Ethnic Differences in Fertility and Assisted Reproduction

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Editor
Fady I. Sharara
Virginia Center for Reproductive Medicine
Reston, VA, USA

Department of Obstetrics and Gynecology
George Washington University
Washington, DC, USA

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To my wife, Roula, and daughters, Yasmeen and Noora, for their unwavering support during the preparation of this book. I would also like to thank all the authors for their hard work in making this project possible.

Fady I. Sharara

To the memory of Diana P. Broomfield, M.D, who passed away during the production of this book

Foreword

This book addresses disparities in fertility care. The time has come to pay attention to this concept. Not only is it an issue of racial and ethnic disparities, which is global, though with particular relevance to the USA, it is also a special area of concern and interest with regard to health care. The differences in health care, including fertility services, on the basis of these disparities, are immense. This book tackles each of the concepts and conflicts in a thoughtful and thorough manner. The basic information is valid and presented in a palatable fashion and the facts, figures, and illustrations are a powerful contribution to the literature. What prompted the editor to put them together is unknown, but he has truly rendered a service to the reproductive endocrine and infertility community locally, nationally, and globally.

The overview by the editor outlines what challenges he has undertaken to address. This is followed by an excellent chapter on research, "How disparities impact on 'who' is studied, 'why' they are studied, and 'how' outcome is measured." This after all defines what makes up a disparate group and whether there are concerns and recognized differences. In Segars' chapter on research, the similarities between groups are shown to greatly outweigh the differences—"only 10–15 % of genetic variation is found between groups." Any research-oriented or clinical manuscript submitted for publication must therefore undergo the scrutiny of sorting out the differences based on disparities.

Although the major portion of patient care in the field of Reproductive Endocrinology represents the treatment of women, one must not ignore the disparity caused by gender.

The mortality rate in African Americans with breast cancer is high; is this a biologic, socioeconomic, or cultural phenomenon? This certainly is addressed in this book. I am not sure that the answers are easily obtained, but it is important for all of us to think about these facets and intricacies when dealing with these issues.

The two chapters on A.R.T., comparing Whites, Blacks, Hispanics, East Asians, and South Asians, are extensive in their breadth and depth. The less-obvious areas have been tackled, including donor egg outcome, frozen embryo transfer, FSH polymorphisms, and fibroids.

An important chapter by Saade on pregnancy outcome is critical for infertility treatment; having a healthy baby is the most important measureable outcome. There are differences that are recognized in regard to premature deliveries as far as African women are concerned, but nevertheless in well-controlled studies it is evident that there might be biological factors responsible for women of African American descent to have a greater number of premature infants than Caucasian women.

Everyone has to address the financial environment, and this too is discussed thoroughly in the book. This of course is a changing scenario, but the information here is sound and will stand the test of time.

The ultimate goal, though, has to be to erase these disparities and certain questions have to be answered: Is this all socioeconomic? Can it be fixed? Is it biologic? It cannot be fixed unless specific very sophisticated futuristic techniques are employed, for instance, gene therapy. Is the problem profound enough that once it is defined, large resources should be allocated for fixing it?

The book is well organized, written, and edited. It is an enjoyable read with wonderful and valuable information, good chapter-to-chapter consistency, and no fear on the part of the writers about being controversial and thinking out of the box.

Bethesda, MD, USA Alan H. DeCherney, M.D.

Contents

Contributors

Ayman Al-Hendy, M.D., Ph.D. Department of Obstetrics and Gynecology, Center for Women Health Research, George Hubbard Hospital, Meharry Medical College, Nashville, TN, USA

Ruben Alvero, M.D. Department of Obstetrics and Gynecology, University of Colorado, Aurora, CO, USA

Katherine S. Anderson, M.D. Department of Obstetrics and Gynecology, William Beaumont Hospital, Royal Oak, MI, USA

Alicia Armstrong, M.D., M.H.S.C.R. NICHD, National Institutes of Health, Bethesda, MD, USA

Diana P. Broomfield (Deceased)

Hakan Cakmak, M.D. Division of Reproductive Endocrinology and Infertility, Department of Gynecology and Reproductive Services, University of California, San Francisco, CA, USA

John M. Csokmay, M.D. Department of Obstetrics and Gynecology, Walter Reed National Military Medical Center, Bethesda, MD, USA

Program in Reproductive and Adult Endocrinology, NICHD, National Institutes of Health, Bethesda, MD, USA

Molina B. Dayal, M.D., M.P.H. Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Saint Louis University School of Medicine, St. Louis, MO, USA

Alan H. DeCherney, M.D. Program of Reproductive Adult Endocrinology, National Institutes of Health, Bethesda, MD, USA

Kate Devine, M.D. Program in Reproductive and Adult Endocrinology, NICHD, National Institutes of Health, Bethesda, MD, USA

Heba Eltoukhi, M.D. Program in Reproductive and Adult Endocrinology, NICHD, National Institutes of Health, Bethesda, MD, USA

Lawrence Engmann, M.D., M.R.C.O.G. Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Connecticut Health Center, Farmington, CT, USA

Karenne N. Fru, M.D., Ph.D. Reproductive Endocrinology and Infertility, Program in Reproductive and Adult Endocrinology, Bethesda, MD, USA

Victor Y. Fujimoto, M.D. Division of Reproductive Endocrinology and Infertility, Department of Gynecology and Reproductive Services, University of California, San Francisco, CA, USA

Laura Gillis, M.B.Ch.B Department of Obstetrics and Gynecology, Doncaster Royal Infirmary, Women's Hospital, Doncaster, UK

Ellen H. Goldstein, M.D. Department of Obstetrics and Gynecology, Dartmouth Hitchcock Medical Center, Lebanon, NH, USA

Emilie Green, B.Med.Sci. University of Sheffield, Sheffield, UK

Lisa Green, M.D., M.P.H. Department of Obstetrics and Gynecology, Howard University, Washington, DC, USA

Stephanie Gustin, M.D. Department of Obstetrics and Gynecology, Stanford University Hospital, Stanford, CA, USA

Heather G. Huddleston, M.D. Division of Reproductive Endocrinology and Infertility, Department of Gynecology and Reproductive Services, University of California, San Francisco, CA, USA

Yetunde Ibrahim, M.D. Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Boston, MA, USA

Tarun Jain, M.D. IVF, Warrenville, IL, USA

Hany Lashen, M.B., B.C.H., M.D., F.R.C.O.G. Department of Obstetrics and Gynecology, NHS Foundation Trust, Sheffield Teaching Hospitals, University of Sheffield, Sheffield, UK

Malinda Lee, B.S. Department of Obstetrics and Gynecology, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA

Richard Legro, M.D. Department of Obstetrics and Gynecology, Hershey Medical Center, College of Medicine, Pennsylvania State University, Hershey, PA, USA

Dmitris Loutradis, M.D. Department of Obstetrics & Gynecology, 'Alexander' Maternity Hospital, Athens, Attiki, Greece

Chi-Wei Lu, Ph.D. Department of Obstetrics, Gynecology, and Reproductive Sciences, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Ramkumar Menon, M.S., Ph.D. Division of Maternal–Fetal Medicine Perinatal Research, Department of Obstetrics and Gynecology, The University of Texas Medical Branch at Galveston, Galveston, TX, USA

Torie Comeaux Plowden, M.D., M.P.H. Department of Obstetrics and Gynecology, Bayne-Jones Army Community Hospital, Fort Polk, LA, USA

Botros R.M.B. Rizk, M.D., M.A., F.R.C.O.G., F.R.C.S., H.C.L.D., F.A.C.O.G., F.A.C.S. Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of South Alabama, Mobile, AL, USA

Monica J. Roth, Ph.D. Department of Pharmacology, UMDNJ–Robert Wood Johnson Medical School, Piscataway, NJ, USA

George R. Saade, M.D. Division of Maternal–Fetal Medicine Perinatal Research, Department of Obstetrics and Gynecology, The University of Texas Medical Branch at Galveston, Galveston, TX, USA

Mohamed Sabry, M.D., A.R.D.M.S. Department of Obstetrics and Gynecology, Faculty of Medicine, IBN-SINA IVF/ICSI Center, Sohag University Hospitals, Naser City, Sohag, Egypt

James H. Segars, M.D. Program in Reproductive and Adult Endocrinology, NICHD, National Institutes of Health, Bethesda, MD, USA

David B. Seifer, M.D. Genesis Fertility and Reproductive Medicine, Maimonides Medical Center, Brooklyn, NY, USA

New York University School of Medicine, New York, NY, USA

Yasunari Seita, Ph.D. Department of Obstetrics, Gynecology and Reproductive Sciences, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Department of Obstetrics & Gynecology, Child Health Institute of New Jersey, UMDNJ-RWJMS, New Brunswick, NJ, USA

Fady I. Sharara, M.D., F.A.C.O.G. Virginia Center for Reproductive Medicine, Reston, VA, USA

Department of Obstetrics and Gynecology, George Washington University, Washington, DC, USA

Reshef Tal, M.D., Ph.D. Department of Obstetrics and Gynecology, Maimonides Medical Center, Brooklyn, NY, USA

Anita P. Tamirisa, D.O. Department of Obstetrics and Gynecology, Summa Akron City Hospital, Akron, OH, USA

Kim Thornton, M.D. Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Nathan Treff, Ph.D. Department of Obstetrics, Gynecology and Reproductive Sciences, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Reproductive Medicine Associates of New Jersey, Basking Ridge, NJ, USA

Shunping Wang, Ph.D. Department of Obstetrics and Gynecology, University of Colorado, Aurora, CO, USA

Lynn Westphal, M.D. Department of Obstetrics and Gynecology, Stanford University Hospital, Palo Alto, CA, USA

Chapter 1
Introduction: The Scope of the Topic

Fady I. Sharara

Over the past 15 years, an emerging body of evidence evaluating racial and ethnic disparities in Infertility treatment, specifically assisted reproductive technologies (ART), has been published. While such racial and ethnic disparities have been studied extensively in other areas of medicine, studies addressing disparities in fertility outcomes have been few and far between. This could be related to multiple factors, including the political correctness of addressing such a controversial topic, and the inherent limitations inherent to defining such groups. We believe that the paucity of published studies only confirm the view that racial and ethnic disparities in fertility research are not a top priority for many researchers in the field, and as such we felt that a book addressing this important topic is long overdue.

Survey data from the National Center of Health Statistics shows that infertility affects women of all race, ethnicities, and level of education, with Black (10.5 %), Hispanic (7 %), and other minority women (13.6 %) reporting infertility more often than White women [1]. Unfortunately, those most likely to be infertile are also those least likely to seek medical help. Recent evidence suggests that infertility is increasing among minority women, particularly blacks, while decreasing among white women [2]. This is particularly concerning since the utilization and outcomes of ART treatment are generally less favorable for Black, Hispanic, and Asian women compared to White women. These disparities appear to be also widening over time [3].

The first paper dealing with ethnic disparities was published as a letter to the editor suggesting poorer outcome in Indian women compared to white women in 1988 [4]. No further reports were published until 1995 in the UK [5], followed by another report in the UK in 1998 [6], all dealing with comparisons between Caucasians and women from the Indian subcontinent, who represent a sizable minority in the UK.

F.I. Sharara, M.D., F.A.C.O.G. (✉)
Virginia Center for Reproductive Medicine, 11150 Sunset Hills Road, Suite 100, Reston, VA 20190, USA

Department of Obstetrics and Gynecology, George Washington University, Washington, DC, USA
e-mail: fsharara@vcrmed.com

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Table 1.1 Racial categories as defined by OMB Statistical Policy Directive No. 15, 1977 [14]

Category	Definition
American Indian or Alaskan Native	A person having origins in any of the original peoples of North America, and who maintains cultural identification through tribal affiliation or community recognition
Asian or Pacific Islander[a]	A person having origins in any of the original peoples of the Far East, Southeast Asia, the Indian subcontinent, or the Pacific Islands
Black	A person having origins in any of the black racial groups of Africa
White	A person having origins in any of the original peoples of Europe, North Africa, or the Middle East
Hispanic	A person of Mexican, Puerto Rican, Cuban, Central or South American or other Spanish culture or origin, *regardless of race*

[a]Revised in 1997 to two separate categories: "Asian" and "Native Hawaiian or other Pacific Islander"

The first publication evaluating ethnic differences in IVF outcome between white and black women in the USA was published in 2000 [7], and since then many studies have been published that have expanded ethnic disparity research into other minority groups in the USA and, to a much lesser extent, in Europe [3–35]. Studies have evaluated ART outcome in East Asians, South Asians, Hispanics, as compared to Caucasians in the USA; and in Europe, between Caucasians and South Asians (in the UK), and in a donor egg model between Caucasian and African women (in Spain) [3–35], all pointing to a lower delivery rate in minority groups. While this book addresses the current state of research in this field, an exhaustive review of the social, cultural, environmental, and economic causes is beyond the scope of this book. We therefore chose to shed light only on the possible medical and biological causes of these disparities, and ways to possibly eliminate or mitigate their negative effects.

The racial categories defined by the government in the USA lump several ethnic groups together. According to the Office of Management and Budget's (OMG) Directive 15 from 1977 (Table 1.1), Asian women are grouped in one category despite the fact that ethnic groups are very different racially and ethnically. For example, no medical researcher believes that women from China or Japan are ethnically (and medically) similar to women from India or Pakistan, or that women from Korea or Taiwan are ethnically (and medically) similar to women from Nepal or Bangladesh. And yet they are all grouped together in one category (Women in East Asian are also distinct ethnic subgroups amongst themselves and therefore Chinese women differ from Japanese, or Korean, or Thai, or Filipino women and comparative studies should be done even among subgroups within an ethnic group). Also, Hispanic women from Buenos Aires or Santiago are ethnically (and medically) distinct from women of the Amazon basin or the highlands of the Andes. In the same token, Mexican women are ethnically (and medically) different than women in the large urban centers of Brazil. This is especially important as stem cell therapy becomes reality. Ethnic groups without adequate stem cell representation will not be able to participate in the new wave of medical genomic therapy, and

Table 1.2 Proposed revised racial categories in the USA

Category	Definition
American Indian or Alaskan Native	A person having origins in any of the original peoples of North America, and who maintains cultural identification through tribal affiliation or community recognition
East Asian or Pacific Islander	A person having origins in any of the original peoples of the Far East, or the Pacific Islands
South Asian	A person having origins in Southeast Asia, or the Indian subcontinent (India, Pakistan, Nepal, Bangladesh, Sri Lanka)
Black	A person having origins in any of the black racial groups of Africa
White	A person having origins in any of the original peoples of Europe, North Africa, or the Middle East
"North and Central American" Hispanic	A person of Mexican, Puerto Rican, Cuban, Central or Caribbean origin
"South American" Hispanic	A person of South American European origin
South American Native	A person having origins in any of the original peoples of South America, and who maintains cultural identification through tribal affiliation or community recognition

therefore adequate studies of appropriately defined ethnic groups is of paramount importance. Twenty-five years after the initial OMB Directive, we believe it is time for a new classification. We therefore propose a revised classification of ethnic groups in the USA (Table 1.2), and we urge researchers in Europe to devise their own classification in light of its' sizable ethnic minority groups (that differ among member countries, for example people of North African descent in France, South Asians in the UK, and Turks in Germany).

A review of the Society of Assisted Reproductive Technologies (SART) database between 1999 and 2007 showed that 35 % of ART cycles lacked the data on race/ethnicity [35]. This could be due to the fact that there is no check box for "mixed" race/ethnicity, a resistance to be classified as one group or another, or more likely, simply to non-reporting. We need to clearly do a better job at collecting this information prospectively, and consider adding a check box for "mixed" on the SART CORS reporting site. Of interest, more than five million Americans identified themselves as more than one race in the last census, and this group is increasing yearly making it hard to define ethnicity and race in our ever changing society. This will represent another layer of complexity to studies of ethnic disparities that needs to be addressed in the future since admixture of ethnic/racial groups will be the rule rather than the exception. Future studies may well report on genomic and epigenomic differences rather than racial or ethnic ones.

While it is heartening that the bulk of the papers have been published over the past 5 years, there are still significant holes in our understanding as to why ethnic minorities have a poorer ART outcome. I have asked few of the researchers with active interest in this field to contribute their expertise to this book, and to them I am deeply grateful. While we loud the formation of the National Institute on Minority

Health and Health Disparities (NIMHD) that was established in 2010 to reduce and eliminate health care disparities as a long overdue step in the right direction, it is our hope that this book will cause accelerated interest in a field that we believe has received anemic attention despite its importance.

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Chapter 2
Racial and Ethnic Groups of Interest in Fertility Research

Ellen H. Goldstein and James H. Segars

Introduction

Physicians consider the differences between patients in order to optimally care for their reproductive health and fertility. The most obvious differences are often physical traits or cultural group affiliations, which may, if unexamined, be simply considered racial or ethnic differences. However, traditional concepts of race and ethnicity are brought into question in the post-genomic era. An examination of race and ethnicity as it relates to reproductive health disparities is urgent: the health of reproductive-aged and pregnant women, if compromised, is both a marker of disparity and a factor in its perpetuation.

Recent changes in US demographics highlight that physicians are caring for an increasingly diverse population. According to the 2009 US census, the total American population increased 9.1 % from 2000 to 2009 (to 307,007,000). For the first time ever, during the 12 month period ending in July, 2011, non-Hispanic white births made up less than half (49.6 %) of all births in America. Among participants reporting only one race, "white" people increased by only 7.1 %, while "black" individuals rose 11.0 %, Pacific Islanders rose 25 % and Asian respondents increased by 32.3 %. Over five million Americans chose to identify with more than one race in the last census, an increase of 36.6 % since 2000, reflecting increasing rates of admixture between groups and an evolving self-concept of "race." Over 48 million

E.H. Goldstein, M.D.
Department of Obstetrics and Gynecology, Dartmouth Hitchcock Medical Center,
1 Medical Center Drive, Lebanon, NH 03756, USA
e-mail: Ellen.Goldstein@alumni.Brown.edu

J.H. Segars, M.D. (✉)
Program in Reproductive and Adult Endocrinology, NICHD, National Institutes of Health,
10 CRC, Room 1E-3140, 10 Center Drive, MSC 1109, Bethesda, MD 20892-1109, USA
e-mail: segarsj@mail.nih.gov

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Americans now consider themselves to be Hispanic, considered "ethnicity" in the census and separate from race, representing 15.8 % of the population and an increase of 37.1 % since 2000 [1].

Despite the large segments of society who fall into one or more minority category and despite improvements in the overall health of the American people, some minority groups have traditionally been underserved or suffer under a disproportionate burden of disease. Socioeconomic, education, and insurance status differences contribute to health care disparities, as do underlying genetic or biological factors. The term "disparity" can be used interchangeably with "inequality" and can refer not only to differences but injustices [2]. The 2005 American College of Obstetricians and Gynecologists Committee Opinion drew attention to the role that patients, providers, and the health care system play in perpetuating disparities and called for redoubled efforts to reduce and eliminate disparity [3]. Some of the well-known examples of disparities in the realm of women's health are shown in Table 2.1.

The reduction and elimination of health care disparities was identified as an important goal by the National Institutes of Health, which formed the National Institute on Minority Health and Health Disparities (NIMHD) in 2010. Health care disparities impact the overall health of the nation and are costly and burdensome to the US Healthcare system. The NIMHD recognizes that the physical environment, the social environment, behavior, and biology all interact to contribute to individual and population health and ultimately to disparities in health. Access to quality health care and the existence of interventions and pro-health policies are also important in the health of populations. The strategy of the NIH/NIMHD to reduce and eliminate health care disparities involves the conduction of research into the etiology of the disparities but also emphasizes the roles of building research capacity, engaging in community outreach and public health education, and integrating all of the above [2]. As of 2002, the NIH requires collection and reporting of data on race and ethnicity for all research it supports that meets the definition of clinical research [4].

Table 2.1 Examples of disparities in women's health care

Disease	Group (compared to non-Hispanic white women)	Disparity
Invasive cervical cancer	American Indian/Alaskan native African-American women Hispanic white women	Higher incidence [72]
Breast cancer	Black women	Higher mortality rate, despite a lower incidence [73]
HIV	Black women	60–70 % of all new cases every year [74]
Preterm birth	Black women	Higher rates [75]
Fetal, infant, and perinatal mortality	Black women	Higher rates [75]
Pregnancy-related death	African-American women	Higher likelihood [76]

Defining Race and Ethnicity

Given the NIH mandate, it is imperative that scientists work towards a definition of race so that groups discussed in a study are recognizable and data can be compared and connected between studies. We emphasize that the goal of this chapter is not to perpetuate stereotypes or delineate "superior" or "inferior" groups, but rather to work within the framework established by NIMHD to further discussion and ultimately reduction of health care disparities. While the differences in health outcomes between groups may be to a degree socioeconomic and access-related, it is clear that genetic, epigenetic, and environmental factors contribute.

Many historical attempts (beyond the scope of this chapter) have been made to classify humans into distinct groups based on their defining physical characteristics. This proves difficult, as human phenotypic and genetic variation is *clinal*; that means there is a gradient of phenotypes over geographic areas with subtle shifting of features from one group to the next [5]. Interestingly, due to the limits of human travel and the subtle variation in physical features that any one traveler might see, the concept of race likely did not exist before the time of the European explorers. This group was the first to be able to depart from one port with humans of one general appearance and then to land amongst humans that must have looked very novel [6]. The typical lay concept of "race" is a sociopolitical one and does not equate to the word "race" in nonhuman taxonomy, which equates with "subspecies" and usually denotes isolated collections of populations that demonstrate objective microevolutionary divergence [7].

Population genetics studies of allele frequency variation show that groups of humans have been evolving separately for a relatively short time period. In the Recent African Origin (RAO, also called Out of Africa) model, an anatomically modern ancestor evolved in Africa about 200,000 years ago (see Fig. 2.1). Groups then started to migrate to the other continents in waves between 50,000 and 100,000 years ago, and even more recently. They displaced and caused extinction of remaining primitive humans like Neanderthals, though there may have been some admixture [5].

At the nucleotide level, humans differ from one another at only 1 in every 500–1,000 nucleotides, making each *Homo sapiens* individual 99.6–99.8 % identical to all others. The remaining three million (out of three billion) nucleotides that may vary between individuals occur mostly in noncoding regions (and are likely "neutral," or not causing any phenotypic change), but also are present in coding and regulatory regions of genes [5, 8]. There are approximately ten million common single nucleotide polymorphisms (SNPs), which are thought to comprise 90 % of the variation in the human genome [9]. Studies using frequencies of these SNPs have shown that approximately 10–15 % of total genetic difference between humans is found *between* the geographic groups Sub-Saharan Africans, Northern Europeans, and East Asians. The F_{ST}, or the proportion of difference found between populations rather than within them, is 0.11–0.23 in most studies of protein polymorphisms, blood groups, and restriction fragment length polymorphisms [5]. This means that

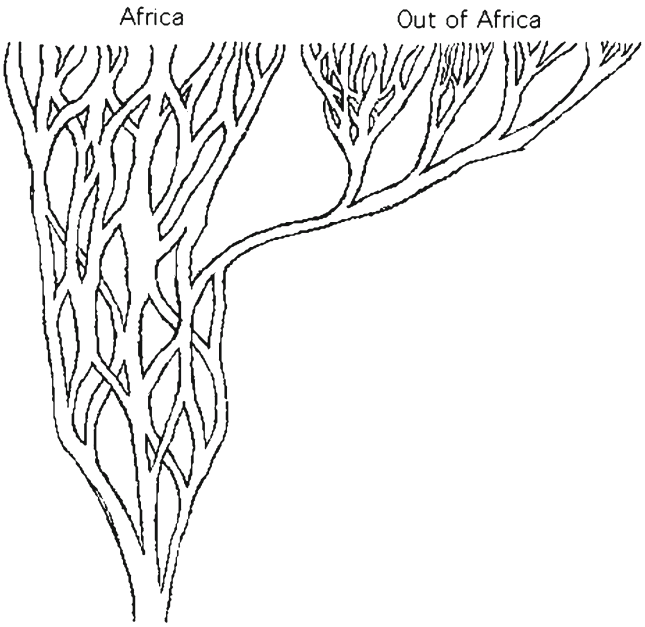

Fig. 2.1 The "wisteria vine" view of human evolution illustrates branching and reuniting of genetic populations throughout the regions of the world. It shows a pattern of decreasing heterozygosity and increasing linkage disequilibrium with distance from Africa, with a marked founder effect due to genetic drift that accumulated in the first population to expand out of Africa. The Eurasian populations each became successively more genetically homogeneous as small subsets of gene pools were carried forward, as illustrated in the right-most branches. Reprinted, with permission, ©1999, Kenneth K. Kidd. http://medicine.yale.edu/labs/kidd/www/wister.html

roughly 85–90 % of nucleotide variation is between *individuals*, regardless of population of origin. Because individuals from neighboring populations typically have more recent common ancestors, their allele frequencies are more highly correlated. This holds true for groups that are widely separate more frequently than for groups that are more typically admixed, like Hispanics or South Asians [8].

Because of this 10–15 % variation between ancestral groups, some genetic markers are informative due to their relatively different frequencies: these are called Ancestry Informative Markers (AIMs) [10]. The international HapMap project seeks to determine common patterns of DNA variation and their frequencies. It also seeks to detect association between particular genomic regions and diseases ("candidate gene" searching). Because each SNP exists in linkage disequilibrium (LD) with the other alleles near which it originally arose by mutation, empirically chosen "tag" SNPs can be genotyped which give information about the rest of the individual's haplotype. The HapMap researchers used subjects from different geographical backgrounds (Europeans in Utah, Han Chinese from Beijing, China, Japanese people from Tokyo, Japan, and members of the Yorubu people from Ibadan, Nigeria) in an attempt to obtain the most variation possible and to test theories of LD [9]. Recent research has shown that fine scale inference of an individual's (self-reported)

ancestry is possible using techniques that have arisen out of the HapMap project and the determination of judiciously chosen AIMs. Only a small fraction of the known genome-wide SNPs must be sequenced to do this [11].

Despite these new developments that may lead to a genetic test to help determine groupings, the primarily self-report paradigm of race in research has led many authors to discuss replacing questions about "race" with questions about *ancestry* [5, 8]. For example, there are many striking disparities in America between African-Americans and other groups. "African-American" is often considered a "race," both in common parlance and in research groupings. However, much of the difference in disease burden is likely due to a complex interplay of social, economic, political, educational, and access differences unique to this particular group of people. Only this group is descended from American slaves and may bear the epigenetic marks and genomic signature of the hundreds of years of deprivation, stress, and inequality that comprised slavery and the long road to integration. Asking patients or research participants about race leads to quandaries such as recent African immigrants or even people of Egyptian or Moroccan descent marking "African-American" [7]. Significant admixture of groups may lead to dilution of what may be true associations. Asking specific questions about ancestry allows researchers to make broad categories and then smaller, more specific categories of patients as needed, and to bear in mind that each subject may not be at all easy to categorize [8].

If this 10–15 % of genetic variation between groups *does* contribute to health care outcomes or disparities, how would it do so? The common disease-common variant hypothesis states that for common heritable diseases, like Type 2 Diabetes, there are common disease susceptibility alleles at a few loci that exist at high frequency across ethnically diverse populations. However, complex and rare diseases may be influenced by susceptibility alleles that are more frequent in certain populations due to drift or natural selection. It is also possible that common alleles may have different effects in different groups based on environment or group-specific epigenetic interactions. Other times, variants may not in themselves be causal but may exist in linkage disequilibrium with the causal variants [8]. Scientists have started to examine these questions. One recent study by Ioannidis et al. [12] showed that among 43 gene-disease associations studied in different "racial" populations, the frequency of the variant differed between racial groups 58 % of the time. However, there was only a very large heterogeneity (difference in the odds ratios of disease susceptibility) between races in 14 % of groups. The authors concluded that while genetic markers for gene-disease associations vary in frequency across populations, the magnitude and direction that of association is usually consistent [12].

The concept of "race" as a social construct deserves mention. Membership in a particular "social group" or "category" is based on a set of socially negotiated terms, including real or perceived biological differences. These terms vary across history and sociopolitical climate. However, much of the correlation between a socially constructed race with biology (both genetic, epigenetic, and physiological) is a result of shared population history, which is dependent on geography and origins [13]. The recent work showing that AIMs do correlate very well with self-reported "race" does not negate the importance of including culture and environment in a complete consideration of this topic.

The Definition of Race in Research

The US census bureau conducts a decennial survey to enumerate the population of the USA in order to apportion members to the House of Representatives. This survey also compiles information about race, using guidelines contained in a document released by the Executive Office of the President's Office of Management and Budget (OMB Statistical Policy Directive No. 15). This document was originally released in 1977, and grew out of the activities of the Federal Interagency Committee on Education (FICE) Subcommittee on Minority Education, whose report in 1973 revealed a lack of useful data on racial and ethnic groups. FICE then convened an Ad Hoc Committee on Racial and Ethnic Definitions, tasked with developing terms and definitions that could be used by federal agencies. After revisions and a testing period, the final categories were delineated in 1977 and have been used since that time (Table 2.2) [14].

The original document also specified that ideally data on "race" and "ethnicity" should be collected separately; this would entail separating the "Hispanic group" and making subcategories that would, for example, delineate Black Hispanic from Black Non-Hispanic [14]. Directive 15 does not specify *how* an individual or an outside observer should classify an individual's racial or ethnic category; all information is supposed to be self-reported. The original governmental documents specify that the categories are a social-political construct and are not meant to be scientifically or genetically based [14].

In 1997, important revisions were made to OMB Directive 15 in response to criticisms that the original categories did not reflect the increasing diversity of the USA. The review document specifies again that the categories are not meant to be genetically or scientifically based, and emphasizes that respect for individual dignity should guide data collection. Respondent self-identification is again encouraged whenever feasible. The attempt was to make categories that were as comprehensive as possible while also being clear and generally understood by the general public, and should be operationally feasible in terms of burden placed upon respondents and upon those analyzing the data [15].

Table 2.2 Racial categories as defined by OMB Statistical Policy Directive No. 15, 1977 [14]

Category	Definition
American Indian or Alaskan Native	A person having origins in any of the original peoples of North America, and who maintains cultural identification through tribal affiliation or community recognition
Asian or Pacific Islander[a]	A person having origins in any of the original peoples of the Far East, Southeast Asia, the Indian subcontinent, or the Pacific Islands
Black	A person having origins in any of the black racial groups of Africa
White	A person having origins in any of the original peoples of Europe, North Africa, or the Middle East
Hispanic	A person of Mexican, Puerto Rican, Cuban, Central or South American or other Spanish culture or origin, *regardless of race*

[a]Revised in 1997 to two separate categories: "Asian" and "Native Hawaiian or other Pacific Islander"

The important changes, which were first implemented in the 2000 census, included the option to check more than one box for race (but no "multiracial" category), a splitting of category 2 (see Table 2.2), and the option to check "some other race." Hispanic ethnicity was again considered separately from race [15].

The NIH requirements for collecting, maintaining, and reporting race and ethnicity follow directly from OMB Directive 15 and closely parallel the census standards. The NIH Policy On Reporting Race And Ethnicity Data: Subjects In Clinical Research, released in 2001, again emphasizes that "categories in this classification are social-political constructs and should not be interpreted as being anthropological in nature." The categories are the same as the revised census categories, with guidance in the form of lists of areas of origin (see complete document available on the web http://grants.nih.gov/grants/guide/notice-files/not-od-01-053.html). Researchers are instructed to collect ethnicity (Hispanic or not-Hispanic) data first, then to separately categorize participants into one or more of the five categories of "race." The NIH stipulates that information should be collected by self report, and requires that investigators report: (a) the number of subjects in each racial category; (b) the number of subjects who selected only one racial category; (c) the "number selecting more than one race"; (d) the number of participants in each racial category who reported their ethnicity as Hispanic. The NIH uses these categories to compare data across agencies. The guidelines are supposed to be minimum standards, and researchers are encouraged to collect more information on subpopulations or to question participants who check two or more races for more details about their backgrounds and personal identification [4].

It is crucial that scientists understand the difference between these required categories, which are important for Federal data collection and health care disparities research, and biological determinism. This is an area of intense debate: one recent anthropological qualitative study [16] interviewed genetics researchers ($n=30$, in the USA and Canada) regarding their methods of racial data collection. Most (24 out of 30) used race/ethnicity as an important part of their study design (in studies of population variation in distribution of markers or in studies of racial/ethnic variation in characteristics of diseases). Others collected racial/ethnic data due to Federal guidelines or because of high prevalence of a disease of interest in a certain group. By conducting qualitative interviews, the investigators uncovered presumptions about group membership that can introduce inaccuracy into the studies (see Table 2.3 for a description of some of their concerns). The authors conclude that using the current paradigm of categorization (even for the research performed under NIH guidelines in the USA) for genetic research is arbitrary and ambiguous and will dangerously perpetuate stereotypes and legitimize reductionist racial thinking. The authors advocate attempts to explore the actual source of the variance, and to thus categorize individuals empirically [16].

To that end, researchers have started to use Ancestry Informative Markers to categorize participants [10, 17]. This is expected to be useful in case–control studies to minimize spurious associations caused by self-reported "race" [18]: in one interesting historical example, a particular HLA type was found to be protective against Type II diabetes in American Indians. It turned out that this HLA type was actually a marker for admixture with European ancestry, a group with a lower rate of

Table 2.3 Conundrums and confounders in defining "race" for genetics research [16]

Individuals from a rural village in China are classified along with Japanese-Americans under the category "Asian," and African-Americans are classified into the same group, "black," as individuals living in Nigeria (*author's note: these are in fact proper groupings under OMB/NIH guidelines*)
A medical doctor notes that in his own study of the genetic basis of chronic disease in African-Americans, he has trouble accepting his own racial categories because he is concerned about intermarriage and admixture making his results invalid
A researcher reveals that he considers the "marrying in" of non-Hispanic family members into a large Mexican family cohort as rare events in an otherwise "pure" bloodline, although intermarriage is extremely common in North America. The authors cite extensive evidence that laypeople and scientists have an incorrect view of the reproductive isolation of racial groups, and most are not aware of how commonplace admixture has been throughout history [16]
None of the interviewed scientists could describe a systematic way to deal with mixed-race participants, and several researchers said that for participants who were difficult to classify, their data would simply be excluded from analysis.
With the (most commonly) used method of self-reporting, there is no way to standardize or even understand how each individual makes this decision. They cite an example of one of the geneticists they interviewed being unable to figure out his own racial category
The racist principle of "hypodescent" (which assigns an inter-racial individual to the member of the less privileged group) may be employed when classifying people as "African-American," whereas, frequently, more attempt is made to "scientifically" classify other groups (such as surname analysis for Hispanics)

diabetes than American Indians. If AIMs are used, ancestry data can be gathered from pooled or banked DNA as well [19].

