more daunting is the tendency for expert analysis to produce more questions and quandaries than satisfying answers. There is no doubt that patients seeking various treatments, and DIVF in particular, will wish to seek the collaborative involvement of spiritual advisors and clergy to work together with their physicians and other medical providers in order to help them reach their individual family-building goals.

Editor's Commentary

Given the precarious and oftentimes contentious relationship between theology and assisted reproduction, it is not surprising that egg and embryo donation has been the focus of much religious scrutiny and criticism. Throughout my years of practice, I have come to appreciate that social sensitivities to the method of egg donation are largely rooted in the conflicts that arise when third parties are introduced into conventional family paradigms. Whether one agrees with it or not, I think that it is fair to say that most of the conventional family images of a man, woman, and child are central to the core teaching of modern religions; and most modern religions are rooted in antiquity. To me, arguing with the proponents of religious teaching that are opposed to third-party reproduction, individuals that typically quote the scholarly work of countless numbers of wise men over thousands of years, is unlikely to accomplish much.

Josh Klein, M.D., notes that followers of strict orthodoxy in any of the major religions are not likely to endorse egg or embryo donation as an acceptable or moral form of reproduction. Yet, it is clear to those of us that practice medicine that many followers of a variety of faiths present themselves every day for advice and assistance in achieving pregnancy, including the use of third-party gametes. It is incumbent upon physicians to recognize the delicate nature of the choice and realize that in many cases patients may be grappling with a great deal of personal guilt as they struggle to make the right decision, and we should be sensitive to their need to take time in reaching the right conclusion.

There should never be a rush to perform egg or embryo donation. Although the therapeutic option may be biologically plausible, egg and embryo donation is often incongruent to the important spiritual and moral values of the individual patient. I have said many times, and to many people, that egg and embryo donation is not for everyone. However, I firmly believe that ultimately it is the right of each patient in consort with their physician to decide whether or not to have a family in this manner and not have that decision dictated to them by a religious authority.

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Ethical Issues in Oocyte and Embryo Donation

29

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Key Points

- Parties involved in the process of donation, which includes both donors and recipients, must understand and agree to the procedure and specifically to all uses of the donated gametes and embryos.
- The role of the donor must be fully described, and the primary parental role of the recipient receiving donor gametes and embryos must be fully defined and unequivocally accepted.
- The issue of payment for oocyte and embryo donation is extremely controversial and deserves close examination by all practicing professionals in the field of assisted reproduction.
- Protecting donors and recipients against all hazards may be impossible, but clinicians have a responsibility to endeavor to protect all parties from known hazards, particularly reproduction without consent.

In this chapter, six important areas of ethical concern for practitioners working in the area of oocyte and embryo donation are reviewed: (1) patient/donor relationships, (2) ethical limits on the amount and manner of payment, (3) ethical issues raised in the law concerning donation, (4) ethical issues in the preimplantation diagnosis of donor embryos, (5) controversy over the use of tissue from aborted fetuses and cadavers, and (6) the ethics of cryopreservation of eggs and embryos, including those retrieved from the deceased.

Throughout the chapter, we emphasize two primary ethical principles. First, no reproduction should occur without consent. All parties involved in the process of donation, donors, and recipients must understand and agree to the procedure and specifically to the uses of donated gametes and embryos. Although protecting donors against all hazards may be impossible, clinicians have a responsibility to endeavor to protect all parties from all known hazards, particularly reproduction without consent. Second, the donation of

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gametes and embryos must be appropriately compensated [1]. The donor of reproductive material must be compensated both at a level and in a manner consistent with the real risks involved in particular procedures, respect for the dignity of the donor, and in financial amounts that are reasonable for the expected use of the materials.

Patient/Donor Relationships

Concern has been expressed about the ethics of using gametes and embryos from donors whose identity is known to the recipient. There are two primary ethical issues: the need to make sure that the role of the donor is fully described and the need to be clear about the primary parental role of the couple receiving donor gametes and embryos.

Directed donation frequently takes place. The American Society for Reproductive Medicine (ASRM) recommends the use of anonymous donation for oocyte gamete recipients but notes that no data are available to show that problems arise with the use of known donors. Almost all programs endorse the use of known donors as well as anonymous donors [2]. Sauer and Paulson found that of 51 ovum donor programs, 53 % made available both anonymous and known donors, 29 % provided only anonymous donors, and 18 % used only known donors [3]. However, historically the majority of gamete materials have been obtained from anonymous or delinked donors. The American Society for Reproductive Medicine 1993 data indicate that 80 % of documented donors were anonymous.

Rosenberg and Epstein conducted a landmark study of donors to gauge medical and psychological reactions to the procedure of anonymous oocyte donation. Overall, most subjects felt "good knowing that a couple who otherwise might not ever have had the chance to be parents were given that chance because (they were given) eggs." But when asked to comment on the outcome of the procedure, many donor women expressed concerns. One donor had difficulty dealing with the possibility that "a woman could give birth to someone with half my genes." Others were concerned "that the parents (might turn out to be) the type of individuals who would be poor parents" [4].

Fifty percent of the anonymous donors had second thoughts about their participation due to general fears about costs to self, physical stress, and concerns about the future for offspring created with the eggs. One donor commented, "After I left that day I felt I'd never know what happened. It's just the wondering and not knowing anything at all." Another, expressing the former concern, asked, "What if my husband and I could not conceive a second child? What if that cycle was my last chance" [4]?

General emotional and physical stress can accompany donation in even routine situations, so it must be understood and monitored as a part of ethical donation practice. Donors focus on the requirement to refrain from intercourse, mood swings, and future menstrual cycles. Side effects of menotropin injections, including loss of appetite, tiredness, headaches, nausea, irritability, cramps, discharge, weight gain, breast swelling, and joint aches, may require more of donors than they expect. Similarly, GnRH-agonist (gonadotropin-releasing hormone) injections may cause sleepiness, dry mouth, hot flashes, mood swings, headaches, and irritability. After the procedure, donors may experience intense bloating. Each of these experiences may create confusing or mixed emotional signals for women in anonymous or directed donation and must be discussed openly prior to donation as well as at the onset of any side effects.

Divulging Information

With directed donors, recipients have the advantage of knowing the genetic makeup, disease history, appearance, and intelligence of the donor. Anonymous donors raise the issue of whether donors, recipients, and children born of donated genetic material *would* want to know about the other party and want the other party to know about them, and whether each party *should* have access to identifying or nonidentifying information about the other [5]. Thirty-three percent of

the donors in the first Finnish oocyte donation program believed that the resultant children from their donations should have access to identifying information concerning the donor, and half of the others agreed to revealing nonidentifying information to the offspring [6].

Such results, however, have been called into question. Broderick and Walker examined multiple studies addressing the issue of identifying donors, offspring, or reciprocal identification and concluded that it is difficult to ascertain whether these studies actually show a desire among donors to know children who are the product of a donation. None of the studies allowed donors and recipients the freedom to detail what they did and did not want to know and what they did and did not want made known, or how strongly they felt about this, nor did any of the studies consistently define identifying and nonidentifying information [5].

There is no consensus as to how much information should be given to recipients, offspring, or donors. In many US clinics, matches are made by doctors and nurses. Recipients are told some of the donors' physical characteristics and a few other nonidentifying facts. An attempt is made, generally, to allay recipients' fears that a donor could somehow find them and claim the child. Donors, it is presumed, do not want a stranger searching for them many years later for financial or emotional support.

