Medical, Social, Legal, and Religious Aspects of Genetic Donation

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Introduction

Sperm, oocyte, and embryo donation are an integral part of the management of infertility when the existing technologies cannot resolve the basic biological problem. Donor insemination is the oldest modern treatment for male infertility and was introduced at the beginning of the twentieth century. Oocyte donation became available once ovarian stimulation became an integral part of assisted reproduction, resulting in surplus oocytes which can be donated to women of advanced age or with an inadequate ovarian reserve. These reproductive options, separately or joined in the form of combined gamete or embryo donations, are a remedy for childlessness, especially in an era of rising maternal age and single parenting. These donations are also significant in the aspect of genetic material donation, which the medical profession and society should consider not only from the interest of the infertile women or couple but also examining the interests of the offspring.

Oocyte Donation

Women of advanced age can conceive and deliver following the transfer of embryos originating from young donor oocytes. Case reports of deliveries in women well over 60 have been reported in peer-reviewed literature and also in popular media [1–4]. Since aging of the uterus is slower than that of the ovaries, the successful

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J. G. Schenker et al. (eds.), *Hot Topics in Human Reproduction*, Reproductive Medicine for Clinicians 3, https://doi.org/10.1007/978-3-031-24903-7_12

implantation of embryos from young donor oocytes into the uteri of perimenopausal and menopausal women is readily accomplished [5, 6]. Embryo implantation is scarcely affected by the endometrial age, and therefore oocyte donation in women of advanced age is as successful in achieving pregnancies and live births as is assisted reproduction in the donors' age group [7]. The uterus retains its receptivity to embryo implantation for a substantial period of time after the ovarian germ cell reserve diminishes, as long as adequate endogenous or exogenous hormonal support exists or is provided. As a consequence, women of very advanced age, even up to the seventh decade of life, are able to conceive, carry pregnancies, and deliver live-born babies to whom they are not genetically related. With the increase in maternal age in developed countries, the number of women contemplating and achieving pregnancies of non-genetic offspring at an age previously considered adequate for grandparenthood is constantly rising.

The medically and ethically adequate availability of oocytes from young donors is the basis for peri- and post-menopausal pregnancies and deliveries. Donor oocytes are used in cases of advanced maternal age and premature ovarian insufficiency, low ovarian reserve, disorders inherited through the mitochondrial DNA, or other maternally inherited disorders in which pre-gestational testing is not feasible. Donor oocytes were historically obtained initially from IVF patients donating surplus oocytes, but currently, most donor oocytes originate from financially compensated volunteers who are termed "donors" despite being paid. The embryos originating from donor oocytes can be transferred fresh if the recipient is synchronized with the donor or cryopreserved and transferred in a different cycle [8]. The latter alternative also facilitates cross border traffic of donor oocytes, fertilized or unfertilized, from countries in which the compensated donors live to the recipients' place of residence.

In menopausal recipients, artificial endometrial preparation with exogenous estrogens followed by addition of progesterone, in a manner similar to artificial cycle for frozen-thawed embryo transfer, is required [5]. After pregnancy is confirmed, the endometrial support administration should be continued until placental autonomy occurs. In cases where ovarian activity still exists, embryos can be transferred based on the endogenous ovarian cycle. The average reported global ongoing pregnancy and delivery rate is currently approximately 50% per transfer [9].

The oocytes are aspirated from paid volunteers compensated for their "expenses." Candidates must be younger than 35, healthy and free of contaminants transmitted through body fluids, such as hepatitis viruses, HIV, or syphilis. They are screened for autosomal and X-linked hereditary disorders, as well as for structural chromosomal rearrangements. Broader screening of recessive traits, including several hundred inherited disorders, is currently under endorsement by quite a few oocyte donation programs in order to minimize the genetic risk associated with this procedure. Those who volunteer to donate oocytes for others undergo moderate ovarian stimulation, because excessive stimulation, in addition to being unsafe for the donor, is also detrimental to the quality of the oocytes. The standard stimulation protocol for oocyte donors is the antagonist protocol with a GnRH agonist, and not hCG, used for triggering oocyte maturation [10]. This approach has a high oocyte yield

and maturity rate, in addition to effectively protecting the donor from early ovarian hyper-stimulation syndrome. The implantation, clinical pregnancy, and live birth rates are unaffected when embryos from oocytes obtained with a GnRH agonist trigger are transferred to the uteri of separately prepared recipients.