One notable study examined skin pigmentation (a common proxy for "race" and a basis for racism) using a spectrometer in five populations of admixed ancestry from various locations in North America and England. Each individual was genotyped at AIMs known to be informative regarding West African, European, and Indigenous American ancestry. Each individual was shown to have a degree of admixture, though the highest genetic proportion of each came from the expected ancestral group (i.e., African Americans were on average 78.7 % West African ancestry with 18.6 % input from European ancestry). There was a significant association between melanin index as measured by spectrometer and proportion of West African and Indigenous American ancestry, though the strength of the relationship was variable. The difference in the strength of the relationship may be due to admixture between groups of widely different pigmentation levels, and the authors explain that with more extensive admixture, this relationship is likely to disappear. The authors concluded that AIMs are very useful for determining proportions of ancestry admixture, and that researchers should not assume that markers such as pigmentation can accurately reflect ancestry [10].

In theory, collecting AIM data for more accurate categorization of study subjects should be increasingly accessible. Programs like AncestrySNPminer (free online, https://research.cchmc.org/mershalab/AncestrySNPminer/login.php) allow researchers

to search all known SNPs to determine which are the most informative to determine ancestry for their particular populations [20]. Applied Biosystems and other industries have platforms for researchers to choose SNPs and make custom arrays for high throughput analysis [21, 22]. However, this adds a significant layer of complexity and expense to any investigation, especially to anthropological or clinical research studies performed by scientists without a genetics lab.

Interactions Between Biology and Environment: Effects of Race and History on Diseases and Fertility

The work of David Barker over the last 20 years [23–25] has led to the concept of Developmental Origins of Health and Disease (DOHaD, also known as Fetal Origins of Adult Disease (FOAD) and the Barker Hypothesis). A full review of DOHaD is beyond the scope of this chapter; this is a lively area of research and a long list of chronic diseases, including diabetes mellitus, obesity, hypertension, coronary artery disease, stroke, kidney failure, lung disease, immune dysfunction, Alzheimer's disease, depression, anxiety, bipolar disorder, and even cancer have been associated with fetal origins. There is tremendous research interest into the study of offspring of obese and diabetic mothers, in both humans and interventional studies in primates. Multiple studies show alterations in neonatal metabolic profiles, markers of placental inflammation, and fat mass [26–31].

Barker originally studied men and women who had been exposed in utero to the Dutch famine of 1944–1945, which was a relatively short (5 month) period of severe food shortage caused by an embargo by occupying German forces. Adult calorie rations dropped as low as 400 calories per day. While malnutrition is unfortunately a chronic problem in developing nations, and historical examples of much longer famines exist, the Dutch famine provides a unique circumstance of severe maternal malnutrition followed by immediate return to normal food availability. The individuals exposed in utero thus had an effective "mismatch" between antenatal and postnatal environment and may have developed an adaptive phenotype to prepare for conditions that then did not play out. This concept is supported by studies of adults who were born during the siege of Leningrad, which lasted more than 800 days. These adults do not have higher rates of coronary artery disease or dyslipidemia, and it is thought that the "thrifty phenotype" of individuals exposed to poor nutrition in utero was well matched to the environment into which they were born. The "mismatch" concept applies well to the modern day first world. Intra-uterine stressors lead to high rates of small-for-gestational-age (SGA) infants in underserved groups, many of whom likely have developed a "thrifty phenotype" to preserve neurodevelopment, but these same children eat a high fat fast food diet and have very high rates of obesity and increasing rates of diabetes. Numerous human and animal studies have shown that the most unhealthy pattern is for low birth weight individuals to "catch up" and have a rapid weight gain during childhood [32].

The Science Behind Environmental Disparities

The question of just *how* the "thrifty phenotype" comes about for infants exposed to in utero stress can be answered by the theory of the "thrifty epigenotype," in contrast to the sometimes discussed "thrifty genotype." Efficient energy metabolism is crucial for survival and fitness; therefore, *all* humans likely possess the capability to enable metabolic thrift as needed. An epigenetic mechanism (see below) addresses several conundrums, including: (a) why a highly heritable disease like Type 2 DM has so few known allele variant associations, (b) why the different rate of obesity in black women does not extend to black men in a genotype–phenotype correlation, (c) why obesity and diabetes rates are climbing in the North American food-rich society *across* a diversity of underlying genotypes. Two groups that have been thought to likely have "thrifty genotypes," the Pima Indians of Arizona and the Nauru people from Micronesia, had extremely rapid increases in diabetes rates after transitioning to a Western lifestyle. However, the rates of diabetes have started to decline recently in the Nauru people despite no change in their lifestyle. This change appears too rapid to represent the culling of alleles for extreme maladaptive thrift, and could demonstrate resetting of epigenetic modifications by a reduction in the "mismatch" between prenatal and postnatal life. The epigenome can adapt much more rapidly to extreme changes in condition than can the genome, whose integrity is paramount [33].

The underlying mechanism responsible for the "thrifty phenotype" is understood to be epigenetic modification of DNA. "Epigenetics" literally means "above" or "upon" genetics. The study of epigenetics encompasses heritable changes of the DNA or the chromatin that is not within the sequence itself. The most well-studied mechanisms of epigenetic modification are DNA methylation and the methylation, acetylation, and phosphorylation of histones. This field may provide biochemical explanations of the adverse effects of the fetal, neonatal, and childhood environment under intense study by the DOHaD researchers. Importantly, especially for consideration of health disparities, these epigenetic changes can carry forward, *perhaps for generations* [34]!

For instance, Pembrey and colleagues (studying cohorts in Sweden and the UK) have shown an inverse, sex-specific relationship between grandfathers' and grandmothers' nutritional status at puberty and their grandsons' and granddaughters' longevity. They have also found an association between early onset paternal smoking with shorter gestational length and greater body mass index at age 9 in their offspring. They conclude that these interactions may be candidates for transgenerational genetic modification but there is not yet an established mechanism [35].

The state of the scientific knowledge now leads us to hypothesize that the source of today's obesity and diabetes epidemic may be a transgenerational effect from hundreds of years past. The conditions (poor nutrition, restricted access to health care, physical and psychological stress) of American slavery from the sixteenth to the nineteenth centuries and the continuing long road to equality thereafter provided an environment and stress for in utero epigenetic modification. One example of the

intersection of socioeconomics with epigenetics comes from a study of low birth weight and African-American women. Transgenerational data sets of African-American infants (born 1989–1991) and their mothers (born 1956–1976) showed that for mothers who had experienced early life impoverishment but then upward economic mobility, preterm birth rates were lower than for women who had experienced lifelong impoverishment. This size of this effect correlated with their level of economic improvement. However, this did not hold true for women who themselves were low birth weight, indicating possible transgenerational epigenetic effects [36].

Toxic exposures may also effect epigenetic change. Groups that are disproportionately represented among lower socioeconomic classes may have disproportionate exposure to toxins. The CDC's National Health and Nutrition Examination Survey (NHANES) collects data on toxic metabolites in blood and urine samples, and reports levels by race and ethnicity like all federal agencies [37]. In rats, exposure of a pregnant female (F0) to plastics, dioxin, and hydrocarbons resulted in early onset of puberty transgenerationally (F3). Hydrocarbon exposure at F0 resulted in higher levels of sperm apoptosis in F3 males. Plastics, pesticides, dioxin, and hydrocarbon exposure at F0 all resulted in fewer ovarian follicles of F3 mice. The investigators performed a genome wide promoter DNA analysis and found differentially methylated regions (DMRs) specific for each exposure vs. controls. This study provides evidence of the existence of epigenetic biomarkers for ancestral environmental exposures [38]. An equivalent controlled interventional study is not ethical in human subjects, but the concepts provide support for a biological basis for health care disparities.

It is impossible to make generalizations about the highly specific in utero environment of each maternal-child dyad, not to mention the epigenetic modifications that may affect more than one generation. However, in the context of some of the known DOHaD associations, we will explore differing rates of disease by racial and ethnic group. History may give us some clues about the etiologies of these differing rates, and epigenetic change may explain their perpetuation. Awareness of this hidden, complex extra level of human disease lends urgency to efforts to reduce health care disparities at the population level.

Common Health Disparities, Obesity and Diabetes, Affect Fertility

Rates of obesity and diabetes mellitus have skyrocketed over the last 30 years in the USA and all over the world. While the statistics below are for the population as a whole, these shocking numbers have special importance for caring for and performing research regarding reproductive aged women. Obesity and insulin resistance are associated with the majority of ovulatory dysfunction and thus contribute to infertility. Obese and diabetic women have much higher rates of complication during pregnancy, both for themselves and their babies.

According to the most recent CDC data, 25.8 million people (8.3 % of the US population) have diabetes. This includes Type 1, classically autoimmune, juvenile diabetes, but these cases only account for 5 % of all adult cases. 90–95 % of all cases of diabetes are Type 2 diabetes, caused by insulin resistance developing over time and associated with obesity and family history of diabetes. 26.9 % of the US population aged 65 and older has diabetes. 1.9 million people aged 20 and older were diagnosed with diabetes in the USA in 2010. After adjusting for population age differences, the rates by racial/ethnic group for adults older than age 20 in 2007–2009 were as follows:

- 7.1 % of non-Hispanic whites
- 8.4 % of Asian-Americans
- 11.8 % of Hispanics
- 12.6 % of non-Hispanic Blacks (this is the group for whom there has been the most dramatic rise in DM prevalence over the last 20 years) [39]
- 14.2 % of American Indians and Alaska natives

This corresponds to a risk of 18 % higher for Asian Americans, 66 % higher among Hispanics, and 77 % higher among non-Hispanic blacks when compared to white Americans. Also reported by the CDC, type 2 diabetes was extremely rare among youth aged <10 years. However, rates of type 2 diabetes in children aged 10–19 are increasing, and there are higher rates among minority children than in white children. Among white children age 10–19, Type 1 DM diagnoses were more common than Type 2 DM diagnoses, but this was reversed for Asian/Pacific Islander and American Indian youths, and the rates are similar for non-Hispanic blacks and Hispanic youth [40].

According to National Health and Nutrition Examination Survey data in 2008, the overall age adjusted obesity rate is 33.8 % in America, and overall combined overweight plus obesity rate is 68.0 %. These rates vary widely with gender, age, and racial category:

- For women, the obesity (BMI >30) rate is 33.0 % among non-Hispanic white women, 49.6 % among non-Hispanic black women, and 43.0 % for all Hispanic women (45.1 % for Mexican-Americans).
- For men, the obesity rate is 31.9 % for non-Hispanic white men, 37.3 % for non-Hispanic black men, and 34.3 % for all Hispanic men (35.9 % for Mexican-Americans).

Similar trends are seen for women for analyses of overweight (BMI >25), class 2 (BMI >35), and class 3 (BMI >40) obesity as well. For men, there is a trend for a less pronounced and more heterogeneous difference than for women across races, as seen above. Non-Hispanic black men actually have a lower rate of overweight (BMI >25 is 68.5 % vs. 72.6 %) compared to non-Hispanic white men, and higher rates of class 2 and Class 3 obesity (14.4 % vs. 10.5 % and 7.0 % vs. 5.2 %, respectively) [41]. These demographic changes are of central importance to fertility research, given the clear association of increased BMI with anovulation and with reduced sperm count in men.

Obstetrical Health Disparities: The Intrauterine Environment and the Next Generation

As noted above, the intrauterine environment is an important determinant of future health. Health statistics demonstrated higher rates of low birth weight and very low birth weight (which do not correct for gestational age) among minorities, but are confounded by higher rates of preterm delivery among these groups. This makes it difficult to tease out small for gestational age (SGA, defined as infants whose birthweight is below the 10th percentile for gestational age [42]) numbers that might indicate prevalence of placental insufficiency and hostile intrauterine environment, rather than preterm deliveries that occur for other reasons such as preterm labor (labor before 37 weeks of gestation [42]) and PPROM (preterm premature rupture of membranes [42]), which also are higher in some minority groups. However, a significant proportion of preterm deliveries *are* for maternal or fetal indications such as severe preeclampsia or SGA, so it is important to be aware of the heterogeneity of the data.

Recent data on preterm (<37 completed weeks gestation) delivery rates, from 2008, show that in the USA, the preterm delivery rate is 12.3 % for all races: 11.1 % for non-Hispanic whites, 17.5 % for non-Hispanic blacks, and 12.1 % for Hispanics. Preterm delivery rates are declining for all groups over the last 3 years, though levels still remain higher than any year from 1981 to 2002 [43].

The most recent CDC birthweight data from 2009 for singleton births, regardless of gestational age, shows:

1. For all races, the rate of low birthweight (<2,500 g) is 6.36 % and very low birthweight is 1.10 %
2. For non-Hispanic whites, 5.23 % and 0.81 %, respectively
3. For non-Hispanic blacks, 11.44 % and 2.51 %, respectively
4. For Hispanics, 5.72 % and 0.96 % [44], respectively

A retrospective study of data from the US natality files from 1975 to 2000 reported rates of term small-for-gestational age. The rate of term SGA in black women declined from 21 to 16 % between 1975 and 2000, and in white women, the rate declined from 12 to 9 %; while these declines are encouraging, the difference in absolute rate must be noted [45].

Some have tried to explain these differences by hypothesizing that there may actually be a racial difference in normal birthweight curves, and that these smaller birthweights are physiological rather than pathological. However, an analysis of 11.5 million births from 1998 to 2000 in the National Center for Health Statistics showed that there was a closer coherence between SGA and neonatal mortality when SGA was defined on a single standard rather than race-specific standards. Rates of live-born neonatal mortality and SGA were lowest among US whites, highest among US blacks, and intermediate for foreign-born US blacks. This intermediate group further supports the likelihood that SGA in African-American babies is pathological. We hypothesize that that this may actually be a transgenerational,

environmentally induced epigenetic phenomenon. Logically, if there was some genetic or biological reason for the difference, the foreign-born blacks should have higher rates and the US blacks should have intermediate values due to underlying genetics and admixture [46]. Even when only "extremely low risk" women are studied (married, age 20–34, adequate prenatal care, vaginal delivery, no reports of health problems or risk factors, tobacco, or alcohol use), the risk of an SGA infant was 2.64 times greater for an African-American woman than a white woman, and the risk of infant mortality was 1.61 times greater. This study demonstrates that existing risk factors cannot completely explain the disparities in birth outcomes; rather, the disparities are consistent with a transgenerational predisposition [47].

The prevalence of gestational diabetes (GDM) varies in direct proportion to the prevalence of type 2 diabetes in a given population; it varies from 1 to 14 % in different studies, with the CDC quoting a 5–10 % rate. These rates vary widely in part because of population differences but also because of differences in screening practices [40, 48]. It has been difficult to tease out whether there is a true association between race/ethnicity and the prevalence of GDM, or whether it is related to differences in obesity rates [48]. However, data from the New York City Department of Health and Mental Hygiene (self-reported as very specific country of origin or ancestral origin) from 1995 to 2003 showed that non-Hispanic white women had the lowest risk (3.6 %) of GDM. African-Americans, sub-Saharan Africans, and Native Americans had adjusted risk ratios (aRR) $\leq$1.5. Hispanic and Caribbean groups showed aRRs of 1.5–2.0. Asians showed much higher risk, though there was considerable variation within the category "Asian." Most South Central Asians showed the highest risk (aRR = 7.1 for women from Bangladesh, 4.6 for women from Pakistan, and 3.7 for women from India), however women from Iran had an aRR of only 1.3. Women from the east Asian regions of Korea and Japan had nearly the same risk as a non-Hispanic white woman [49]. There is some evidence that Asian women develop GDM at lower BMIs than women of other ethnicities [50].

Studies on ethnic differences in preeclampsia are limited, but data from New York City in 1995–2003 (again subdivided very specifically by geographic origin) showed that East Asian women had the lowest incidence (1.4 %) and Mexican American women had the highest incidence of preeclampsia (5.0 %). Compared to non-Hispanic white women, Mexican women had the highest risk of preeclampsia (aRR 2.9) while African Americans had the second highest risk (OR 2.3). Women from Iran had the lowest risk for preeclampsia, with an aRR of 0.3 [51]. One recent study examined The US Collaborative Perinatal Project (cohort study, n = 60,000), from 1959 to 1966, and found a higher risk ratio for "ischemic placental disease" (IPD, including preeclampsia, small for gestational age, and placental abruption) both at term and preterm for black women [52]. The authors concede that much has likely changed in obstetrical care in the last 60 years, but they stipulate that the pathophysiology of these illnesses should be the same over time [52].

Disparities in Infertility and Assisted Reproductive Technologies

With the caveat that each study mentioned in this book faced the limitations inherent to "defining" racial and ethnic groups, there is a growing body of evidence that health care disparities extend to infertility rates, care utilization, etiologies, and treatment outcomes. Here is an introduction to some of the differences that make these groups interesting to our field; detailed discussions will be provided in subsequent chapters.

Many studies have examined the utilization of reproductive endocrinology and infertility (REI) and assisted reproductive technology (ART) services by ethnic group. Infertility patients tend to be white, educated, and wealthy [53]. Even in states where REI services are covered by insurance, and therefore, total utilization rate is higher, African-Americans have a longer period of infertility before presenting for care and have had less frequent past ART utilization [54]. Black women tend to receive their REI care in low-volume clinics, which can have lower success rates [54]. Hispanics are consistently shown to have lower utilization rates [55]. In a military, equal access to care model, African American patients sought care at levels proportional to their representation, but Hispanic patients did not [56, 57]. Asian patients also have demonstrated a longer delay in seeking care [58].

Infertility etiology or "fertility disease" also varies by ethnic group. Many studies demonstrate significantly higher rates of uterine factor (fibroids) infertility in the African-American populations [56, 59–61]. African-Americans [53, 54, 56, 59–62] and Hispanic patients [53, 55] frequently have higher rates of tubal factor infertility, while white patients have higher rates of endometriosis [54, 55, 60, 61] and ovulatory dysfunction [54, 60]. Lower rates of male factor infertility (which can be easier to overcome) have been demonstrated in infertile black populations [54]. Hispanic women show higher rates of PCOS in some populations, while PCOS rates are comparable between blacks and whites [63].

Outcomes of ART also vary by race. The reasons for this difference is unknown, but may be related to etiology of infertility and the fact that research and development of ART protocols are primarily conducted with Caucasian patients. There may be underlying epigenetic factors as well, as explored above. Many studies report that their African-American patients have reduced success with ART, with lower implantation rates (IR), Clinical Pregnancy rate (CPR), and Live Birth Rate (LBR) [54, 64, 65] though others have shown no differences [61, 62]. Some studies show that pregnancy rate and live birth discrepancies between African Americans and white patients in fresh IVF cycles are actually eliminated for frozen cycles [54]; a group from Walter Reed demonstrated this in a military population [59]. SART CORS data shows a lower pregnancy rate (PR) and lower live birth rate (LBR) for Asian, Hispanic, and black women compared to white women even within BMI categories [60, 66]. However, other studies show that Hispanic women have PR and LBR comparable to white patients, though they have higher ectopic pregnancy rates [55].

Asian patients have demonstrated a lower PR and LBR despite multivariate analysis [67]. Some work shows a trend toward reduced pregnancy rates after IVF in Asian patients [58]. In Asian women receiving donor eggs, there was no significant difference in IR, CPR, and LBR, but the *donors* (all Asian themselves) had higher peak estradiol levels [68]. Studies have also shown Indian patients to have lower CPR and LBR following IVF [69] or transfer of good quality blastocysts [70], though others have not shows any differences [71]. In many analyses, spontaneous abortion is more common after ART in black women, which has been partially attributed to fibroids [65].

Conclusion

The wealth of information about ancestry informative markers and possible ancestry informative epigenetic markers adds a layer of complexity to considerations of race in research and clinical encounters. Especially in modern society, with admixture of groups and rapid cultural changes, humans inherently resist classification. Rather than excluding research subjects with mixed ancestry, researchers should cultivate an understanding that admixture is the rule rather than the exception and seek to include everyone; to do this they may often need to delineate more specific groups. Analysis of AIMs can help, as may future use of panels of epigenetic markers.

For now, clinicians and researchers may use patients' ancestry to help them get a general sense of their underlying genome and epigenome, or as a proxy for socioeconomic, cultural, or educational differences, though this is by no means perfect. Until the era of truly personalized medicine, an awareness, appreciation, and respect for our similarities and our differences will go a long way towards addressing and reducing disparities. Identification of the underlying causes of health disparities and intervention is urgently needed; otherwise poor health is likely carried forward for generations to come.

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Chapter 3
The Impact of Sociocultural and Economic Factors in Seeking Fertility Services

Molina B. Dayal

Introduction

Many studies within the USA and other countries describe the existence of health care access and delivery disparity along racial, ethnic, and socioeconomic lines [1]. According to the National Healthcare Disparities Report published by the Agency for Healthcare Research and Quality (AHRQ) in 2004, "disparities related to race, ethnicity, and socioeconomic status pervade the American healthcare system" [2]. In this report, it is observed that compared to their Caucasian counterparts, African American and Hispanic individuals have worse access to medical care 40 and 90 % of the time, respectively.

While much research encompasses general medicine, a growing body of evidence exists regarding similar disparities within the field of reproductive health. Despite the widespread use and rapid growth of in vitro fertilization (IVF) centers worldwide, the utilization of IVF services has been relatively limited to a highly selective group of individuals. In the USA, multiple studies and national surveys show that those individuals who seek infertility treatment tend to be married, older, more educated, and with higher annual incomes [3–6]. Furthermore, the National Survey of Family Growth (NSFG) show low minority use of infertility care and treatment in the USA [7]. Indeed, Hispanic, non-Hispanic black, and other-race women are more likely to be infertile but are significantly less likely to have ever sought fertility treatment compared to Caucasians [8, 9]. Data from the NSFG indicate that the prevalence for infertility in Black, non-Hispanics is nearly double that of White, non-Hispanics but the utilization of infertility services by Black,

M.B. Dayal, M.D., M.P.H. (✉)
Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Saint Louis University School of Medicine, 6420 Clayton Road, St. Louis, MO 63117, USA
e-mail: molinadayal@yahoo.com

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non-Hispanics is approximately one-third that of White, non-Hispanics [9]. It is unclear whether the observations from these studies are due to a higher prevalence of infertility in certain populations or whether certain populations are better able to access and use fertility services, or a combination of both factors.

Infertility is associated not only with medical factors such as advancing maternal age and pelvic inflammatory disease, but also with socioeconomic, behavioral, and cultural factors including access to fertility care, treatment seeking behavior and cultural beliefs [10]. While rates of seeking infertility treatment are comparable in developed and less developed societies [11], access to care is much more limited in developing societies [12, 13]. Indeed, issues related to cost and access make infertility treatment particularly vulnerable to inequity. However, differences in cultural beliefs between and amongst racial and ethnic groups can further contribute to disparities in fertility service utilization.

On a basic level, infertility is as a condition that affects a couple regardless of which partner may have a functional impairment, thus impacting relationships between an individual and a medical professional, within the couple and larger social networks [14]. This chapter will examine the impact of sociocultural and economic factors that limit access and use of fertility services amongst ethnic groups.

Behavioral and cultural influences on individuals and groups of individuals have historically been difficult to assess given the wide range of qualitative responses, small sample sizes, use of non-standardized measures, and lack of adequate control groups. These ethnographic and survey studies are extremely important as they provide insight regarding the meaning of infertility in an individual's own words [15, 16]. Despite these limitations, reports of several cross-cultural ethnographic surveys assessing these important factors amongst various racial and ethnic groups in both developed and developing countries have been published.

Perceptions of Infertility

Significant differences exist between the experience of infertility in developed and developing societies. Developed societies more often treat infertility as a medical or psychological issue, and pay limited attention to sociocultural issues whereas studies of infertility in developing societies have the opposite emphasis [17].

In many developed societies, women without children are often presumed to be voluntarily childfree. However, in developing countries such as India and Chad, voluntary childlessness is rare [18–20] and is linked to a woman's well-being and social status. In cultures in which there is no concept of being voluntarily childfree, it is impossible to hide infertility [14]. The stigma of infertility, therefore, is likely to be greater in developing countries and can have significant social consequences for a woman and/or couple [15] though it is also seen in multiple racial and ethnic groups within the USA [16, 21, 22]. Forty-nine percent of respondents in a survey conducted in Massachusetts were concerned about the social stigma associated with seeking fertility treatment [16]. While social stigma is more likely to be mentioned

as a point of concern amongst African Americans (OR 3.7. 95 % CI 1.8–6.0) and Asian Americans (OR 7.3. 95 % CI 2.8–19.0), Chinese patients are 59-fold more concerned than Caucasians (OR 59; 95 % CI 6.0–579) regarding the social stigmatization related to fertility treatment. This is further supported by the self-report of Chinese patients being more concerned about friends or family finding out about treatment (OR 18.4, 95 % CI 3.5–96.2) compared to Caucasians [16]. In this survey, all other races or ethnicities sampled are 7–13 times more concerned about friends or family finding out about their fertility treatment. Indeed, for Hispanics, couples without children face derision and public scrutiny, with males experiencing more stigmatization for male causes than their female partners for female derived causes for infertility [15]. For these reasons, couples may decide to face their fertility problems alone, in isolation, and opt not to seek or delay seeking assistance with fertility.

Many societies emphasize motherhood as central to a women's identity more than others [14]. In a study done in Israel, no woman surveyed believed that there was such a thing as voluntary childlessness [23]. Procreation is highly valued, and a source of social status in many cultures within developing societies as well as in African American, Hispanic, and Arab American groups within the USA [21, 22]. Having children is the key to women achieving status and acceptance within the family and the community [24]. The birth of children gives a woman the right to share in her husband's property and wealth in many African societies [25] and in others, is considered essential in the continuation of family lineages [26].

Interviews with infertile women reveal a consistent pattern of thought [27]. These include a feeling of worthlessness and inadequacy, a sense of lack of personal control, anger, resentment, grief, depression, anxiety, stress, and a sense of isolation. Studies on depression and anxiety report mixed findings, with some studies noting women with infertility exhibit more depression and anxiety than others who conceived naturally [28], while other studies [29] find that women undergoing IVF do not differ from their fertile counterparts. In many patriarchal societies, women carry the burden of infertility [14], thus possibly enhancing these feelings. For instance, Egyptian women bear the burden of infertility even when they know there is a male cause [30]. Studies of men also report mixed results. Baluch et al., finds that Iranian men with infertility have higher scores for depression and anxiety, especially if their infertility diagnosis is secondary to a male-factor [31]. A study from Zimbabwe reports that one-third of infertile men show signs of mild clinical depression [32], and another study, longitudinal in design in Europe, concludes that infertility is stressful for men regardless of the source of infertility [33]. In contrast, Monga et al., notes that men in infertile couples do not differ from fertile male controls measured on a scale of psychological well-being [34].

Childless women often complain of domestic violence and disrespectful treatment by their extended families and spouses while some women are completely abandoned, regardless of the cause of infertility [35]. In Bangladesh slums, the "treatment" for infertility is remarriage, even if the cause is due to a male factor, as women are held responsible for infertility [36]. Some traditional beliefs include that male infertility is explained by the belief that the "worms" (or sperm) are weak in Egypt [30], and that infertility may be attributed to a husband's and wife's blood failing to mix or a

woman's marriage to a spirit in Madagascar [37]. In Latino cultures, husbands feel that infertility threatens their masculinity [22] and refuse even to be tested. These beliefs are examples that potentially perpetuate erroneous beliefs and delay appropriate evaluation and treatment of infertile couples.

Delays in Seeking Fertility Services

Interestingly, African Americans and Hispanics delay seeking treatment by more than 15 and 14 months, respectively, compared to white Caucasians [16]. This delay in seeking care corroborates the findings with African Americans in a previous study by Jain, et al. where African Americans have a mean duration of infertility of 4.3 ± 2.6 years compared to 3.3 ± 2.2 years in Caucasians ($p = 0.03$) [38]. In the same study by Jain et al., duration of infertility was similar, however, between Hispanics (3.3 ± 2.0 years), Chinese (3.3 ± 2.3 years), other Asians (3.1 ± 1.9 years) and Caucasians.

On the most basic level, many ethnic groups are uncomfortable receiving gynecological care from a male physician due to their notions of modesty [15]. According to Inhorn, proposed barriers that prevent African American women from seeking treatment include high costs of treatment, lack of knowledge regarding fertility treatment, lack of referrals to fertility specialists and the male partner's refusal to participate in the assessment and treatment of fertility [15]. In the same case study by Inhorn, lack of economic capabilities, lack of awareness of possible treatment resources, and that infertility is a private matter are reported by Hispanics; this population also reports frequent use of traditional, non-biomedical, infertility treatments.

Seeking assistance from traditional health care providers and more Western-style practitioners is common in developing countries [39]. In many societies, Western biomedical interpretations of infertility can coexist and interact with traditional ones [37, 40, 41]. In many developing societies, couples with infertility often will seek the aid of traditional healers before using a more, Western biomedical approach [40]. These traditional healers often are more available and socially accepted [42, 43]. In South Africa, Dyer et al. discovers that one-quarter of female infertility patients had been seeking care for over 5 years with other practitioners before their first appointment at an infertility clinic, therefore significantly delaying appropriate treatment [44]. Thus, the use of traditional interpretations in understanding and treating infertility can greatly delay an individual's access to more appropriate treatment.

Cost of Fertility Treatment

Infertility affects approximately 15 % of all married and cohabitating couples worldwide [45]. Despite the staggering prevalence of infertility, many health care plans do not consider it a medical disease. For this reason, infertility treatment is often regarded as an elective intervention with in vitro fertilization (IVF) services

remaining essentially privately funded in the USA. This is in contrast to many other developed countries such as Australia, Denmark, Finland, France, Germany, Iceland, The Netherlands, Norway, and Sweden that cover infertility treatment, including IVF, within their national health care plans [46].

In addition, the cost of IVF in the USA is prohibitive for many couples affected by infertility. In 2002, the mean cost for a single fresh IVF cycle, without the associated medications, was approximately $9,547 [47]. According to the US Census Bureau, the median household income in 2002, before taxes, was $42,409 [48]. With the cost of an IVF cycle approaching 25 % of an average household income, IVF would be exceedingly difficult to afford, especially if the cost of a multiple pregnancy is included [49].

A similar pattern for IVF cost is seen in developing countries as well. Although the mean cost for an IVF cycle in developing countries can be as low as $1,300 (in Iran), the cost of an IVF cycle in any developing country is greater than half of an average individual's annual income [47]. For this fundamental reason, affluent women in developing countries access and utilize fertility treatments and IVF more readily than poor and middle-class women [50, 51].

In a study conducted by Jain et al., IVF utilization rates are examined using 1998 US national IVF data in states with complete, partial, or no mandated insurance coverage [52]. They note that the utilization rate, defined as the number of IVF cycles per 1,000 women of reproductive age, in states with complete insurance coverage for fertility services, is three times greater (3.35) than is seen in states without any fertility coverage (1.21). These findings suggest that infertile women residing in states without insurance coverage for IVF do not undergo IVF, likely due to financial constraints.

Further disparity exists as certain racial groups, specifically African Americans and Hispanics, are more limited in their ability to undertake diagnostic testing and fertility treatments as their annual incomes are significantly lower than their Caucasian and Asian counterparts [48]. Many minority families, especially recent immigrants, lack health insurance of any kind, further marginalizing these populations from fertility treatment.

Access to Fertility Treatment

As a response to concerns regarding the expense of fertility treatment and possible unequal access to fertility care, multiple states within the USA have passed health care insurance mandates ensuring some degree of insurance coverage for infertility. As a result, many middle-class and working-class couples are able to undertake IVF and other fertility treatments. But, does improving access to fertility care by expanding insurance coverage increase IVF utilization by minority women?

To answer this question, two different equal-access, low cost medical systems in the USA have been examined to determine if fertility service utilization would improve if the cost of IVF is reduced. To assess the impact of insurance mandates

on IVF utilization by various ethnic groups, Jain, et al. conducted a mail survey of 561 women who were treated at a large infertility center in the state of Massachusetts [8]. These investigators note that those individuals who undertake fertility treatment are primarily Caucasian, highly educated and wealthy. African Americans, Chinese and Hispanic patients comprise only 4.5, 4.3, and 3.9 % of the total patients attending this infertility center. These percentages are in contrast to the total population of Massachusetts (in 2000) which was composed of 5.4 % African Americans, 1.3 % Chinese, and 6.8 % Hispanics [53]. This data indicates that African American and Hispanics are under-represented within this infertility population despite having equal access. In contrast, more Chinese patients seem to seek care (4.3 %) than would be expected, based on the overall number of Chinese in the Massachusetts population (1.3 %). All patients within this study, regardless of race or ethnicity, had at least a high school education and more than half had a mean annual income of at least $100,000. African Americans and Hispanics did not seek fertility care despite ease of access and low cost, more education and high average incomes. This study highlights that even in a state with mandated insurance coverage for infertility, disparities continue to exist amongst different racial groups.

Feinberg et al. examined the use of fertility services in the military heath care system at Walter Reed Army Medical Center [54]. In the military health system, any barrier to expensive subspecialty care is reduced regardless of rank or socioeconomic status. In this manner, patients have easy access to the evaluation and treatment of infertility. In this model, it is observed that the proportion of African Americans that undergoes IVF in the military (17.4 %) is similar to the proportion of African Americans being represented within the entire population of the Department of Defense (19.1 %). Most importantly, the proportion of African Americans seeking infertility care within the military is four times greater than the proportion noted in the general infertility population of the USA, thus underscoring the importance of economic factors in IVF service utilization.

McCarthy-Keith et al. specifically addresses IVF utilization by Asians within the same military medical system [55]. Of 1,929 patients that undertook IVF between 2000 and 2005, 5.7 % were Asian compared to approximately the same proportion of Asians being represented in the Department of Defense demographics (4.3 %) and the US SART data (4.5 %). For Asians, lowering the cost of IVF did not appear to significantly increase Asians utilization of IVF.