By contrast, a few clinics in the USA, such as the Center for Surrogate Parenting and Egg Donation in Beverly Hills, allow couples to receive a dossier on the donor and her extended family, including photographs and her social security number, in case they ever need to contact her. The center urges donors and recipients to meet. Dr. Hilary Hanafin, of the Beverly Hills clinic, California, supports this system of what might be termed "open donation" because she feels that other clinics may intentionally leave out information in order to "dress up donors" in their desire to make a match [7].

Whether or not donors and recipients choose to divulge information, there is a key set of issues about which both should be aware. First, it is not possible to guarantee beyond a shadow of a doubt that legal protections will be strong enough to prevent contact between parties for all time. As tempting as such protections are to offer, clinicians must temper their need to secure agreements with a need to preserve privacy for a couple or donor who really does not want to participate if such a risk exists.

Moreover, while open arrangements offer some advantages to families and donors alike, the unconventional nature of such arrangements demands what can be termed "protracted consent," that is, a series of meetings with all parties to determine what the likely future needs and responsibilities in such an arrangement will be. The need for consent extends beyond legal and financial protections for the parties. There must also be, beyond the consent form itself, an attempt to counsel these future parents so that their awareness of the responsibilities is ascertained at a conversational level. The competing needs of all parties in donation situations demand a high level of surveillance and oversight and may require municipalities, professional organizations, and legislative bodies to think about supervising donation relationships in ways analogous to adoptive relationships. In the short term, ethical conduct at the level of the physician-patient relationship can go much further than regulations in ensuring good and appropriate outcomes, and only through foresight and planning can such relationships be ensured.

Payment

The issue of payment for oocyte or embryo donation is extremely controversial and deserves close examination by all practicing professionals in the field [8]. French bioethics law forbids in its general principles any payment for organ donation or parts or products of the human body. The Human Fertilization and Embryology Authority (HFEA) of the UK stated in its 1994 annual report the intention to reconsider phasing out payment of gamete donors [9]. In 1994, £15 plus reasonable expenses was the maximum payment allowed by law in the UK. In 1996, the HFEA moved to outlaw all forms of cash payments to brokers of oocyte donation [10].

The USA is still struggling over the issue of payment. In its 1993 guidelines for oocyte donation, the American Fertility Society declared that "donors should be compensated for the direct and indirect expenses associated with their participation, their inconvenience and time, and to some degree, for the risk and discomfort undertaken" [11] (p. 65). The guidelines make clear that payments are intended to compensate donors and not act as an inducement for offering their oocytes. However, in practice, some argue that this distinction is not persuasive [12].

Reimbursement costs have escalated over the years. Ten years ago, donors received roughly $250. By 1997, $2,500 was not uncommon. Is a tenfold increase really merited by increased costs, inflation, risks, or inconvenience to patients [1, 13]? One prominent practitioner commented that while attending the World Congress of IVF, he was impressed by the "almost unanimous criticism levelled at practitioners in the USA by colleagues abroad with respect to the payment of donors" [13] (p. 1150).

At issue, of course, is the more basic question of whether at some point donation might be construed as "selling" oocytes or embryos. Shenfield, for example, contends that if society intends to pay gamete donors, then the operational term *donation* should be changed to *sale* of gametes. This leads directly into the question of whether trading and buying organs and gametes is demeaning and an affront to the respect due to human beings [9]. Should society choose to pay donors, negative consequences could be the discouragement of a voluntary supply, increased risk of transmitting disease of donors motivated by gain and willing to falsify personal health information, and the potential exploitation of vulnerable socioeconomic groups [14].

Exploitation has already become a concern. The *New York Times* noted in the January 1996 series "The Fertility Market" that in the USA, fees of paid donors are rising as demand soars. Many journalists, politicians, and cultural critics are troubled by advertisements in college newspapers. While clinic rates range from $1,500 to $3,000, some potential recipients run their own advertisements offering to pay even more. For example, a common advertisement that runs in the *Harvard Crimson* requests a "Jewish ovum donor needed for infertile couple willing to pay fee of $3,500 plus expenses" [7]. Some experts believe that donors' motives have shifted from altruism to financial motives [7]. Rosenberg and Epstein asked anonymous donors what they did with the $2,000 they were paid. Thirty percent paid bills, 24 % paid college-related expenses, 15 % used the money to buy a car, and 15 % put the money into savings and used the rest for various expenses [4].

The motivations of donors can cloud the consent process [1]. A potential donor with serious debt problems and little income is not making the same decision as an affluent woman eager to make a gift to a couple she knows. A study by Greenfield et al. [15] compared directed and anonymous candidates for oocyte donation within a single program. There were marked differences in donor motivation between the two groups. Anonymous donors were paid $2,000, while the directed donors were not reimbursed. The motivations among the anonymous donors were sometimes financial. Directed donors were universally motivated by their relationship with the recipients. Many of these women would not have considered donating anonymously but wanted to help their sisters or friends have a baby [15]. It is crucial to ensure that patients whose motivation is financial and who are known to have such a motivation are made to understand fully the risks entailed by the procedure. Further, it is crucial to ascertain whether they truly understand the process in which they are participating.

The prominence of media accounts about the practice of payment reflects societal ambivalence about the mixture of money with gamete and embryo procurement [8]. Popular magazines such as *Redbook* have painted grim pictures of naive college girls needing cash and turning to what seems to be easy money. Barbara Nevins writes, for example, of one college student who had a credit card bill of $3,000, prompting her to contact a fertility clinic offering $1,500 for her eggs. "I didn't worry about the emotional things," she said [12]. Although these stories too often rely on anecdotal evidence, when considered

together, these anecdotes have painted a disturbing picture in the popular literature.

Concern also must be directed to the question of who should donate. Some would argue that college students and teenagers are too young to appreciate the consequences of donating or the risks they take to their health in doing so [7, 8]. They hold that without the experience of having their own children, donors cannot possibly understand the significance of letting someone else bear a child with their eggs [12].

Although no programs currently permit 14-year-old girls to donate eggs, no law exists to stop donation from adolescents who hold signed parental consent forms. Many programs do have an age limit of 21 years, although some accept women as young as 18 years of age. There is substantial controversy about how adolescence and young adulthood bear on informed consent [16].

Alternatives to Payment

A well-known alternative is that of oocyte sharing, the use (with or without compensation) of eggs harvested from one patient for the use of another. In the USA in 1992, at least 45 % of the clinics offered egg sharing within the context of the guidelines of the ASRM, which recommended reasonable compensation for egg donors. In Israel, egg sharing is the only acceptable form of donation permitted by law. In this scheme, women who wish to undergo in vitro fertilization (IVF) treatment may consider donating an agreed proportion of their oocytes to an unidentified recipient. In return, such women will themselves receive free or subsidized treatment. The HFEA actually set guidelines for prohibiting direct payment to donors but accepting the provision of lower cost or free IVF treatment to women in recognition of oocyte donation to anonymous recipients [10].

Ahuja and Simons note four advantages of shared egg donation: (1) egg sharing achieved in this way enables two infertile couples to benefit from a single surgical procedure; (2) infertile donors require hormonal treatment anyway for their own needs; (3) as the center is responsible for compatibility and anonymity, it acquires the medical and social histories of participants; and (4) disadvantaged groups who are denied help from the UK National Health Service benefit without recourse to financial inducements or direct personal transactions [10].

There are some disadvantages to egg sharing. The donor's success might possibly be compromised if her eggs are shared with a recipient. Conversely, the recipient, who pays for the treatment, might receive suboptimal oocytes because the donors are not necessarily multiparous women and of proven fertility [10]. However, studies such as the one by Ahuja et al. show that success rates with shared eggs are comparable to those obtained through other forms of donation [17].