Medical Complications in Recipients of Donor Oocytes

In countries in which oocyte donation from designated compensated volunteers is performed, relevant legislation or directives exist, set to protect the health, rights, and anonymity of the volunteers [11] and minimize the health hazards to which they are exposed. On the other hand, there is a relative paucity of regulations, other than a maximal age limit, concerning the management of the recipients, most of them women of advanced age. The medical pregestational evaluation required for ascertaining the suitability of these women for pregnancy and delivery is not rigorously defined despite the significant hazards that pregnancy might impose on them. Thus, while the use of oocytes from young (paid) volunteers reduces the fetal genetic hereditary and non-hereditary risk, it is quite well-established that pregnancy in the older population potentially constitutes a major maternal-fetal health risk during pregnancy.

The respiratory, hemodynamic, renal, and endocrinologic changes in pregnancy are a stressful event in young women. The cardiac output gradually increases to 140% of the baseline value and transiently even more than that during labor. At advanced age, the adaptation capacity of the cardiovascular system might be impaired, even in apparently healthy patients. The pulmonary respiratory volumes and effort, as well as the renal glomerular filtration rate, rise significantly during pregnancy [12]. Additionally, occult hypertension, heart diseases, diabetes, chronic lung diseases, renal diseases, and other conditions might exist at an advanced age [13, 14], jeopardizing the health of the mother and fetus, up to the point necessitating premature termination of the pregnancy. Age is also a risk factor for the occurrence of gestational trophoblastic diseases, fibroids, and urinary tract infections that might complicate pregnancies as well [15–17].

Setting up an age limit for conception attempts and determining the medical evaluation required for the candidates in order to go through pregnancy safely is under constant discussion.

The prevalence of pregnancy-induced or exacerbated hypertension, preeclampsia, impaired glucose tolerance, and frank diabetes are all in correlation with age [13, 18]. Moreover, in women over 50, the occurrence of these conditions is even more elevated in comparison to the 40–49 years age group [14]. These observations have been confirmed by other studies, reaching a peak of 63% for risk for any complication requiring hospitalization [18–20]. In singleton live births of women over 45, the risk for preeclampsia in oocyte donation recipients was 12.6% compared to 1.1% in spontaneous pregnancies at the same age. In contrast to natural conceptions, the preeclampsia risk in oocyte donation recipients over 45 was constant and was unaffected by previous parity [21].

Age is also an independent risk factor for placental abruption and malpresentation (placenta previa) [16, 18], probably as a result of uterine microvasculature changes [22]. In the case of multi-fetal gestations—a common result of assisted reproduction—the prevalence of hypertensive and placental complications is even higher [19]. Additionally, the likelihood of preterm labor or complications necessitating premature delivery is also increased with maternal aging [2, 14, 18–20, 23, 24]. The risk of preterm deliveries and low birth weight is significantly increased over age 50 for all types of gestations—multiples and singletons [19]. Therefore, taking into consideration the high success rates of assisted reproduction with young donor oocytes on the one hand, and the very high-risk that multifetal gestation bears at an advanced age on the other, a mandatory single embryo transfer policy is strongly recommended under these circumstances.

Direct and indirect maternal mortality also correlate with age. In developed countries, the primary reasons for such tragedies are mainly exacerbations of preexisting medical conditions or the occurrence of dramatic severe preeclampsia, placental abruption, postpartum hemorrhage, and thromboembolic events [25]. The almost universal performance of cesarean sections for delivering women of advanced age who conceived through oocyte donation does not contribute to the maternal mortality [2]. Sporadic maternal deaths of oocyte recipients of advanced age were reported [25], but underreporting of such cases can be assumed. Nevertheless, even at advanced age, maternal mortality is still a rare event in developed countries in which up-to-date prenatal care is available. Although the relative risk of maternal mortality at advanced age is increased, the absolute risk with proper screening and adequate antenatal care is still very low. After adequate screening of a healthy population, the maternal morbidity and mortality is low enough not to ban oocyte donation and pregnancy at an advanced maternal age [26]. With proper maternal-fetal antenatal care, both the maternal and neonatal outcomes are reasonably good.