A very different observation has been noted in the degree of IVF utilization in Hispanics [56]. In a retrospective study of 1,387 patients who undertook IVF from 1999 to 2003 within the low cost military medical system, only 4 % of patients undergoing IVF were Hispanic compared to the 9 % of Hispanics that comprise the population of the Department of Defense. Given equal access to and decreased overall cost for IVF, the difference noted in the proportion of Hispanics using IVF and the proportion of Hispanics within the Department of Defense is significantly greater than expected if only socioeconomic factors impacted IVF utilization. These findings suggest that behavior and cultural beliefs may impact access and utilization of IVF services by Hispanics.

Given the disparate results from the current body of literature, it remains unclear if enhancing access to fertility care by simply decreasing cost improves IVF service utilization. In some racial and ethnic groups, decreasing cost does improve service utilization whereas in others there is little or no impact. However, while this data is informative, it still does not address the relative underutilization of services by all those in need, including minority populations. This data suggest that other influences, such as social, behavioral and cultural factors, must therefore play important roles in IVF service utilization.

It is well described that the level of education attained correlates directly with fertility treatment utilization [3]. Based on a large, nationally representative, general US population survey, the National Survey of Family Growth (NSFG), from 1995, reports that 56 % of all women using fertility services have at least a college degree [57]. While educational level is not assessed within racial groups it was notable that of those that visit fertility clinics, Hispanics and non-Hispanic blacks are 20 and 40 % less likely to undergo IVF, insemination or surgery compared to non-Hispanic whites, a difference which is not significant.

Additional evidence supporting that a higher education leads to more utilization of IVF resources has been found in Massachusetts, a state with mandated insurance coverage for infertility. In Massachusetts, 85 % of infertility patients seeking fertility care have at least a 4-year college degree; 29.6 and 20 % of patients have a Master's or professional/doctorate degree, respectively, compared to the Massachusetts population where 9.3 % of people have a Master's degree and 3.1 % have a professional/doctorate degree [8]. Further support for a higher educational level correlating with IVF utilization is the example of the Chinese population in Massachusetts where greater than 80 % of Chinese women have a Master's or professional/doctorate degree; these women are over-represented in this IVF clinic, comprising 4.3 % of the patients, compared to the percentage of Chinese women in the general Massachusetts population, 1.3 % (difference in percentages significant; $p<0.001$) [38].

Hispanics, as before, display a different pattern of IVF utilization despite their educational level achieved in both the military and mandated insurance setting. Fewer Hispanics within the Department of Defense have less than a high school education (6.5 %) compared to the general US population (36.4 %). In this setting, a higher level of education does not correlate with IVF utilization. In fact, Hispanics comprise 9 % of the Department of Defense population but only 4 % of the patients seen in the Walter Reed ART program [56]. Despite being more educated, Hispanics within the Department of Defense utilize IVF less frequently, a finding that contrasts other studies that observe high utilization of IVF with advancing education [5, 6]. Studies indicate that nearly 60 % of Hispanics in a Massachusetts clinic have at least a 4-year college degree. Again, despite the high level of education achieved, Hispanics tend to underutilize IVF, even with mandated insurance, as only 3.9 % of IVF patients are Hispanic compared to the 6.9 % of Hispanics that comprise the general population of Massachusetts.

Studies have shown that Hispanic patients are intimidated by biomedical language, suggesting that language barriers may prevent access to fertility care in the USA [22].

However, this explanation might be too simple as it does not explain the IVF utilization amongst Hispanics within the military health care system. All Hispanics within the military must pass the English Comprehension Level test, thus ensuring that at least one member of a Hispanic couple comprehends and speaks English [56]. In this specific instance, a language barrier should not have impacted these patients' utilization of IVF.

In many studies, it appears that the female partner is much more likely to seek initial treatment than male partners [58, 59]. Despite being treatment-oriented, women find the experience of treatment highly stressful and unpleasant [60–62]. In the USA, Missmer et al., observe that African Americans are 4.6-fold more likely (95 % CI 1.0–22.3) to self-refer to a fertility clinic compared to Caucasians, whereas Hispanics are 4.3 times more likely (95 % CI 1.9–9.9) to be referred by a friend or family member [16].

More recently, a survey study was undertaken to assess demographic, cultural, and socioeconomic characteristics among 743 women attending a fertility clinic in the state of Illinois (has mandated fertility coverage) [16]. Based on these self-reported questionnaires, African Americans are 6 times more likely to report difficulty in finding a physician with whom they were comfortable (OR 6.6; 95 % CI 2.8–15.4), 4.6 times more likely having difficulty taking time off from work (4.6; 95 % CI 2.4–9.0), and 10 times more likely to experience difficulty getting an appointment with a physician (OR 9.9; 95 % CI 3.3–29.8) compared to white Caucasians. Hispanics fare similarly with regards to finding a physician with whom they were comfortable (OR 3.4; 95 % CI 1.4–8.3), taking time off of work (OR 6.8, 95 % CI 3.3–14.0), and in scheduling an appointment (7.2; 95 % CI 2.5–21.0) compared to Caucasians.

It could be that, as new fertility treatments become available and more widely used that they will become more acceptable to a variety of ethnic groups. However, certain family-building strategies are not acceptable to some ethnic groups. In general, the biomedical description of procreation and associated treatment strategies can be disturbing and even threatening to many ethnic groups seeking fertility treatment [63]. Religion plays a major role in the determination of fertility treatment options. Islam prohibits adoption because there are no blood ties to the father and no maternal bond [64] Use of donor eggs and donor sperm is also disallowed for the same reason within the Islamic belief system [21, 32]. Thus, treatment options are limited in couples with a severe male sperm abnormality or multiple unsuccessful treatments. In Latin American countries, the Catholic Church does not approve of IVF and attempts to limit infertile couples' access to IVF centers. Adoption is socially acceptable for treating infertility within the Catholic Church [65]. In a survey performed in the USA, God's will (OR 3.1, 95 % CI 1.5–6.1), personal control (OR 4.3, 95 % CI 2.3–8.1), chance (OR 4.2, 95 % CI 2.3–8.1), and religious faith (OR 2.8, 95 % CI 1.5–5.4) are more frequently cited as possible factors in the ability to bear children by African Americans compared to Caucasians in the USA [16]. A similar belief system is noted with Hispanics where Hispanics were more likely to cite personal control, God's will, chance, and religious faith compared to Caucasians. However, compared to Caucasians, Asian Americans are less likely to cite God's will (OR 0.3, 95 % CI 0.1–0.9), chance (OR 0.6; 95 % CI 0.2–1.6), and

religious faith (0.3, 95 % CI 0.1–0.7) as important factors [16]. In the same study by Missmer et al., Catholic women are five times more likely than Protestant women to have self-referred for fertility treatment and nine times more likely to report difficulty in obtaining fertility treatment due to their religious beliefs.

Some racial and ethnic groups believe that their access to fertility care is limited due to their race. In the USA, African Americans self-report having 72 times the difficulty in getting infertility care due to their race (OR 72; 95 % CI 14–378), compared to Caucasians [16]. They are also 33-fold more likely to worry about fertility treatment based on the historic misuse of medical treatment in their community compared to Caucasians (OR 33.2, 95 % CI 7.7–143). The same increased difficulty in accessing care due to race is reported by Hispanics compared to Caucasians (OR 36, 95 % CI 6.6–195). Asian Americans, however, do not report any increased difficulty in accessing care based on their race.

Concluding Remarks

This chapter summarizes the contributions of sociocultural and economic factors, in addition to known physiological pathology, that can impact a women's desire to seek fertility care. The data on economic factors suggest that if access to fertility services is indeed equal, then a greater number of minority women would be expected to seek care. As noted, equal access does not equate to equal utilization. Income and educational characteristics may lead to improved access to fertility care but cultural differences in the acceptance of certain fertility treatments are likely as important [66].

Indeed, little is known regarding the social, behavioral and cultural factors that dictate seeking fertility care. Studies are beginning to emerge assessing some of these factors. Research and analyses are moving in the direction of placing the experience of infertility within its social context by bringing sociological and sociopsychological theories to bear on the experience of infertility [14]. However, it can be argued that many of these studies provide little, if any, information about half of the infertile female population, as these women have not sought treatment. Without studies of women opting not to seek fertility treatment, it is impossible to determine what factors differentiate those who do seek treatment from those who do not [14].

Utilization of medical resources by different racial and ethnic groups is dependent on a myriad of factors. While lack of appropriate information, racial discrimination, and lack of referrals from primary care physicians may impact an individual's decision to seek fertility care, a complex and dynamic interplay of socioeconomic, behavioral, and social influences can also significantly influence decisions regarding medical care at both the individual and the greater racial and ethnic group level. As the USA attempts to provide better individual access to high quality fertility services with insurance mandates, it will be exceedingly important to become culturally competent, to understand these racial and ethnic groups based on their anthropologic influences, so that the pervasive and persistent disparities between groups can disappear.

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Chapter 4
Fertility Differences Among Ethnic Groups

Kate Devine, Lisa Green, Heba Eltoukhi, and Alicia Armstrong

Introduction

As a result of its strong immigrant history, the USA has a racially and ethnically diverse population. Within this diverse population, women's reproductive experiences vary considerably by demographic characteristics such as education, income, and race [1]. According to the National Survey of Family Growth (a large, longitudinal women's health study conducted by the US Department of Health and Human Services and the Center for Health Statistics) approximately 2.1 million married women (7.4 %) are estimated to be infertile. Black, non-Hispanic females reported higher rates of infertility (11.5 %) compared to white non-Hispanics (7.0 %) and to Hispanics of any race (7.7 %). It is unclear whether this difference is due to a true racial disparity in natural fecundity rates, given the racial/ethnic differences in the utilization of infertility services that could account, at least in part, for this difference. Older, educated Caucasian women are more likely to utilize medical care for

K. Devine, M.D. • H. Eltoukhi, M.D.
Program in Reproductive and Adult Endocrinology,
NICHD, National Institutes of Health, 10 Center Drive, Bethesda, MD 20892, USA
e-mail: kate.devine@nih.gov; heba.eltoukhi@nih.gov

L. Green, M.D., M.P.H.
Department of Obstetrics and Gynecology, Howard University,
2041 Georgia Avenue, Washington, DC 20060, USA
e-mail: lisa.green@howard.edu

A. Armstrong, M.D., M.H.S.C.R. (✉)
NICHD, National Institutes of Health, 10 Center Drive, MSC 1109,
Bethesda, MD 20892, USA
e-mail: armstroa@mail.nih.gov

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infertility [2], and in certain states with mandated insurance coverage for infertility, ethic disparities in utilization persist. In a cross sectional survey by Jain et al., 1,500 consecutive females presented for evaluation in a state with mandated infertility service coverage, and African American women reported a longer duration of infertility prior to seeking treatment compared with Caucasian women (4.3 vs. 3.3 years, respectively; $p = 0.03$) [1].

Historically, fertility research has focused on consumers of high cost elective procedures, such as ART. Since this population has included only small numbers of minority participants, exploration of racial/ethnic disparities in fertility has been limited. In the USA, the military health services system provides a model where income-based access to service is largely negated. Within this system, universal insurance covers indicated infertility evaluations, and ART is offered at a relatively lower cost, resulting in greater access to care across racial groups. Therefore, within the military health system, minority representation more closely mirrors that of the population at large. A study by Feinberg et al., conducted within this military health system, demonstrated enhanced access by African American patients but not Hispanic patients. The study also found a significant decrease in live birth rate and increases in spontaneous abortion and uterine leiomyomas in African American women compared to Caucasian women [3].

This chapter explores ethnic/racial disparities surrounding fertility/infertility issues and provides evidence from the literature supporting hormonal, metabolic, anatomic, and cultural factors which may affect natural fertility. The focus will be on *unassisted* reproduction. Current available information on racial and ethnic differences in unassisted reproduction and infertility, specific to patients outside the USA is also reviewed.

Ethnic Differences in Male Fertility

Male factor accounts for approximately 40–50 % of couples' infertility, making it the most common identifiable reason for difficulty conceiving [4]. There is a reasonable body of evidence to suggest that ethnic differences exist in semen parameters, testicular architecture and function [5], sperm susceptibility to medications [6–11], and incidence of genetic changes associated with infertility [12]; however, these findings are preliminary, resulting from small studies, generally comparing only two populations. Few data are available defining the relationship of ethnicity to incidence and etiologies of male factor infertility.

Sperm Parameters

The most recent World Health Organization (WHO) semen analysis manual provides the lower reference limits of semen parameters based on samples from men whose partners conceived in 12 months or less. Samples were from men on three continents: Australia, Europe, and North America [13]. The other continents, Asia,

Africa, and South America, and many regions of the included continents, such as Southern Europe, were not represented in the raw data used to generate the reference limits. This is significant, given that regional differences in sperm parameters are well established [14–18]. Furthermore, sub-analyses of semen parameters according to ethnic group were not reported.

Comprehensive, normative sperm parameters for fertile men by ethnic group have not been defined, even for sperm concentration. Were sperm production to be equivalent among ethnic groups, it is still possible that ethnic differences exist in competency of sperm for fertilization. These might manifest themselves grossly as differences in sperm motility or morphology. Alternatively, there may be ethnic differences in sperm characteristics not evaluable by current clinical testing. For example, normal fecundity could result at different levels of sperm production, motility, and/or morphology in different ethnic groups, altering the 5th and 95th centiles and necessitating distinct normal ranges for different ethnic groups. For example, in a population where a higher percentage of men were successful in impregnating their partner within 12 months, the lower limit of normal for some or all parameters may need to be lowered [19]. The WHO manual acknowledges this with the statement: if "differences are revealed, their mechanism and significance for fertility will need to be studied before it can be decided whether there should be specific reference values for different ethnic groups or regions" [13].

One factor likely contributing to the paucity of data regarding ethnic differences in male fertility/infertility is the difficulty that has been encountered in obtaining volunteers for reproductive studies involving semen analysis. Rates of acceptance for requests to donate semen for research purposes have been in the range of 13–19 %. Low response rates may introduce bias [13]. In the setting of low response, certain ethnic groups are often underrepresented, making comparison impossible while also compromising generalizability. Though this barrier will be difficult to overcome, understanding the impact of race and ethnicity on baseline normal and abnormal fertility states and their responses to treatment is essential to providing the best individualized care to infertile couples from varied backgrounds.

Anatomic Differences

While androgen or androgen-progestin contraceptives induced azoospermia in only 60–70 % of Caucasian men [6, 7], they successfully induced azoospermia in >90 % of Chinese and Indonesian men [8–11]. Johnson et al. [5] sought to determine why spermatogenesis in Asian males is more susceptible to steroidal contraceptives via postmortem studies of testes from Chinese, Hispanic, and Non-Hispanic Caucasian men at a mean age of 29. Chinese men were found to have lower parenchymal weight, number of primary spermatocytes, spermatocyte density, and diameter of seminiferous tubules. Hispanic men had a lower Sertoli cell density. Chinese men had higher density Leydig cell cytoplasm. Though fertility data on these men were not available for correlation with these findings, the data provides basis for the concept of difference in the structure and function of spermatogenic anatomy among ethnic groups.

Genetic Differences

If significant ethnic differences in male fertility exist, genetic variation provides a likely explanation. Ethnic variation in mutation frequency in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which is associated with congenital bilateral absence of the vas deferens (CBAVD) is well documented. Caucasians of European or Ashkenazi Jewish descent demonstrate a carrier frequency of 1/24 to 1/25, while African Americans, Hispanics, and Asian Americans have carrier rates of 1/61, 1/58, and 1/94, respectively [20, 21]. In a recent report of unselected infertile men, 14.3 % of 2,242 patients had karyotypic abnormalities, of which Klinefelter syndrome (47 XXY) was the most common, and incidence is not known to vary significantly by ethnicity: 3.6 % of 2,749 patients had Y-microdeletions by PCR-based assessment [22].

The azoospermia factor (AZF) region on the long arm of the Y chromosome includes three discrete regions, mutations of which are associated with varying degrees of impaired spermatogenesis [23]. Widely variant incidences of Y-microdeletions have been reported from study to study, largely owing to differences in patient selection with regard to degree of oligospermia. Logically, the frequency of Y-deletions increases with severity of spermatogenic defect [24], with microdeletions detectable in approximately 15 % of azoospermic and 5–10 % of oligospermic men [25]. However, Osterlund et al. evaluated 192 consecutive Swedish men with <5 million sperm per milliliter via multiplex PCR using 13 primer pairs and found microdeletions in only 4 men, all of whom were azoospermic, suggesting a very low mutation frequency in the Swedish population and implicating that Y-chromosome microdeletions likely vary widely by ethnic group [26].

Sachdeva et al. propose that the wide variation in reported mutation frequency is partially attributable to the number of markers tested. Furthermore, ethnicity-specific Y-microdeletion panels may be warranted [27]. In the 200 Indian males tested, all of whom had sperm concentration less than or equal to 5 million/mL, 3 % had microdeletions when the six sequence tag site (STS) markers prescribed by the European Academy of Andrology (EAA) were used. In 1999, Simoni et al. reported that the EAA panel detected over 90 % of AZF microdeletions [28]. However, when an additional 16 STS markers, derived from studies in Indian men were tested, an additional 7.5 % of their population were found to have microdeletions, suggesting a role for ethnicity-specific STS panels for maximal detection of Y-microdeletions among azo/oligospermic men.

The much studied Y chromosomal DAZ (deleted in azoospermia) gene family is located in AZFc and has two autosomal analogues: BOULE and DAZ-like (DAZL). A single nucleotide polymorphism (SNP) in the latter has been reported as a susceptibility factor to infertility in the Chinese population, occurring in 7.39 % of infertile men vs. 0.86 % of controls [29]. In contrast, the SNP was not detected among 242 infertile and 229 normo-spermic Italian men [12]. In combination, the existing data strongly suggest ethnic differences in the genetic determinants of male fertility, and further study is warranted in order to optimize testing of infertile males.

Male Patients' Utilization of Medical Services for Fertility

Finally, it is clear that within the USA, as with women, racial and cultural background are associated with varied norms in terms of sexual behavior and age at onset of parenthood, which inversely correlate with ultimate rates of childlessness (voluntary and involuntary) and the need for infertility services. Interestingly, survey data showed that though socioeconomic status was highly associated with male respondents having "reported a visit for help with having a child at some point in their lifetime," race/ethnicity was not [30]. In the study, Hispanics and blacks were sampled at higher rates than whites in order to obtain greater adequate data on these groups for analysis; however, fewer than half as many responses were obtained from blacks and Hispanics relative to whites. Overall response rate was 78 %. Response rates by race were not given. Response rates may have been lower in these groups, and minorities of higher socioeconomic status may have been more likely to respond. Encouragingly, race was still not significantly associated with utilization of fertility services among males, when multiple logistic regression was performed to control for socioeconomic status.

Though it is encouraging to see equal reporting of fertility service utilization in these minority groups of males, there is discord with regard to the proportion of fertility patients minority couples comprise relative to their proportion of the general population [2]. This is likely secondary to the overall lower socioeconomic status of minority groups, which makes high-cost fertility services inaccessible, rather than unwillingness to use them or unawareness of their availability.

Ethnic Differences in Tubal/Peritoneal Infertility

Tubal factor infertility (TF) constitutes the second most common etiology of infertility. Tubal and pelvic pathology is reported as a cause of infertility in 35 % of couples regardless of age [31]. According to the CDC, TF is the *primary* diagnosis for approximately 9 % of patients using ART [32]. Common gynecologic pathologies associated with tubal obstruction and/or functional impairment include postsurgical adhesive disease, pelvic inflammatory disease (PID), and endometriosis, the latter two of which are thought to exhibit ethnic variation in incidence. Another common reason why patients may require IVF is a history of tubal sterilization, which also varies significantly by ethnic/cultural background.

Multiple recent studies have demonstrated higher rates of TF infertility in African-American patients vs. white women: in a 2011 study looking differences in FET pregnancy rates by ethnicity, 64 % of African-American (AA) vs. 31 % of white patients met criteria for this diagnosis [33]; in 2010 Seifer et al. reported that black non-Hispanic patients were 2.5 times more likely to have TF at presentation for first IVF [34]; and in 2009 Dayal et al. reported 23 % TF in AA patients vs. 9 % in Caucasian women presenting for initial IVF [35].

This section will focus on the etiology of these ethnic differences in pathologic conditions affecting the fallopian tubes and peritoneum.

Endometriosis

Endometriosis varies widely in its clinical presentations, and one common manifestation is fallopian tube obstruction and/or functional impairment. The relatively low incidence of TF infertility in Caucasian patients exists despite a historic belief that an increased susceptibility to endometriosis exists in this group relative to AA. An incidence of 1.6 per 1,000 has been reported in white females [36]. A large study of 116,678 women from the Nurses' Health Study II demonstrated 241 cases per 100,000 person-years for white vs. 145 cases per 100,000 person years in AA women, resulting in a statistically significant multivariate rate ratio of 0.6. The study population was overwhelmingly white [37].

Interestingly, Asian women are thought to have the highest risk of disease, with an OR of 6.3–8.6 relative to white women [38]; however, the data from the Nurses' Health Study II population does not confirm this difference [37]. A study comparing findings at laparoscopy in 202 Malaysian infertile women vs. 464 British infertile women uncovered a diagnosis of endometriosis in 51 % vs. 22 % respectively [39].

Ethnicity-associated polymorphisms have been identified and postulated to underlie the increased susceptibility to endometriosis among Asian women [40, 41]; however, Tempfer et al. concluded in their 2009 systematic review of 114 publications that polymorphisms are unlikely causative of endometriosis [42].

Overall prevalence of endometriosis remains unknown, given that it is a surgical diagnosis and that asymptomatic women are generally not operated upon. Therefore, the above noted ethnic differences may be largely attributable to differences in laparoscopy rates. Some studies have suggested that the lower observed incidence in AA and African-indigenous women may be due to lifestyle factors (such as early pregnancy and increased prevalence of STIs, resulting in tubal occlusion, which may prevent efflux of endometrium-derived cells into the peritoneum) and/or to methodological problems interfering with accurate detection. For example, lower suspicion for the disease among clinicians may result in less rigorous diagnostic evaluation and lower rates of laparoscopy in AA women [43]. Undoubtedly, prospective, standardized studies are needed in order to determine definitively whether black women are truly at lower risk of this disease, as inappropriately low suspicion for disease by clinicians may propagate under-diagnosis and under-treatment.

More studies are also required comparing response to treatment for endometriosis according to race. A recent meta-analysis revealed two studies comparing dienogest and GnRH analogue response rates in a European endometriosis population vs. a Japanese one. No heterogeneity in response was observed according to ethnicity, and the two agents were shown to have equal efficacy in controlling pelvic pain in women with endometriosis [44]. Response to other treatment modalities and among other groups warrants evaluation.

Pelvic Inflammatory Disease

The disparately higher rates of TF in AA women derive from the documented higher incidence of PID in this population. Incidence of infertility increases with number and severity of pelvic infections. Women with laparoscopically confirmed salpingitis and three prior episodes of clinically recognized PID have a relative risk (RR) of 28.3 for infertility compared with controls [45]. In 2010, Miller et al. published that from 2004 to 2005 there was a 6.8/10,000 female population hospitalization rate for PID among blacks vs. 3.4/10,000 among white women in Texas. Hispanic women had the lowest PID-related hospitalization rate at 1.8/10,000 [46]. In California, from 1991 to 2001, AA aged 20–39 years had the highest hospitalization rates compared with other racial groups [47].

The higher rates of PID among AA are linked to an established higher prevalence of chlamydial and gonococcal infections in this population. As recently as 2011, it was reported that at 8.3 % positivity, AA high school students continue to be significantly more likely than students of any other ethnicity to screen positive for these infections [48]. Clearly, greater education and outreach is needed in this population with regards to the importance of STI prevention and its relationship to future fertility.

Tubal Sterilization

Tubal sterilization is the most common means of contraception among women older than 30 years in the USA [49] and is accompanied by up to 7 % regret and 1 % request for reversal [50, 51]. Women who choose to pursue child-bearing post surgical sterilization require costly therapy, in the form of either IVF or surgical reversal. The latter is associated with ectopic pregnancy rates up to 12 % [52]. Data from the 2002 National Survey of Family Growth, which surveyed 7,643 women, revealed AA women to have a 1.43 odds ratio (OR) compared with white women, with regards to likelihood of undergoing tubal sterilization (95 % confidence 1.08–1.88) [53]. A separate survey performed by the same group attempted to determine the reasons for this difference and found that AA women were more likely to list the following as important factors leading to their decision to undergo sterilization: their mother's influence, prior unintended pregnancy, and avoidance of foreign object insertion. The following misconceptions were also more common among black than among white women: sterilization reversal easily restores fertility; spontaneous reversal of sterilization occurs after 5 years; men cannot ejaculate post-vasectomy [54]. Better patient education and physician counseling is again needed in this domain.

Ethnic Differences in Uterine Leiomyoma

Uterine fibroids, particularly those submucosal in location, have been associated with impaired fertility and miscarriages, as well as with symptoms of menorrhagia and pelvic pain.

Many studies have reported increased leiomyoma rates among AA patients. Baird et al. performed ultrasound on 1,364 randomly selected 35–49 year old women and found that the cumulative incidence of fibroids at the upper age limit was >80 % for AA women. Interestingly, it was notably high for white women as well at nearly 70 %. Age-specific cumulative incidence was plotted and was significantly higher for AA women (OR 2.9 95 % CI 2.5–3.4, $p<0.001$) [55]. Data from the Nurses' Health Study II revealed AA women nearly three times more likely to be diagnosed with fibroids by any mode of detection [56]. In a 2011 study looking at differences in FET pregnancy rates by ethnicity, 40 % of AA vs. 10 % of white patients carried a fibroid diagnosis [33]. Weiss et al. reported on 203 women undergoing hysterectomy for benign conditions, and leiomyoma was the indication in 85 % of AA vs. 63 % of Caucasian women ($p=0.02$) [57].

Ethic Differences in Clinical Presentation of Fibroids

Fibroids appear to be more severe, faster growing, and earlier in onset in AA women. Huyck et al. collected data on 285 sister pairs with uterine leiomyomata and found that on average, AA women were diagnosed 5.3 years younger than white women ($p<0.001$) matched for socioeconomic status. In addition, AA women were more likely to report menorrhagia and/or having had multiple myomectomy or hysterectomy ($p<0.001$) [58].

Studies provide evidence that at time of surgical management, the fibroids of white women are smaller than those of AA women. In one study, hysterectomy specimens, weighed an average of 102 g less in white women [59], whereas in another, specimens weighed 208 g less [60]. White women also had a statistically significantly lower number of fibroids at myomectomy and were half as likely to have a complication or require blood transfusion. Differences in complications and need for transfusion did not hold, however, after controlling for size and number of fibroids [61]. In addition, it is important to bear in mind that the size and number of fibroids may be affected by such factors as the duration of disease prior to surgery as well as surgical approach and treatment goals, which may be vary by race.

There is also evidence that, at least in older women, fibroids exhibit a faster rate of growth in AA women. A study followed 262 fibroids by MRI over the course of a year in 38 black and 34 white premenopausal women and observed an overall median growth rate of 9 %. In women <35 years old, there was no difference in growth rate between AA and white women; however, growth rates were lower in white women 35 years and older, compared with their younger counterparts, while in AA women, rate of growth did not decline with age ($p<0.05$) [62].

Risk Factors for Fibroids May Vary by Race

In a multicenter study of 1,585 women assessed at time of laparoscopy for tubal sterilization, 16 % of AA women and 9 % of white women were found to have uterine fibroids. Advancing age was a risk factor for both AA and white women; however, nulliparity, length of time since last delivery, one pack/day or greater lifetime cigarette use, prolonged menstrual cycle, and prolonged menses were risk factors for white women but not for AA women [63].

Proposed Etiologies for Increased Prevalence and Severity of Fibroids Among African Americans

On a molecular level, polymorphisms, especially in genes involved in estrogen processing, have been postulated as contributing to the high prevalence, larger size, and more aggressive course of fibroids in AA women [64]. Importantly for steroidogenesis, *CYP17* encodes cytochrome P450 C17-alpha, which is involved in 17-alpha-hydroxylase and 17, 20 lyase activation [65]. A *CYP17* single base pair polymorphism has been associated with increased estrogen and progesterone levels [66]. Homozygosity for the A2 genotype of this polymorphism was associated with higher risk for fibroids on hysterectomy specimens in black South African women [67].

Catechol-O-methyltransferase (COMT) conjugates 2,4 methoxy estradiol from 2,4 hydroxy estradiol. There exists a common single base pair polymorphism resulting in a protein with one-fourth the enzymatic activity of the wild type [68]. Homozygosity for this polymorphism (from myometrial tissue and serum) was statistically associated with the presence of fibroids at hysterectomy, and among AA, Hispanic, and white women, AA women had the highest frequency of this genotype at 47 % (vs. 19 % in white women) [69]. Two polymorphisms encoding differences in estrogen receptor restriction sites have also been identified and found to vary by ethnicity. Homozygosity for polymorphism encoding the absence of the site recognized by the P*vull* endonuclease has been associated with a higher risk of fibroids in AA and white women. Hispanic women did not demonstrate this association. This genotype was most frequent in AA women at 35 % [70].

A study of 31 AA, 34 Caucasian, and 36 Japanese women compared aromatase mRNA levels in fibroids vs. surrounding myometrium. Transcripts were 83 fold higher in leiomyoma tissue relative to myometrium in AA women vs. 38 fold in Caucasian women and 33 fold in Japanese women. The authors further isolated the increased aromatase expression in AA women to the proximal promoter II of the CYP18A1 gene (the gene encoding aromatase). The authors hypothesized that the marked increase in aromatase expression in the fibroids of AA women may lead to higher estrogen levels which could have a mitogenic effect, accounting for the greater size and number of fibroids observed in African-American women [71].

The same study sought to evaluate myoma estrogen receptor alpha and beta expression in the same three groups. Estrogen receptor (ER) alpha expression was 1.8–2.6 fold higher than in corresponding myometrium in all groups. Interestingly, fibroids of Japanese women also had elevated transcripts of ER-beta and had higher levels of progesterone receptor transcripts than did the other two groups [71]. Wei et al., via immunohistochemical assessment of high-density micro-array, found ER alpha was more highly expressed in both leiomyomata and normal myometrium of AA women but that the relative expression (leiomyoma: myometrium) did not differ significantly from Asian, Hispanic, or white women. However, progesterone receptor A (PR-A) was upregulated in fibroids of AA women relative to myometrium, and retinoid acid receptor alpha as down-regulated, both statistically significantly, relative to other ethnic groups [72].

Retinoic acid metabolism has been shown to be aberrant in leiomyomata [73], and treatment of leiomyoma cells with all-trans retinoic acid has been shown to inhibit their proliferation and to induce an extracellular matrix protein expression pattern more similar to that of myometrium [74].

These potential differences in pathophysiologic mechanisms may indicate different first line medical therapies for fibroids depending on ethnicity. For example, some have postulated that given higher levels of aromatase expression in fibroids of AA patients, aromatase inhibitors may provide better symptom reduction than other agents such as gonadotropin releasing hormone analogues, combined oral contraceptive pills, and anti-progestins [75]. Clinical trials are currently under way to address this question [76].

Characteristics of Fibroids in Other Races

There is little available evidence regarding fibroid prevalence, character, and treatment response in groups other than blacks and whites. The largest cohort is again that of the Nurses' Health Study II, which indicated that prevalence in Asian and Hispanics is equivalent to that in white women [56]. On the other hand, a study performed among school teachers suggested that Hispanics are significantly more likely than whites to have fibroid surgery (OR 1.3; 95 % CI 1.1–1.6) [61].

In addition to further study of fibroid characteristics in Asians and Hispanics, more rigorous clinical study and more effective recruitment of AA, who are clearly the most severely affected, is also necessary. Taran et al. recently reviewed 106 studies that were included in the Agency for Healthcare Research and Quality (AHRQ) report on fibroids and found that the vast majority did not report race and ethnicity. Black women made up approximately 50 % of study participants in the studies reporting race. However, modeling used to estimate the enrolment of black women in studies where race was *not* reported indicated 15 % of all study participants to be black women, which is far fewer than representative, give the high disease prevalence in this group [77].

Ethnic Differences in Obesity and Metabolism and Their Effect on Fertility

Obesity, defined as a body mass index (BMI) greater than 30 kg/m^2 in adults, is a complex and multi-factorial chronic disease affecting both general and reproductive health. Established influential factors on BMI include genetics, metabolism, diet, exercise, environment, culture, and socioeconomic status.

The association between obesity and infertility has been extensively investigated and well documented. It appears that the effect of obesity on reproductive function can occur as early as adolescence, with obese adolescent girls presenting with a younger age of menarche than average sized controls [78].

Adipose tissue is an active participant in steroid production and metabolism. It converts androgens to estrogens, estradiol to estrone, and dehydroepiandrosterone to androstenediol. In peripheral obesity there is no significant difference in circulating androgens, though rate of clearance seems to be affected. However, in central obesity, altered androgen levels and clearance rates are observed [79].

Obesity's interference with the hypothalamic pituitary ovarian (HPO) axis leads to an-/oligo-ovulation, menstrual irregularities, and reduced conception rate. The presence of obesity also portends poor obstetrical outcomes, increasing the rate of miscarriage and adverse maternal and perinatal outcomes. The current recommendation is that obesity, particularly abdominal obesity, be treated prior to or concurrently with fertility treatment. Although detrimental, obesity is a modifiable risk factor with various treatment options, ranging from diet and exercise to pharmacological and/or surgical interventions.

Racial Disparities in Obesity

Although there has been an overall increase in obesity in the USA across all racial/ethnic groups and ages, the greatest increases have occurred amongst Hispanic and AA women. The prevalence of obesity (BMI $\geq$ 30) in Non-Hispanic black women is 49.6 % compared to 43 % in Hispanic and 33 % in Non-Hispanic white women. Currently, there is no gender-specific data available for Asian Americans, Native Americans, Alaska Natives, and Native Hawaiians or Other Pacific Islanders, but the overall prevalence of obesity is lower in these ethnic groups with 8.9 % of Asian Americans, 32.4 % of Native Americans and Alaska Natives, and 31 % of Hawaiian or other pacific islanders affected [80]. The origin of these differences in obesity prevalence amongst racial and ethnic groups is complex and not well understood. A multitude of dietary, behavioral, genetic, and socioeconomic factors likely contribute [81].