There are also reports of rare oocyte donation programs that have proven successful offering absolutely no incentives. In a summary of 3 years' experience with a donor program at the University of Southern California, Sauer and Paulson reported the success of the program without a single advertisement. In the first year, patients in need of an oocyte donor were required to locate such an individual on their own and present her for formal screening. As cases accumulated, women wishing to become donors contacted the office directly and were screened. Without any advertisements, the oocyte donor program grew and allowed the clinic to build up a register that could be used for couples in search of donation services [18]. For purely altruistic motives, gainfully employed educated women were willing to experience the inconvenience of repeated cycles of ovarian stimulation and follicle aspiration in order to help another woman conceive. Women interested in becoming oocyte donors had usually thought through the process prior to entering the screening [18].

At the Infertility Clinic of the Family Federation of Finland in Helsinki, established in 1991, the donated oocytes originated from fertile volunteer women recruited through newspaper accounts based on information supplied by the clinics. Of 30 women, 21 were married, and almost all were professionally educated. All donors expressed the desire to help other people as their primary motive for donation. Most had experienced infertility problems among relatives

and close friends or in connection with their work. The findings indicate that with this type of recruitment method, it was possible to obtain a group of educated and mature donors who were highly motivated to help infertile women without the need for a financial reward. Seventy-eight percent of the donors said they would donate again if asked to do so. Not one of the women reported regretting their donation [6].

Legal Concerns

The 1993 guidelines for oocyte donation issued by the American Fertility Society state that clinics should issue documents "that state the commitment, on the part of the donor, to give up all rearing rights and duties in any offspring and on the part of the recipient, to take on all the rights and duties of the legal mother" [11]. Similarly, in India and the non-Muslim countries in Eastern Asia, a child conceived by gamete donation is treated, under the law, as the legitimate child of the recipients [19].

Misbehavior can lead to serious legal quandaries. Dr. Ricardo H. Asch, formerly of the University of California, Irvine, is alleged to have transferred to other patients eggs harvested from women who were unaware of their "donation." Records suggest that five patients' eggs were taken and given without their consent to other women. One 36-year-old woman said that Asch never asked her permission to give her eggs to other women. She is troubled by the idea that "I could have a child out there." One couple felt robbed of the opportunity to have more children: "If we had the additional eggs, we would have had that chance." Another woman whose eggs were allegedly taken said she dreams about the children born to another woman because in her mind they are her children and she wants to see them. The scandal raises profound legal questions. Who should have custody of the child if neither the genetic nor the birth mother was aware the eggs were stolen [20]?

Several lessons can be gleaned from the Asch affair. Many experts believe that reproductive technology is underregulated in the USA and some other nations [20–22]. At a minimum, those handling eggs and embryos must always secure the permission of those from whom they were obtained prior to use for research or procreation.

Preimplantation Diagnosis

Preimplantation diagnosis makes it possible to investigate the genetic makeup of an embryo produced by IVF so that embryos with unwanted genetic characteristics can then be destroyed and only "healthy embryos" implanted. It may be psychologically easier to destroy an eight-cell zygote than to undergo abortion Holm (1997), Ethical issues in preimplantation diagnosis.

Preimplantation testing involves the biopsy of single cells taken from preembryos formed in vitro. The relevant gene sequence is then amplified [23]. Technical problems do exist, and in most cases, preimplantation diagnosis should still be considered experimental. But the technology will likely improve, and already there is a demand for the technique, both in families with known genetic disease and for other purposes such as sex selection Holm, Ethical issues in preimplantation diagnosis.

Holm presents three groups of users likely to demand access to preimplantation diagnosis: (1) infertile couples in IVF treatment wanting to screen their embryos for chromosomal abnormalities prior to the transfer of the embryo to the woman's womb, (2) couples with a known risk of genetic disease wanting to avoid prenatal diagnosis and possibly abortion by having IVF and preimplantation diagnosis, and (3) couples wanting to choose a child of a specific kind, for instance, a child of a specific sex. Holm notes that two of the groups are not infertile, suggesting that the development of preimplantation diagnosis will create a redefinition of the purpose of IVF for treatment of infertility to a more general element of the possible procreational choices facing a couple wanting to have children Holm, Ethical issues in preimplantation diagnosis. McGee suggests that demand for preimplantation diagnosis is likely to grow as couples express reticence about aborting for some conditions that they would nonetheless prefer to eliminate in potential offspring [21].

Often suggested is that preimplantation diagnosis should be restricted to looking for serious or severe conditions. Some have supported the idea of creating a list of conditions for which preimplantation diagnosis will be available, as well as conditions for which it will be prohibited. However, establishing a dividing line between severe and nonsevere conditions is very difficult [21]. Whose assessment of severity should count? There are differences between the nature and validity of observations about disease severity made by the general population, politicians, physicians, persons with the condition, and prospective parents Holm, Ethical issues in preimplantation diagnosis.

A recurrent feature of preimplantation debates is the suspicion these techniques may be used to promote the selection or creation of children with certain characteristics that the parents prefer. Fears have been raised that the testing of genes might be one short step away from manipulating them and trying to alter characteristics having nothing to do with disease prevention [21, 24]. Such choices could be about the sex, height, eye color, hair color, intelligence, and sexual orientation of the child. Consensus points to restricting certain uses of the technique but not prohibiting all uses of preimplantation diagnosis Holm, Ethical issues in preimplantation diagnosis. Experts contend that limits should be placed on what sorts of traits should be tested for and possibly manipulated [21, 24].

Use of Ovarian Tissue from Aborted Fetuses and Deceased Women

Assuming that it will become possible to retrieve ovarian tissue from aborted human female fetuses and from deceased women and to grow human eggs from that tissue, would this be acceptable? Technical feasibility is not a reason, in itself, for doing such a thing. In 1994, the UK's HFEA produced a public consultation document addressing the issue of the use of donated ovarian tissue. The report stated that only 3 % of 8,946 respondents felt fetal ovaries and 5 % felt that cadavers would be acceptable sources of eggs for infertility treatment [25].

However, in 1994 Lyall et al. surveyed 1,210 women involved in family planning, infertility, and abortion clinics to gauge their views of the use of donated ovarian tissue. More than 89 % of the women thought that ways should be sought to increase the supply of eggs for research and treatment. Although live donors were found by 90 % of the women to be the most acceptable source, the majority of women supported the use of fetal eggs/tissue and the use of cadavers as a source of eggs for both treatment and research [26].

One reason for countenancing the use of tissue from aborted fetuses and dead women is the need for oocytes and ova both for use in research and in assisted conception techniques. However, those considering posthumous donation must be made fully aware of the implications of having their gametes procured.

Consent is a crucial element of reproduction. Aborted fetuses or persons who die without prior statements concerning their views about gamete or embryo procurement cannot give consent. Nor can minor children. In such circumstances, oocyte and embryo harvesting ought to be prohibited [27]. Even when consent is available, it is vital to examine the impact on a child of knowing that his or her mother was a dead woman. Follow-up is a requirement for any program using gametes obtained postmortem until sufficient information is obtained to allay concerns about the impact of such a practice on the well-being of children created by this means.

Cryopreservation of Eggs and Embryos

What is to be done with excess eggs and fertilized embryos being held in frozen storage? France has issued new laws declaring that a couple who stores embryos for future use should decide how they will be disposed of in situations where the couple ceases to pursue treatments. However, when confronted with disagreement of couples, a lack of explicit directives, or termination of a couple's union, the storage authority gains responsibility for appropriate action regarding frozen embryos [28]. In 1992 in France, a woman whose husband was killed in a car accident

requested that two embryos the couple had frozen be implanted. The physicians refused to comply with the widow's request, and the case went to court. In 1994, the court ultimately ruled the widow did not have a valid suit against the hospital, and thus she was not allowed to undergo the implantation procedure with her frozen embryos. On July 29, 1994, a law was passed in France prohibiting the transfer of embryos after a partner's death. This same law stipulates that storage must end if the embryos have not been used after 5 years [28].