The Neonate at Advanced Maternal/Parental Age

While the use of oocytes from young donors reduces the fetal aneuploidy and malformation risk expected in the advanced maternal age group [7], the prevalence of obstetrical complications such as low birth weight, prematurity, and stillbirths is increased in neonates of mothers of advanced age [2, 7, 14, 23, 27, 28]. This is the result of the increased prevalence of complications necessitating pre-term delivery, such as pre-term labor and abnormal placental function. On the other hand, the prevalence of low Apgar scores, neonatal asphyxia, and metabolic acidosis is not increased in comparison to younger women [18, 23].

The long-term psychological and social impact of being the child of an elderly mother, father, or parents varies greatly between countries, populations, and societies, in accordance with culture, social norms, life expectancy, and quality of life at

the advanced age. Opponents to pregnancies in older women or parents reason this position based on the interest and welfare of the future offspring, thus implying that older individuals might be or are less suitable parents [29], based on a greater generation gap, growing up without grandparents, or parental age-associated medical morbidities and a shorter life expectancy [30]. On the other hand, older people are more mature and experienced than younger ones and have more free time, as well as emotional and material resources to nurture children. The deep-seated desire for an offspring might be of more benefit than harm to the child [31]. Taking all these into consideration, it is reasonable to assume that in societies with a longer healthy life expectancy, advanced parental age has little if any negative impact on the offspring.

Sperm Donation

IVF and intracytoplasmatic sperm injection (ICSI), especially in combination with testicular sperm retrieval procedures, facilitate genetic parenthood for a vast majority of couples with male factor infertility [32]. Still, donor sperm is a treatment modality for severe male infertility, either as a first line or second line of treatment, when exploration for testicular sperm in azoospermic men failed or if the fertilizing capacity of the available partner spermatozoa is reduced. Sperm donations are also used by women without a male partner or with a trans male partner [33].

The most prevalent form of sperm donation is an anonymous donation through a sperm bank service, and limitations do exist in different countries concerning the number of recipients one sperm donor can donate to. Directed donations in which sperm is donated by an individual to a particular female recipient who is familiar (but not intimate) with him, without bearing paternal duties, are accepted in some countries. Sperm donors are compensated volunteers of the local legal consent age, who have a normal spermatogram. They are screened meticulously for physical and mental health conditions, genetic conditions, and carriership of occult infectious agents such as HIV, hepatitis B and C, and syphilis. Once a donor is enrolled, a 3–6-month quarantine period before the sperm can be used is warranted in order to ensure that repeated serology is negative, ruling out an infection that might have been present when the sperm sample was provided. Fresh sperm donations are currently outside the standard medical practice because the risk of transmitting infectious agents cannot be eliminated without a proper quarantine period [33].

Donated sperm can be used for artificial insemination (AID) or for IVF. The outcome of the treatment depends on its type, the patients age, and other patient data, not on the sperm used. In a meta-analysis of the clinical outcomes of sperm donation including eight studies, donor sperm neonates were not at increased risk of being born with low birth weight, preterm, or with increased incidences of birth defects, than were spontaneously conceived neonates [34].

Ethical and Legal Considerations

The principal ethical considerations regarding gamete donation are protection of the donors' (male and female), recipients', and offspring privacy, as well as the medical safety of the oocyte donors and recipients. While the latter are mainly medical issues previously discussed, the privacy dilemma is a major ethical consideration. The other ethical and legal dilemma is the financial compensation of those who volunteer to donate their gametes and the complicated issue of embryo donation.