According to Behavioral Risk Factor Surveillance System (BRFSS) 2005 data, the estimated prevalence of eating fruits and vegetables five or more times per day was significantly higher among Asian/Pacific Islander women (35.9 %) than Non-Hispanic white women (28.8 %). AA tend to eat higher-calorie, nutrient-poor foods that are

highly palatable and inexpensive. Theses dietary choices, which are contrary to current health recommendations, may be secondary to habit, cultural norms, and accessibility. Potential barriers to healthy food access include the following: [1] paucity of supermarkets and produce stores in neighborhoods with large minority populations and [2] higher cost of healthful, energy-dense foods [82].

Minority and low-income populations also have limited access to physical activity facilities and safe areas in which to engage in non-occupational physical activity. According to the BRFSS 2005 data, regular (non-occupational) physical activity was significantly lower among non-Hispanic blacks (36.3 %) and Hispanics (42.3 %) than among non-Hispanic whites (49.8 %). AA also tend to engage in physically demanding jobs with low pay, which may discourage leisurely physical activity. In inner city neighborhoods, crime and traffic are not conducive to outdoor, inexpensive exercise (e.g. walking). According to the Centers for Disease Control, only 24–36 % of AA adults participate in regular physical activity.

Ethnic disparities in body image may also contribute to higher minority obesity rates. Both non-Hispanic black and Hispanic women are more satisfied with their body size than non-Hispanic white women. These differences in cultural attitudes regarding body weight may dissuade them from actively trying to lose weight [83].

Metabolic Consequences of Obesity

Male and female obesity adversely affect fertility and reproductive outcomes. In a prospective study of 12,000 American women by Hartz et al., obesity and waist-hip ratio were found to be independently and positively correlated with the presence of irregular menstrual cycles, oligomenorrhea (menstrual cycle >36 days), and hirsutism. These changes arise secondary to increased androgenicity, insulin resistance, and increased levels of luteinizing hormone [84]. They are central to the pathophysiology of polycystic ovary syndrome, which disproportionately affects AA and Hispanic women and is discussed in detail later in this chapter.

Obesity is the principal cause of insulin resistance. Insulin resistance syndrome (IRS) commonly referred to as metabolic or dysmetabolic syndrome is defined as the presence of three or more of the following criteria [85]:

1. Abdominal obesity (waist circumference more than 102 cm in men and more than 88 cm in women)
2. Hypertriglyceridemia [≥150 mg/dl (1.69 mmol/l)]
3. Low level of high density lipoprotein (HDL) cholesterol [<40 mg/dl (1.04 mmol/l) in men and <50 mg/dl (1.29 mmol/l) in women]
4. High blood pressure (≥130/85 mmHg); or
5. High fasting glucose [≥110 mg/dl (≥6.1 mmol/l)]

An analysis of NHANES III data showed [86] that the prevalence of IRS may not perfectly mirror obesity prevalence. Although AA women have the highest prevalence of obesity, the prevalence of IRS is highest in Mexican American women, followed by Mexican American men, then by AA women [86].

Another predictive marker of IRS, low HDL levels, may also have a paradoxical relationship in the AA population. Previous longitudinal studies have shown that HDL levels are negatively correlated with age. A cross-sectional analysis of 2,420 participants in the Jackson Heart Study, found that HDL-C levels actually increase with age in AA [87]. These findings illustrate that although AA tend to have and increased cardiovascular risk profile (i.e. increased insulin resistance, prevalence of diabetes, blood pressures, and BMI) they may have a more favorable lipoprotein profile than Caucasian Americans.

Effect of Obesity on Menstruation

The effect of excess body fat on menstruation has long been recognized. A classic study by Mitchell et al. reported that menstrual dysfunction was four times more likely in obese women than in normal weight women [88]. In a cross sectional study of 726 women aged 26–36 years of age, Wei et al. found obese women to have two-fold greater odds of irregular menses (OR = 2.61; 95 % CI = 1.28–5.35) [89]. In a study by Lake et al., using the 1958 British Birth Cohort Study, data was extracted for 5,799 females at varying ages on height, weight, and presence of menstrual irregularities. The authors found that obesity at ages 23 years (OR = 1.75) and 7 years (OR = 1.59) independently increased the risk of menstrual irregularity by age 33 after adjusting for other confounders. Women who were overweight at 23 years (BMI 23.9–28.6 kg/m^2) were 1.32 times more likely to have menstrual irregularities [90]. Such irregularities are generally due to ovulatory disorders, which are discussed in detail in the following section of this chapter.

Obesity and Obstetric Outcomes

In addition to its metabolic derangements, obesity and its comorbidities adversely affect a woman throughout her reproductive lifespan. Obesity leads to greater risk of unfavorable obstetric outcomes, spanning the entirety of pregnancy. Early pregnancy loss, stillbirth, congenital anomalies, hypertensive disorders, and cesarean section/operative vaginal delivery rates are all increased in the setting of obesity [91–93]. In a longitudinal study by Mandal et al. of 442 women who were obese (BMI $\geq$ 30.0 kg/m^2) prior to pregnancy compared to normal weight controls, obesity was associated with an increased risk of gestational DM (19.43 vs. 3.79 %; $p < 0.001$), pre-eclampsia (8.76 vs. 3.31 %; $p < 0.001$), preterm labor less than 34 weeks (7.58 vs. 3.55 %; $p < 0.001$), cesarean section (36.72 vs. 17.53 %; $p < 0.001$), operative vaginal deliveries (12.32 vs. 5.21 %; $p < 0.001$) and postpartum infectious morbidity (9.95 vs. 3.79 %; $p < 0.001$) [92].

Fetal Demise

There is no established etiology for increased rates of stillbirths in obese mothers, but several pathophysiologic mechanisms have been proposed. One theory involves increasing adiposity, which can lead to the disruption of normal lipid metabolism and hyperlipidemia. Studies suggest that hyperlipidemia may then trigger a reduction in prostacyclin secretion yielding a subsequent rise of thromboxane production. These elevated thromboxane levels are associated with an increased risk of placental thrombosis and decreased placental perfusion which could lead to subsequent fetal demise [94].

In a large prospective study of 54,505 women from the Danish National Birth Cohort, the authors noted a fivefold increase in the rate of stillbirth in obese women [95]. In another study by Salihu et al. the authors found that obese mothers were approximately 40 % more likely to experience stillbirth than non-obese women (adjusted HR 1.4; 95 % CI 1.3–1.5) [96].

Gestational Hypertension and Diabetes

Two of the most common obstetrical risk factors, diabetes and hypertension, are directly associated with obesity. Through separate mechanisms, maternal obesity can result in opposite extremes in terms of fetal growth disorders. Macrosomia, which increases risk for cesarean delivery, or low-birth weight, which is associated with hypertensive disorders, may occur [97]. A prospective multicenter study of 16,102 patients, by Weiss et al., demonstrated that obesity was an independent risk factor for adverse obstetric outcomes such as gestational diabetes, gestational hypertension, pre-eclampsia, fetal macrosomia, and increased risk of cesarean delivery. Patients with a BMI <30 kg/m^2 served as controls for the two study groups: patients with a BMI of 30–34.9 kg/m^2 and patients with a BMI > 35 kg/m^2. The rates of gestational hypertension, pre-eclampsia, gestational diabetes and macrosomia were considerably higher in patients with a BMI > 30 kg/m^2, and patients with a BMI >35 kg/m^2 were more likely to undergo cesarean delivery (47.4 %) compared to the controls (20.7 %) [98].

Neonatal Anomalies

There is a large body of evidence supporting the long-term consequences of maternal obesity on the fetus, ranging from neural tube defects to cardiac malformations and orofacial clefts [99]. The association between obesity and neural tube defects was first documented by Waller et al. in 1994. They demonstrated an increased risk of spina bifida and neural tube defects in children of obese mothers [100]. This positive correlation between risk of neural tube defects with increasing BMI has been further confirmed [101]. In 2009, a meta-analysis by Stothard et al. corroborated these findings. Using data from 39 studies, they demonstrated that obese mothers were more

likely to have a neural tube defect, including anencephaly, compared to mothers with a normal BMI (OR: 1.9, 95 % CI: 1.62–2.15, $p<0.001$). In this same analysis, children of overweight mothers were also found to have an increased risk of neural tube defects (OR: 1.2, 95 % CI: 1.04–1.38, $p=0.01$), but not of anencephaly [102].

Using the Atlanta Birth Defects Risk Factor Surveillance Study, Watkins et al. demonstrated pregnancies in obese and overweight mothers to have double the risk of risk of a cardiac defect compared to mothers with a normal BMI [103].

Effects of Obesity and Its Metabolic Consequences on Male Reproduction

The impact of obesity on male factor fertility has not been as widely investigated as in females. Obesity in male partners has been found to have a significant and multifaceted impact on fertility. Hormonal modifications associated with obesity, lifestyle factors, and accumulation of toxins in adipose tissue likely contribute [104–106]. In a study by Magnusdottir et al. looking at 72 male partners of couples that presented for a fertility evaluation, the incidence of obesity (BMI 30 kg/m^2) was threefold higher in the men with an abnormal semen analysis [107].

Altered Spermatogenesis

The hypogonadotrophic hyperestrogenic hypoandrogenic state found in the obese male is distinctive. Reduced androgen, SHBG, and Inhibin B levels (without compensatory increase in FSH), coupled with increased estrogen levels, are characteristic of obesity-related male endocrine dysfunction [104]. Serum total and free testosterone levels are negatively correlated to increasing body weight, and this decrease is associated with a progressive decrease in SHBG. Common clinical signs of hypogonadism may not be present because obesity primarily affects bound (rather than active, free) testosterone.

Inhibin B is an established marker of Sertoli cell function and correlates to spermatogenic activity. There are multiple reports in the literature regarding the finding of decreased inhibin B levels in obese men compared to controls. In a study by Winters et al., mean inhibin B levels in young adult males (18–24 years) were negatively correlated to BMI. The mean inhibin B was 248 pg/mL in those with BMI <25 kg/m^2, 231 pg/mL with BMI 25–30 kg/m^2, and 183 pg/mL with BMI >30 kg/m^2 ($p<0.05$) [108].

Overweight and obese men have a lower mean sperm concentration and increased prevalence of oligospermia [104, 107, 109, 110]. In a recent meta-analysis by Sermondade et al., within a cohort of 9,779 men, overweight men were at significantly increased odds of oligozoospermia (OR, 1.11; 95 % CI, 1.01–1.20) or azoospermia (OR, 1.39; 95 % CI, 0.98–1.97) compared with normal-weight men. These risks further increased among obese men: oligozoospermia (OR, 1.42; 95 % CI, 1.12–1.79) or azoospermia (OR, 1.81; 95 % CI, 1.23–2.66) [111].

Considering the racial/ethnic disparity in obesity prevalence, with 31.6 % of non-Hispanic black men, 27.8 % of Hispanic men, and 25.4 % of non-Hispanic white men being obese [81], it has been postulated that increased obesity prevalence in minority groups could impact fertility in minority groups. However, confirmatory studies have yet to be performed.

Erectile Dysfunction

A recent study demonstrated that 79 % of males who self report symptoms of erectile dysfunction are overweight or obese [112]. Proposed mechanisms include decreased Testosterone levels and elated levels of pro-inflammatory cytokines in obese males. Obesity is also associated with multiple comorbidities that can contribute to erectile dysfunction, such as diabetes, hypertension, and dyslipidemia [113].

Accumulation of Toxic Substances

There is some evidence that environmental substances can also affect male fertility [114, 115]. The majority of candidate toxins are fat soluble with the potential to collect in adipose. The most concerning toxins include pesticides, phthalates and polychlorinated biphenyls (PCBs). Obese men are logically at increased risk for the accumulation of these toxic substances.

Increased Testicular Heat

The elevation of the scrotum to that of the core body temperature can lead to failure of spermatogenesis. Occupational heat exposure (e.g. baking, welding, ceramics) can produce these results. Additionally, prolonged sitting (e.g. professional driving and paraplegia) reduces air flow to the scrotum and can cause a similar effect [116–118]. Obese men are known to possess a distinctive scrotal fat pattern, which has been hypothesized to affect the local scrotal temperature and negatively affect spermatogenesis [119].

Ethnic Differences in Anovulation

Anovulation is defined as failure of the ovarian follicle to release a mature oocyte for over 3 months. One of the classical clinical markers of anovulation is irregular/absent menses or oligomenorrhea. Oligomenorrhea is defined as >36 days between menstrual cycles or less than eight menstrual cycles per year [120]. These ovulation defects lead to infertility because an ovum is not available for fertilization. Defects in the hypothalamic–pituitary–ovarian axis lead to ovulatory dysfunction and can occur at any level.

Hypothalamus

Hypothalamic causes of anovulation are typically secondary to absent or decreased production of gonadotropin releasing hormone (GnRH). There are multiple congenital defects which lead to hypothalamic hypogonadism.

Stress-mediated anovulation can be physical, emotional, or nutritional, the latter of which has been suggested to be most prevalent in Caucasians. Cortisol, often called the "stress hormone," is a glucocorticoid produced by the adrenal gland in response to stress and has the ability to affect various reproductive hormones (e.g. to decrease LH, estradiol and progesterone). Excess cortisol can suppress GnRH secretion leading to a subsequent decrease in ovulation [121]. Cortisol has been reported to lead to an increased risk of miscarriage and temporary infertility, with resumption of fertility when cortisol levels return to normal [122, 123].

Anorexia Nervosa, the classic example of nutritional stress resulting in hypothalamic anovulation, is characterized by a self imposed food restriction secondary to a distorted body image and irrational fear of weight gain [124]. Gonadotropin, leptin, and estradiol levels are all decreased in females with anorexia nervosa. In a 989,871-subject Swedish national cohort study, gender, ethnicity, and socioeconomic status were large influences on the chance of developing anorexia, with women descended from non-European parents less likely to be diagnosed and those descended from wealthy families of European descent at greatest risk [125]. A cross-sectional survey of participants from the National Heart, Lung, and Blood Institute (NHLBI) Growth and Health Study found that anorexia nervosa and bulimia nervosa were more commonly found in whites, compared to blacks [126]. In contrast, pooled data from three national databases, The National Survey of American Life (NSAL11), The National Latino and Asian American Study (NLAAS12), and the National Comorbidity Survey Replication (NCS-R), revealed no statistical difference in the prevalence of anorexia among Hispanic, Non-Hispanic whites and non-Hispanic blacks in the USA but did report a higher rate of utilization of mental health services by non-Hispanic whites. Bulimia Nervosa was found to be more prevalent among Hispanic and Non-Hispanic blacks, when compared to non-Hispanic whites in this study [127].

Pituitary

The pituitary is an endocrine gland, located at the base of the brain, which secretes nine hormones involved in the regulation of homeostasis. Ovulation requires the pituitary to act as a mediator between the ovary and the hypothalamus in the HPO axis. Pituitary tumors can lead to disruption in this communication by compressing the pituitary or by producing elevated levels of prolactin which can induce release of dopamine, resulting in decreased GnRH [128]. Vascular insult to the pituitary as can occur from local ischemia (Sheehan's), compression, intra-cranial hemorrhage

or thrombosis can also lead to pituitary damage and, ultimately, amenorrhea. It is not known whether there exists an ethnic difference in the prevalence of pituitary tumors as studies have yielded mixed results, ranging from no significant difference to considerable differences [129, 130]. In a retrospective analysis of Surveillance Epidemiology and End Results (SEER) Program data, researchers at the University of Iowa reported that the highest incidences of pituitary adenomas were found amongst blacks (4.4 cases per 100,000). The lowest rates were observed among the American Indian/Alaskan Native Population (1.9 per 100,000) [131].

Ovary

Primary Ovarian Insufficiency

Average age of menopause, defined as cessation of menses for at least 12 months, is 51 years of age [132]. The classical triad of early onset hypergonadotropic, hypoestrogenic amenorrhea diagnostic of primary ovarian insufficiency (POI) was first reported by Fuller Albright et al. in 1942 [133]. POI is not natural menopause and occurs by either ovarian dysfunction, loss of ovarian follicles, or by destruction or removal of the ovaries at a young age [134, 135]. Approximately 5–10 % of patients with this diagnosis will go on to conceive spontaneously. Most cases are sporadic with prevalence rates of approximately 1 in 10,000 US women by age 20, 1 in 1,000 by age 30, and 1 in 100 by age 40 [136]. Though many cases are idiopathic, POI has been linked to autoimmune disease, genetic disorders (e.g. Turner's syndrome and Fragile X Syndrome), and chemotherapy and radiation [134, 137–140]. Data on prevalence of Turner's syndrome and Fragile X among different ethnic groups has not been reported, and investigation is warranted. Infertility is just one of the many medical implications of this diagnosis. POI patients also carry an increased risk of osteoporosis, heart disease, and hypothyroidism [140, 141].

Polycystic Ovary Syndrome

First described by Stein and Leventhal in 1937, polycystic ovary syndrome (PCOS) presents with the classic triad of hyperandrogenism (characteristically manifested as hirsutism), obesity, and oligo/amenorrhea [142–144]. As stated, PCOS is a metabolic disorder that is highly associated with obesity and largely believed to be associated with ethnic background. Although not a part of the diagnostic criteria, hyperinsulinemia and insulin resistance play a large role in the regulation of this disorder [78]. Hyperinsulinemia increases GnRH pulse frequency, LH dominates over FSH, ovarian androgen production increases, follicular maturation decreases/arrests, and SHBG binding decreases [145, 146]. These changes comprise the metabolic cascade that is PCOS.

Disparity in PCOS Prevalence

PCOS is the most common female endocrinopathy in the world, with a prevalence ranging from 5 to 10 % [143]. Observed ethnic differences in prevalence may be attributable to genetic, cultural/ethnic, or lifestyle factors, and/or to studies' utilization of different criteria for diagnosis (generally, NIH versus Rotterdam) [147]. There are few studies in the literature which have compared the prevalence of PCOS among ethnic groups under the same conditions and diagnostic criteria, and systemic reviews of population-based data or analyses of large clinical databases are needed [148]. In a study by Dunaif et al., a higher prevalence of PCOS was noted in Hispanic-Caribbean women compared to Non-Hispanic black women [149]. In a longitudinal cohort study by Azziz et al., no statistical difference was found in the incidence of PCOS among Non-Hispanic blacks compared to Non-Hispanic whites using the NIH criteria [150].

Phenotypic Differences in PCOS by Ethnicity

There is substantial support in the literature that ethnicity and culture play a role in the phenotypic variations observed in PCOS women among different ethnic groups [150–157, 159]. In a study by Welt et al., authors reported that Non-Hispanic black women with PCOS had a higher BMI and body weight compared to Non-Hispanic whites with the syndrome, but the prevalence of clinical signs of hyperandrogenism were the same [157]. In a study by Knochenhauer et al., no racial difference in hirsutism was identified between black and white women with PCOS, but hirsutism in women of East Asian decent was found to be less prominent [158]. In a retrospective analysis of phenotypic characteristics in a cohort of 547 Chinese and 427 Dutch women with PCOS, Guo et al. reported a higher incidence of hyper-androgenism ($p < 0.001$) and amenorrhea ($p < 0.001$) in Chinese compared to Dutch women [159].

Metabolic Sub-types of PCOS by Ethnicity

There exist clear variations in the metabolic phenotypes of PCOS. In a cross-sectional analysis of 71 self-identified Mexican Americans and 120 Non-Hispanics, Kauffman et al., found a higher incidence of insulin resistance among Mexican Americans [160]. The risk of concurrent metabolic syndrome varies greatly among various ethnic groups: East Asians are at lower risk than South Asians, Hispanics, and Non-Hispanic blacks [160, 161]. Abnormal glucose tolerance is more commonly found in Asians and Hispanics when compared to Southern and Eastern Europeans [162]. In summary, there is a large body of evidence to support the effect of geographic location, ethnic origin, and cultural/social practices on the phenotypic variations observed in women with PCOS. There has been some thought given to creating ethnically appropriate thresholds for metabolic screening in high risk ethnic groups; however, more data is needed prior to implementation of such programs.

Effect of Obesity on PCOS

In women with PCOS, obesity exacerbates the reproductive and metabolic consequences. It is possible that the increased production of estrogen from conversion by peripheral tissues leads to worsened HPO dysfunction or that hyperinsulinemia induces androgen secretion from the ovary [79]. These hypotheses are supported by the fact that obese women are prone towards hyperinsulinemia, insulin resistance, hyperandrogenemia, increased peripheral aromatization of androgens to estrogens, and altered gonadotropin secretion [79, 163].

Obesity has also been associated with delayed responses to ovulation induction in PCOS patients, including clomiphene citrate and gonadotropins [164]. It has been reported that, after losing as little as 5 % of initial body weight obese women with PCOS improved spontaneous ovulation rates and spontaneous pregnancy.

International Issues in Racial and Ethnic Fertility Differences

In this section, selected information regarding how racial and ethnic differences in unassisted reproduction affect patients outside the USA will be reviewed.

Male Fertility

Incidence and etiology of male infertility varies globally, due to both environmental and genetic factors. Johnson reviewed data from ten Western studies of a cumulative 9,766 men with oligo- or azoospermia and found the incidence of chromosomal abnormalities to be 5.8 %, with sex chromosome abnormalities representing 4.2 % and autosomal abnormalities representing 1.5 % [164]. A study of severely oligospermic men in Northeast China reported that 9.26 % had chromosomal abnormalities, which was higher than that reported by studies of severely oligospermic men from other Asian countries (e.g. India 6.52 %) [165].

As stated above, Cystic Fibrosis (CF) is a common genetic disorder among those of European descent and is a relatively frequent cause of male infertility in Europe because of its association with congenital bilateral absence of the vas deferens. Men with this disorder are azoospermic and carry mutations for cystic fibrosis trans-membrane conductance regulator (CFTR) gene [166].

Most cases of male factor infertility in Africa are caused by infections of the male genitourinary tract. Studies from Nigeria showed that prevalence of male infertility is 26–43 % [167–169, 207]. The genitourinary tract is the most common anatomic site of infection by *Chlamydia trachomatis* and *Neisseria gonorrhea.* These can cause male infertility when urethritis progresses to chronic epididymitis, resulting in oligo- and/or asthenospmermia. Lepromatous leprosy is endemic to Africa and is associated with semen abnormalities including azoospermia. Testicular

biopsy patients affected by leprosy often reveals spermatogenic arrest and complete hyalinization of seminiferous tubules and interstitial tissue [170]. Studies from Tanzania showed lower fertility in men who suffer from malaria; however the pathogenesis is still unkown [171]. Infection with HIV, which is extremely prevalent in sub-Saharan Africa, causes male infertility by induction of hypogonadism, altered spermatogenesis, and increased susceptibility to other STIs [172, 173].

Female Fertility Worldwide

According to a 2004 WHO report on developing countries, more than 186 million ever-married women between 15 and 49 year old had either primary or secondary infertility. Infertility increased sharply with age: while only 5 % experienced significant difficulty conceiving at the age of 24 years old, 65 % carried an infertility diagnosis in the 45–49 year old age group [174]. Infertility rates are significantly lower in Europe, where ovarian aging, ovulatory dysfunction (including that associated with obesity and/or PCOS), and an increasing incidence of sexually transmitted disease are the most common causes of infertility [175]. What follows reviews international trends in female fertility worldwide.

Ovarian Aging

The development of Assisted Reproductive Technologies (ART), and increased access to it, especially in Europe, has enabled childbearing in some couples who have chosen to delay parenthood beyond the natural age of highest fecundability. The rise in the average age at birth of first child in developed countries reflects the trend of intentionally delayed parenthood, which has also resulted in more women presenting with ovarian factor infertility (i.e. diminished ovarian reserve) [176–179]. ART is widely available in many European countries, especially those with state-administered infertility healthcare.

International Differences in Polycystic Ovary Syndrome

European studies have estimated the prevalence of PCOS to be between 5 and 10 % [180–182], while in China prevalence was 2.2 %. This degree of difference is likely due to environmental and lifestyle differences as well as obesity rates [154]. While PCOS incidence may be decreased among Asians, international data suggests that Asian women may be more severely affected than their counterparts, particularly with regards to metabolic aberrations. A large study performed in the Netherlands

focused on ethnic differences among normogonadotropic anovulatory women [183]. Subgroups included women of Northwestern European, Mediterranean European, African, Southeast Asian and Indian descent. The insulin resistant phenotype (high fasting insulin and glucose levels with decreased SHBG) was most common among women of Indian origin. These findings were consistent with those of Norman et al., which previously revealed higher insulin resistance in Indian women compared with white women with PCOS in South Africa [184]. Wijeyaratne et al. compared South Asian Sri Lankan to Caucasian British women with PCOS and found higher rates of fasting glucose and insulin resistance among the Sri Lankan women [185]. European women with PCOS also tend to have lower rates of metabolic disturbance than corresponding Maori and Pacific islanders women [186].

Asian women may also be more likely to exhibit hyperandronemia, despite the finding that hirsutism is *less* common in this group. A comparative study between the phenotypic characteristics in Chinese and Dutch women with PCOS and oligo-/amenorrhea showed that Chinese women with the diagnosis have higher incidence of hyperandrogenism and amenorrhea as well as increased BMI. Hyperandrogenism (HA) in both groups was associated with increases in age, fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR) and serum LH [159]. Valkenburg et al. found that hyperandrogenism was most common among Indian (74.7 %) and Mediterranean (75.9 %) women and lowest among Northwestern Europeans (41 %). Mediterranean European ancestry was associated with markedly elevated serum androgen levels [186].

With regards to metabolic-syndrome-associated body type, women of African descent had the highest mean waist circumference and BMI, with 39.1 % being obese. Women of Mediterranean European and Indian descent demonstrated intermediate levels of obesity, at 37.6 and 28.9 %, respectively. The lowest BMI values were seen among Northwestern European (26.9 %) and Southeast Asian (21.6 %) descended women. Polycystic appearance of the ovaries and higher antral follicle number was observed more frequently in women of African descent compared to other groups (20.8 vs. 16.5 follicles, $p = 0.002$) [186].

These studies indicate that racial and ethnic differences have an influence on phenotypic characteristics and clinical presentation of PCOS in international populations.

Infectious Morbidity

As discussed above, tubal factor infertility varies by race and ethnicity. Additional data demonstrates that it also varies geographically, largely on account of variable prevalence of pelvic inflammatory disease. A study done in 33 World Health Organization centers located in 25 countries included 5,800 couples and showed that about 50 % of infertile African couples had TF, vs. 11–15 % among infertile couples from other continents [187]. Studies from Egypt, Nigeria, and South Africa

have reported that tubal pathology accounts for 42–77 % of infertility. Chlamydial and gonorrheal infections constituted the main causes of tubal damage in these patients [188–192].

Non-African developing countries also have high prevalences of STIs, and therefore, of tubal disease. In a study conducted at university hospital in Brazil, chlamydia positivity was 51.8 %, with 56 of 106 women screening positive [193].

Endometrial and tubal tuberculosis (TB) remains a known cause of infertility especially in developing countries. The fallopian tubes are usually the first reproductive structure to be affected, with subsequent extension to the endometrium and other pelvic anatomy [194]. Fibrosis and scar formation results in loss of function in the fallopian tubes, peritoneal cavity and endometrium. However, early detection of Mycobacterium Tuberculosis (MTB) DNA using TB-PCR and anti-tubercular treatment can reduce the damage to genital organs [195]. A retrospective study of Nigerian patients reviewed 661 infertile women evaluated by endometrial biopsy from 1997 to 2004 and reported a low incidence of endometrial TB (0.45 %) [196]. In India the prevalence was higher, with 169 (38.15 %) of 443 infertile patients having positive TB-PCR analysis [195].

International Variance in Uterine Pathology

As discussed above, uterine fibroids are more frequent among women of African descent than among Caucasian women, with the lowest incidence among Asian women [197, 198]. Studies from Africa reported the incidence of fibroids as 13.6 % in Southeast Nigeria, 6.6 % in Western Nigeria, and 10.0 % in Ghana [199].

Postpartum pelvic infection, obstetric trauma, unsafe abortion practices, intrauterine synechiae, and Asherman's syndrome are very common in developing countries [200]. These result from lack of adequate medical care, especially in rural areas where home deliveries in unsterile conditions without a skilled attendant are common practice. Stanton et al. in 2007 reported that only 40 % of deliveries in Sub-Saharan Africa were performed by trained personnel [201].

International Trends in Obesity and Fertility

In general, obesity rates tend to be inversely related to poverty levels. Obesity ranges from 5 % in some developing countries to up to 30 % in developed countries. As discussed, obesity impacts fertility via its association with ovulatory disorders, and it has reached epidemic levels in the USA. A similar trend has been observed in many Western countries [202].

A study by Agyrmang et al. was particularly elucidative with regards to the impact of international urbanization on rates of obesity [203]. The study compared obesity among Ghanaian residents of the Netherlands with those remaining in urban

and rural Ghana, respectively. The authors found that Dutch-Ghanaian women had the highest prevalence obesity (79.0 %), followed by urban Ghanaian women (50.0 %), with the lowest obesity rates observed among rural Ghanaian women (19.0 %). Urbanization and sedentary lifestyle may even correlate more strongly with obesity than ethnicity does. A large meta-analysis estimated the prevalence of obesity among West African population to be 10 %, with women and urban residents more likely to be obese than men and rural residents [204].

Chapter Summary

- Semen parameters are known to vary by ethnicity and geography, even among fertile men. More research is warranted to determine whether race-specific normal ranges might better diagnosis and treatment of male infertility.
- The frequency of genetic abnormalities, especially micro-deletions and SNPs (primarily along the Y chromosome), have been shown to vary widely by study population. It is likely that ethnicity-specific Y-microdeletion panels should be developed and used to optimize diagnostic accuracy for individual patients.
- African American patients exhibit higher rates of tubal disease than Caucasian women, likely secondary to increased rates of PID and (though less so) because of increased rates of surgical sterilization and subsequent regret. Rates of tubal factor infertility are lower in white and Asian women, despite some studies showing higher rates of endometriosis in these groups.
- Fibroid incidence, severity, and need for surgical intervention are higher in black women than in any other race. Molecular and genetic characteristics may account for these differences and provide insight into appropriate therapies, e.g. aromatase inhibitors.
- Obesity prevalence is markedly increased among Hispanics and blacks in the USA, likely secondary to dietary, behavioral, genetic, and social economic factors. Given their association with ovulation disorders, the higher obesity rates among minority populations may negatively impact fertility.
- Racial/ethnic disparities in *male* obesity may have adverse fertility effects via hormonal modifications, impaired spermatogenesis, increased testicular heat, increased incidence of erectile dysfunction, or the accumulation of toxins in adipose tissue.
- Physical, psychological, and nutritional stress affect the hypothalamus and can lead to anovulation. Diseases of nutritional stress, i.e. anorexia nervosa, may be more prevalent in Caucasians.
- In women with PCOS the risk of concurrent metabolic syndrome varies greatly among ethnic groups. East Asians are at lower risk than South Asians, Hispanics, and Non-Hispanic blacks. The creation of ethnically appropriate thresholds for metabolic screening may be warranted given the phenotypic variations observed in different geographic locations, ethnicities, and cultural/social practices.

- Internationally, environmental and genetic differences account for variation in male infertility causes: Y-chromosomal abnormalities may be more common in the Chinese population; CBAVD associated with *CFTR* mutations is more common among those of European ancestry, and infectious morbidity (e.g. urethritis, TB, leprosy, and HIV) is more common in developing countries, particularly in Africa.
- Diminished ovarian reserve as a reason for infertility is becoming increasingly common in developed nations, secondary to voluntary delay of childbearing.
- As in men, women residing in developing countries are more likely to experience infertility secondary to infectious morbidity (e.g. PID and TB), manifesting primarily as tubal disease.
- Unsafe obstetric and abortion practices in developing countries are associated with increased rates of postpartum pelvic infection, obstetric trauma, intrauterine synechiae, and Asherman's syndrome, all of which are associated with infertility.
- International data on obesity suggests that urbanization and sedentary lifestyle may be more directly associated with up-trending collective BMI (and its associated ovulatory dysfunction) than race itself.

Future Directions

More than 70 million couples worldwide have fertility problems [205, 206]. Growing evidence suggests ethnic differences in the incidence, etiology, and even best therapies for infertility. A more in depth understanding of these differences is essential, both to decrease infertility rates from a public health perspective and to provide better, individualized care to patients from diverse backgrounds. Further research on disparities by race, ethnicity, and geography is greatly needed. In addition, minority groups would benefit from a heightening of patient fertility education efforts and improved access to diagnostic and therapeutic modalities. The direction of resources towards prevention of urogenital infections, provision of safe obstetric care, and mitigation in the rise of obesity could significantly decrease infertility rates both in the USA and abroad.

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Chapter 5
Disparities Between Black and White Women in Assisted Reproductive Technology

Reshef Tal and David B. Seifer

Introduction

Racial disparities are pervasive throughout the US health care system, as evidenced by minorities having more severe disease and poorer outcomes [1, 2]. The obstetric literature reports higher rates of maternal mortality, increased perinatal and neonatal mortality, and increased incidence of low and very low birth weight neonates among African Americans [3–6]. It is therefore reasonable to question the impact of racial disparity in gynecology, and more specifically, infertility and assisted reproductive technology (ART) outcomes.