Who has ultimate authority in deciding what is to be done with frozen-stored embryos and eggs? Salem and Novaes note that this dilemma is an outgrowth of the displacement of the reproductive act from the private sphere to a laboratory situation, which results in an increased complexity of the network of actors surrounding the issue. They claim we seem to be headed from a situation where there is unequivocal hierarchy between the woman, her partner, and the medical staff, with indisputable priority granted to the woman, toward another situation characterized by an assumed equivalence between gamete donors and physicians responsible for fertilization and impregnation. Deprived of its "natural" setting and traditional references to the woman's body, the embryo seems to be presently immersed in an ambiguous "no-(wo)man's land" with an increasing number of people who, for different reasons, feel responsible for its destiny [28].

Excess embryos from IVF programs make thousands of frozen embryos potentially available for donation. The growing demand for less expensive infertility treatments makes this option of embryo donation more likely to occur with greater frequency. Couples who have created embryos as part of their own IVE treatment may be willing to donate excess embryos to infertile couples. Couples who themselves have struggled with infertility undoubtedly feel great sympathy for couples in such a position [29].

The couple's willingness to donate will be strongly influenced by their attitudes toward embryos. A couple that views embryos as having the status of persons is likely to prefer donating the embryos rather than discarding them, storing them long term, or donating them to research. Clinics should inform IVF patients of the option to donate unwanted embryos. If consent is ignored or options are not presented, commercial embryo banks, akin to sperm banks, may develop to coordinate donation and placement of donor embryos and eggs [29].

Editor's Commentary

When I decided to write a second edition of *Principles of Oocyte and Embryo Donation*, it was apparent to me that so much had changed since the first edition was published that essentially it was as if commissioning a new text. It was 15 years ago that I asked Drs. McGee, Anchor, and Caplan to write a chapter on the ethics of egg and embryo donation. Of the 23 original chapters published in 1998, this is the only one that I chose to reprint in the new "updated" edition. Simply stated, that is because medical ethics really hasn't changed, and the points made by the authors back then are still poignant and very pertinent today and well worth restating.

Since its inception, there has been much controversy surrounding egg and embryo donation. Critics of the method, and there are quite a few, are not likely to go away. The "unnatural" and sensational conceptions made possible through assisted reproduction are probably most dramatically illustrated to the general public when egg donation has been employed. These would include births in seventy-year-old women, gestational carriers delivering babies for same-sex male couples, and "grandmothers" carrying the embryos of their children, to name just a few examples. Additionally, the payment of fees to young women providing eggs remains a divisive issue. And most recently, the payment of fees to egg donors enrolled in research protocols with the sole intent of procuring gametes for stem cell lines has sparked fierce debate involving members of the lay public and scientific community as to the ethics of "egg donation."

Are donors motivated by altruism or by greed? Are payments rendered fairly or are they outrageous enticements? Is the procedure safe or dangerous? Should parents tell their children or keep it a secret? The questions go on and on. I heard them asked in 1984, and I continue to hear them today, and as far as I'm concerned, they remain unanswerable.

Despite the challenges, I have always felt very comfortable with the ethics of egg and embryo donation. To me, the guiding principle goes back to something so simply and elegantly stated by Dr. Robert Edwards in the preface of the first edition of this book:

> Today, many voices are heard on ethics and law, and many countries have legislated strict or liberal laws in attempts to regulate every possible aspect of this field. My own opinion is that the ethics of care should be paramount and raised above many of the other issues… We must accept a fundamental truth—that virtually all of our patients are searching for happiness, and usually within a framework of love for a child and a partner.

Cognizant of the essential elements of medical ethics that include beneficence, nonmaleficence, autonomy, and justice, each request for egg donation must be carefully considered, and a judgment rendered. These decisions may not always be popular, but they should always be ethically defensible.

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30 Ethical Issues: Addressing the Sensational Cases and Analyzing the Clinical Practice

Andrea L. Kalfoglou and Glenn McGee

Key Points

- Oocyte and embryo donation have always been controversial because of public divisiveness regarding sensational cases and the social concerns that attend changes in conventional reproductive patterns, capacities, and roles.
- A growing body of empirical data is accumulating on issues, such as the potential psychological effects oocyte and embryo donation has on donors, families, and offspring, to further inform our ethical discussions.
- Values that govern medical practice must also be extended to women who are willing to donate oocytes.
- It is incumbent upon physicians to treat oocyte donors with as much care and respect as they normally extend to patients for whom their goal is to cure.

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Oocyte and embryo donation have long been lightning rods for controversy about assisted reproduction, both because of public divisiveness regarding sensational cases and because of the social concerns that attend changes in reproductive patterns, capacities, and roles. In particular, there is much discussion regarding the minimization of physical risks to oocyte donors, the iteration and development of consensus around what ought to be included in information provided to donors before they give consent to oocyte or embryo donation, and both whether and what children have a right to know about their genetic origins [1].

Among the most dramatic changes in the social perception of oocyte and embryo donation is the presence of a growing body of empirical data to shed light on issues such as potential psychological outcomes of oocyte and embryo donation for donors, families, and offspring [2–4] to inform our ethical discussions.

In the USA and many other countries, there is also now legal precedent and legislation that helps predetermine legal parentage and other potential disputes about oocyte and embryo donation as well as other forms of third-party reproduction.

Multiple professional associations like the American Society for Reproductive Medicine (ASRM) and European Society of Human Reproduction and Embryology (ESHRE) and not-for-profit organizations such as the National Research Council-Institute of Medicine (NAS-IOM), the California Institute of Regenerative Medicine advisory committee, New York Stem

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Cell Foundation ethics committee, New York Task Force on Life and the Law, the Nuffield Council, and UK's Human Fertilisation and Embryology Authority (HFEA) have provided guidance on many of the ethical and legal issues surrounding the donation of oocytes and embryos for reproductive and research purposes.

Across these three changes in the environment and institutions of assisted reproduction, five trends and technological advances have altered the ethics landscape for oocyte and embryo donation most recently.

First, the number of fresh oocyte donor cycles has more than doubled from 1997 (4,498 cycles) to 2010 (9,866 cycles), and the number of frozen embryo transfers with donor oocytes has increased fivefold (from 1,482 cycles in 1997 to 6,665 cycles in 2010) [5]. Fully 12 % of all IVF cycles in 2009 used donor oocytes [6]. This growth in the use of donor oocytes is due to the fact that regardless of age, cycles using fresh embryos from donor oocytes result in a live birth 47–52 % of the time, whereas fresh embryos using the intended mother's oocytes result in an average live birth rate of 30 % [5]. For women of advanced reproductive age who have virtually no chance of having a live birth using their own oocytes, the use of donor oocytes or embryos improves their odds of a live birth to that of most 20–30-year-olds.

Second, there has been an explosion in embryonic stem-cell research. In the late 1990s, although embryo research was occurring, it was mostly to improve the outcomes of assisted reproductive technologies in private clinics. Embryonic stem-cell research was in its infancy, and no one at that time could envision that the National Institutes of Health (NIH) would eventually fund embryonic stem-cell research. The development and growth of embryonic stem-cell research and the need for donors to supply gametes for research purposes have created additional demand for oocytes.