Gamete donors can be either anonymous or known to the couple, partially or fully [33]. In most countries the anonymity of the donors is preserved. Traditionally, sperm donation was mostly clandestine and was not accepted as a social and marital norm. Donor insemination was considered in some societies as being illegitimate or constituting adultery. Secrecy was also in the male partners' interest since it protected him from the social stigma of sterility, associated with male dysfunction in many cultures. Since female infertility is more acceptable and described in different, older scripts, cases of oocyte donation in which the conception results from assisted reproduction are more socially acceptable even in traditional, conservative societies. Nevertheless, in most countries both sperm and oocyte donor anonymity are protected by law for the following reasons:

1. Donors' concerns about legal and social parenthood liability if their identity is disclosed might preclude gamete donation altogether.
2. Protection of the future privacy of the donors and especially their future families.
3. Prevention of social embarrassment for the recipients.
4. Prevention of parental confusion among gamete donations' offspring.

On the other hand, several universal and particular arguments for identifying gamete donors were raised, especially for the potential psychological benefit of the offspring. The main ones are:

1. Truthful disclosure as a universal value that outweighs accidental discovery based on physical discrepancy or blood type mismatch.
2. The individual's universal basic right to explore and uncover his/her biological identity, ancestors, and origin.
3. Equality with the offspring of spontaneous gestations who are familiar with their biological parents.
4. The relevance of the donors' evolving medical history to the health of the offspring.
5. Prevention of accidental consanguinity in the next generation.

It is interesting that despite these arguments, even where the disclosure of donor identity is the legal norm, most children that were conceived by sperm donation are not interested in this disclosure [35]. The bottom line is that consideration for protecting the donors and parents overcomes any considerations for protecting the rights of future, but presently unborn, offspring. If the theoretical rights of the latter

were the dominant consideration, then gamete donations would be reduced to scarce or even null numbers in many countries. Some programs offer a form of compromise between absolute anonymity and full disclosure in the form of partial disclosure. This includes a variety of details regarding the physical appearance and biography of the gamete donor, hobbies, personality traits, and even exposure of the recipients to childhood and recent photos of the donor. In this manner a feeling of acquaintance is achieved without revealing the donor's identity.

Payment for Donation of Genetic Material

Most international ethical committees are against financial compensation for individuals who volunteer to donate their gametes to others. On the other hand, financial compensation is a serious drive for gamete donation. Local regulations in different countries provide a solution to this dilemma by authorizing compensation for the "time and expenses" of the volunteer and not for the gametes [33, 36]. Obviously, such payment would be lower for sperm donation than for oocyte donation. Ideally, there are almost no donor expenses in donating sperm, so it should be donated altruistically, and payment should not be the main motivation for donation [37]. Unfortunately, this is not the case in most of the world, and sperm donors are compensated in a financially attractive manner. In most countries, donor sperm for IUI or IVF is not covered by the public health system and the cost of the sperm donation is paid by the patient.

Oocyte donation is associated with a substantial donor effort, time input, and risk in undergoing ovarian stimulation and oocyte pick up, so an adequate compensation is warranted.

The Voluntary Licensing Authority for Human in Vitro Fertilization and Embryology in the United Kingdom has decided to allow centers to offer free procedures in return for donated eggs. Some centers offer a free IVF cycle treatment as compensation for excess egg donation. The American Society for Reproductive Medicine guidelines state that the donor should be compensated for direct and indirect expenses associated with their participation, inconvenience, and time and, to some degree, for the risk and discomfort undertaken. Payment should not be predicated on the number of oocytes donated and should not be the primary incentive for the donation [33]. Nevertheless, despite this statement, in the United States, a sum as high USD 8000 is paid to oocyte donors [38], much higher than one would expect as compensation for expenses.

Embryo Donation

With the introduction of cryopreservation as a routine practice in IVF, there is an excess of stored surplus embryos up to the point of a cryostorage space crisis. Donation of these embryos to patients or couples in need is an appealing idea, but raises substantial ethical and legal problems:

1. Who is the owner of undesired human cryopreserved embryos?
2. Can human embryos be sold or bought just as gametes are?
3. Who controls the disposition of the stored embryos in case of death of both or one of the progenitors or in the case of divorce?

The answers to those questions were provided by several ethical committees and legislators regulating ART. The legal status of the human embryo in cryostorage is difficult to establish. A cryopreserved embryo is not considered a human being for the purpose of criminal law. On the other hand, the cryopreserved embryo is not property. If a dispute arises between the couple who provided the sperm and oocyte from which the embryo was formed about its disposition, the embryo will remain cryopreserved until a legal or judicial decision has been reached.