Infertility is a major public health issue affecting more than six million women in the United States [7]. The number of ART clinics has been increasing steadily (from 300 clinics in 1995 to 361 clinics in 2008) as has the number of ART cycles being performed (from 59,142 cycles in 1995 to 140,795 cycles in 2008) [8, 9]. Despite increasing use of ART, black women in the United States have experienced an increase in the prevalence of infertility at the same time that infertility is decreasing among white women [10]. The population-based rates of 12-month infertility determined by the National Survey of Family Growth in 1982 and 2002 were 7.8 and 11.6 %, respectively, for black women and 11.6 and 7.1 %, respectively, for white women [10]. Among women seeking infertility treatment, black women are significantly different with regard to socioeconomic position [11, 12] and marital status [12]. They have a higher prevalence of some risk factors for infertility such as

R. Tal, M.D., Ph.D.
Department of Obstetrics & Gynecology, Maimonides Medical Center,
4802 Tenth Avenue, Brooklyn, NY 11219, USA
e-mail: resheft@gmail.com

D.B. Seifer, M.D. (✉)
Genesis Fertility and Reproductive Medicine, Maimonides Medical Center,
1355 84th Street, Brooklyn, NY 11228, USA

New York University School of Medicine, New York, NY, USA
e-mail: drseifer@genesisfertility.com

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uterine fibroids [13], tubal disease [11, 13], and excess weight [14, 15]. In addition, the proportion of ART cycles provided for black and white women indicates that there was a racial disparity in the use of ART services in the United States at the beginning of the twenty-first century. The US census data for the general population in the year 2000 showed 12.9 % of the population to be black and 75.1 % to be white [16, 17]. While black and white women made up 7.8 and 72.1 %, respectively, of married, reproductive-age women in the United States during 2002 [10], there were 3,666 (4.6 %) cycles among black women and 68,607 (85.4 %) cycles among white women during 1999–2000, demonstrating underrepresentation of black women in this national dataset [18]. These social, environmental, and anatomic factors most likely play a significant role in infertility disparities among black compared to white women. In addition, these and other factors are likely responsible for the growing evidence in the literature suggesting racial differences in ART outcomes.

Disparities in Infertility Care Access and Utilization

A growing number of studies have investigated the association between race/ethnicity and ART outcomes. The first US study of racial determinants of ART outcomes was published in 2000 by Sharara and McClamrock [15], studying black and white women seeking care at a university-based program in an insurance-mandated state. Women were excluded from analysis if they had specific anatomic predictors of poor outcome (hydrosalpinges and intracavitary lesions) or if they had biochemical evidence of diminished ovarian reserve (FSH of 11 IU/L or greater). Multiple cycles per women were studied. Compared with whites, black women were more likely to have a diagnosis of tubal factor infertility ($P<0.001$), had higher mean BMI ($P=0.038$), and were more likely to require microdose Lupron Flare protocol during stimulation ($P=0.012$). On average, black women had 1.3 more years of infertility before treatment than whites ($P=0.016$). The groups were comparable by age, day-3 FSH levels, cycle cancellation rate, and multiple embryologic predictors of pregnancy (number of oocytes retrieved, number of embryos transferred). Black women had significantly lower implantation and clinical pregnancy rates per cycle than white women (implantation rate 9.8 % in blacks vs. 23.4 % in white women, $P=0.0005$; clinical pregnancy rate 19.2 % in blacks vs. 42.2 % in white women, $P=0.009$). The ongoing pregnancy rate per cycle (a pregnancy beyond 20 weeks gestation or a live birth) was also significantly lower in black than in white women (14.9 % vs. 38.8 %, $P=0.005$) [15]. The significant effect of race on ART outcomes in this study was likely mediated in part by differences in BMI and duration of infertility, which were not controlled in the analysis, making it difficult to determine the strength of race as an independent predictor of ART treatments. Conducting the study in a state with an insurance mandate to cover infertility services is a specific strength of this study, minimizing the impact of socioeconomic factors on ART outcomes. Indeed, 28 % of the patients treated in the study were black, significantly more than the reported proportion of black women receiving ART treatments nationwide [13].

However, despite the presence of a mandate, there was still a racial disparity in the duration of infertility before ART was initiated suggesting relative underuse of ART treatments by black women. This difference confirms the growing literature showing that insurance mandates have not been able to completely bridge the racial gap in access to infertility services [9, 11, 19, 20]. For example, a survey of over 500 women attending a fertility clinic in Massachusetts demonstrated that, even in a state with mandated insurance coverage for infertility services, those seeking services are predominantly white, highly educated, and wealthy [19].

To explore the reasons why those populations of women with the greatest need for infertility care do not seek them out even when available, Missmer et al. [9] conducted a survey among 743 women receiving infertility care at a university-based fertility center in a mandated state. Compared with whites, African-American women had been attempting to conceive for 20 months longer ($P<0.0001$). African-American women also found it more difficult to find a physician with whom they felt comfortable, to get an appointment with a physician, to take time off from work for their appointment, and to pay for treatment ($P<0.0001$). In addition, they reported that it was more difficult to get treatment specifically because of their race or ethnicity ($P<0.0001$) or income level ($P<0.0001$). Compared with white women, African-American women were three to four times more likely to be concerned about using science to conceive, the social stigma of infertility, and disappointing their spouse. Specifically, the social stigmatization of infertility was of great concern to African-American women as they were 6.6 times more likely to be concerned about friends and family finding out about their infertility treatment compared with white women [9]. Data from this survey suggest that there are cultural factors in addition to known pelvic pathology (i.e., tubal and/or uterine factor) that most likely contribute to lower and/or delayed use by nonwhite women of infertility care.

Feinberg et al. used a unique approach to control for the influence of limited health care access and other social factors on ART outcomes. The investigators compared ART utilization and outcomes in black and white women within the military system, where improved access to care would be expected given the full access to diagnostic modalities and greatly reduced cost of IVF regardless of economic status or military rank. They examined a total of 1,457 patients undergoing first-cycle fresh, nondonor ART [13]. In this equal-access-to-care setting, 17.4 % of the women studied were black: a fourfold increase in use compared with the US ART population. Black and white women were comparable with respect to age, day-3 FSH levels, amount of gonadotropin administered during stimulation, peak estradiol levels, number of mature oocytes retrieved, and number of embryos transferred. However, black women were nearly three times more likely than white women to have leiomyoma as a stated cause of infertility (odds ratio [OR] 2.85, $P<0.0001$) and nearly twice as likely to be diagnosed with tubal factor infertility (OR 1.91, $P<0.0001$). In an analysis that adjusted for the presence of fibroids (an independent predictor of outcomes in this series), the association between race and ART outcomes (clinical pregnancy rates, spontaneous miscarriage rates, and live birthrates) was not significant [13]. While using a very specialized population such as the military enables to minimize the impact of limited health care access and other social factors on ART

outcomes, it compromises the generalizability of findings to other groups of women. The investigators also acknowledge that sample size limitations may have hindered the ability to detect subtle differences in treatment outcomes by race [13]. It is possible that other investigations have also been limited by sample size constraints despite valid methodologic approaches. Of the four studies that found no association between race and ART outcomes the sample sizes ranged from 251 to 1,135 subjects, and none were as large as the Feinberg study, which showed no association [13, 21–23].

Studies Based on Society for Assisted Reproductive Technology (SART) Database

As this area of investigation has evolved, larger datasets have been examined allowing a more thorough evaluation of ART outcomes in multiple racial/ethnic groups. Specifically, studies using data from the national registry of ART cycles in the United States collected by the Society for Assisted Reproductive Technology (SART) and maintained by the Centers for Disease Control and Prevention have circumvented issues of limited sample size and potential type two errors. As these reports have relied on registry data, a unique set of limitations in the interpretation of results must be considered. Specific information regarding socioeconomic status and other potential confounders such as BMI and direct measures of embryo quality is not uniformly available. The units of measure to determine treatment outcome must also be taken into consideration: registries track total number of cycles completed, which allows for individual patients to be represented in the dataset more than once, thus creating potential repeated-measure bias. Women who choose to repeat cycles when previous attempts have failed may be different than women who stop trying in ways that relate both to the risk factor of interest (race/ethnicity) and the outcome (pregnancy). Finally, in a recent systematic review of publications that used SART data from years ranging from 1999 to 2007, it was found that more than 35 % of cycles could not be used for comparisons of racial/ethnic groups and reproductive outcomes because the data on race/ethnicity were lacking [24], raising concern for a potential selection bias.

Five large database studies have recently noted consistent findings indicating racial/ethnic differences in ART outcomes between black and white women [18, 25–28] (Table 5.1). One of the first of these studies examined 80,390 nondonor cycles (both fresh and frozen) from SART for the years 1999 and 2000 [18]. Additional inclusion criteria included cycles from clinics that performed at least 50 ART cycles annually and reported race >95 % of the time. Of the 80,390 cycles evaluated, 3,666 were among black women (4.6 %), 68,607 were among white women (85.4 %), and 8,036 (11.9 %) were among women of other races and ethnicities. Only outcomes in blacks and whites were compared. In this series, black women had a greater duration of infertility before ART than white women (40 vs. 34 months for those having their initial cycle and 48 vs. 36 months for women

Table 5.1 Summary of studies examining racial/ethnic disparities in ART outcome between black and white women based on SART data

Authors	SART data years	SART cycles analyzed (*n*)	Clinical intrauterine gestation rate (%)			Live birthrate (%)		
			Black	White	*P*-value	Black	White	*P*-value
Seifer et al. [18]	1999–2000	80,309	27.7[a]	33.6[a]	<0.001	18.7[b]	26.3[b]	<0.001
Fujimoto et al. [26]	2004–2006	139,027	32.0[b]	40.1[b]	<0.0001	75.0[c]	83.7[c]	<0.0001
Seifer et al. [25]	2004–2006	158,693	29.3[a]	38.3[a]	<0.001	22.2[a]	32.3[a]	<0.001
						76.9[d]	84.8[d]	
Baker et al. [28]	2004–2006	225,889	32.2[b]	40.5[b]	<0.0001	75.1[c]	83.7[c]	<0.0001
Luke et al. [27]	2007	31,672	35.5[b]	44.8[b]	<0.0001	76.3[c]	84.5[c]	<0.0001

[a]Rate per cycle started without prior ART
[b]Rate per cycle started
[c]Live birthrate/pregnancy
[d]Live birthrate/pregnancy without prior ART

who had previously undergone ART [$P<0.001$]). This translated to older mean ages for black women at treatment than for white women. When analyzing all cycles in the dataset, black women were less likely to experience a live birth per cycle of ART initiated compared with whites after controlling for age, parity, diagnosis, and clinic factors. It was also noted that the overall live birthrate per fresh nondonor cycle for black women (18.7 %) was below the lower 95 % confidence interval (CI) for the rate among all races in the United States during 1999–2000. In contrast, the live birthrate among whites (26.3 %) was above the 95 % CI for all races nationally (*P* value for difference in live birthrates between blacks and whites, <0.001). When restricting the analysis to patients receiving their first ART cycle, black women were 24 % less likely to experience a live birth than whites when adjusting for the same confounders ($P<0.001$). Black women who had been treated with ART previously were 38 % less likely to have a live birth per cycle ($P<0.001$). There were no racial differences in live birth when comparing frozen embryo transfer cycles [18].

In a follow-up study, Seifer et al. [25] investigated trends in ART outcomes in black and white women by comparing SART database outcomes for 2004–2006 with previously reported outcomes for 1999–2000. A total of 158,693 nondonor IVF cycles were analyzed. The proportion of cycles in which black women were treated for the first time increased from 5.4 % in the 1999–2000 series to 8.4 % in the 2004–2006 series ($P<0.001$) as did the proportion of cycles for black women with previous ART cycles (4.6–7.1 %, $P<0.001$). However, trends in ART outcomes were significantly worse for black women over time, representing an expansion of the disparity demonstrated in the analysis of 1999–2000 SART data. This widening of the gap in treatment outcomes may be explained in part by worsening of prognostic indicators in black women over time. The proportion of black women undergoing ART for the first time who were over 35 years old increased in the 2004–2006 assessment (57.9 %) compared with the 1999–2000 assessment (49.9 %) ($P<0.001$).

In addition, the proportion of black women treated for the first time with the diagnosis of diminished ovarian reserve nearly doubled between these time points (7.5 % in 1999–2000 vs. 14.4 % in 2004–2006, $P<0.001$). Significant upward trends were also noted in the diagnosis of unexplained infertility and uterine factors in black patients ($P<0.0001$) [25]. In accordance with these trends was a plateau in the likelihood of clinical pregnancy and live birth per cycle of ART in black women. The live birthrate per cycle initiated in black women (first cycle of ART) in 1999–2000 was 20.7 % compared with 22.2 % in 2004–2006 ($P=0.19$). In contrast, trends in white women showed improvements in both clinical pregnancy (first-cycle ART clinical pregnancy rate/cycle of 33.6 % in 1999–2000 vs. 38.3 % in 2004–2006, $P<0.001$) and live birthrate over time (first-cycle ART live birthrate/cycle 28.4 % in 1999–2000 vs. 32.3 % in 2004–2006). In the 2004–2006 assessment, black women treated for the first time were 31 % less likely to achieve a live birth than white women (adjusted relative risk 1.31, 95 % CI 1.26–1.37). Compared to the adjusted relative risk of first-cycle treatment failure for blacks compared to whites in the 1999–2000 series (1.24) this updated result represents a significant widening gap in treatment outcome. Black women who had ever had prior ART treatment were 33 % less likely than whites to achieve a live birth ($P<0.001$), which was comparable to the risk in the 1999–2000 assessment (adjusted relative risk 1.38). Finally, a 10 % lower adjusted odds of live birth after transfer of cryopreserved embryos was noted in black women compared with white women, a difference which was not demonstrated in the 1999–2000 cycle data analysis [18]. This analysis raises concern of a growing disparity in ART outcomes over time.

Additional studies have used SART to investigate disparities in ART outcomes. Fujimoto et al. have investigated ART outcomes in multiple racial/ethnic groups based on SART registry data [26]. A total of 139,027 nondonor ART cycles between 2004 and 2006 were assessed. Outcomes were compared between white, black, Asian, and Hispanic women. Compared with the referent group of white women, all other groups had lower live birthrates adjusting for maternal age, number of embryos transferred, and infertility diagnosis ($P<0.0001$). Black women (8,903 cycles, 6.5 % of total cycle number) had similar clinical pregnancy rates as white women but were 38 % less likely to achieve a live birth. All ethnic groups studied had significantly higher miscarriage/stillbirth rates than white women ($P<0.0001$) [26]. Baker et al. have published the largest evaluation to date of ART outcomes based on SART registry data [28]. Their study population included 225,889 fresh nondonor ART cycles between 2004 and 2006 in multiple racial/ethnic groups. Compared with white women all other racial/ethnic groups were less likely to achieve a clinical intrauterine pregnancy. Black women had significantly lower rates of clinical intrauterine gestation compared with white women (32.2 % vs. 40.5 %, $P<0.0001$). Compared with white women, Hispanics and Asians had a significantly greater risk of pregnancy loss in the second and third trimesters, and blacks had a significantly greater risk of pregnancy loss in all trimesters ($P<0.0001$). In addition, black women had significantly decreased live birthrate/pregnancy compared with white women (75.1 % vs. 83.7 %, $P<0.0001$). In an attempt to eliminate the effects obesity may have on racial disparities in

reproductive outcomes following ART, Luke et al. examined a total of 31,672 ART cycles from the SART database in 2007 and stratified them according to patient BMI categories [27]. Within BMI categories, there were substantial racial and ethnic disparities, with black women significantly more likely to have adverse treatment and pregnancy outcomes. Among normal-weight women, the adjusted odds ratio (AOR) of failure to achieve a clinical intrauterine gestation was 1.18 for black women (1,954 cycles, 6.0 % of total cycle number) compared with the reference group of white women, although this difference did not reach statistical significance ($P=0.10$). Compared with white women, the AOR of failure to achieve a live birth was 1.45 for black women ($P=0.04$). These racial differences in ART outcomes were more pronounced in the obese population. Compared with obese white women (BMI > 30), the AOR of failure to achieve a clinical intrauterine gestation and the AOR of failure to achieve a live birth were 1.47 ($P<0.0001$) and 1.84 ($P=0.002$), respectively, for obese black women [27].

Despite the acknowledged limitations of these large studies, there is a consistent finding of race/ethnicity as a risk factor for poor ART outcomes after adjusting for many confounders. While environmental, socioeconomic status, behavioral, and anatomic factors are likely contributors to disparities in ART outcomes between black and white women, significant differences still remain even when these factors are controlled for, suggesting that genetic factors may also play an important role.

Possible Genetic Factors and ART Outcome Disparities

Seifer et al. reported a significant difference in the mean level of anti-Mullerian hormone (AMH), a surrogate marker of ovarian aging, as a function of race or ethnicity [29]. After controlling for age, BMI, smoking, and HIV status, black women had lower average AMH values compared with white women (25.2 % lower, $P=0.037$). This study presented the first biochemical evidence of a difference in ovarian aging between black and white women. Implications of these findings may have potential broad applications for the life planning of minority women. As such, this information may influence minority women and their physicians to seek/provide infertility treatment earlier if pregnancy is not easily accomplished.

Another genetic risk factor which is likely related to racial disparities in ART outcome is estrogen receptor alpha polymorphism. The estrogen receptor (ER) plays an important role in mediating estrogen action on target tissues. Two subtypes of ER are known, ER-alpha encoded by the ESR1 gene on chromosome 6 [30] and ER-beta encoded by the ESR2 gene on chromosome 14 [31]. ER-alpha, the first identified and the most abundant, is found in all human reproductive tissues. The overall prevalence of the ER-alpha PvuII homozygous (PP) genotype is significantly higher in black women (35 %) than white (13 %) or Hispanic (16 %) women [32]. The higher prevalence of ER-alpha PP genotype in blacks has been associated with the increased occurrence of uterine leiomyoma [32], a well-known poor

prognostic factor in ART. Independent of the association with uterine fibroids, Georgiou et al. found ESR1 PvuII polymorphism in women to affect pregnancy rate following IVF [33]. Sundarrajan et al. corroborated their findings [34]. In a study of 200 IVF patients who had normal cycles with unexplained infertility despite extensive workup, PvuII polymorphisms were evaluated and correlated with ART outcomes. The pregnancy rate showed a strong negative correlation to the severity of PvuII polymorphism, being highest in the no polymorphism group (pp) and lowest in the homozygous (PP) group (88.9 % vs. 14.7 %, $P<0.001$) [34]. These studies suggest a role for ER-alpha polymorphism in poor ART outcomes in black women. The ER gene could underlie variable responses to estrogens, from fetal to adult follicular growth and differentiation. ESR variability may also suggest a variability in the rate of germ cell depletion throughout reproductive life.

Vitamin D levels have been shown to be lower in black compared with white women [35]. Causes related to lower vitamin D levels include deeper skin pigmentation, decreased exposure to sunlight, and obesity. Low vitamin D levels have been associated with reduced pregnancy rates following IVF [36], suggesting that vitamin D may be a factor contributing to racial disparities in ART outcome. Interestingly, AMH has been shown to correlate with vitamin D levels [37, 38], providing further support for a biological role for vitamin D in ovarian reserve and ART outcome.

Gleicher et al. reported that the distribution of fragile X mental retardation (*FMR1*) genotypes varies between Caucasian, African, and Asian women [39]. Based on a normal range of 26–34 (median 30) CGG repeats the authors used CGG counts on the two X chromosome alleles to define whether a genotype is normal (*norm*), heterozygous (*het*), or homozygous (*hom*). An individual was defined as *norm* when both alleles were within range, *het* by one allele outside, and *het-norm/low* or *het-norm/high*, depending on the abnormal count allele being above or below normal range. Both alleles outside range defined *hom*. The authors reported *het-norm/low* to be associated with a PCO-like ovarian phenotype [40], rapidly depleting follicles (and ovarian reserve) [41], significantly reduced pregnancy chances in IVF, and high risk towards autoimmunity [40]. In their study, African women demonstrated significantly reduced odds of pregnancy compared to white women after controlling for BMI and age (OR 0.27, 0.10–0.70; $P=0.007$) [42]. African women demonstrated a preponderance of abnormally low-count CGG outliers [42], corresponding to *het-norm/low*, providing a possible explanation for their reduced IVF pregnancy rates.

In summary, accumulating evidence suggests that race/ethnicity is a risk factor for poor ART outcomes after adjusting for many confounders. The impact of race/ethnicity on accessibility to ART centers requires additional study. Such research is needed to better understand if race/ethnicity reflects genetic factors that may influence ART outcomes or if these categories are proxies for socioeconomic status, environmental influences, or behavioral differences that contribute to outcomes. It is likely that some combination of these factors is responsible for the disparities that have been demonstrated.

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Chapter 6
Assisted Reproductive Outcomes in Hispanic Patients

Ruben Alvero and Shunping Wang

Introduction

Research on health outcomes in Hispanic or Latino subjects is a priori a difficult endeavor because of the considerable heterogeneity inherent in the definition of ethnicity. The National Institutes of Health definition of what constitutes minority status was initially defined in 1997 by the Office of Management and Budget (OMB) Directive 15 and further revised and refined in 2001 [1]. Two ethnic categories (Latino/Hispanic and Non-Hispanic/Latino) and five racial categories (American Indian/Alaska Native, Asian, Black or African American, Native Hawaiian/Pacific Islander and White) are defined. Latino subjects are further described as "A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race." The term "Spanish origin" can also be used in addition to "Hispanic or Latino." The Federal Government agencies governing these reporting requirements do recognize that the assignations are "sociopolitical" constructs and are not meant to be anthropological in nature. In research and other necessary designations, ethnic and racial assignments are collected by self-report. Further fluidity is introduced since "mixed" background is generally collected for race but not for Hispanic ethnicity. Of particular importance to reproductive research for Latinos, the Society for Assisted Reproductive Technologies (SART), in the required annual IVF clinics reporting system has a field for racial and ethnic

R. Alvero, M.D. (✉)
Department of Obstetrics and Gynecology, University of Colorado,
12631 East 17th Avenue, P.O. Box 6511, Mail Stop B198-3, Room 4411,
Aurora, CO 80045, USA
e-mail: ruben.alvero@ucdenver.edu

S. Wang, Ph.D.
Department of Obstetrics and Gynecology, University of Colorado,
1635 Aurora Ct., AOP Bldg #3400, PO Box 6510 MS F701, Aurora, CO 80045, USA
e-mail: shunping.wang@ucdenver.edu

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background but, in addition to combining race and ethnicity into the same category, which is at odds with federal guidelines, allows the cell to go unfilled if the patient does not self-report. This permissiveness in reporting is a missed opportunity for increasing our knowledge of ART outcomes in Latino couples since this field goes unreported significantly.

Although a minor point, the terms Latino and Hispanic are, in common usage interchangeable, and this leads to some additional confusion. For the remainder of this manuscript the terms will be used interchangeably. A more important potential distinction is the genetic background among the various Latino subgroups. For instance, a native of the American southwest with Pima Indian antecedents would very likely have a different predisposition to adult onset diabetes mellitus than a Chilean with a significant northern European background. It is quite possible that the heterogeneous Latino population would benefit greatly from personalized medical care. With progressively decreasing costs of gene sequencing and microchip array technologies, genetic predispositions can be more accurately determined and intervention developed for this varied population [2].

Using the previously cited definition of "a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin regardless of race," the 2010 Census identified 50.5 million, or 16 % of the total population in the USA, as being Hispanic or Latino. The Hispanic population increased from 35.3 million in 2000 when this group made up 13 % of the total population (2010 US Census Bureau). This demographic change accounts for more than half of the growth in the total population of the USA during this time period. In spite of the growing preponderance of Hispanics in the population and considering the level of growth, the group is underrepresented in ART in the USA although the reasons remain murky. Nevertheless, significantly more research needs to be conducted to investigate the assisted reproductive outcomes in Hispanic patients.

Despite the constraints due to definition and reporting, a modest number of studies have been conducted to investigate the association between assisted reproductive technologies (ART) outcomes and patient demographics. As with all populations, increased maternal age has long been proven to have negative impact on the success rate. Other factors, such as day 3 cycle FSH level, anti-Müllerian hormone (AMH), Body Mass Index (BMI), also have been extensively studied [3, 4]. There is a growing interest focusing on racial and ethnic disparities in assisted reproductive technologies and the potential for negative outcomes. Several studies have indicated reduced pregnancy rates and live birth rates among Asian and African-American patients compared to their Caucasian counterparts, although some other studies found no significant differences [5–7]. Surprisingly, there are relatively few studies focusing on the assisted reproductive outcomes in Hispanic patients.

In addition to biologic factors, many other factors impact ART outcomes. It is critical that all these factors be investigated carefully to determine the reasons for adverse ART outcomes in Hispanic patients. This chapter will examine the IVF outcome disparities in Hispanic patients from biological, social/cultural, and economic aspects and systematically review current publications on racial/ethnic disparities for assisted reproductive technology outcomes in Hispanic patients.

Biological, Social/Cultural, and Economic Status

Ethnic/racial disparities in terms of infertility diagnosis have been documented. Several studies suggested that Hispanic infertile patients have higher proportion of tubal infertility, compared to non-Hispanic white women who tend to have higher rates of endometriosis [8, 9]. The higher prevalence of tubal infertility in Hispanic patients may be attributed to the increase exposure to Chlamydia, but the true etiology remains unclear [5, 10–12]. The duration of infertility was also found to be longer in Hispanics than in whites and African American patients [13, 14]. The reason for this is unclear although some have suggested that this may in part be due to patient discomfort with sharing the diagnosis, even with a health care provider. No significant difference has been found with respect to uterine factor, diminished ovarian reserve, idiopathic infertility, or male factor infertility.

Access to fertility care and treatment is also a major contributing factor to the success of assisted reproductive outcomes. A clear association exists between fertility service use, especially advanced reproductive technology, and higher socioeconomic status. In the USA, fertility treatment, in vitro fertilization in particular, is prohibitively expensive if without insurance coverage. Patients with lower socioeconomic status are often left with limited option treatment options.

In recent years, several states have mandated broader insurance coverage of infertility treatment. Additionally, certain health care systems, such as the US military, provide increased access to care at low cost, essentially equalizing access across socioeconomic groups. However, even in these lower-cost, equal-access-to-care settings, disparities in service utilization persists even when access to fertility treatment is economically feasible. Feinberg et al. found the Hispanic use of assisted reproductive technology was less than half of what would have been expected based on patient demographics [6]. In comparison, the proportion of African Americans who use ART services was representative of the general military population. There are several plausible explanations for this underutilization. A recent, unpublished qualitative study of Latino couples in the Denver, Colorado metropolitan area sheds some light on possible reasons. First, Latino couples had a limited understanding of the health care system (Sterne, Rodriguez, Alvero, unpublished data). Many Hispanic patients, even those born in the USA, struggle to navigate the unfamiliar infrastructure and lack the knowledge and awareness of available sources. Additionally, poor communication between care providers and Hispanic patients often exists, due to language and cultural barriers. Patients' unwillingness to pursue in-depth discussion and questioning about infertility may suggest to physicians that infertility is not a complaint of great importance. Reciprocally, patients perceived (whether or not the perception is real) that health care providers regard the Latino population as generally fertile and therefore do not pursue the topic to any great extent. Patients also related that physician awareness of the cost burden of infertility treatment limited their discussion of these treatment options. The patients interviewed also placed a great deal of trust in alternative fertility treatments and frequently truncated their efforts to access care under a western medical model. Interestingly, although much more

familiar, the alternative approaches were still very expensive. Another social factor that surfaced in the study was the machismo and denial of male-factor infertility, which highlights the gender imbalance which may still be present in Latino culture. In this study, US-born study participants expressed greater awareness of and willingness to address male causes of infertility. Surprisingly, religion does not appear to be a primary deterrent to accessing fertility care among Hispanic patients and many couple expressed surprise that the Catholic Church had a negative view of assisted reproduction. Virtually all participants in the study suggested that education for the Latino community, through media and community centers, as well as consciousness-raising among non-Latino health care providers about infertility in this population, would empower couples to overcome these obstacles and seek care.

Success Rates

There is no consensus among the existing research confirming that there is a disparity in assisted reproductive technology outcomes of Hispanic patients. Many studies accessed the ART outcomes by using the Society for Assisted Reproductive Technology Clinical Outcome Reporting System (SART-CORS) national database. This dataset contains more than 90 % of the IVF clinics in the USA. The data are reported by these IVF clinics annually and verified by SART, and in turn are reported to the Centers for Disease Control and Prevention in compliance with the Fertility Clinic Success Rate and Certification Act of 1992. These SART-based studies suggest a significant racial/ethnic disparity in assisted reproductive technology outcomes in Hispanic patients versus non-Hispanic whites. In some studies with live birth rate as the measurement outcome, Hispanic women have shown to have lower live birth rate compared to whites. One study suggested that black and Hispanic women had more embryos transferred compared with white women [15]. However, there is no significant difference in the development of ovarian hyperstimulation syndrome (OHSS), as might be expected if Polycystic Ovary syndrome were over-represented in Latinas, between these and non-Hispanic whites. Consistent with previous findings, Hispanic women were found to be more likely to have tubal factors. In addition, all three minority groups, including African American, Hispanic, and Asians, are less likely to have a live birth compared to white. Baker et al. also found significantly lower odds of clinical pregnancy in Hispanics compared to whites [16]. Hispanic women also showed significantly higher pregnancy loss in the second and third trimesters. In another study which body mass index (BMI) was adjusted, normal weight Hispanic women still showed a significantly lower pregnancy rate. Overweight and obese Hispanic women also has higher tendency to have pregnancy wastage [8]. Ovarian hyperstimulation syndrome (OHSS), which is a rare, but serious complication of controlled ovarian hyperstimulation, was found to be less prevalent in Hispanic women. Finally, the use of elective single embryo transfer, increasingly used to reduce multiple pregnancies, is less likely to be used in Hispanic patients compared to whites [17].

The large sample size of these SART-CORS based studies provides a large dataset which reduces many of the concerns associated with small-scale studies. In addition, the almost universal submission of ART cycles nationally yields a census-like collection of data points. However, there are significant shortcomings, one of which has already been highlighted. Reporting error of ethnicity and race is likely since there is no clear definition for the individual entering the data and in fact reporting is not truly required at all. Some studies have noted that more than 35 % of cycles evaluated could not be used for comparisons of racial/ethnic groups and reproductive outcomes because the data on race/ethnicity were either missing or unspecified [18]. In fact, the cycle numbers of Hispanic patients in the SART CORS datasets significantly under-represent the general population of Hispanic population. This may be due to the underutilization of assisted reproductive technology treatment among Hispanic patients, the underestimation of IVF cycles of Hispanics, or a combination of both. Furthermore, the socioeconomic status information, which is known to be strongly associated with access to fertility treatment, is not readily available in this dataset.

In addition to socioeconomic status, many confounders which may have great impact on the study outcomes are not available, or the data is missing, from these SART-CORS based studies. Several studies have been conducted in order to address these limitations. A study conducted in San Antonio, where Hispanics makes up 23 % of the total IVF patient population, also indicated there is no statistical difference with regards to clinical intrauterine gestation rate and live birth rate between Hispanic and non-Hispanic white women [9]. No significant difference was found between the two groups with respect to gravidity, previous births, or history of spontaneous abortion (SAB). In terms of cycle characteristics, Hispanic patients demonstrated no difference in the total amount of medication used, number of oocytes retrieved, or cycle cancellation rate. However, Hispanic women did show higher rate of tubal infertility diagnosis, while non-Hispanic whites were more likely to have a diagnosis of endometriosis. Worth noting and consistent with what other studies have shown, although Hispanics make up 23 % of the IVF patients in the study, this considerably under-represents the 58 % of Hispanics in the community, according to the US census data. Feinberg et al. reported that even in the lower cost, equal-access-to-care military medical setting, Hispanic use of assisted reproductive technology was less than half of what would have been expected based on patient demographics [19]. The group did not find any significant difference with regards to cycle characteristics, clinical pregnancy rates, live birth rates, spontaneous abortion rates, and implantation rate between Hispanic and Caucasian women. Additionally, there was no difference in terms of infertility diagnosis between the two groups, which is at odds with previous findings. Bendikson et al., in a retrospective cohort study between August 1994 and March 1998, found there was no difference in terms of pregnancy outcomes among different ethnic groups, including African American, Asian, Hispanic, and Hispanic women compared to Caucasian women, although there were only 18 Hispanic patients recruited, compared to the 1,039 white women who participated [5].

The limitations of these studies, compared to those SART-CORS based studies, is obviously the smaller sample size. However, these studies do have several

advantages with regards to study design and data collection. These smaller-scale studies usually presented a stricter, more well-defined and validated criteria for race/ethnicity, compared to the self-report, loosely defined race/ethnicity category in SART CORS dataset. It is reasonable to assume that the standardization of racial categorization among clinics, or even among patients, varies widely. In addition, the large percentage (near 35 %) of the missing values on the race/ethnicity in SART dataset cannot be ignored since this significant percentage may considerably impact the study outcomes. Moreover, some well-known confounders, such as BMI, gravidity, and socioeconomic status, are included in these studies while they are not consistently available in SART dataset. It is imperative that readers recognize these limitations and interpret the results of the studies with caution.

PCOS: A Special Concern in Latino Reproductive Health Care

Polycystic Ovary Syndrome (PCOS) is one of the most common female endocrine disorder and cause of infertility. It is a condition associated with chronic anovulation, and/or polycystic ovaries, insulin resistance, and androgen excess. The diagnosis of Polycystic Ovary syndrome has evolved over time. In 1990, a conference sponsored by National Institutes of Health (NIH) proposed that PCOS is defined by the following: (1) hyperandrogenism and/or hyperandrogenemia, (2) ovulatory dysfunction, (3) other entities that would cause a phenotype similar to PCOS are excluded. A consensus workshop in Rotterdam, 2003, sponsored by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), suggested that PCOS be diagnosed if two out of three of the following criteria are present: (1) oligo- and/or anovulation, (2) excessive androgen activity, (3) polycystic ovaries on ultrasonography. In addition, the Androgen Excess Society also published its own diagnostic criteria for PCOS in 2006, which requires the presence of hyperandrogenemia or hyperandrogenism. Depending on the diagnostic criteria used the prevalence of PCOS ranges from 5 to 10 % in the reproductive age female population.

The association of PCOS and insulin resistance and adult onset diabetes mellitus is quite strong, with elevated insulin levels contributing eliciting thecal androgen production and creating the vicious cycle that maintains PCOS. Obesity is also a contributing and exacerbating factor. It is estimated that 10 % of all Hispanics have adult onset diabetes mellitus and they are twice as likely to have diabetes as non-Hispanic whites. Various subgroups among Hispanics have a greater vulnerability insulin resistance and diabetes and this is a good example of the importance of knowing the specific background of any given patient rather than just assigning patient risk based on self-reported ethnic background. It is well-recognized that certain populations derive their vulnerability from a so-called “thrifty gene” which was adaptive to episodes of “feast or famine.” For example, the Pima Indians of the American southwest likely have the highest rate of diabetes in the world due to this susceptibility. A genetic strategy that previously may have been effective became

maladaptive when these native peoples encountered a western diet. Similarly, some Latino sub-groups may share a similar predisposition to insulin resistance and diabetes when acculturating to new dietary environments and the overlap with PCOS has become significant.