Third, a precedent-setting surrogacy case in California changed expectations about parental responsibilities in assisted reproductive activities and subsequent parentage, as a judge decided that a surrogate mother, pregnant with an embryo created from the intended parent's genetic material, was not the legal mother of the baby [7]. Because the intended parents were the gamete providers, they were awarded full custody of the resulting child. The judge referred to the woman who gestated the fetus as a "foster parent." As a result, many intended parents who use a surrogate mother believe there will be less maternal bonding and more support from the courts if the surrogate tries to keep the baby when the gestating woman does not provide the oocyte(s) that creates the fetus(es).

Fourth, the banking of reproductive material has expanded to include oocytes, in an environment where other banking and use is now better established. Sperm banks are routine. Embryos can be frozen, thawed, and transferred in later cycles, but success rates from previously frozen embryos were low until recent years. Oocyte freezing was purely experimental, and success rates – even in bench and preclinical research – were so low that it was not a viable option. A process called vitrification has radically improved the process of oocyte cryopreservation. This technological advance has changed the landscape of oocyte donation. Oocyte banks are increasing in number across the USA and the rest of the world claiming that cryopreserved oocytes are cheaper and faster to use than recruiting an oocyte donor and then cycling her with the recipient patient. Although many of the ethical issues related to oocyte banking are similar to sperm banking, this new technology has had little in the way of ethical analysis.

Similarly, though live birth success rates from frozen embryos are not as good as fresh embryos, they are climbing into the range of 35 % [5]. According to a 2002 RAND study, there were approximately 400,000 cryopreserved embryos in the USA [8]; however, fertility patients appear to be very reluctant to donate excess stored embryos to other couples for reproductive purposes [9, 10]. Fertility clinics and private companies have attempted to create embryo banks so that reproductive material is readily available to couples seeking fertility treatment; however, most of these ventures have been abandoned.

Fifth, an experimental technology that made a splash in the USA before the FDA shut down the

research in 2001 is now emerging in the UK. It has many names – cytoplasmic transfer, mitochondrial DNA transfer, maternal spindle transfer, and pronuclear transfer – but the research has two primary goals. In the UK clinical trials, the goal is to help a couple have a child that is free from mitochondrial disease; however, this is not the only target market for this technology. The larger market, should this technology prove safe and effective, is infertile women of advanced maternal age who want to have a child that shares their DNA. If this technology becomes widely available, it is possible that demand for oocyte donors will increase. It also creates new ethical questions because the resulting child will have genetic material from three rather than two individuals and the phenotype of the oocyte donor no longer matters. Like gestational surrogacy, oocytes could be obtained from women willing to accept much less in compensation, putting donors at increased risk of exploitation.

Across three technologies and five new kinds of problems, there are four important kinds of ethical concerns for practitioners working in the area of oocyte and embryo donation. These include the following: (1) Who gets to decide what happens to donor oocytes and embryos? (2) Who are the parents of children created from donor gametes? (3) Why are we still debating donor compensation? and (4) What new ethical dilemmas will we need to navigate as cytoplasmic transfer technologies improve?

Who Gets to Decide What Happens to Donor Oocytes and Embryos?

We have learned a great deal about how to improve the consent process for oocyte donors in the past 20 years. Research conducted by the New York State Task Force on Life and the Law [11] as well as at least one other study [7] have shown that donors were not always receiving all the necessary information they needed to make an informed decision about donating, and many were given no information about the potential uses of their oocytes. Should donors have a voice as to whom and how many people receive their oocytes for reproductive purposes? For instance, should a donor be able to specify that she only wants to donate to a Jewish, nonsmoking couple? We would not permit this with blood donation because it would feed into prejudice and racism, but is contributing to the creation of a child somehow different? Many donors feel a sense of stewardship over their reproductive potential and the children they help bring into the world; they want to know that the child will be raised by a loving family [12].

Because donors represent a resource that is in very high demand, they may have more power to make these kinds of requests than many donors realize. Some clinics are, in fact, willing to work within the constraints a donor places on her donation. If a clinic is unwilling to work with the donor, not only are there other clinics to choose from but some donors have turned to the Internet to appeal directly to infertile couples. In this open market, oocyte donors have negotiated higher compensation and more open relationships than what many clinics permit [12].

In clinics with anonymous donation programs, most donors are told that their oocytes will be used to attempt to create a child for a deserving couple. Does the clinic or oocyte donor organization have an ethical obligation to inform the donor if embryos created with her gametes are going to be transferred to a surrogate or used by a single person or same-sex couple? During the consent process, should the donor be asked about her wishes for the disposition of excess embryos? Or does her right to make decisions about what happens to her oocytes end when they are removed from her body or combined with sperm? Many different organizations and ethics committees have made recommendations regarding the donor's consent to the disposition of her oocytes [12], but the New York Task Force on Life and the Law's guide *Thinking about being an egg donor? Get the facts before you decide!* makes that group's then articulated consensus for New York's State Health Department clear: "Once you donate your eggs, their fate is entirely up to the recipient. You have no say about what happens" [13]. It could be argued that this view can be extrapolated to the point of universal ethical norm

and that medical professionals who are informing potential oocyte donors have an ethical obligation, at a minimum, to let women know all the potential used of donated oocytes and embryos created with their oocytes based on individual clinic policies (e.g., some clinics routinely split oocytes between recipients if a minimal number are harvested).

Oocyte banking is one of the newest trends in third-party reproduction. Oocyte banks claim that banked oocytes are cheaper and faster to produce for infertile couples than waiting to match cycles with an oocyte donor, and they can provide a wider selection of donors. Some offer money-back guarantees if the recipient does not get pregnant [14]. How does donating to an oocyte bank differ from donating to a specifically matched couple or individual? In this case, a business "owns" genetic material that can be used to create life rather than it being controlled by individuals who might have more of a personal sense of stewardship over these cells. Certainly, this has been the case with sperm banks for many decades. It is unclear that there will be any differences for oocyte banks, but as we are discovering, there are implications for them. First, with growing improvement in success rates for single or double embryo transfers, there is the possibility that a single stimulation cycle could result in multiple children born into one or multiple families. Children created from sperm donation are now using the Internet to find half-siblings and sperm donors. Europe is moving toward more openness in gamete donation. In fact, those who donate gametes after 2005 in the U.K. are required to provide identifying information [15]. For many oocyte donors, it is especially important to know whether a child was born and the sex and birth date of that child. As donors age and become parents themselves, some have persistent concerns that their own children could end up in an incestuous relationship with a half-sibling, and they believe having this information would be reassuring [12].

Banking oocytes is not as simple as banking sperm. Donors go through medical procedures including hormone injections and invasive surgery. Although there is no clinical evidence that donating leads to long-term medical problems, some of these women are likely to experience short-term problems [16]. Clinicians have an obligation to both adequately inform women undergoing a stimulated cycle and to provide follow-up care. Eventually, a former oocyte donor will experience infertility and may blame it on the oocyte donation. If her oocytes are still in storage, she may want her oocytes returned. Does the donor have the right to demand that they be returned to her if they are still available? Should she have to pay for her own gametes? Should she be entitled to free fertility treatment? What if the oocytes are now embryos stored by another patient?

With the advent of oocyte banks, women have begun using them to expand their own reproductive options. Extend Fertility was the first prominent company to begin offering personal oocyte banking services, but it now has much competition [17, 18]. The most obvious use of these services is to preserve future fertility among women and girls who are undergoing treatments like radiation for cancer where they may be left infertile, but women who intend to postpone childbearing until they find the right partner or meet their career goals may be the larger market for this service. Is this option empowering to women, or is it an opportunistic chance to play on women's fears in order to make money [19, 20]?