Documentation and Registration

There is a consensus among medical professionals that keeping accurate medical records is essential. Record keeping has always been an important part of both medical practice and of quality assurance. In cases of gamete donation, it is also crucial for follow-up of the parties involved. It raises particularly difficult ethical and legal questions with regard to medical confidentiality and family privacy. The right to privacy is a fundamental human right. In the context of medical information that is personal and intimate, the concern for respect for the privacy of the participants is paramount. Truth-telling and candidness are values to be respected in the communication between physician and patient, and in the case of gametes and pre-embryo donation, it may be considered in the relationship between the physician, the donor, and the recipient. Candidness with the family after the birth of a child as to the method of his conception, or later as to the identity of the donor, is of a different nature. Society's (or the state's) intervention in the privacy and intimacy of the familial relationship, in order to force a greater openness, could be an invasion of the freedom of procreation decision-making that extends beyond the legitimate concern for the quality of services and for proper follow-up of the offspring. Registration and regulations in different countries, where gametes and pre-embryo donation are practiced, take into consideration the nature of the information to be maintained about the parties involved in the gametes and pre-embryo donation program. Thus, a distinction has been drawn between non-identifying and identifying information. The non-identifying information includes:

(a) Detailed description of physical characteristics, ethnic origin, etc.
(b) Medical history and genetic background.
(c) Social characteristics: education, profession, habits, interests, etc.

When identifying information is required, it will include full names, addresses, dates, and places of birth, as well as the IDs of the parties involved.

The responsibility for the collection of information should lie with the physician performing each stage of the donation procedure. There are different opinions regarding the storage of information: Where should it be kept? Who should have access to it? What kind of information should be released to the parties involved in the program?

In most countries where genetic material donation is practiced, the records of identifying and non-identifying information are kept and maintained by the physicians or medical institutions according to the regulations of the particular country. In some countries, it was suggested that the identifying information of the parties involved should be stored in the Central Government Registry. The advantages of a central state registry are:

(a) The information can be safely kept for long periods.
(b) There is a protected central control on the release of information.
(c) A central computerized national register may provide control over the number of donations made by each donor.
(d) It is of importance to restrict to a minimum the personnel who have access to this information.

Identifying material may be released in extreme situations according to the legislation in a specific country. The legislation should not be retrospective on current or past participants in the program. The identifying information can be released only if the parties involved have given their consent to it prior to the procedure. Conflicts of interest may arise between the parties involved—sperm, ovum, and pre-embryo donors, offspring, and parents—regarding disclosure and access to information.

Religious Aspects of Genetic Material Donation

Roman Catholic Church

The issue of human reproduction was discussed in the Congregation for the Doctrine of the Faith in February 1987, signed by Cardinal Joseph Ratzinger, and approved by Pope John Paul II (Doctrine of the Faith, 1987). The key value in the instructions is respect for the dignity of the human being. Fertilization is allowed when it is the result of a conjugal act, that is, sexual intercourse between husband and wife. Consequently, the instruction prohibits IVF—embryo transfer, surrogate motherhood, and cryopreservation of embryos. It also rejects AID and IVF on the grounds that this involves a separation between "the goods and meanings of marriage." This position eliminates any use of donor semen for artificial insemination or for IVF. Furthermore, artificial fertilization of a woman who is unmarried or widowed, whoever the donor may be, cannot be morally justified. The practice of ovum and embryo donation is prohibited on the same basis as sperm donation.

Other Christian Churches

The Eastern Orthodox Church supports the medical and surgical treatment of infertility. IVF and other assisted reproductive technologies are not absolutely rejected. However, the Church opposes gamete donation, especially AID, on the grounds that it constitutes an adulterous act.

The Baptist, Methodist, Lutheran, Mormon, Presbyterian, Episcopalian, United Church of Christ, Christian Science, Jehovah's Witness, and Mennonite religions have liberal attitudes toward infertility treatments. All denominations except Christian Science accept IVF with the spouse's gametes and no embryo wastage [39]. Christian Science poses no objection to artificial insemination but opposes IVF because of the drugs and surgical procedures used. The aforementioned religions oppose IVF with donated gametes and the practice of surrogacy.