Treatment of PCOS involves first determining what the patient's goals are. Regardless whether the patient wishes to conceive or not, if she is overweight or obese, then treatment is likely to involve weight loss. Return to ideal body weight with a body mass index in the normal range is not necessary but the patient may need to lose approximately 5–10 % of her current weight to improve overall hormonal effectiveness. If the patient is interested in ovulating effectively in order to become pregnant, then the weight loss may be sufficient to return the ovary to a more estrogenic milieu. If normal menstrual cycles do not return or are insufficiently frequent for adequate trials of pregnancy, the addition of ovulation induction agents such as Clomiphene citrate is important. The patient may be refractory to conservative means of ovulation induction and may require more aggressive treatments such as with gonadotropins. Given the concerns of excessive response with ovulation induction agents which may lead to ovarian hyperstimulation syndrome and multiple pregnancy, these patients frequently are treated with ART. In spite of the fact that patients with PCOS have a large number of oocytes retrieved, these are frequently of poor quality and may lead to poorer pregnancy outcomes than would be expected. Strategies for improving oocyte and subsequent embryo quality frequently involve cycle stimulation with little or no LH and with attempting to control the external hormonal and substrate milieu in order reduce exposure to an environment that is, for instance, hyperglycemic[19]. A patient only wishing to regain normal menstrual cyclicity may achieve this with weight loss alone or with the addition of cyclic hormonal oral contraceptives.

Summary

There is an appropriately growing interest in the racial and ethnicity disparities in assisted reproductive technology (ART) outcomes. A modest number of studies have been conducted to compare the in vitro fertilization (IVF) success rates of African Americans and white women. There is more limited information available with regard to the various Hispanic populations with regard to reproductive outcomes and pregnancy rates in ART. Based on the SART-CORS (Society for Assisted Reproductive Technology Clinical Outcome Reporting System) national database which contains comprehensive data reported by more than 90 % of the clinics nationwide, several research groups have reported reduced IVF success rates among Hispanic populations. However, other publications using much smaller databases, while adjusting for factors known associated with pregnancy outcomes, suggest that rates may be comparable to the population at large but that Latino access to assisted reproduction, even in situations where ART is no or low cost, is limited compared to other populations. The discrepancy in rates may be attributable to the complex

nature of the study. The self-reporting system used by SART-CORS is not standardized and may not truly represent the racial and ethnic variety in these studies. Furthermore, several other factors, such as social, cultural, and economic status, which may play critical roles in the success of assisted reproductive technology outcomes, may not be easily collected by quantitative studies. Qualitative studies have suggested that suspicion in Latino communities of conventional treatments, preference for alternative treatments and lack of cultural awareness by health care providers may prevent Hispanic patients from accessing effective care. However, education, both of patients and providers, may reduce the chasm and allow patients to obtain optimal treatments, especially in situations where assisted reproduction is a covered benefit. Polycystic Ovary Syndrome (PCOS), the most common endocrine disorder in reproductive aged females, and a cause of ovulatory infertility, should be especially considered in Latina populations given the genetic predisposition for diabetes, insulin resistance, and the metabolic syndrome in this population.

The limited understanding of the health disparities occurring among Latino couples, especially with regard to access to assisted reproduction and then the uncertainty with regard to outcomes emphasizes the need for enhanced education among those involved in the care of these patients as well as the patients themselves as well as the critical need for quality research. An understanding of the heterogeneous nature of the Hispanic population is critical in order to effectively conduct this research.

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Chapter 7
Reproductive and Assisted Reproductive Technology (ART) Outcomes in East Asian Women

Hakan Cakmak, Heather G. Huddleston, and Victor Y. Fujimoto

Introduction

Racial and ethnic disparities in many health outcomes are highly prevalent in the United States [1]. For instance, diabetes mellitus and coronary artery disease disproportionately impact certain racial and ethnic groups compared to Caucasians [2, 3]. Health disparities research in women's reproductive health is evolving; that said, racial and ethnic disparities have emerged in many areas, including pregnancy-related mortality, spontaneous abortion, preterm birth, and infertility [4]. Observed differences in racially diverse populations may reflect true biologic differences because of genetic background or may result from various environmental exposures, lifestyle factors, cultural factors, access to care, and specifics of treatments once care has been accessed [5, 6].

Issues related to cost of treatment, access to services, and variation in utilization by minority groups, including East Asians, render the treatment of infertility especially prone to disparity [7, 8]. However, there can be other factors that make assisted reproductive technology (ART) outcomes prone to disparity. For example, the reproductive factors that may negatively affect fertility can be more prevalent or response to treatment may differ in certain racial/ethnic groups [9, 10].

Differences in reproductive outcomes across racial and ethnic groups have been described in a growing number of reports [11–13]. Differences have been demonstrated in outcomes after treatment with ARTs and in reproductive aging. In this chapter, we aim to present the existing information in areas where differences in reproductive and ART outcomes between East Asian and other racial groups have been described.

H. Cakmak, M.D. • H.G. Huddleston, M.D. • V.Y. Fujimoto, M.D. (✉)
Division of Reproductive Endocrinology and Infertility, Department of Gynecology and Reproductive Services, University of California, 2356 Sutter Street, 7th floor, San Francisco, CA 94115, USA
e-mail: cakmakh@obgyn.ucsf.edu; HuddlestonH@obgyn.ucsf.edu; fujimotov@obgyn.ucsf.edu

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Reproductive and Assisted Reproductive Technology Outcomes

Ethnic differences in utilization and response to infertility therapy have emerged as an important area for research in recent years. A growing body of work has examined differences in outcomes between Asians and Caucasians undergoing infertility treatment and has consistently found decreased pregnancy outcomes among Asian women [11–15].

Differences in access to care may also have an impact on infertility prevalence and treatment outcomes by leading to decreased treatment of antecedents of infertility and/or delayed treatment of infertility. Several studies have shown that Asian women present with a longer durations of infertility, which may associate with poorer ART outcomes [14, 16]. Whereas decreased access to care likely plays the most significant role in the low utilization rates of some Asian women, more complicated sociocultural forces may also be relevant. Infertility can lead to emotional stress among all women but, in particular, East Asian women tend to conceal their circumstances more due to social stigma [17, 18]. There is a strong sense of shame associated with the infertile condition within East Asian populations that may lead to decreased utilization. Whether or not this factor also plays a role in delaying East Asian couples from presenting for care is still unknown.

Lamb et al. demonstrated that Asian ethnicity was associated with lower pregnancy rates following intrauterine insemination (IUI) treatment, typically the first-line treatment for unexplained or mild male factor infertility, compared to Caucasians [14]. In this retrospective study, 2,327 IUI cycles were analyzed from a total group of 269 Asian and 545 Caucasian women undergoing ovarian stimulation and IUI treatment. Clomiphene citrate- and letrozole-only cycles constituted the majority of all IUI cycles (over 2/3) in the study compared with gonadotropin-augmented IUI cycles. The baseline characteristics, including average number of IUI completed, infertility diagnoses, age, basal follicle-stimulating hormone concentration, antral follicle count, total motile sperm count per cycle, and parity, were similar in both groups. Asians had lower mean clinical pregnancy rate per cycle (7.1 % vs. 9.3 % for all cycles) compared to Caucasians [14]. Although not statistically significant, lower cumulative pregnancy rates were also observed in Asian women relative to Caucasian women (56/269 (20.8 %) vs. 143/545 (26.2 %)) [14]. However, after adjusting for age, gravity, parity, stimulation protocol, and duration of infertility, cumulative pregnancy rates after IUI were significantly lower in Asians (adjusted odds ratio (OR) 0.68, 95 % CI 0.47–0.98) [14].

Several studies have shown that Asian women have fewer pregnancies after in vitro fertilization (IVF) treatments when compared with Caucasian women (Table 7.1) [11–13, 15]. Purcell et al. performed a parallel analysis in Asian women compared with Caucasians using cycles reported to Society for Assisted Reproductive Technology (SART) and from the University of California, San Francisco (UCSF) [13]. A total of 27,272 cycles from SART were studied, of which 1,429 (5.2 %) were in Asian women. Of the initial cycles studied from UCSF (567 total cycles),

Table 7.1 Fresh autologous oocyte ART outcomes in Asian patients compared to Caucasian cohort

	Number of cycles		Clinical pregnancy rate		Live birthrate	
References	Caucasian (*n*)	Asian (*n*)	Caucasian (%)	Asian (%)	Caucasian (%)	Asian (%)
Purcell et al. [13] (UCSF)	370	197	45.9	37.1[a]	37.5	28.6[a]
Purcell et al. [13] (SART)	25,843	1,429	41.3	33.3[a]	34.9	26.9[a]
Langen et al. [12][b]	112	68	59	43[a]	48	31[a]
Fujimoto et al. [11]	107,484	13,671	40.1	30.9[a]	33.6	25.2[a]
Luke et al. [15]	24,896	2,891	44.8	38.1[a]	37.9	30.8[a]

[a]Statistically significant
[b]All blast transfer

197 were performed in Asian women (34.74 %). Type of protocol, total dose of gonadotropins, the number of follicles produced during stimulation, the number of oocytes retrieved, and the number of embryos transferred did not differ by race. Interestingly, the Asian women had significantly higher peak estradiol (E_2) levels, even though the total number of follicles was similar [13]. In both data sets, Asian women had lower odds of clinical pregnancy and live birth than Caucasian women [13]. Multivariate logistic regression using the SART registry data demonstrated that Asian women were 24 % less likely to achieve a live birth after ART (OR 0.76, 95 % CI 0.66–0.88) [13]. The UCSF data confirmed this disparity with comparably diminished odds of pregnancy in Asian patients compared with Caucasians (OR 0.59, 95 % CI 0.37–0.94) [13]. Poor embryo quality is often identified as a reason for ART failure. However, data from this study revealed a lower embryo fragmentation rate and similar cleavage rates in the transferred embryos of Asian women compared to Caucasian women which suggests against embryo quality as an etiology for lower pregnancy rates in Asian women [13].

In a later study, the pregnancy rates after blastocyst transfer were compared in East Asian and Caucasian women to further evaluate the impact of embryo quality on disparity of IVF outcomes [12]. In that retrospective analysis, 68 East Asian and 112 Caucasian women undergoing blastocyst transfer cycles were evaluated. Type of protocol, total dose of gonadotropins, the number of oocytes retrieved, the use of intracytoplasmic sperm injection, fertilization rates, the number and quality of blastocysts, and the number of blastocysts transferred were similar in both groups [12]. Despite all these similarities, East Asian women had significantly lower implantation (28 % vs. 45 %), clinical pregnancy (43 % vs. 59 %), and live birthrates (31 % vs. 48 %) compared to Caucasian women [12]. Moreover, logistic regression analysis showed that East Asian women were significantly less likely to have a clinical pregnancy (OR 0.52, 95 % CI 0.28–0.95) or live birth (OR 0.48, 95 % CI 0.25–0.90) after blastocyst transfer than Caucasian women [12].

Fujimoto et al. have published the largest evaluation to date of ART outcomes in multiple racial/ethnic groups based on SART registry data [11]. A total of 139,027 non-donor ART cycles between 2004 and 2006 were assessed. Outcomes were

compared between Caucasian, black, Asian, and Hispanic women. Compared with the reference group of Caucasian women, all other groups had lower live birthrates adjusting for maternal age, number of embryos transferred, and infertility diagnosis [11]. Asian women, who comprised 9.8 % of the cycles evaluated (13,671), had a 14 % lower odds of clinical pregnancy and a 10 % lower odds of having a live birth than Caucasians after ART [11]. But among those who did achieve a pregnancy, their live birthrates were comparable to those for Caucasian women, without an increase in pregnancy loss [11]. Moreover, Asian women averaged the longest gestations within each plurality and were less likely to deliver preterm [11].

In a more recent study, to determine whether a higher prevalence of overweight and obesity was one of the underlying reasons for the racial and ethnic disparities, the effect of maternal race and ethnicity within body mass index (BMI) categories on ART pregnancy and live birthrates was evaluated using SART registry [15]. A total of 31,672 ART embryo transfer cycles in 2007 were assessed. Asian women, who comprised 9 % of the cycles evaluated (2,891), were significantly lighter than the women in the other groups; more than two-thirds were normal weight [15]. The study demonstrated a significantly greater likelihood of failure to achieve a clinical pregnancy among obese women, and failure to achieve a live birth among overweight and obese women after ART treatment [15]. Within BMI categories, Asian women were more likely to fail achieving a clinical pregnancy and a live birth compared to Caucasians [15]. Specifically, after controlling for BMI, compared with Caucasian women, the adjusted OR of failure to achieve a clinical pregnancy was 1.38 (95 % CI 1.25–1.52) and failure to achieve a live birth was 1.33 (95 % CI 1.11–1.60) for Asian women [15]. Within BMI categories, also compared to Caucasian women, the adjusted ORs of failure to achieve pregnancy were 1.36 (95 % CI 1.22–1.53) for normal-weight, 1.21 (95 % CI 0.98–1.50) for overweight, and 1.73 (95 % CI 1.21–2.47) for obese Asian women [15]. Similarly, the adjusted ORs of failure to achieve a live birth was 1.21 (95 % CI 0.96–1.51) for normal-weight, 1.56 (95 % CI 1.07–2.27) for overweight, and 2.20 (95 % CI 1.18–4.08) for obese Asians compared to Caucasians [15]. Overall, similar to previous reports, this study demonstrated that Asian ethnicity is a negative predictor for ART pregnancy outcomes independent of BMI.

In a recent retrospective cohort study, the oocyte donor–recipient model was used to separate the impact of oocyte quality and endometrium on pregnancy outcomes [19]. First-time anonymous oocyte donors of Asian ($n=63$) or Caucasian ($n=156$) ethnicity were included to the study. There were no differences in cancellations for poor response, total dosage of gonadotropins used, number of stimulation days, follicles greater than 13 mm, oocytes retrieved, or oocytes fertilized between two groups. Asian and Caucasian recipients showed no difference in age or endometrial thickness measurements. Similar to an infertile cohort study [13], Asian donors had peak E_2 levels that were 23 % higher than their Caucasian counterparts. The elevated E_2 level did not appear to be due to increased follicular response in Asians [19]. E_2 per total number of follicles, per follicle greater than 13 mm, and per oocyte retrieved were also significantly higher in Asian donors [19]. In contrast to infertile women using autologous eggs, no differences were noted in

implantation (47.4 % vs. 40.9 %, OR 1.12, 95 % CI 0.61–2.07), clinical pregnancy (60.3 % vs. 62.4 %, OR 0.92, 95 % CI 0.50–1.66), or live birthrates (55.5 % vs. 59.9 %, OR 0.84, 95 % CI 0.47–1.50) achieved using an Asian vs. Caucasian oocyte donor [19]. This lack of difference in pregnancy success rates among Asian and Caucasian recipients would suggest that ovarian stimulation per se plays a pivotal role in the lower pregnancy rates seen among Asian women. Unfortunately, there are no linked studies at this time to demonstrate that Asian women can "correct" their relative lack of success with fresh autologous IVF through the use of frozen embryo cycles.

All of the studies investigating the disparities in ART outcomes between Asian and Caucasian women demonstrated significantly low implantation, clinical pregnancy, and live birthrates in Asian women using autologous eggs [11–13, 15, 20]. In attempts to explain these findings, the concept that Asian women might suffer from an acceleration in ovarian aging has been proposed [21]. The study comparing the first IVF cycle outcomes in 29 consecutive Caucasian and 17 Chinese oocyte donors demonstrated that Chinese women had higher cycle cancellation rate (5/17, 29.4 %) either before cycle start or during stimulation due to poor response compared to Caucasians (0/29; RR 1.42, 95 % CI 1.04–1.9) [21]. In the same study, Chinese donors had significantly fewer oocytes retrieved per initiated cycle (9.3 ± 9.7 vs. 15.3 ± 7.1) [21]. However, this difference lost statistical significance when cycle outcomes were compared for cycles that reached retrieval (13.3 ± 8.9 vs. 15.3 ± 7.1) [21]. FMR1 premutations, consisting of 55–199 CGG repeats, have been associated with premature ovarian insufficiency [22]. Moreover, milder forms of premature ovarian senescence have also been reported to be associated with increasing CGG counts with the highest risk (18.6 % prevalence) in those with 80–99 CGG repeats [23, 24]. Therefore, one would expect Asian women to have disproportionally higher CGG repeats. However, studies failed to demonstrate differences in the prevalence of high CGG repeat number between Asians and Caucasian women [25, 26].

In all the studies mentioned above except the one published by Gleicher et al. [21], Asian women had similar baseline characteristics, response to ovarian hyperstimulation, and even embryo quality compared to Caucasians, suggesting similar ovarian reserves. Moreover, Wang et al. recently demonstrated that Asian women had higher spontaneous fecundability and shorter time to pregnancy when accounted for age, socioeconomic status, and motivational behavior [27]. All these findings suggest that factors mediating the reduced pregnancy and live birthrate among Asian women are restricted to the infertile population and factors other than ovarian function or embryo quality may be causing this discrepancy.

The decreased pregnancy and live birthrates may indicate fundamental biological or genetic differences between the ethnicities. Both infertile and donor Asian women were noted to have higher E_2 per follicle during ovarian stimulation compared to Caucasians. The impact of serum E_2 levels on ART success rates during ovarian stimulation has been a controversial issue. Excessive E_2 exposure might lead to insufficient secretory transformation of the endometrium with dyssynchronous glandular and stromal development at the time of expected endometrial receptivity [28, 29]. Indeed, several reports have indicated that elevated E_2 levels in autologous oocyte IVF cycles may decrease IVF success [30–33]. Moreover, the expressions of

the endometrial receptivity markers integrin-β3 and leukemia inhibitory factor were negatively associated with high E_2 levels [34]. Other reports did not confirm the negative association between serum E_2 levels and pregnancy outcomes [35–37]. However, the possibility remains that certain subgroups of patients, like Asians, may be more susceptible to adverse effects of supraphysiologic E_2 achieved during gonadotropin stimulation than others.

Differences in E_2 levels during ovarian stimulation seen between Asians and Caucasians likely represent differences in steroid hormone production or metabolism. The distribution of FSH-receptor polymorphisms is different in Asians and Caucasians; the European population more frequently carries the SS variant, which requires higher doses of gonadotropin stimulation and produces less E_2 than does the NN variant, which is more common in the Asian population [38]. Alternatively, the higher E_2 levels could result from polymorphisms of the genes involved in estrogen synthesis and metabolism, such as the CYP19 gene [39]. In women treated with pituitary down-regulation and transdermal E_2, markedly higher E_2 levels were demonstrated in Asian women compared to Caucasians, implicating differential metabolic clearance as a likely explanation for the observations seen during ovarian stimulation [40]. E_2 and its oxidative metabolites are cleared by the liver through conjugation by either glucuronidation or sulfation [41]. The degree to which metabolic efficiency may vary across ethnicities has not been adequately explored. It is possible that differences in steroid-conjugating enzyme activities in Asians might also explain higher E_2 levels during ovarian stimulation.

Reproductive Aging

There is a growing body of research indicating that reproductive aging may be influenced by race and ethnicity. Several reports have suggested an association between race/ethnicity and timing of natural menopause [42–45], whereas others have not supported this conclusion [46–48].

Investigators from the Study of Women Across the Nation (SWAN), a racially diverse, multicenter, prospective study of the natural history of the menopausal transition, have reported on multiple factors associated with age at natural menopause, including race and ethnicity. In this cross-sectional study of nearly 15,000 women, menopausal age was comparable in Caucasians, Hispanics, blacks, and Chinese women [44]. However, lower proportion of Japanese women reported menopause between ages 40 and 55 years (10.9 %) compared to other ethnicities (11.7–18.5 %), suggestive of a later onset of natural menopause [44]. Another study also found a later age of natural menopause in Japanese Americans compared to Caucasians within a large multiethnic cohort (n=95,704) [49]. These findings contrast with reports that have described earlier or comparable menopause in various Asian populations compared with Caucasian women in the United States and Europe [47, 50, 51].

In a separate study from SWAN database, the prevalence of premature ovarian failure (cessation of menses before age 40) across several ethnic groups was

investigated [52]. In a cross-sectional survey of 11,652 women, the prevalence of premature ovarian failure was significantly less common in Chinese (0.5 %, 3/592) and Japanese women (0.14 %, 1/727) than in Caucasian (1.0 %, 61/6,063) [52]. Premature ovarian failure was not significantly different between Chinese and Japanese women. In addition, Chinese (2.2 %, 13/592) and Japanese women (0.8 %, 6/644) were less likely to enter menopause before age 45 than were Caucasians (2.9 %, 177/6,063) [52].

The SWAN study investigators performed a cross-sectional analysis of hormones in women with different ethnic backgrounds [53]. In the unadjusted analysis of race/ethnicity and its association with hormone levels, Chinese women were noted to have significantly lower E_2 levels compared with all other groups studied [53]. Although this relationship became nonsignificant in a multivariate regression model, E_2 concentrations were still 13 % lower in Chinese women, a finding that has been demonstrated by other investigators [42, 53–55].

Another study from SWAN cohort demonstrated that Asian women (Chinese and Japanese) complained of the fewest vasomotor symptoms and the fewest menopausal symptoms overall [56]. The diminished frequency of vasomotor symptoms in Asian women in this report was consistent with other studies that have described less frequent vasomotor symptoms in Asian women than in women of European descent [55, 57]. Lower E_2 levels in pre- and perimenopausal Chinese women that decline less markedly during the menopausal transition have been proposed as an explanation for diminished reporting of menopausal symptoms in this group [53]. It has also been suggested that there may be cultural differences in characterization of menopause by Asian women and difficulties translating terms relating to perimenopausal symptoms [58]. It is possible that these differences may be less pronounced in Asian American women than in Asian women who have not immigrated to the United States.

Conclusions

Outcomes following ART treatment and the menopausal transition both represent women along a natural continuum of the reproductive life cycle. Each stage is sensitive to genetic and environmental influences that may correlate with race and ethnicity. In the last decade we have begun to fully appreciate the importance of health care disparities within various racial and ethnic groups. Our review of the literature provides the evidence that Asian ethnicity is an independent negative predictor for ART pregnancy outcomes. Based on current evidence, higher E_2 levels during the ovarian stimulation creating glandular–stromal dyssynchrony may be one of the explanations of the worse pregnancy outcomes in Asian women. There is no evidence that embryo quality is compromised in Asian women undergoing IVF either at early-cleavage or blastocyst stages.

The ultimate goal of identifying racial disparities in reproduction is to isolate the basic determinants of disparities and formulate strategies to improve outcomes for

women at risk. There are still major knowledge gaps in our understanding of these racial and ethnic disparities in East Asian women. Further research to improve our understanding of the source of these disparities is critical to optimizing the delivery of reproductive care across our increasingly diverse society.

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Chapter 8
Differences in Fertility and Assisted Reproduction in South Asian Women

Stephanie Gustin, Malinda Lee, and Lynn Westphal

Introduction

As racial and ethnic disparities are being recognized in all areas of medicine, interest in outcomes of assisted reproductive technology (ART) in different groups, such as South Asian women, has increased significantly. Unfortunately, the true incidence of infertility in these women at a national level within the United States is unknown, as there is a lack of literature examining fertility across multiple ethnic groups living in the same geographic region. One reason for this limited information is lack of reporting. One study that systematically reviewed SART data from 1999 to 2007 found it difficult to draw conclusions on disparity outcomes due to the lack of universal reporting of race and ethnicity by practices. The study concluded that 35 % of cycles could not be used in their analysis because the data on race/ethnicity were indeterminate [1]. A recent study has shown an increased reporting in race, suggestive of a trend in the right direction [2]. However, many studies group all Asian women together (Chinese, Japanese, Indian, etc.), which makes analysis of data more difficult.

Despite the lack of information, we can use other data to extrapolate the prevalence of infertility in South Asian women. Overall, infertility in the United States

S. Gustin, M.D. (✉)
Department of Obstetrics and Gynecology, Stanford University Hospital,
900 Welch Road, Suite 350, Stanford, CA 94304, USA
e-mail: sfisher@stanford.edu

M. Lee, B.S.
Department of Obstetrics and Gynecology, Harvard Medical School,
Massachusetts General Hospital, 25 Shattuck Street, Boston, MA 02115, USA
e-mail: malinda.shinrhei@gmail.com

L. Westphal, M.D.
Department of Obstetrics and Gynecology, Stanford University Hospital,
900 Welch Road, Suite 20, Palo Alto, CA 94304, USA
e-mail: lynnw@stanford.edu

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is estimated to affect almost 11 % of all women of reproductive age [3]. Some studies have guided us toward believing that the total prevalence of infertility amongst Asian women is similar to that of Caucasian women. An analysis of women with spontaneous conceptions in the San Francisco Bay Area concluded that Asian women did not have decreased fecundability as compared to Caucasian women [4].

Another way to determine prevalence is to look at the utilization of fertility treatment among Asians. A study of women in the San Francisco Bay Area observed that Asian women tended to have delayed utilization of fertility treatment when compared to Caucasian women, with a significantly higher percentage having a duration of infertility of greater than 2 years prior to beginning treatment (43.9 % vs. 24.6 %) [5]. Presenting with a longer duration of infertility may be associated with decreased utilization of treatment options, as well as poorer outcomes.

The decision to seek infertility treatment in and of itself is dictated by multiple factors, many of them cultural. Racial disparities have been reported in infertile women seeking care [6]. Some studies have suggested that there are inherent differences in the ethical beliefs of Asian versus Caucasian women. A large US multiethnic study surveyed women about whether ART presented no ethical concerns, some ethical concerns, or serious ethical concerns. The survey showed that Asian women had greater ethical concerns about infertility treatment as compared to Caucasian women [7]. The study also found that ethical concerns were associated with lower odds of getting tests and receiving treatment. Another barrier to access is the associated social stigmatization of seeking fertility treatment. Asian women are less likely to express interest in infertility research and less willing to be contacted for recruitment in ongoing studies. In addition, women born outside of the United States are less likely to consent to be contacted than women born in the United States [8]. This unwillingness may result in decreased access or utilization of fertility treatments.

Etiologies of Infertility

There are many causes of infertility, although the breakdown for different ethnic groups within the United States is unknown. The 2009 ART success rates, published by the Center for Disease Control and Prevention, reported the following primary diagnoses: male factor (18.8 %), unexplained infertility (13.5 %), diminished ovarian reserve (11.5 %), tubal factor (7.7 %), ovulatory dysfunction (6.8 %), endometriosis (4.2 %), uterine (1.4 %), multiple factors (28.4 %), and others [9].

Polycystic Ovarian Syndrome

PCOS is thought to be the most common endocrinopathy affecting women. In Westernized countries, the prevalence of PCOS has generally been estimated to be

5–10 %. While the prevalence of polycystic ovaries as detected by ultrasound in the general population is approximately 20–33 %, a study conducted in England found the prevalence of PCOS in women of Indian ancestry to be as high as 52 % [10]. South Asian women present at a younger age, and have more acne and hirsutism, as well as more secondary infertility [11]. Whether these differences are due to varying diagnostic criteria, lifestyle/cultural factors, or intrinsic biologic differences is unknown. Asian patients with PCOS might be phenotypically different from their Caucasian counterparts, which may affect the outcomes of ART.

Genital Tuberculosis/Tubal Factor

Genital tuberculosis is associated with infertility, recurrent pregnancy loss, and menstrual disorders. Various studies have shown genital tuberculosis as a cause of infertility in 1 % of the cases in developed countries and 18 % in India [12]. A study of patients seeking IVF in India showed that 50 % of the cohort had tubal factor infertility; of these patients, 48.5 % had genital tuberculosis, 82.8 % had been previously treated for tuberculosis, and 28.5 % showed signs of extra-genital tuberculosis [13]. Successful pregnancy in patients with genital TB is rare, even after complete treatment. Thus, for many patients of this population, IVF and embryo transfer remain the only options for successful pregnancies [14]. There are little data on genital tuberculosis in the United States, as it is relatively uncommon except in immigrant populations. Shahine et al. [15] and Sharara coworkers [16] showed no difference in the incidence of tubal factor between the South Asians and Caucasians in their studies.

Uterine Factor

Uterine leiomyoma is the sole factor for infertility in less than 10 % of cases, with submucosal fibroids most likely to cause infertility. Asian American women are thought to have similar incidences of fibroids as compared to white and Hispanic women. Black women have significantly higher rates of uterine leiomyoma than other ethnicities. A study of premenopausal US nurses showed that the incidence of leiomyoma among Asian, white, Hispanic, and black women were 10.4, 12.5, 14.5, and 37.9 %, respectively [17].

Unexplained

In a Boston study of infertile women, 50 % of Chinese patients and 42.4 % of other Asian patients had unexplained infertility, compared to 33.9 % of Caucasian patients

Table 8.1 Examining etiologies of infertility among Caucasian and South Asian women

Etiologies of infertility among Caucasian and South Asian women				
	Asian		*Caucasian*	
Diminished ovarian reserve				
Sharara 2011	7.0 %	(4/54)	19.0 %	(45/238)
Shahine 2009	6.0 %	(5/80)	10.0 %	(15/145)
Male factor infertility				
Sharara 2011	72.0 %	(39/54)	69.0 %	(164/238)
Shahine 2009	38.0 %	(30/80)	36.0 %	(52/145)
Unexplained				
Sharara 2011	2.0 %	(1/54)	3.0 %	(7/238)
Shahine 2009	16.0 %	(13/80)	18.0 %	(26/145)
Endometriosis				
Sharara 2011	9.0 %	(5/54)	15.0 %	(36/238)
Shahine 2009	15.0 %	(12/80)	11.0 %	(16/145)
Tubal factor				
Sharara 2011	22.0 %	(12/54)	21.0 %	(50/238)
Shahine 2009	10.0 %	(8/80)	9.0 %	(13/145)
PCOS				
Sharara 2011	50.0 %	(27/54)	29.0 %	(69/238)
Shahine 2009	24.0 %	(19/80)	14.0 %	(20/145)

and only 20.0 % of black women [6]. However, two studies of South Asians showed no difference in the rate of unexplained infertility compared to Caucasians [15, 16].

Table 8.1 shows the relative causes of infertility reported in these two studies of South Asians.

ART Outcomes Among Women of South Asian Ethnicity

As researchers continue to examine disparities in success of ART in different ethnicities, the available data are insufficient for strong conclusions [18]. Despite these inadequacies in national reporting, the research that has been performed examining ethnicity as an independent predictor of treatment response has been provocative. Because prior reporting, at best, allotted subsets of ethnicity as Caucasian, African American, Hispanic, and Asian, much of the literature examining ethnic-mediated outcomes group South Asian, East Asian, and Pacific Islanders together as one ethnicity. As previously described, studies have eluded to differing etiologies for infertility among Asian women, e.g., higher prevalence of PCOS among South Asian women. Here, we discuss treatment outcomes among self-reported "South Asian/Indian" women with infertility.

Few studies look specifically at ART outcomes in South Asian women. From the reports that currently exist, it appears that a significant cause of infertility in

South Asian women is oligoovulation or anovulation secondary to PCOS [10]. Despite this high prevalence, reported as high as 52 % of South Asian women with infertility, many are able to conceive with mild ovulation induction using oral agents, such as clomiphene citrate. For those who are not able to conceive with ovulation induction alone, most often in women with multiple factors contributing to their infertility, ART is a viable option. One study from the United Kingdom compared ethnic variations in response to IVF/ICSI treatment in women with PCOS refractory to standard ovulation induction [19]. Using women with tubal disease for comparison, the two ethnic groups compared were South Asian immigrants from the Indian subcontinent and British Caucasians. Examining outcomes of 668 IVF or ICSI cycles using a GnRH agonist down-regulation protocol and cleavage-stage fresh transfers, they found that South Asian women with PCOS presented at an earlier age for management of fertility. Also, women with PCOS (both ethnic groups) had significantly higher serum LH concentrations than the comparison tubal factor group; however, the basal FSH concentrations, body mass index (BMI), and median stimulation lengths were comparable in all groups. When examining treatment outcomes, they found that South Asian patients diagnosed with PCOS required significantly lower dosages of gonadotropins/day as compared to the South Asians with tubal factor and Caucasians (both with and without PCOS). Despite requiring lower doses of gonadotropins during the stimulation phase, significantly more oocytes were retrieved from the South Asian women with PCOS, whereas the remaining three groups had similar number of oocytes. However, even with this increase in oocyte production, the four groups had similar number of mature oocytes, with a reduction in fertilization rates in the South Asian women with PCOS; the fertilization rates among the other groups were similar. Furthermore, South Asian women with PCOS were 3.53 times more likely to experience miscarriage than their Caucasian PCOS counterparts [19].

In another study of IVF outcomes of Indian women in Britain, Mahmud et al. found evidence of poorer IVF performance compared to Caucasian women [20]. Specifically, they found that a higher proportion of Indian patients experienced cycle cancellation (22.7 % vs. 9.1 %) and lower live birthrates (LBR) (22.7 % vs. 9.1 %) as compared to the matched Caucasian controls. However, other cycle parameters such as number of oocytes, fertilization rates, embryos transferred, and clinical pregnancy rates were similar. These findings were not seen in a larger study also performed in the United Kingdom. Lashen et al. [21] compared IVF outcomes among 108 first-generation Indian patients and 216 Caucasian controls that were matched by age, FSH, and infertility diagnosis. With a median age of 32 years in both groups and a higher incidence of PCOS and longer duration of infertility among the South Asian women, they reported that under the same IVF protocol, the Asian patients exhibited a similar response to controlled ovarian stimulation and subsequent IVF outcomes to the Caucasian controls. Interestingly, they did find a nonsignificant reduction in clinical pregnancy rate among the Asian women (16 % vs. 22.6 %), and postulated that perhaps the longer duration of infertility within this group contributed to this discrepancy.