Society will be faced with many of the same questions that have arisen from banked sperm: Do others, such as spouses or parents, have the right to use the oocytes to attempt to create children or the right to donated banked oocytes to research in the event the woman dies? One can envision a situation where a 14-year-old child dies from cancer and her own mother, now premenopausal, wants to use her daughter's oocytes to attempt to give birth to her own granddaughter. Does it make a difference if the woman who has banked the oocytes has specified her desires regarding the disposition of her oocytes prior to her death? The ethics committee of the ASRM recommends that gametes only be used for posthumous reproduction when there is an advanced directive from the provider granting consent [21]. Knowledgeable ART providers will ask these kinds of questions at the time oocytes are banked to help deal with

these inevitable requests and legal petitions. In a 2004 document, ESHRE argued that when the donor is a child or adolescent, the stored gametes should be destroyed upon the death of that child or adolescent. In adults, if there is prior authorization to use sperm for reproductive purposes, it can be donated or used by a surviving spouse. In 2004, ESHRE felt that because stored ovarian tissue or oocytes were both too experimental and would require the use of a surrogate, use after death, even if the oocyte provider gave consent, should not be permitted [22]. The ASRM practice committee outlines the elements of informed consent for women wishing to cryopreserve oocytes for their own use and stresses that this is still an experimental procedure [23].

Because oocytes are such a valuable commodity for both reproductive and research purposes, perhaps we will learn how to harvest them – like organs – from young women who have died. Should society permit family members to harvest gametes in order to create children whose genetic mother is dead? We have plenty of examples where this is a natural reaction of grieving widows and parents who want to harvest sperm from dead men, and many institutions are now writing policies on how to handle these kinds of requests. Should gametes be treated like other organs of the body? If a woman has signed an organ donor card, or if her family agrees to organ donation, does this mean that ovaries are fair game for harvesting? What law should govern such protocols or should estate law be the paradigm for transfer? Or should society require explicit consent from potential organ donors because gametes' reproductive potential makes them much different than bone marrow or liver cells? Reviews of the literature show that oocyte donors do not think of oocytes the same way they think of the donation of other organs [24].

For the most part, as a matter of policy, clinics typically treat embryos created from donor gametes as the "property" of the intended recipient(s). When a couple decides they have completed their family and still have frozen embryos, it is often extremely difficult for them to make a decision about what to do with the frozen embryos [9, 25– 27]. There are three options for these leftover embryos: (1) Allow them to die and dispose of them, (2) donate them to others seeking fertility treatment, or (3) donate them for research purposes. When those making the donation decision are the providers of the gametes used to create the embryos, they still may wish to put restrictions on the types of research for which the embryos are used [28]. When embryos were initially created with donor oocytes, couples are more likely to donate rather than destroy excess embryos [29]. When the embryos were made from one or more donor gametes, there is no clear answer about whether or not gamete donors must be informed or provide their consent for options 2 and 3. It is possible to ask the oocyte donor, at the time of donation, whether she consents to having excess embryos donated for reproductive or research purposes, but is it ethically necessary to do so? This is not normal practice for sperm donation, and perhaps an oocyte donor's rights to determine the disposition of her oocytes end once they are fertilized. The National Research Council-Institute of Medicine (NRC-IOM) report states that for embryo research protocols, each of the gamete donors must provide explicit consent for that particular protocol [30]. This would mean that in order to donate excess embryos for research purposes, the oocyte donor would need to be recontacted, informed about the protocol, and provide consent. As a result, many studies using embryos recruit their own gamete donors because the NRC-IOM recommendation is unduly burdensome.

As well, new conflicts are arising as the result of third-party reproduction. For instance, what if a couple, who still has embryos in storage, divorces? Most courts in the USA have sided with the parent who does not want their embryos to be used to produce children, but what if the woman is no longer producing oocytes and the embryos are her only chance of having biological children? Should courts give the woman "custody" of those embryos but absolve the biological father from all parental responsibility? Of course, this still would not absolve the father from what society sees as a parental obligation that comes from the genetic relationship with the child. What if one or both of the gamete providers die while

embryos are in storage. Should other members of the family such as intimate partners or parents "inherit" the embryos? If there is documentation of the gamete providers' wishes for the disposition of the embryos in the case of death, should this trump family member's wishes or state legislation?

Fertility clinics and private companies have also attempted to create embryo banks so that reproductive material is readily available to couples seeking fertility treatment; however, it appears that all of these ventures in the USA have been abandoned. There is public discomfort with organizations "owning" and "selling" the seeds of human life [31–33]. Still, there is the possibility that embryo banks could become an accepted service provided by fertility clinics or private companies. Alternatively, couples who cannot contribute genetically to creating a child can now customize their child by selecting an oocyte and sperm donor. In any case, because obtaining oocytes requires the participation of a physician, physicians must ask themselves whether they are prepared to participate in providing this kind of service.

Who Are the Parents?

When the first child was born as the result of an embryo donation in 1984, the headlines of the *Los Angeles Times* read "Woman Delivers Donor's Baby." The headline made the assumption that genetics trumped both gestation and intention to parent in determining who the "real" mother was. With the advent of ART, there are potentially five different adults who can be involved in the creation of a child – the two providers of the genetic material, the adult(s) who raise the child, and the woman who gestates the fetus. Laws vary by state in terms of who is recognized as the legal parent(s) at various stages in the process, but usually there is a person or couple who are intending to raise the child. Advocates of fertility services have lobbied to change laws so that intended parents have legal parentage, but there are still debates about who are the rightful parents when disputes erupt.

Women and couples who avail themselves of oocyte donation and gestate the fetus typically do not have to be concerned about retaining custody. The fact that oocyte donation requires the participation of the medical community, compared to "do it yourself" sperm donation, creates an advantage for intended couples. In many cases, the recipients of the oocytes are completely anonymous to the donor. The donor is not even told if a child resulted from the donation. While clinics have claimed this is to prevent the donor from being concerned about her own fertility or feeling as though her efforts were in vain if a child is not born, the secrecy also serves to assuage any concerns that the recipients might have that the donor could attempt to become part of the child's life. There are no cases on record of oocyte donors attempting to fight for custody of children particularly when the gestating woman is also the intended mother.

Custody has only been disputed when oocytes or embryos from would-be intended parents have been mistakenly transferred into the wrong patient's uterus or intentionally misappropriated. Laboratory errors occur. Embryos were transferred into the wrong woman's uterus in Connecticut [34], Wales [35], Hong Kong [36], and Japan [37]. In the first three cases, the mistake was discovered immediately, and the women took the morning after pill to prevent the embryos from implanting. The woman in Japan was not informed until weeks into her pregnancy, and though there was actually a chance that the fetus was from her genetic material, she chose to abort the pregnancy [37].

In the most tragic case, a clinic in Ohio transferred the wrong embryos into Carolyn Savage's uterus in 2009 [38]. The clinic informed her of the error on the day they informed her she was pregnant. The clinic told her she had one of two options: Abort the fetus or carry the baby to term and permit the biological parents to adopt the child. As a deeply religious couple that believed life begins at conception, the Savages chose not to abort the fetus. Carolyn carried the fetus to term and gave the boy to his biological parents.

The ASRM has written an ethics statement to address medical errors. Although laboratories

have strict protocols to avoid mix-ups, humans make mistakes. The guidelines recommend that any medical errors be immediately disclosed to all parties affected by the error [39].