Islam

The procedure of IVF embryo transfer is acceptable, but it can be performed only if it involves the gametes of a husband and wife. A third party is not acceptable, whether in providing the egg, spermatozoon, embryo, or uterus. If a marriage has come to an end through divorce or death of the husband, artificial reproduction cannot be performed on the woman even by using spermatozoa from her late husband. Islamic law strictly condemns the practice of AID on the grounds that it is adulterous. According to the Muslim faith, for example, a Muslim man can marry a Jewish or Christian woman, as the religion of offspring is linked to the father.

Oocyte donation is not permitted in Islam, since it involves the intervention of a third party [40, 41]. Islamic law limits a man to the marriage of four wives simultaneously. Donation of oocytes between wives is not permitted. Donation of embryos, according to Islam, is prohibited. Frozen embryos are the property of the couple alone.

However, according to Fatwa from Ayatollah Hussein Khomeini in 1999, egg donation was approved only for the Shia sector. According to Iranian law, oocyte donation can be permissible under certain circumstances.

According to the Druze religion (a minority group of less than 1,500,000 persons living in the Middle East and originating from Islam), donation of oocytes can be permitted only between sisters.

Judaism

Therapeutic insemination with donor spermatozoa (AID) is accepted by a portion of the Jewish population in Israel and is unacceptable to most rabbinical authorities. Rabbis have been discussing the principles involving AID for many centuries. Their discussions are based on ancient sources in the Talmud and codes of Jewish law dating back to the fifth century that mention procreation without intercourse.

Jewish law prohibits AID for a variety of reasons: resemblance to incest, lack of genealogy, and problems related to inheritance. In addition, donors are violating the severe prohibition against masturbation. Many rabbinical scholars consider a child conceived through AID as having the status of "mamzer" (bastard), which severely limits prospects of marriage and implies a severe social handicap. Some rabbinical authorities permit AID if the donor is not a Jew. Rabbi Moshe Feinstein ruled that with the husband's permission and in the case where the infertile couple is suffering considerably, one may permit donor insemination, but specifically with the sperm from a non-Jewish donor. This eliminates some of the legal complications related to the personal status of the offspring. If the donor is a gentile, the child is not a "mamzer," but if the child is a girl, she is forbidden to marry a Cohen (a person with temple priest ancestry). Another reason for preferring non-Jewish donor sperm is to prevent future accidental consanguinity among the offspring of anonymous donors.

Oocyte (from single women) and embryo donations are allowed in Judaism, and the main issue is whether the religious status of the offspring should be based on the oocyte donor or the recipient. Jewish law dictates maternal determination of the religious status of the child. For purposes of lineage, the woman receiving the egg, rather than the woman donating the egg, is the mother, although the latter is certainly the genetic parent. If the recipient is Jewish, then the child is considered Jewish.

Hinduism

Assisted reproductive technologies are acceptable in Hinduism because there is no single authority to accept or reject on behalf of the faith. The most important condition is that the oocyte and sperm are from a legally married couple. In practice, artificial insemination with donor sperm and oocyte or embryo donation are performed with an anonymous donor. It is preferable that the sperm donor be a close relative of the husband.

Buddhism

The Buddhist religion is practiced by about 500 million people, representing 7–8% of the world's population. The largest Buddhist populations reside in China, Thailand, and Japan.

Buddhism of all types in various countries is individualistic, and even their scripture is not rigid.

There is no central Buddhist authority to pronounce on religious positions. Marriage within Buddhism does not have the high priority that it has in monotheistic religions. Any technology that is used to achieve pregnancy is morally acceptable, and treatment can be given to the married as well as to the unmarried.

In China, sperm, oocyte, and embryo donation for research is controlled by governmental regulation. Sperm donation is completely anonymous; only donors

between the ages of 22 and 44 years are eligible for selection; donor sperm cannot be provided to single women or same-sex couples; and each sperm donor can only impregnate up to five women via AID or IVF.

In Japan, anonymous sperm and oocyte donation is practiced. Commercial oocyte donation is not permitted.

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