To further study the reduced pregnancy rates in South Asian (Indian) patients, Shahine et al. sought to control for embryo quality by comparing LBR between

Table 8.2 A comparison of two US centers examining IVF outcomes after blastocyst transfer among Caucasian and South Asian women

	Caucasion	South Asian	*p* value
Shahine et al.	*N* = 145	*N* = 80	
Age (mean ± SD)	36.71 ± 3.9	34.03 ± 4.09	0.03
Cycle day 3 FSH (IU/L) (mean ± SD)	6.5 ± 2.0	6.2 ± 1.8	0.4
Gonadotropin use (IU) (median)	3,714	3,106	0.2
Oocytes retrieved (mean ± SD)	16.8 ± 5.9	17.1 ± 5.9	0.6
Embryos transferred (mean ± SD)	2.0 ± 0.8	1.9 ± 0.7	0.6
Implantation rate	38 %	28 %	0.06
Clinical pregnancy rate	52 %	36 %	0.02
Miscarriage rate	22 %	31 %	0.4
Live birth rate	41 %	24 %	0.003
Sharara et al.	*N* = 238	*N* = 54	
Age (mean ± SD)	33.5 ± 3.6	30.5 ± 3.5	<0.001
Cycle day 3 FSH (IU/L) (mean ± SD)	8.5 ± 3.6	7.1 ± 2.8	0.008
Gonadotropin use (IU) (median)	2,775	2,475	NS
Oocytes retrieved (mean ± SD)	13.0 ± 5.9	13.4 ± 6.8	NS
Embryos transferred (mean ± SD)	21 ± 0.7	1.9 ± 0.4	NS
Implantation rate	37.3 %	41.1 %	NS
Clinical pregnancy rate	65.5 %	62.9 %	NS
Miscarriage rate	11.5 %	23.5 %	NS
Live birth rate	57.6 %	48.2 %	NS

(Asian) Indian and Caucasian women after blastocyst transfer. Both groups had comparable baseline characteristics, with the exception that the Indian patients were younger than the Caucasian patients by a mean of 2.7 years. Predictably, a larger proportion of the Indian patients had PCOS (24 %) compared to Caucasians (14 %). In contrast to the study by Palep-Singh et al., the two groups had similar number of oocytes retrieved, fertilization rates, and mean number of blastocysts. Despite a younger average age, similar response to ovarian stimulation, and comparable embryo quality, the Indian patients had significantly lower clinical pregnancy rates (36 % vs. 52 %) and LBR (24 % vs. 41 %) than the Caucasian patients [15].

Sharara et al. performed a similar study in Virginia, comparing South Asian women to Caucasian women undergoing fresh blastocyst transfer (see Table 8.2). Interested in controlling for embryo quality, they compared 292 fresh blastocyst transfers (54 were South Asian). In concordance with previous studies, they found that South Asians had significantly higher rates of PCOS and a lower incidence of diminished ovarian reserve [16]. They also found that South Asians were significantly younger with lower FSH levels than their Caucasian counterparts. In response to treatment, they found no difference in gonadotropin dose, number of oocytes retrieved, number of embryos transferred, implantation and clinical pregnancy rates, or LBR. Only women under 40 years of age were included in their study, and they postulated that perhaps a younger cohort of women may have contributed to the similarity in outcomes reported.

Understanding Disparity in Treatment Outcomes

As previously delineated, a large proportion of South Asian women experience infertility as a consequence of anovulatory cycles, most commonly caused by PCOS. Although the first line of treatment is ovulation induction with oral agents, some patients will require superovulation with gonadotropins. Prior studies examining ART outcomes among women with PCOS have reported higher oocyte yield per cycle, but lower fertilization rates, suggesting a compromise in the oocyte quality [22]. A study comparing ART outcomes between South Asian and Caucasian women with PCOS found that South Asian women exhibited a higher sensitivity to gonadotropins [19]. Compared to their Caucasian counterparts, the South Asian patients required significantly less gonadotropin stimulation with a resultant higher oocyte yield, although a lower fertilization and implantation potential, suggesting an ethnic-mediated discrepancy in hormonal receptivity or metabolism [19].

Hyperinsulinemia and insulin resistance, both common findings in PCOS patients, are thought to affect ovarian steroidogenesis, leading to an elevation in androgen production and reduction in sex hormone-binding globulin (SHBG) [22]. Further, women with insulin resistance, in the setting of PCOS, are at significant risk of developing type 2 diabetes mellitus [23]. In fact, 50–60 % of women with PCOS exhibit central obesity, which significantly contributes to the risk of emerging diabetes and heart disease [22, 23]. Examining unique clinical and biochemical parameters in South Asians and Caucasians with PCOS, Wijeyaratne et al. [11] reported a higher prevalence of acne, acanthosis nigricans, and secondary infertility among South Asian women. In concordance with prior investigations, despite similar BMI, waist:hip ratios, and fasting glucose, South Asians exhibited significantly higher fasting insulin levels and lower insulin sensitivity [11, 19]. Perhaps even more concerning, the South Asian women presented with evidence of systemic disturbance earlier than their Caucasian counterparts, suggesting a combination of younger onset and a more severe form of the condition.

During the past decade, metformin has been evaluated as a treatment for PCOS. Studies have demonstrated that metformin successfully improves hyperinsulinemia and hyperandrogenemia, and improves ovulation and pregnancy rates when used in combination with clomiphene [24, 25]. Recently, investigators have looked at metformin as a form of "pretreatment" in women with PCOS, and reported improved pregnancy rates and LBR among patients who took metformin as compared to placebo [26]. Given the prior reports of heightened insulin resistance among South Asians diagnosed with PCOS, treatment with insulin sensitizers may be considered.

Conclusions and Future Directions

As made evident throughout this chapter, insufficient reporting of ethnicity to the national database has perpetuated a gap in our understanding of the etiology behind the reproductive disparity in infertile Asian patients. Despite these limitations, there

appears to be an elevated incidence of PCOS among South Asian women, with a significantly higher prevalence of insulin resistance. In addition, patients with PCOS and abnormal elevations in serum insulin production have a higher predisposition toward developing diabetes than those without PCOS. Thus, our efforts should focus on early diagnosis and a multidisciplinary approach to the management of such patients.

Access to care is another issue that must be considered when studying ethnic differences. Different cultural norms and values can affect when and how patients seek medical care. In South Asian communities, infertility is a highly stigmatized condition. Although most studies examining South Asian women undergoing ovulation induction or ART report lower mean ages among these women, many exhibit longer durations of infertility [11, 15, 19]. Since South Asian women tend to seek motherhood at a younger age than Caucasians, physicians should be sensitive to duration of infertility, and patients should be referred to a specialist when they have exceeded their age-expected average time to conception. Finally, with evidence to suggest that ethnicity is a major factor involved in treatment response, efforts should focus on better understanding of these differences and using available data to provide the best individualized care.

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Chapter 9
Ethnicity and IVF

Emilie Green, Laura Gillis, and Hany Lashen

Ethnicity

Ethnicity constitutes one's biology, culture, language, religion, health beliefs and behaviours, and is a complex concept that is difficult to define succinctly [1]. The terms "race" and "ethnicity" are sometimes considered synonymous, though "race" usually relates to biological variation due to the underlying genetic construct of an individual [2]. Ethnicity is generally considered to encompass both biological and environmental factors, and thus is likely to play a key role in determining disease prevalence, particularly when the changing demographics of the Western World are considered. The 2001 UK Census revealed that 4.6 million of the UK population was classified as "ethnic minority", a rise of 53 % from the 1991 census [3]. This trend is also seen in the USA. In the 2000 census, an estimated 24.9 % of the population reported their ethnic origin to be something other than white [4], an increase from the 1990 census during which 19.7 % of the population allocated themselves to the "ethnic minority" category [5].

There is evidence to suggest that migrants develop the disease profile of the land to which they migrate within a few generations. Consequently, by exploring

E. Green, B.Med.Sci.
University of Sheffield, Beech Hill Road, Sheffield S10 2RX, UK
e-mail: mda07eg@shef.ac.uk

L. Gillis, M.B.Ch.B.
Department of Obstetrics and Gynecology, Doncaster Royal Infirmary, Women's Hospital, Armthorpe Road, Doncaster DN2 5LT, UK
e-mail: laura.gillis@hotmail.co.uk

H. Lashen, M.B., B.C.H., M.D., F.R.C.O.G. (✉)
Department of Obstetrics and Gynecology, NHS Foundation Trust, Sheffield Teaching Hospitals, University of Sheffield, Tree Root Walk, Jessop Wing, Sheffield S10 2SF, UK
e-mail: h.lashen@sheffield.ac.uk

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health-related states amongst various ethnic groups, disease aetiology may be better understood. In addition, prognostic factors related to treatment modalities such as IVF may become apparent [6, 7].

Data from the 2001 UK census demonstrates that within the ethnic minority population, the majority are Asians of Indian-subcontinent descent [3]. However, from a US perspective, the black population is the second most prevalent ethnicity. The largest subgroups within the Asian population constitute those originating from East Asia, for example countries such as China, Japan, Korea and Thailand [4].

Relationship Between Ethnicity and IVF Outcome

Extensive research has been undertaken in the field of assisted reproduction over the past 30 years. However, the extent to which ethnicity impacts upon the outcome of techniques such as in vitro fertilisation (IVF) remains unclear due to a scarcity of published data. Only a few studies have attempted to explore the link between ethnicity and IVF, both in the UK and the USA, though no steadfast conclusions have been drawn. Fertility and IVF success is measured predominantly by clinical pregnancy rate, but the outcome live birth rate has more logical and economic values.

On a global scale, the demand for IVF is increasing. The UK figures suggest that sub-fertility affects 3.5 million people at some point during their lives. Further, from 2005 to 2006, a 5.6 % rise in the number of IVF cycles performed has been noted. It must be remembered that the UK live birth rate remains relatively low at 23.1 % per cycle [8]. In the USA, over 100,000 couples undergo IVF each year, most of which are Caucasian [9]. However, there has been a recent increase in the proportion of African Americans using this technology [10].

Certain conditions are more prevalent in certain ethnic groups; for example the South Asian population is more susceptible to type 2 diabetes mellitus [11, 12]. Ethnicity therefore offers an opportunity to define and explore, through comparison with a native population, the true aetiological agents of disease. Many studies currently advocate that ethnicity influences many important milestones throughout the reproductive process. However, it remains to be seen whether the impact of this demographic factor is due to its environmental, social, cultural or genetic components [13].

Health disparities are defined as “differences in the incidence, prevalence, mortality, and burden of diseases and other adverse health conditions that exist among specific population groups” [14]. Ethnic diversity in terms of disease profiles, and consequently its proposed association with sub-fertility, may be attributed to genetic biological variation or environmental lifestyle factors [15, 16].

Despite a dearth of studies focussing on ethnicity, data from a large US epidemiological study of IVF treatment suggests that African Americans have a higher risk of sub-fertility than their Caucasian counterparts. The precise rationale behind this association remains unknown, though factors such as health inequality and low socioeconomic status have been implicated, as they may cause a failure to treat conditions that predispose to sub-fertility [17]. Similarly, Gleicher et al. established

that pregnancy rates following IVF were significantly lower in the African race, 10.2 % compared to 25.9 % in Caucasians and 29.2 % in the predominantly East Asian group. Further, there is evidence to suggest that although non-Caucasian women may experience lower levels of fertility than Caucasian women, this group often has limited access to assisted reproduction technologies [18]. This inequality of healthcare provision emphasises the need for a better understanding of the potential variation in fertility of women of differing ethnic backgrounds.

Numerous potential reasons for fertility variation have been proposed; for example the retrospective research carried out by Sharara et al. also concluded that black women have inferior IVF outcomes compared to their Caucasian counterparts. This disparity was attributed to factors such as a higher BMI, a longer duration of sub-fertility and a higher incidence of tubal disease among black women [19].

Further to the higher rates of sub-fertility that have been demonstrated in black-African women, many studies have suggested that this ethnic group often experience a longer duration of sub-fertility after having presented for treatment. This implies a degree of inequality in access to care, which may be attributable to socioeconomic factors [14]. Future studies, particularly those based in the USA, must consider the socioeconomic status of participants, as some states do not have mandates that cover IVF costs. Consequently a higher socioeconomic status becomes imperative in order to fund IVF treatment, which may confound the success rates obtained from ART data [19, 20].

The definitive identification of a causative relationship between ethnicity and sub-fertility will enable healthcare professionals to improve outcomes for women deemed to attain lower chances of success. Accordingly, whether ethnic disparity can have a direct effect on oocyte endowment or quality or embryo implantation is not known despite alluding to such possibilities in the literature.

Numerous potentially influential factors, which have been implicated in the causal pathway linking IVF and ethnicity, will now be discussed.

Potential Factors Causing Ethnic Differences in Fertility

Fragile X

Among the many proposed explanations for differences in IVF outcomes between ethnic groups is the fragile X mental retardation 1 (FMR1) genotype. The distribution of this genotype varies between Asian, Caucasian and African American ethnicities. In women, the FMR1 mutation is less destructive and does not cause the neuro-psychiatric disease seen in males, though it can cause premature ovarian failure.

A recent study classified the FMR1 genotype into “normal”, “heterozygous normal/high” and “heterozygous normal/low”, indicating the abnormal allele count above or below the normal range. The African group showed a higher expression of the “heterozygous normal/low” genotype than Asian and Caucasian counterparts.

(The Asian groups of participants predominantly originated from China, India and Pakistan.) Therefore, after logistic regression for BMI and age, it was found that the African ethnicity predisposed individuals to a reduced chance of pregnancy. The authors concluded that further research, involving a higher number of participants, is required to investigate the FMR1 genotype in relation to IVF [21].

Vitamin D

Vitamin D deficiency is a global issue and is significantly more prevalent in black and Asian populations. For example, cultural habits such as the wearing of a burka by certain Islamic populations, or the lack of milk fortification in Middle Eastern countries, have the potential to adversely affect vitamin D levels [22].

Vitamin D levels have been implicated in the inconsistency between IVF success and ethnicity. The formation of calcitriol, the active form of vitamin D, is dependent on the enzyme 1-alpha-hydroxylase. The gene coding for 1-alpha-hydroxylase is said to be expressed at a higher level within early pregnancy decidua than other tissues, as are vitamin D receptors. Calcitriol is produced by the endometrium as the embryo enters the uterine cavity, subsequently binds to vitamin D receptors present in uterine, ovarian and placental tissue and regulates genes that control implantation [23].

A cohort study by Ozkan et al. found that levels of calcifediol (25-hydroxyvitamin D), a pre-hormone for vitamin D, were greatly reduced in black participants compared to those of other ethnicities ($p = 0.001$). Patients with high levels of vitamin D and calcifediol were four times more likely to achieve clinical pregnancy. A study by Rudick et al. recently reported lower pregnancy rates among non-Hispanic whites with low vitamin D levels, though Asian participants did not adhere to this pattern. No association between ovarian stimulation parameters or embryo quality and vitamin D levels was found, which suggests that the primary impact of vitamin D may be on the endometrium, as previously mentioned [24].

The possibility that vitamin D supplementation could improve success in women undergoing IVF is a novel concept requiring further investigation [25]. Furthermore, the diagnosis and correction of this metabolic deficiency are both simple and economically viable [26]. Inadequate vitamin D levels could be extrapolated to other gynaecological conditions such as polycystic ovary syndrome (PCOS), as vitamin D therapy could and could serve to regulate the menstrual cycle of such women, thereby increasing their chances of conception [27].

Endometrial Thickness

Kovacs et al. suggest that endometrial thickness has a significant impact on the outcome of IVF. Results from their study showed that the endometrial thickness of women who successfully achieved clinical pregnancy following a cycle of IVF was significantly greater than in women who did not fall pregnant [28]. Another study

advocated that the ideal endometrial thickness is between 7 and 14 mm, and that women outside of this range at both extremes were less likely to conceive [29]. These findings implicate endometrial thickness variation as a potential causative factor for sub-fertility, though Kovacs et al. stated that pregnancy could not be predicted based on endometrial thickness alone [28]. Further research is required to ascertain whether endometrial thickness varies between women of different ethnicities, thus contributing to the disparity in fertility levels. There has been no studies comparing implantation rates or endometrial thickness between ethnic minorities and white European population.

Socioeconomic Factors

Socioeconomic status is a combined measure of education, income and occupation. A recent meta-analysis by Clark et al. showed that African American and American Asian women have a lower pregnancy rate after IVF than Caucasian women. The authors found the live birth rate variation to be statistically significant between Caucasians and African Americans (odds ratio 0.59), Caucasians and American Asians (odds ratio 0.79) and Caucasians and Hispanic women (odds ratio 0.9) [30]. Following this meta-analysis, it was suggested that the differences in fertility and pregnancy outcomes in African Americans and other racial minorities could be attributed to socioeconomic factors. For example, the authors proposed that barriers to healthcare resulting in the late presentation for sub-fertility treatment of certain ethnic groups might reduce live birth rates. African American women were found to have higher levels of obesity and tubal factor sub-fertility, which may also relate to socioeconomic status [30].

There is a tendency for migrants to settle in inner city areas that are known for social deprivation. This sets the trend for the future socioeconomic development of many migrants, which reflects in more ways than one on their health. However, Smith et al. reported that upward intergenerational social mobility did not impact positively on the health of the second generation [31].

Data from the National Centre for Education Statistics demonstrates that African Americans are more likely to attend schools with higher poverty levels than their Asian American and Caucasian counterparts [32]. Education has a significant influence on health-seeking behaviour, so this data may provide important insight into the reasons that certain women present at a late stage for fertility treatment, and also for their lower birth rates following IVF.

According to a recent study by Morris et al., the UK women of high socioeconomic status are more likely to report fertility problems. However, trends in the subsequent investigation and treatment of these women compared to their counterparts of lower socioeconomic status have not been clearly defined. Further studies are planned, specifically to explore the potential role of family income in access to fertility treatment [33]. Evidently, the potential link between low socioeconomic status and sub-fertility has not yet been established in the UK, and additional research is required.

Confounding Factors

Risk factors that are associated with the exposure of interest but do not lie on the causal pathway are known as confounders. They may independently affect the risk of developing the outcome of interest, and may therefore affect the results of the study [34]. Confounding factors may introduce bias into study findings, potentially threatening the internal validity of the research. It is often extremely difficult to completely eliminate the effect of confounding variables. However, by thoroughly randomising the allocation of patients to study groups in randomised controlled trials (RCTs) or by strictly matching participants according to their confounding risk factors in case–control studies, the compromise of the validity of research would be minimised [35].

For clarity, this statistical concept will now be related to IVF outcomes among women of varying ethnicity. For example, Asian women that do not become pregnant after IVF therapy may attribute their lack of success to vitamin D deficiency, which is the exposure of interest in this case. However, these women may smoke more than Caucasian women. Smoking is therefore the confounding factor that does not lie on the originally hypothesised causal pathway but independently reduces fertility.

Age

Of the many confounding factors, increasing patient age is deemed the most important in terms of female fertility. It is therefore extremely relevant to the success of IVF [36]. Templeton et al. supported this theory by demonstrating a steep decline in pregnancy rates following IVF in women over the age of 35 years. Further, no pregnancies in women over the age of 45 years have been recorded in the HFEA data [8, 37]. Therefore, if studies exploring the potential association between ethnicity and IVF outcome fail to limit the age of their participants, the poor outcomes of patients within certain ethnic groups may be magnified. Study participants are usually age matched, thereby reducing the effect of this confounding factor [38].

Smoking

Another major confounding factor that is often unreported in research is the smoking status of the participants. Smoking is a significant risk factor for sub-fertility and other obstetric conditions such as preterm labour and miscarriage. A meta-analysis exploring the influence of smoking on IVF outcome found that female smokers required twice as many cycles of IVF to produce a pregnancy. Further, anti-Mullerian hormone (AMH) levels were lower among smokers, indicating a poor ovarian reserve [39]. If studies do not account for this potential confounding factor, findings may be overestimated.

BMI

BMI may limit the success of IVF treatment. Findings from a study by Thum et al. demonstrated that women with a BMI of 36 or above were more likely than those with a normal BMI (19–25) to experience a miscarriage and hence lower live birth rates were common among this group of women [40]. Both maternal and foetal morbidity and mortality are increased in obese women, and the success of ART is compromised [41]. Current National Institute for Clinical Excellence (NICE) guidelines suggest that the ideal BMI range for successful assisted reproduction is between 19 and 30. The guidance also states that if a woman has a BMI of greater than 30, it would take her longer to conceive when compared to a woman with a "normal" BMI [42]. This potential confounding factor is important with respect to ethnicity, as black women are more likely to have a higher BMI than their white counterparts [20].

Interestingly, Lashen et al. found that extremes of BMI (>27.9 and <19) did not negatively affect the outcome of IVF, though women with a high BMI did have lower levels of oestradiol even after receiving the same gonadotropin dose [43]. A subsequent case–control study explored the relationship between obesity and miscarriage. Primiparous women with a BMI >30 were compared to a matched control group with a normal BMI. Obese women had a significantly higher risk of early and recurrent miscarriage ($p=0.04$) [44].

The precise effect of BMI on IVF outcome remains indistinct, as it is complicated by the presence of PCOS, which is common among women with a high BMI. A limited number of epidemiological studies estimate the prevalence of PCOS to be around 6–10 % among females of reproductive age [45]. Up to 34 % of women seeking fertility treatment have PCOS, which constitutes only a fraction of the total number of women with the condition, as many remain asymptomatic [46]. PCOS is the commonest ovulatory cause of sub-fertility, and a significant proportion of these women are obese [40]. A recent study by Swanton et al. showed no difference in IVF outcome between women with polycystic ovaries (PCO), PCOS or normal ovaries. However, patients with PCO or PCOS did have an increased risk of developing ovarian hyper-stimulation syndrome [47].

Evidently, the interplay of many confounders makes it difficult to assess the effect of each individual factor. For example, a recent study investigating the impact of both age and BMI on IVF outcome revealed that a high BMI alone did not have a significant effect on fertility. However, when combined with increasing age, this interaction resulted in a considerable decline in fertility. As expected, clinical pregnancy rates decreased as both age and BMI increased. The negative effect of a high BMI on fertility was at its peak among patients in their twenties, but diminished as the patient age increased. Authors reported that BMI has a negligible impact upon fertility in women aged 36 or above [48].

These studies demonstrate that extremes of BMI could adversely affect outcomes of both normal pregnancy and successful assisted conception. Such research could aid clinicians in supporting, encouraging and educating patients about weight loss, and its potential role in improving fertility.

The effect of ethnicity on the prevalence of obesity in the UK is controversial with many studies providing conflicting results [49].

Barriers to Research

Health disparity is becoming an increasingly significant component of modern medicine as the Western world continues to diversify ethnically. However, research involving ethnic minority populations is laden with obstacles. The publication of many studies, each demonstrating a unique perspective, has made the interpretation of this issue challenging [13]. The impact of ethnic diversity upon reproduction needs to be further explored in order to develop techniques that will improve outcomes for susceptible women. Therefore, if certain ethnic groups are not involved in research, the ability of researchers to explore potential variation in fertility and response to assisted reproduction treatment is limited [13].

Ethnic minority couples still constitute a small proportion of the total population undergoing IVF treatment. In addition, the US IVF database controlled by the Centers for Disease Control and Prevention does not include ethnicity-related data [9]. It is therefore difficult to both quantify the usage of and response to IVF amongst the ethnic minority population [10, 50].

The majority of studies comparing reproductive outcomes involve blacks and whites, though Asians and Hispanics are considered to be the two other main ethnic groups. White Caucasians are often used as a reference against which to compare other ethnicities [13]. Previously, many studies attempting to evaluate the participation of various ethnic groups in research have paradoxically excluded Asians. Consequently, there is a dearth of evidence on which to determine the willingness of Asian women to participate in research [51].

A recent cross-sectional study suggests that both Asian and Middle Eastern women are less likely than their Caucasian counterparts to participate in medical fertility research. Reasons remain unclear, though authors propose that factors such as limited education, concerns about time commitment and a perception that clinical care may be compromised by participation in research may hinder the involvement of all subgroups of Asian women. Findings from this study demonstrate that minority populations require education about the importance of their participation in clarifying the implications of possible variations [52].

Patients of ethnic groups other than Caucasian may be excluded from research for numerous reasons. For example, such groups may have inadequate access to research centres. Further, healthcare professionals may be reluctant to refer ethnic minority patients to trials for fear that they may feel exploited [53]. Both cultural and language barriers may also limit the involvement of such patients in studies [54]. Some studies may deliberately exclude patients of ethnic minority groups to simplify data interpretation [55].

Difficulties related to the categorisation of individuals into discrete ethnic groups have been reported to hinder research. The classification of ethnicity is imperative

to ensure valid findings, as this factor is used as a proxy genetic marker of disease. However, due to rising racial admixture, rigid categorisation is becoming increasingly complex and potentially obsolete. Further, concerns that the identification of health disparities could pose problems have been raised. Individuals needing additional care and support may be marginalised if stereotypical perspectives emerge [11, 56].

In the majority of the studies undertaken, a larger number of Caucasian women were recruited than women of other ethnic backgrounds. This could be attributed to the simple fact that Caucasians constitute the majority of the population in the developed world, and therefore a smaller number of ethnic minorities seek fertility treatment than Caucasian women. Is this because of healthcare inequality, or are ethnic minority groups less inclined to access fertility services for cultural reasons? Future research should involve participants from a diverse range of ethnic backgrounds.

Conclusion

The precise aetiology and clinical significance of varying fertility rates within the increasingly ethnically diverse society of the Western world remain unclear, as many studies exploring this potential association have yielded diverse results. Research exploring fertility among women of differing ethnic backgrounds is extremely complex, and involves multiple potentially influential factors; thus it is difficult to attribute a particular outcome to a specific variable [57]. Further research is required to address gaps in knowledge in this field. Healthcare professionals need adequate evidence on which to base clinical practice so that the delivery of care to patients of all ethnic backgrounds may be optimal [58].

Both patients and healthcare professionals should be educated regarding the potential aetiology of fertility problems that may be experienced by women of ethnic minority backgrounds. For example, the fertility of Asian patients may be adversely affected by low vitamin D levels. If healthcare professionals are aware of such potentially causative factors, they could ensure that patients are vitamin D replete before commencing fertility treatment [25]. In addition, healthcare professionals should be able to deliver appropriate counselling so that patients are fully aware of their prognosis and treatment options [59].

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Chapter 10
Ethnic Disparity in Oocyte Donation Outcome

Fady I. Sharara

Introduction

Infertility is a major public health problem affecting millions of women worldwide. Over the past three decades, the acceptance, advancement, and growth of assisted reproductive technologies (ART) to treat infertility have been significant [1, 2]. The initial report of racial differences in ART outcomes was reported by Anand Kumar in India in 1988 [3], followed by two reports in the UK [4, 5], before the first report in the USA [6]. Since then there has been a mounting body of evidence identifying racial disparities related to ART access and outcomes, in the USA and worldwide [7].

The ART outcome for fresh and FET cycles have been addressed in prior chapters. This chapter deals with the outcomes of oocyte donation cycles across ethnic groups. While the paucity of data is concerning, the only published report on whites compared to black women showed a poorer outcome in black women utilizing donated oocytes [8]. However, there seems to be no such disparity in outcome between East Asian women and whites using oocyte donation in the only two reports in Asian women [9, 10].

White vs. Black Recipients

In the only report to date addressing racial disparity in oocyte donation outcome between black and white women, Bodri et al. reviewed their experience in Barcelona,

F.I. Sharara, M.D., F.A.C.O.G. (✉)
Virginia Center for Reproductive Medicine, 11150 Sunset Hills Road, Suite 100, Reston, VA 20190, USA

Department of Obstetrics and Gynecology, George Washington University, Washington, DC, USA
e-mail: fsharara@vcrmed.com

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Spain [8]. In that retrospective study, 280 black recipients undergoing their first oocyte donation cycle (African and Caribbean descent) were each compared with 560 age-matched white recipients also undergoing their first cycle (a 2:1 ratio of white to black recipients achieved an 82 % power). Race was determined by patient self-questionnaires and by taking into account the birthplace of the recipients. The black women had a higher incidence of tubal factor, fibroids, BMI, and a longer duration of endometrial preparation. The black male partners also were significantly older than the white controls. After adjusting for multiple cofounding variables, black race was an independent risk factor for not achieving an ongoing pregnancy (adjusted OR: 0.62, 95 % CI: 0.43–0.89, $P = 0.009$) [8]. Of importance, two of the clinically most plausible variables (tubal factor infertility and uterine fibroids) that might be responsible for decreased implantation rates were found to be not significantly associated with decreased pregnancy rates. This however may become significant in a larger sample size.

The authors then evaluated the 43 women of Southeast Asian descent. There were few patients of Asian descent, so the authors lumped the South Asians and the East Asians in one group, even though these racial groups are different ethnically and biologically. These were matched with 129 age-matched white recipients (power was only 21 %). The authors could not find any differences in ongoing pregnancy rates between the two groups, possibly because of the low number of recipients in the Asian group [8].

White vs. East Asian Recipients

Gleicher was the first to evaluate the outcome of donor oocyte cycles in East Asians (specifically Chinese) women [9]. He noted in a small number of donors that Chinese donors had a much higher incidence of diminished ovarian reserve compared to age-matched white donors. Specifically, the 17 Chinese donors undergoing ovarian stimulation had a higher baseline FSH levels (7.5 ± 1.9 mIU/ml) and a higher cancellation rate (5/17, 29.4 %) was noted compared to a basal FSH of 5.1 ± 1.7 mIU/ml ($P = 0.004$) and no cycle cancellation in the 29 white donors ($P < 0.01$). In addition, fewer oocytes were retrieved in the Chinese donors (9.3 ± 9.7 compared to 15.3 ± 7.1, $P < 0.05$). However, the clinical pregnancy rates per transfer were not different between East Asians and white recipients (6/12 [50 %] compared to 15/29 [51.7 %]), but the clinical pregnancy rates per initiated cycle were lower in the East Asian recipients (6/19 [31.6 %] compared to 15/29 [51.7 %]) [9].

More recently and in a larger patient population of donor oocyte cycles in Asian women, 63 Asians were compared to 156 white recipients [10]. Ethnicity was self-reported, and only the first cycle was evaluated. The Asian donors were Chinese (21 %), Japanese (22 %), Southeast Asians (5 %), and Korean (4 %) and the rest did not specify beyond Asian ethnicity (47 %) [10]. This is again unfortunate as the ethnic groups, especially South Asians, are distinctly different from their East Asian counterparts. Asians showed a trend toward a lower BMI and lower starting

gonadotropin dose, and their peak estradiol levels were 23 % higher than their white counterparts, which did not appear to be due to increased follicular response. There were no differences in the number of oocytes retrieved, implantation rate, or live birth-rates (55.5 % vs. 59.9 %). The rate of multiple gestation was slightly higher for women using an Asian donor (51.2 % vs. 31.4 %; OR 2.3, CI 1.1–4.8) [10]. In contrast to Gleicher's prior results with Asian donors [9], Huddleston et al. could not find higher cancellation rates or basal FSH levels in Asian donors compared to their age-matched white counterparts [10].

A limitation of Huddleston's study is their classification of Asian ethnicity as a homogeneous group, and because donors self-reported their ethnicity, misclassification bias may have influenced their findings [10].

Donor–Recipient Attitudes and Ethnic Origin

In a recent study, Laruelle et al. evaluated the anonymity and secrecy options of donor and recipient couples in a donor oocyte program in Belgium [11]. In Belgium and much of Western Europe, and unlike the USA, payment of oocyte donors is prohibited with the exception of reasonable reimbursement of their expenses. In their program, three options are therefore available for couples wishing to undergo oocyte donation:

1. Known donation: Couples receive the oocytes of the donor they brought to the program.
2. Known-anonymous donation: Each recipient brings a donor whose oocytes are usually shared among four other recipients. In return, each recipient can have up to four or five successive cycles.
3. Anonymous donation: Concerns couples who do not bring a donor to the program.

Laruelle evaluated 135 recipients and 90 donors. Of these, 90 (66.7 %) came with a donor and 45 (33.3 %) came without. The majority of the recipients were from Europe (66.7 %), 20 % were from sub-Saharan Africa, and 13.3 % were from North Africa. Taking ethnic origin into account, Europeans preferred the anonymous donation option (68/90, 75.6 %), and couples from North Africa even more so (15/18, 83.3 %). However, couples from sub-Saharan Africa mainly opted for known donation (17/27, 63 %). A significant group difference was found in the ethnic origin between the three types of donation ($P < 0.01$) [11].

Conclusions

While there is a significant body of evidence showing a lower success and worse obstetric outcomes for ethnic minorities in fresh IVF cycles, the situation with oocyte donation is inconclusive mainly because of the very small number of published studies to date. Studies are also needed to address the different models of donation

between the USA and other countries, especially Western Europe, as the attitudes toward donation differ significantly between known and anonymous donations for both donors and recipients. Larger studies are clearly needed to evaluate whether a racial disparity exists when using a donor oocyte model, and, if such disparities do exist, evaluate and treat the possible culprits to optimize outcome.

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Chapter 11
Frozen Embryo Transfer Outcomes Among Racial and Ethnic Groups

Katherine S. Anderson, Anita P. Tamirisa, John M. Csokmay, and James H. Segars

Introduction

African American and Hispanic women are significantly more likely to be infertile compared to women of other ethnicities, OR 1.9 (95 % CI 1.5–2.3) and OR 1.7 (95 % CI 1.4–2.0), respectively [1]. Despite higher rates of infertility, both groups are underrepresented in artificial reproductive technology (ART) populations [2, 3]. Conversely, Asian women have been shown to be overrepresented in ART clinics in a state with mandated insurance coverage for infertility services [4], potentially reflecting their higher education levels compared to Caucasian, African American, and Hispanic women [5]. However, there is evidence that Asian women still present after a longer duration of infertility compared to Caucasians [6], suggesting continued cultural and/or social differences.