Perhaps the darkest events in the history of ART occurred at the University of California, Irvine's Center for Reproductive Health between the late 1980s and 1995. Two reproductive endocrinologists, Drs. Ricardo Asch and Jose Balmaceda, intentionally misappropriated fertility patients' oocytes and embryos and transferred them without consent into the uteri of other infertility patients, as well as provided embryos to embryo researchers. Once the misdeeds came to light, the two physicians fled the country, Asch to Mexico and Balmaceda to Chile, in order to avoid prosecution, where they continue to practice reproductive medicine to this day. The US government is still in the process of attempting to extradite them, but it is unclear as to what the actual criminal charges will be, since there were no specific laws covering gamete and embryo theft.

Medical records are sketchy, but it appears that approximately 15 children were born as the result of misappropriated embryos at the University of California, Irvine. Medical records show that Loretta Jorge was one of the women whose oocytes were used to create embryos and were transferred into another woman's uterus. The Jorges, who were never able to have their own biological children, know that another woman gave birth to twins using Loretta's eggs. The Jorges filed suit seeking custody of the children, but the recipients refused to allow a genetic test to determine whether the children were genetically related to the Jorges [40]. Similarly, medical records show that the embryos of Shirel and Steve Crawford were transferred into the uterus of another woman who gave birth in two separate pregnancies to a boy and a girl. The Crawfords hired a private detective to try and locate the children, who are now adults, but to no avail. They live with heartache believing they may never know their biological children. In all, UC, Irvine, has paid settlement claims for 137 separate incidents in which oocytes or embryos were either unaccounted for or given to other women without consent [41], and the decimation of this major reproductive medicine and research organization under the weight of scandal caused a collapse of faith in reproductive medicine among many in society.

Why Are We Still Debating Compensation to Donors?

Oocyte donation, like many ARTs, developed outside the traditional experimental process of most new therapies. In many fields, new technologies go through an extended experimental period that has some measure of oversight. If oocyte donation research had been funded by the National Institutes of Health (NIH) or was developed in a research facility that accepted federal funds, the protocols would have been reviewed by an institutional review board (IRB). Frequently, health participants in research protocols are compensated for their time, inconvenience, and the risk of participation. The practice of oocyte donation developed in a much different environment. When consent forms were used, there was evidence that the risks to oocyte donors were minimized when compared to the risks listed for the same process with fertility patients [11]. Rather than recruiting oocyte donors directly, many fertility centers relied on third parties to recruit, screen, pay, and *inform* oocyte donors. Donors described feeling less like patients and more like guinea pigs when they went in for the clinic visits [42].

As donors became more experienced and networked through the growth of online social networking, many of them realized that they could set the terms of their donation. Women began marketing themselves directly to infertile couples, and couples and brokers began recruiting primarily through college newspaper classified ads. Donors with particular phenotypic characteristics were in higher demand, and the market was all that controlled the compensation to donors. Offers of compensation as high as $100,000 made headlines [43]. Eventually, attempts were made to put limits on the compensation provided to oocyte donors. The ASRM issued an ethics committee statement that

compensation should be approximately $5,000 and making the claim that there is no justification for compensation of $10,000 [44], but demand to recruit the limited number of potential donors in certain communities like New York City drove these compensation rates to $10,000 and higher.

Much has been written about how selecting gametes based on the phenotype of the donor (along with a number of social traits such as education) is a step too far toward commodifying children. The concern is that there is still a great deal of uncertainty in the creation of a child, but when you put a dollar value on one, you begin to expect a certain quality for your investment [45, 46]. There are no guarantees with human reproduction. Much can happen when DNA from gametes combines, which is unpredictable.

Had oocyte donation developed within the same regulatory framework as research, with compensation amounts reviewed and approved by an IRB that were deemed to be fair but not coercive, it is unlikely that we would still be debating payment to donors almost three decades after the first birth from an oocyte donation. It is the complicity of the medical community with this market-based system of compensation that most critics object to. Additionally, if we pay a donor who is tall, with blonde hair and blue eyes, and a high IQ much more than we would pay a woman of color, this implies that babies with these characteristics are more valuable.

Other countries have taken a very different approach to compensating oocyte donors. In the UK, oocyte donor compensation is permitted only for donor expenses, though the HFEA recently increased the amount donors may be compensated [47]. The ESHRE ethics committee stated in its 2002 ethics guidelines that compensation for reproductive material is unethical [48]. Compensation for the donor's time and effort is acceptable; however, the compensation could not be high enough where it would be perceived as a profit or entice people who otherwise would not donate or cause them to withhold information that might be important for the safety of the donation. The committee argued that excessive compensation would undermine "the very notion of informed consent by the donor" [48].

An alternative model of compensation has developed particularly in the UK, where payments are limited, but also in the USA. Women undergoing IVF for their own infertility treatment are offered a reduction in treatment costs in exchange for donating some of their oocytes. These oocyte-sharing arrangements have garnered both praise and criticism [49–51]. The oocyte donor is not subjected to invasive medical treatments where there is no benefit to her as traditional oocyte donors are asked to do, fertility patients often produce more oocytes than are needed, and this arrangement appears to benefit both parties. Others have argued that this arrangement takes advantage of women who could not otherwise afford IVF because each donated oocyte potentially reduces her changes of obtaining a pregnancy. This may be less true today as success rates using fewer embryos per transfer are resulting in better success rates than a decade ago.

If reproductive oocyte donors are well compensated, equity would assume that donors for research purposes would also be well compensated. Similarly, couples who have stored embryos left over from fertility treatment might be expected to be able to recoup some of their investment by selling embryos to researchers. Oddly, in the USA, this is not the case. The committee that wrote the NRC-IOM report [30] recommended that individuals who donate gametes for research purposes not be compensated. Similarly, the ASRM ethics committee has recommended that fertility patients being offered the chance to donate embryos to research not be compensated [52]. Other prominent ethics advisory committees have come to the conclusion that donors ought to be compensated just like individuals who participate in research that has no therapeutic benefit [53–55]. Payment for gametes and embryos for research purposes has become a contentious issue [56–60]. On the one hand, there are those who argue that embryonic stem-cell research will be unable to proceed unless we are able to pay donors because there simply are not enough women who will go through all that is involved to donate altruistically [58]. On the other hand, there are great concerns that because the phenotype of the donor is no

longer important, women in other countries where the regulations and laws are less stringent will be coerced into donating for little compensation, contributing to a research agenda they and members of their community will never benefit from [56, 57].

Mitochondrial DNA from Donor Oocytes

There are two potential purposes for developing a technology that can combine the DNA of one woman's oocyte with the mitochondrial DNA of another woman's oocyte. The first is that it can permit a woman at risk of transmitting a mitochondrial DNA disorder to have a potentially healthy, genetically related child. The second purpose is that the technology might allow women of advanced maternal age to have genetically related children with the assistance of donor cytoplasm. There are three scientific procedures under study, and donor oocytes are required for all three.

The first technique is *cytoplasmic or ooplasmic transfer (CT)*. Researchers remove a fraction of the cytoplasm from the donor oocyte and inject it into the recipient's oocyte prior to or at the same time as fertilization.

The second technique is called *pronuclear transfer (PNT)*. IVF is performed using the intended parent's sperm and oocyte. Once the oocyte is fertilized, it contains the separate genetic material of the sperm and that of the oocyte cell each enclosed in a membrane. These are called the male and female pronuclei. The embryo also contains the mother's mitochondria, which originates from the cytoplasm in her oocyte. When the embryo is still a single undivided cell, the two pronuclei are removed from the single-celled zygote. A donor oocyte is then fertilized. At the same state of development, the two pronuclei within the donor's zygote are removed and discarded. The parent's pronuclei are then placed into the enucleated zygote. The reconstructed embryo cell now contains the pronuclear DNA from the intended parents and the mitochondria from the donor's oocyte.

The third technique is called *maternal spindle transfer (MST)*. Maternal spindle transfer (also known as "metaphase II spindle transfer") is a transfer technique that works on a similar principle to PNT. The main difference between the two techniques is that MST uses two unfertilized eggs to reconstruct an egg with healthy mitochondria that can then be fertilized.

The birth of the first baby using CT was announced in a letter to the editor of the Lancet by a US-based fertility clinic [61]. A year later, another clinic in the USA reported a live twin birth following CT from frozen donor oocytes [62]. In addition, a Chinese team of researchers reported live births (five healthy infants and three ongoing pregnancies in nine patients) after the injection of sperm and the cytoplasm of tripronucleate zygotes into metaphase II oocytes of patients with repeated implantation failure [63]. In 2001, the original US-based fertility clinic reported on 28 cases of CT. They claimed 12 clinical pregnancies and that there had been 30 live births worldwide following CT [64]. Later that year, the clinic admitted that, in addition to the 15 healthy live births, there were two additional fetuses with Turners Syndrome (one miscarried and the other was aborted) and one case of Pervasive Developmental Disorder [65]. Some of the children born after CT had mtDNA from both oocytes. This heteroplasmy of different variants of mitochondria has prompted safety concerns [64, 66]. Italian researchers report in 2001 the birth of healthy twins following CT [67].

In July of 2001, the US Food and Drug Administration (FDA) sent a letter to sponsors and researchers stating that they need an IND before continuing research into CT. The two primary US-based research institutes that are developing this technology continue conducting research on animal models and claim to be working with the FDA to establish an IND, so the research can continue. CT is not legal in the UK under the HFE Act because it alters an egg before it is transferred to a woman. There were media reports of US couples traveling abroad to seek CT after the ban, however, including the parents of a child who had been born following CT [68]. Indeed, at present, CT is offered with IVF in

many countries. For example, in 2011, reports from Chennai, India, noted the births of healthy twins after CT, which were reportedly the "first in Asia" [69], although this may not be the case. In 2012, commercial websites have listed clinics offering CT in India, North Cyprus, Ukraine, Armenia, Georgia, Israel, Turkey, Thailand, Singapore, Germany, and Austria [70].

Since the 1990s, experiments using PNT in mice have shown that reconstructed embryos continue to develop after pronuclear transfer. These experiments show promise that PNT might be an effective means of preventing mtDNA disorders. There are no reported live human births following PNT; however, at the 2003 meeting of the American Society for Reproductive Medicine, Dr. Jamie Grifo from New York University and his colleagues at Sun Yat-Sen University in Guangzhou, China, announced a triplet pregnancy following PNT [71]. The multiple gestation pregnancy was selectively reduced to twins. Unfortunately, some months later, the pregnancy ended in a miscarriage. PNT and MST research using animal [72] and human gametes that were not transferred to the uterus has continued in the UK [73]. CT is illegal in the UK because it is considered to be genetic modification.

The guiding principle for governance of all these technologies to date has been safety, a difficult bar to say the least. The Nuffield Council, an ethics board in the UK, declared PNT and MST to be ethical for the purpose of mitochondrial disease prevention if the technologies prove to be safe and effective [74]. It must be noted that the Nuffield Council is funded by the Wellcome Trust which also funds the Wellcome Centre for Mitochondrial Research at the University of Newcastle. The Human Fertilisation and Embryology Authority (HFEA) report recommended that before PNT and MST could be used in treatment, specific safety must first be established [75].

Safety of these technologies is also the principle focus of the US FDA and the UK HFEA, two organizations that have taken essentially opposite approaches to governance of new reproductive technologies to date. Both maintain that if these technologies can be developed to the point where safety and efficacy can be established, the next ethical question is whether these technologies may amount to germ-line genetic modification [76]. The media has focused on the notion that the child born from these technologies will have "three genetic parents" [77]. While this technically may be true, it will only express the DNA of two parents. The third would only contribute mtDNA which does not influence the phenotype of the child. But, what are the implications of intervening with mtDNA both physically and psychologically? Physicians engaged in this research ought to keep databases of these children so that long-term follow-up studies can be conducted. Finally, like oocyte donation for research, the phenotype of the donor does not matter with these technologies. Unlike reproductive donors who are carefully selected for characteristics and traits that tend to make the women less likely to be exploited (presumable college-aged women can read and comprehend a consent form, have the financial means to support themselves, and access to the Internet where they can research and talk to other former oocyte donors), the DNA of oocyte donors for CT, PNT, or MST does not matter. It would be very easy to outsource, obtaining this commodity to India in much the same way we see happening currently with gestational carrier surrogates [78].

Physicians engaged in oocyte and embryo donation must bear a measure of responsibility for what is taking place in their own clinics and also for knowledge of and ability to relay to patients the current national and international trends. The physician/nurse-patient relationship is grounded in trust. Just as laboratory procedures that are anything but meticulous can lead to lifelong heartache, caregivers must rigorously study those guidelines provided by the ASRM and ESHRE and identify best practices for recruiting, counseling, and informing potential oocyte and embryo donors in order to minimize potential harm. Values that govern medical practice must also be extended to women who are willing to donate oocytes. Although there is an inherent conflict of interest in the doctor/nurse-donor relationship [79], it is incumbent upon the physician to treat patients who merely act as donors

with as much care and respect as physicians would give the patients for whom their goal is to cure. This includes providing adequate follow-up care and even engaging in follow-up research to determine the long-term risks of oocyte donation and also means being aware of trends in society that could lead to the exploitation of economically disadvantaged donors [80]. Physicians will likely be held responsible for their participation in the use, for example, of gametes and embryos obtained from banks or international organizations, that is, to ensure that they are reputable organizations in full compliance with standards designed to protect both the donors and recipients of genetic material.

Editor's Commentary

Public debate over the ethics of assisted reproduction occurred long before the birth of Louise Brown, and it continues to draw interest. Of course this is not surprising, as it is deserving of such attention. After all, our field of medicine abuts with religion, law, and ethics, and we deal with the most primal elements of life. There will never be a unanimous decision reached on the majority of our basic tenets, but that does not mean that we cannot reach a reasonable consensus opinion on many, if not most, of our challenging issues.

Drs. Kalfoglou and McGee focus on contemporary issues that have been spotlighted in the media. This chapter serves as a nice companion piece to the earlier commentary on ethics written for the 1st edition of the book. Some of the newer controversies have been generated as a result of the natural evolution of egg and embryo donation over time. For instance, it was questionably ethical to pay egg donors $250 to participate in "research" in 1984 at UCLA; it is certainly more reasonable to question the payment at today's rate of $8,000 per cycle. Egg banking, a technique which will likely revolutionize the manner in which we store and utilize donor eggs in the future, ushers in a whole new set of circumstantial dilemmas, including posthumous use of stored gametes. Extending services to single menopausal women, gay men using gestational carriers, or other less than traditional recipients has become increasingly commonplace and yet far from accepted standard of practice, at least in many parts of the world.

I believe that we need to be particularly aware of the general public's social sensitivities. As a field of medicine, we have come very far, very fast. Our general charge is to enhance the quality of a woman's life by making her a mother, and yet our techniques, including those developed using egg donation, may now produce children who by design will never know their genetic parents. Certainly there exists a chorus of voices opposed to such actions, and therefore we need to be methodically focused on assuring ourselves, and the public, that the actions we take "do no harm." Harm in this case means not only to the individual but to society at large.

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