K.S. Anderson, M.D.
Department of Obstetrics and Gynecology, William Beaumont Hospital,
3601 West 13 Mile Road, Royal Oak, MI 48073, USA
e-mail: kay.anderson@beaumont.edu

A.P. Tamirisa, D.O.
Department of Obstetrics and Gynecology, Summa Akron City Hospital,
525 East Market Drive, Med II, Akron, OH 44309, USA
e-mail: tamirisaa@summahealth.org

J.M. Csokmay, M.D.
Department of Obstetrics and Gynecology, Walter Reed National Military Medical Center,
Bldg 10, Floor 2, FM 2138, 8901 Wisconsin Avenue, Bethesda, MD 20889, USA

Program in Reproductive and Adult Endocrinology, NICHD, National Institutes of Health,
10 CRC, Room 1E-3140, 10 Center Drive, MSC 1109, Bethesda, MD, USA
e-mail: John.M.csokmay.mil@health.mil

J.H. Segars, M.D. (✉)
Program in Reproductive and Adult Endocrinology, NICHD, National Institutes of Health,
10 CRC, Room 1E-3140, 10 Center Drive, MSC 1109, Bethesda, MD, USA
e-mail: segarsj@mail.nih.gov

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With a higher proportion of minority women experiencing infertility compared to Caucasians it is important to understand disparities in ART outcomes and the etiologies of these differences. While demographic factors and access to care may contribute [4, 5], there is evidence that ethnic differences in ART outcomes persist in equal access to care settings [3, 4]. In this chapter, variables that may contribute to racial differences in frozen embryo transfer (FET) outcomes are reviewed. As ethnic disparities in fresh embryo transfer after ART are detailed elsewhere in this text, only a brief overview of fresh cycles will be outlined to serve as background for a discussion of racial variation in FET.

Racial Differences in ART Outcomes

In the first published study of race and ART outcomes, Sharara and McClamrock [7] reported that African American women experienced significantly lower implantation rates (9.8 % vs. 23.4 %, respectively) and lower clinical pregnancy rates (19.2 % vs. 42.2 %, respectively) compared to Caucasians. This study prompted increased interest in evaluating racial disparities in ART, and numerous studies have since demonstrated decreased ART success among minority groups [8–13]. In one of the largest studies of ART outcomes in minority ethnic groups, Fujimoto et al. [12] evaluated 139,027 non-donor ART cycles from the Society for Assisted Reproductive Technology (SART) database (a national registry of ART cycles in the USA). African American, Asian, and Hispanic women all experienced significantly lower live birth rates compared to Caucasian women [12]. While some studies have found no difference in ART outcomes between races, these studies have been comparatively smaller than those utilizing the SART database and may have been limited by sample size and/or composition [14, 15]. The number of large studies demonstrating significantly different outcomes offers compelling evidence that ethnic disparities in ART outcomes exist.

Proposed etiologies for racial disparities in success with ART include differences in the prevalence of tubal factor infertility [5, 7, 14–17] and leiomyomas [18], extremes of BMI [7], premature ovarian aging (POA) [9, 19], and differences in estradiol metabolism with subsequent variance in endometrial receptivity [10, 11, 20–26]. Despite controlling for many of these factors minority women still have decreased implantation rates, clinical pregnancy rates, and live birth rates with fresh embryo transfer [8, 10–13]. These findings evoke consideration of possible inherent biological differences between ethnicities that influence ART outcomes.

Single-Embryo Transfer and Frozen Embryo Transfer

Single-embryo transfer (SET) use has increased within ethnic groups [2]. For African American women, 5.3 % of transfers were SET in 1999–2000, compared to 8.8 % in 2004–2006 ($P < 0.001$) [2]. Caucasian women had a similar increase in SET rates,

from 4.6 to 8.6 % for the study periods, respectively ($P<0.001$) [2]. SET has been shown to decrease the rate of multiple gestations without negatively impacting pregnancy rates [27, 28]. By implementing education regarding the risks of a multiple gestation pregnancy into their protocols, ART providers have demonstrated that with increased knowledge more women desire a singleton pregnancy [27, 28]. With increasing utilization of SET, more embryos from the stimulated cycle will be cryopreserved for possible transfer at a later time [28]. This highlights the importance of understanding factors that influence FET success, and possible racial differences therein.

Not unexpectedly, one of the main predictors of success with FET is the outcome of the fresh cycle pregnancy test [29, 30]. Other factors that influence FET success include, but are not limited to, an endometrial thickness of at least 8 mm, ovarian reserve status, and the number of high-quality thawed embryos available for FET [29, 30]. As outlined below, when controlling for several confounders there may be little variation in FET outcomes between patients of different ethnic backgrounds.

Racial Differences in Frozen Embryo Transfer

There are limited data on racial differences in FET success rates. In a study of 80,196 ART cycles from the SART database for 1999 and 2000 [31], African American and Asian women had significantly reduced fresh cycle live birth rates compared to Hispanic and Caucasian women. However, when further examining the 11,684 cycles using thawed frozen embryos there were no significant differences in either clinical pregnancies or live birth rates between racial groups [31].

To further examine racial differences in FET outcomes, 72,273 women undergoing IVF using non-donor embryos from 1999 to 2000 were identified using the SART database [8]. Consistent with the findings of Grainger et al. [31], African American women had significantly decreased live birth rates compared to Caucasian women in fresh cycles, but there was no difference in clinical pregnancy or live birth rates for FET cycles [8]. In a follow-up study, the authors used SART data from 2004 to 2006 and again showed no difference in implantation or clinical pregnancy rates between African American and Caucasian women in FET cycles [2]. However, in contrast to the findings in the initial study, African American women in the second analysis had a lower live birth rate after FET than Caucasian women.

Seifer et al. [2] proposed that the lower FET live birth rate for African American women may have been detected in the second study due to improved cryopreservation and thawing techniques. The authors further postulate that the results suggested that thawed embryos of African American women are more likely to abort compared to those of Caucasian women [2]. While African American women have been shown to have a higher incidence of spontaneous abortion after ART compared to Caucasian women [13, 31], the exact mechanism responsible for this difference is yet to be determined and warrants evaluation [18]. Of note, the 10 % difference in live birth rate between races after FET is much less dramatic than the 31 % disparity

observed in fresh cycles [2]. This point was emphasized by the authors and suggests differential success for minorities undergoing fresh versus frozen cycles.

Csokmay et al. [32] also compared outcomes between 50 African American women and 119 Caucasian women who underwent a frozen blastocyst transfer between 2003 and 2008. Live birth rates after fresh embryo transfer in African American women were significantly lower than those in Caucasian women (16.7 % vs. 39.7 %, respectively) [32]. However, there was no significant difference in pregnancy outcome between the two groups after frozen blastocyst transfer, despite African American women having four times the incidence of leiomyomas [32].

The available data therefore suggest that ethnic disparities in fresh embryo transfer cycles may not persist in subsequent FET cycles. There are variables that may differentially affect success in fresh versus frozen embryo transfer. In the following sections the factors that might contribute to racial disparities in ART outcomes are outlined, focusing on how these factors may, or may not, contribute to the observed difference between fresh and frozen embryo transfer cycles. It is important to identify the etiology responsible to determine whether intervention might improve success in fresh cycles for minority populations.

Tubal and Uterine Factors

African American and Hispanic women are more likely to present with tubal factor infertility compared to Caucasian women [5, 7, 14–17]. Although some studies have not found a difference in the rates of tubal factor infertility between Hispanic and Caucasian women [18], multiple other studies suggest that it is more prevalent in the former group [5, 17]. In vitro fertilization (IVF), however, bypasses the fallopian tubes, and tubal factor infertility is one indication for IVF. It is possible that scarring from pelvic inflammatory disease could cause a hydrosalpinx, which may result in an unfavorable environment for embryo implantation [33]. If this were the primary reason for disparities in ART outcome, it is logical that the effect would persist regardless of treatment in fresh versus frozen cycles. However, as outlined above, disparities between ethnic minorities in FET outcomes are not as significant as those in fresh cycles, if they exist at all. Furthermore, in a study that excluded women with a known hydrosalpinx, African American women still had decreased implantation and clinical pregnancy rates in fresh embryo transfer cycles [7].

Uterine leiomyomas are more common in African American women compared to women of other racial backgrounds [18, 32], with an incidence as high as 30.8 % in one study [18]. Feinberg et al. [18] studied 1,457 women undergoing fresh, non-donor IVF cycles and found a decreased live birth rate in African American women, postulating that these differences were due to the higher prevalence of leiomyomas. Indeed, when adjusting for leiomyomas within their study there was no difference in fresh ART outcomes between African American and Caucasian women [18]. Conversely, in a much larger study of 80,309 non-donor IVF cycles, Seifer et al. [8] found that despite controlling for tubal and uterine factors African

American race remained an independent risk factor for not achieving a live birth with fresh embryo transfer [8].

While tubal and uterine factors certainly contribute to outcomes in ART, any negative effect that these variables may have would be expected to be present in both fresh and frozen cycles, provided no interim intervention was performed. Given the improved outcomes for minorities undergoing FET relative to fresh cycles, and recognizing that the effect of tubal/uterine factors remains constant between fresh and frozen cycles, it is unlikely that the decreased success of minorities undergoing fresh embryo transfer can be attributed solely to differences in the rates of tubal or uterine factor infertility.

Body Mass Index

Extremes of body mass index (BMI) have been associated with decreased success in ART [34–41]. Underweight and overweight women have been shown to have increased miscarriage rate and produce fewer number of developed embryos in IVF cycles [37, 39]. Overweight and obese women have lower clinical pregnancy and live birth rates after ART [34–41]. Proposed etiologies for these differences include technical difficulties in ultrasound-guided transvaginal oocyte retrieval, inadequate dosing of gonadotropins during stimulation [36, 39, 41], and potentially decreased embryo quality in obese women [41].

African American women undergoing IVF tend to have a higher BMI compared to Caucasians (mean BMI of 28.6 vs. 26.7, respectively) [7] and, as described above, have significantly lower implantation and pregnancy rates in fresh cycles. African American women may also require more aggressive ovarian stimulation due, at least in part, to an increased BMI [7, 34, 36]. In the limited available literature, no significant difference in BMI between Hispanic women and African American, Caucasian, or Asian women pursuing ART has been demonstrated [14, 17].

Women with a low BMI may also have decreased success with ART. Similar to overweight women, underweight women experience increased risk of miscarriage and reduced pregnancy rates [35, 37]. In a study of fresh blastocyst transfer IVF cycles, Asian women had significantly lower BMI compared to Caucasians (22.6 and 24.2, respectively) [11]. Clinical pregnancy and live birth rates were lower for Asian women in the fresh cycle (FET outcomes were not analyzed) [11]. The significant difference in BMI between Asian and Caucasian women is of interest given the association of both low BMI and Asian ethnicity with poor ART outcomes.

To further evaluate the effects of BMI and race on IVF outcomes, Luke et al. [42] analyzed 31,672 ART embryo transfers from the SART database for 2007. Asian women weighed significantly less than women of other racial groups and African American women were significantly heavier ($P < 0.0001$) [42]. Interestingly, even within BMI categories, non-Caucasian (African American, Asian, and Hispanic) women had decreased clinical pregnancy and live birth rates [42]. Thus, while BMI may vary between racial groups, the results of this study suggest that there may be inherent differences between weight-matched women of separate ethnicities that affect ART outcomes.

Premature Ovarian Aging

Diminished ovarian reserve (DOR) or POA has also been proposed as a contributor to decreased pregnancy rates in minorities pursuing ART. After controlling for age, BMI, smoking, and HIV status, African American and Hispanic women were found to have decreased serum levels of Mullerian inhibiting substance (MIS) (25 and 24.6 % decrease, respectively) compared to Caucasian women [9]. Subsequently, an increase in the diagnosis of DOR in African American women was demonstrated between 1999–2000 and 2004–2006; however, the women in the latter analysis were older in comparison to the initial study [2].

Although conflicting results exist, there is also evidence of a high rate of POA in Asian women [19]. In one study evaluating oocyte donors, Chinese women were 30 times more likely to receive a diagnosis of POA compared to age-matched Caucasian women (POA was diagnosed if the baseline FSH level exceeded the 95 % confidence interval for the age group) [19]. Conversely, Purcell et al. [10] conducted a secondary data analysis of 567 cycles from an academic clinic with a high proportion of self-identified Asian women. There was no difference in day-3 FSH values between Asian and Caucasian women (7.02 and 7.27, respectively) [10]. Furthermore, DOR was diagnosed less frequently in Asian women compared to Caucasians (29.1 and 38.5 %, respectively, $P = 0.03$); however, no data were provided on how DOR was diagnosed [10]. The significantly different results in the few studies that exist on this topic speak to the need for more research in this area.

Oocyte and Embryo Quality

Despite some evidence of differential rates of POA diagnoses between races, oocyte and embryo quality have been shown to be similar. Purcell et al. [10] found that embryo fragmentation was lower in Asian women, compared to their Caucasian counterparts. In theory, this should increase pregnancy rates; however, the Asian cohort still had fewer clinical pregnancies and live births in the fresh cycle [10]. Similar embryo quality between Asian and Caucasian women was also observed in a study of oocyte donors, as there were no differences in implantation, clinical pregnancy, or live birth rates in women receiving Asian or Caucasian oocytes [22]. Furthermore, Csokmay et al. [32] found similar live birth rates between African American and Caucasian women after FET, suggesting equivalent embryo quality between the two groups.

Much attention is given to oocyte and embryo quality during IVF cycles in what may be considered an “embryocentric” idea of infertility treatment [43]; however, the apparently similar embryo quality between ethnicities suggests a different mechanism for decreased success of minority groups in ART. Endometrial-embryo synchrony is imperative for successful implantation and, as outlined below, may be particularly important when considering ethnic differences in ART outcomes.

Endometrial Receptivity

When evaluating outcomes in FET, it is important to recognize factors that will remain relatively constant between fresh and frozen cycles. In general, tubal and uterine factors, BMI, and ovarian reserve are all unlikely to significantly change from one cycle to the next [32]. However, there are differences in hormonal profiles between fresh cycles and FET, as fresh cycles involve controlled ovarian stimulation and supraphysiologic estradiol (E2) levels. Elevated E2 levels have been associated with adverse outcomes in fresh embryo transfer, such as decreased implantation and pregnancy rates [44–46]. Interestingly, it has been shown that women with high E2 levels in the stimulated cycle experience improved implantation and pregnancy rates in subsequent FET, suggesting that the reduced implantation in the fresh cycle may have been due to divergent serum hormone levels and endometrial receptivity [45].

General Effects of Controlled Ovarian Stimulation on Endometrial Receptivity

The theory that controlled ovarian stimulation negatively affects implantation is not novel. In 1988, Forman et al. [44] demonstrated a reduced implantation rate after fresh embryo transfer when preovulatory E2 values were >90th percentile for their patient population (2,320 pg/mL), hypothesizing that the findings were due to altered endometrial receptivity. Subsequent studies produced results in support of this theory, leading many to view implantation as the "rate-limiting step" in IVF cycles [47–49]. Check et al. [50] retrospectively compared pregnancy and implantation rates between oocyte recipients and their donors (who also underwent IVF embryo transfer). In the stimulated cycle, there was a significantly higher implantation rate in the recipients (39 %) compared to the donors (22.5 %) [50]. In subsequent non-stimulated FET cycles there was no significant difference in outcomes. The results suggest that the supraphysiologic estrogen in the fresh cycle altered endometrial receptivity, as embryo quality was apparently not affected based on FET outcomes. In a recent randomized controlled trial, women undergoing their first IVF cycle were randomized to either fresh blastocyst transfer ($n=53$) or FET ($n=50$) [51]. The implantation rate was 70.8 % in the FET group compared to 38.9 % in the fresh transfer group ($P<0.0001$) [51], further supporting the theory of impaired endometrial receptivity in fresh IVF cycles.

Effects of Elevated Estradiol and Progesterone on Endometrial Receptivity

The mechanism by which ovarian stimulation impairs implantation is likely through high serum E2 and/or progesterone causing advanced stromal morphology and delayed glandular development [51–53]. This was confirmed by comparing

endometrial biopsies taken on day 7 after human chorionic gonadotropin (hCG) administration in stimulated cycles, to biopsies from day 7 after the LH surge in natural cycles [52]. Women with the highest estradiol concentrations showed delayed secretory advancement of the endometrium, causing "gland–stromal dyssynchrony" [52]. Furthermore, high serum E2 levels cause up-regulation of progesterone receptors, resulting in endometrial hypersensitivity to progesterone [49, 51, 54]. Elevated progesterone levels, particularly in an environment hypersensitive to this hormone, may negatively affect endometrial receptivity by altering the window of implantation, leading to decreased pregnancy rates [55]. This theory, however, remains in question as a recent meta-analysis failed to show an association between elevated progesterone and poor fresh IVF outcomes [56]. Some reports have not correlated high E2 levels with impaired endometrial receptivity [22, 57–60], suggesting that certain women may respond differently to elevated E2 during stimulation [22] or that the threshold E2 above which ART outcomes are decreased may be quite high (>5,000 pg/mL) [60]. Importantly, supraphysiologic E2 seems to affect the endometrium with insignificant to no impact on the oocyte and embryo [10, 22, 50, 61]. Likewise, elevated progesterone in the fresh IVF cycle does not adversely affect subsequent FET outcomes [55, 62], suggesting that embryo quality is unaffected. The impact of elevated E2 and/or progesterone on IVF outcomes remains a subject of debate, and a full review of this topic is beyond the scope of this chapter.

Endometrial Thickness

Endometrial thickness is an important predictor of IVF outcomes [29, 30], and differences in endometrial thickness have been observed between ethnicities [10, 11, 21, 63]. In a study of 180 fresh blastocyst transfer cycles, Asian women had a significantly thicker endometrial lining compared to Caucasians (10.9 and 10.2, respectively) and significantly lower implantation, clinical pregnancy, and live birth rates [11]. In another study of 113 fresh IVF cycles, minority women (self-identified as black, Hispanic, Asian, or other) were shown to have increased endometrial thickness and lower implantation rates compared to Caucasian women [63]. A thicker endometrial lining in these women may be evidence of the effect of high E2 levels. Furthermore, it appears that increased endometrial thickness is not an independent predictor of improved receptivity, as women with elevated E2 levels have increased endometrial glandular–stromal dyssynchrony [52]. This finding is consistent with previous reports that implantation may depend not only on endometrial thickness but also on the pattern [64–66] and histological composition [52] of the endometrium. In a prospective study of 103 IVF cycles, Sharara et al. [66] showed that women with a homogenous endometrial pattern had lower implantation and pregnancy rates than women with a triple-line pattern on the day of oocyte retrieval, regardless of endometrial thickness. The fact that some studies have not demonstrated differences in endometrial thickness between

ethnic groups [7, 22, 23] suggests that if endometrial receptivity does vary between races it may be due to differences in either endometrial thickness or histologic and morphologic response to E2.

Racial Variation in Estrogen Metabolism

There is some evidence to suggest that differences in estradiol levels and, therefore, endometrial receptivity after gonadotropin stimulation, may contribute to ethnic disparities in ART outcomes [10, 11, 20]. African American and Asian women have been shown to have elevated peak E2 levels compared to Caucasian and Hispanic women [7, 10, 14, 32, 67]. In an analysis of 567 cycles from a university-based clinic containing a high proportion of self-identified Asian women, Asian women had significantly higher E2 levels on the day of hCG administration compared to Caucasian women and had significantly fewer pregnancies and live births in the fresh cycle [10]. Csokmay et al. [32] evaluated 169 patients undergoing FET between 2003 and 2008. Data from the fresh IVF cycle was available in 58 % of these women. In the stimulated cycle, African American patients had higher E2 levels (5,355 pg/mL) compared to Caucasian patients (4,541 pg/mL), and the fresh cycle live birth rates were significantly different between African American and Caucasian women (16.7 and 39.7 %, respectively) [32]. However, as mentioned above, there was no difference in the live birth rate between the ethnic groups after FET [32].

Consistent with the findings of ethnic variation in E2 levels, a single-site cohort of women undergoing their initial IVF cycle demonstrated that African American and Asian women had significantly higher E2 levels (2,270 and 2,247 pg/mL, respectively) compared to Caucasian and Hispanic women (2,043 and 2,011 pg/mL, respectively) [67]. The women with higher E2 levels experienced poorer outcomes in the stimulated cycle (subsequent FET cycles were not available for analysis) [67]. The evidence suggests that elevated estradiol levels in certain ethnic groups are associated with decreased pregnancy rates in stimulated cycles.

High levels of serum estradiol or progesterone may impair implantation by altering endometrial gene expression [53]. Furthermore, there may be ethnicity-specific genetic differences in estrogen metabolism and/or end-organ sensitivity to the hormone. Disparities in rates of hormonally mediated conditions, such as leiomyomas, endometriosis, and osteoporosis, support this theory [23, 68, 69]. In the reproductive literature, varying response to estrogen has been demonstrated between women of different racial backgrounds. Increased end-organ sensitivity to estrogen was demonstrated in an observational study of normo-cycling African American ($n=40$) and Caucasian women ($n=27$) [21]. African American women had increased endometrial thickness, bone mineral density, and suppression of early follicular phase FSH when compared to Caucasian women, despite similar E2 levels [21]. African American women were also found to have significantly elevated progesterone levels compared to Caucasians [21] which, as discussed, may or may not adversely affect pregnancy outcome [55, 56, 62].

Variations in estrogen metabolism have also been demonstrated between Asian and Caucasian women [23]. In 181 women treated with equivalent doses of transdermal E2 in preparation for FET, Asian women had 52 % greater E2 levels compared to Caucasians ($P = 0.0004$) [23], suggesting decreased metabolic clearance of estrogen in the Asian group. Proposed mechanisms for these differences include FSH-receptor polymorphisms between Asians and Caucasians and/or polymorphisms of genes involved in estrogen synthesis and metabolism [10, 23–26].

If there are inherent racial differences in estrogen metabolism, controlled ovarian stimulation may have differential adverse effects on the endometrium depending on ethnicity. The decreased success of minorities undergoing fresh embryo IVF cycles may be related to elevated levels of E2, the endometrial response to the elevated hormone levels, and/or the physiology of estrogen metabolism. Thus, it is possible that certain ethnic groups have a higher rate of embryo–endometrial dyssynchrony in fresh ART. This might explain, in part, why the decreased success among certain ethnic minority groups in fresh embryo transfer cycles has not been observed in FET.

Conclusion

Understanding etiologies for ethnic differences in ART outcomes is important because an unequal proportion of minority women experience infertility [1]. The evaluation of racial and ethnic disparities in assisted reproduction is challenging due to many factors that may influence success, including socioeconomic, cultural, and biological factors. Despite advancing knowledge of possible etiologies of racial disparities in ART, the exact mechanism for differences in fresh versus frozen cycle outcomes is not known. Identifying and correcting modifiable risk factors for poor outcomes among ethnic groups may result in improved pregnancy rates. For example, adverse outcomes associated with leiomyomas or obesity may be overcome with surgery or weight loss. However, it also seems that there may be inherent racial or ethnic differences that affect ART outcomes, such as genetic variability affecting estrogen metabolism and/or function, which may create embryo–endometrial dyssynchrony leading to lower success and FET. Identification of the reasons for these differences and implementation of customized treatment protocols may prove critical for increasing ART success among all ethnic groups.

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Chapter 12
Understanding Racial Disparity in Adverse Pregnancy Outcome

Ramkumar Menon and George R. Saade

In the past decade, tremendous technological and scientific advances have been made in scientific research and medical care; however, there are continuing disparities in the burden of disease experienced by ethnic minorities in the United States. These minorities include African Americans, Hispanics, Native Americans, Alaska Natives, and Asian Pacific Islanders, compared to the population as a whole. The Minority Health and Health Disparities Research and Education Act by the US Senate in 2000 defined a population as having a health disparity if "there is a significant disparity in the overall rate of disease incidence, prevalence, morbidity, mortality or survival rates in the population as compared to the health status of the general population" (United States Public Law 106-525 (2000), p. 2498). The law mandates the setup of a National Center to address disparity issues in all health care fields through the National Institutes of Health (NIH) to further understand disparities, its causalities, and consequences, and take necessary action to reduce the rate of disparities. The NIH defines health disparities as differences in the incidence, prevalence, mortality, and burden of diseases and other adverse health conditions that exist among specific population groups. Health disparities are rampant in every branch of medicine and it is our opinion that it starts with pregnancy and child birth. Understanding the underlying factors and their manifestations in adverse pregnancy outcome seems extremely important to address the issues of health disparities during other phases of life.

This chapter is intended to assess racial/ethnic disparities in pregnancy-related complications, overview our current knowledge, and provide recommendations to fill knowledge gaps to reduce the disparity. Disparity in adverse pregnancy outcomes impacts not only neonatal mortality but also morbidities of living children which can persist throughout the lifetime of the individual. This trend is demonstrated in the

R. Menon, M.S., Ph.D • G.R. Saade, M.D. (✉)
Division of Maternal–Fetal Medicine Perinatal Research, Department of Obstetrics and Gynecology, The University of Texas Medical Branch at Galveston, 301 University Blvd., MRB, Room 11.138, Galveston, TX 77555-1062, USA
e-mail: Ram.menon@utmb.edu; gsaade@utmb.edu

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rate of adulthood diseases such as diabetes, hypertension, and many forms of cancers. The racial disparities we describe in this chapter are broadly defined as differences in pregnancy outcome that systematically and negatively impact one group over the other groups [1, 2]. Despite the advances in medical care and improvement of our understanding of the problems, disparities still persist and the gap between various ethnic groups have widened in many pregnancy-related complications [3–12].

Disparities in Adverse Pregnancy Outcome

Neonatal morbidities and mortalities are major public health concerns and three major pregnancy complications, stillbirth (SB), indicated preterm births due to preeclampsia (PE), and gestational diabetes and spontaneous preterm births (PTB), contribute to this condition [8, 10–23]. Recent estimates as reported by March of Dimes, USA Peristats (http://www.marchofdimes.com/peristats/Peristats.aspx), indicate that the infant mortality rate in the United States is approximately 6.7 deaths per 1,000 live births. The stillbirth rate is 6.2 per 1,000 deliveries, and preterm birth accounts for 12.3 % of live births. The rates among non-Hispanic African Americans are higher, nearly double the infant mortality at 13.0 infant deaths per 1,000 live births, and nearly double the stillbirth rate at 11.1 stillbirths per 1,000 deliveries, and one-third higher with preterm births at 17.5 % of live births [11, 18]. The disparity in rates of PTB and very PTB (<32 weeks gestation) translates into approximately 2.4-fold greater infant mortality for African American compared to Caucasian infants.

Several laboratories have prioritized understanding racial disparities in pregnancy complications as their research agenda and identified multiple factors including genetic, epigenetic, biodemographic, and clinical factors as potential contributors [10, 18]. Much scientific literature on stillbirth [10, 12, 24], preeclampsia [16, 17, 21, 25], gestational diabetes [19, 22, 23, 26–28], and spontaneous [6, 8, 29–39] preterm birth has been published in the past few years. Both epidemiologic and biologic studies have identified several areas of consensus, irrespective of the pathologic phenotype. Epidemiologic factors that contribute to racial disparity include, but are not limited to, socioeconomic status, access to care, nutrition, neighborhood factors, psychosocial stressors, and biodemographic factors such as body mass index (BMI). However, heterogeneities in etiology, environment, pathophysiologies, and clinical presentations make it difficult to point to specific factors as contributors to disparity [12]. Poor understanding of complex interactions between various factors has also limited our ability to explain combinations of factors as contributors of racial disparity in adverse pregnancy phenotypes. A series of recent systematic reviews examined BMI, infection/inflammation, nutrition, inter-pregnancy interval, and sociodemographic and biodemographic factors as potential contributors of racial disparity associated with spontaneous preterm birth [40–45]. As mentioned above, all these reviews derive a common conclusion that a single indicator is insufficient to determine racial disparity in preterm birthrate. However, each of these factors can be used as surrogate to understand underlying mechanisms of preterm birth, a primary step towards understanding causality of racial disparity.

A workshop conducted by the National Institute of Child Health and Human Development in 2010 focused on the disparities in preterm birth, stillbirth, and infant mortality, and identified several factors associated with disparities and above-mentioned pregnancy complications. The workshop also suggested recommendations to overcome such disparities [11]. Although conclusive evidence from research reports is limited to distinguish factors associated with disparity, the workshop reported the strongest support for infection and inflammation. This is logical, since infection is one of the most common risk factors associated with stillbirth and preterm births [46–57]. Inflammatory pathophysiology is also suspected in preeclampsia. Inflammation is an underlying factor in preterm birth irrespective of etiology, as stress, poor or malnutrition, high BMI, uterine anomalies, and allergies can all cause inflammation resulting in preterm birth. Therefore inflammation also plays a major role in racial disparity [51, 57]. This reporting by NICHD is in line with ongoing research activities in our laboratory.

We have studied infection and inflammation as a major factor associated with racial disparity in *spontaneous* preterm birth and have identified several knowledge gaps that need further investigation. As there are several epidemiologic, biodemographic, and socioeconomic reviews that exist on racial disparities associated with adverse pregnancy outcome, we have adopted to review the mechanistic components based on our own data and other published reports. Understanding the phenotype of interest and the pathophysiology leading to this phenotype is of utmost importance. Our approaches are twofold: (1) document racial disparity and (2) document pathophysiology of the phenotype where race can be used as a risk modifier. Our phenotype of interest is spontaneous preterm birth, as the causality of this condition is still unclear and understanding the mechanisms resulting in preterm labor and delivery is important to prevent further increase in rates and racial disparity. In this chapter we review our current research data on racial disparity in spontaneous preterm birth, discuss how multitudes of factors and their interactions may contribute to this condition, and attempt to portray similar research strategies needed to understand mechanistic factors contributing to disparity for other adverse pregnancy outcomes.

Intrauterine Infection: A Factor Associated with Preterm Birth and Racial Disparity

Ascending infection (from the vagina and cervix) is one of the most common routes of infection. It can manifest as vaginitis, cervicitis, deciduitis, and chorioamnionitis, eventually reaching the amniotic cavity (microbial invasion of the amniotic cavity—MIAC) and establishing an intra-amniotic infection (IAI). Several lines of evidence support the hypothesis that very early preterm delivery (gestational age <28 weeks) has an association with infection, including the following: (1) inverse relationship observed between the likelihood of upper tract microbial colonization or chorioamnionitis and the gestational age at delivery; (2) the percent of positive cultures in the chorioamnion and the amniotic fluid (AF) increases as the gestational age at delivery

decreases; (3) ~40 % of spontaneous preterm births are associated with IAI and over 70 % of very preterm births are associated with infection. Establishing an infection in the amniotic fluid, which is rich with antimicrobial peptides, is not an easy process as it requires compromise of innate immune mechanisms [46]. Host inflammatory response to IAI is overwhelming, and that is hypothesized to lead to preterm labor [48, 58, 59]. IAI triggers a vicious cycle of events in the intrauterine tissues that involve cytokines, chemokines, matrix metalloproteinases, adhesion molecules, pro-apoptotic factors, coagulation factors, stress-related hormones (e.g., CRH), and reactive oxygen species. These factors lead to cyclooxygenase (COX)-mediated prostanoid response (prostaglandin production) that eventually results in early labor [60, 61]. Although these pathways may not explain the causality and actual risk factors leading to infection, inflammation remains a major component of PTB. Based on these pathophysiologic pathways of PTB, several biomarkers have been studied to predict preterm labor risk, and many of them have been tested in clinical practice [62–67]. However, recent advances in medical care, community-based educational and intervention programs, progress in high-throughput research (genomics, proteomics, metabolomics, etc.), new biomarker and genetic marker screening, and new intervention strategies (e.g., progesterone trials) have not reduced the rate of PTB or reduced the racial disparity.

Racial Disparity and Infection

The inconsistencies described in the literature regarding causality, pathophysiology, and response to an intervention led us to postulate that our understanding of PTB, its etiology, and pathophysiology are far from reality. Many risk factors and biomarkers associated with PTB and biomolecular pathways that culminate in PTB are not generalizable. Although risk exposure may be the same for ethnic groups in a given population in a specific region, pathophysiologic manifestation of risk factors in different racial groups may be different. Factors that can influence infection rate and pregnancy outcome in different races can include, but are not limited to, genetics, epigenetics, environment, behavioral and psycho–social factors, and their interactions. Using race as a surrogate, we examined the role of infection to better understand PTB risk.

Inflammatory Markers Show Marked Imbalance Favoring Proinflammatory Response in African Americans But Not in Caucasians

Cytokines are considered as effectors of the labor process. The role of TNF-α as a marker of preterm labor has been established due to its pluripotency. Using an in vitro model of fetal membranes and AF from women experiencing preterm labor and MIAC, we examined the changes in this marker and its two soluble receptors: soluble TNFRI and soluble TNFRII (sTNFRI and sTNFRII). In vitro, fetal membranes from

both African Americans and Caucasians were found to have higher TNF-α response, in response to bacterial infection. However, soluble TNF receptor responses (molecules that buffer TNF-α and neutralize their functions) were significantly decreased in African Americans and but were unchanged in Caucasians. Similarly membrane-bound TNF receptors, whose action is to promote TNF function, were increased in African Americans but decreased in Caucasians. These data suggest a balance in TNF-α response in Caucasians but an imbalance in African Americans that favor TNF-α biological activity. In vivo studies confirmed the in vitro findings. They demonstrated an imbalance in African American TNF-α response to infection. Soluble TNF receptors were higher in Caucasian cases and decreased in African American cases compared to their respective controls. This was also evident in cases with MIAC where the molar ratio between the ligand and the soluble receptors favored higher bioavailability of TNF-α in African Americans in cases with MIAC, whereas the TNF/soluble TNF receptor response was balanced in Caucasians [81, 83].

Can Different Bacterial Pathogens Associated with Preterm Birth Produce Different Immunologic Responses?

Previously, we had used lipopolysaccharide as a surrogate to study differential immune response by different races. We further tested the possibility of differential responses to different intra-amniotic pathogens. For this, normal membranes from African Americans and Caucasians were stimulated with 10^7 colony-forming units or color-forming units of *Ureaplasma urealyticum*, *Ureaplasma parvum*, *Mycoplasma hominis*, *E. coli*, Group B Streptococcus, *Polyporhans gingivalis*, and *Gardnerella vaginalis*, all known pathogens associated with preterm birth. Each bacterium produced a distinct cytokine signature, and racial disparity was also evident in immune response with some bacteria/biomarkers. These data suggest that the response is not just limited to in vitro experimental agents such as LPS but also extends to different bacterial pathogens [84].

Infection and inflammation may produce an imbalance, and this can lead to pro-labor cytokine functions in African Americans. However, it is highly unlikely that one cytokine and its receptor(s) may explain complex phenotype such as preterm birth or racial disparity.

Racial Disparity in Biomarkers of Preterm Birth Defines Distinct Biofunctions That May Underlie Preterm Birth Pathophysiology in Different Races

To further delineate, we have undertaken a larger study to address the following questions: (1) Does racial disparity exist in other biomarkers of preterm birth? (2) Do maternal–fetal compartments contribute differently to preterm birth in different

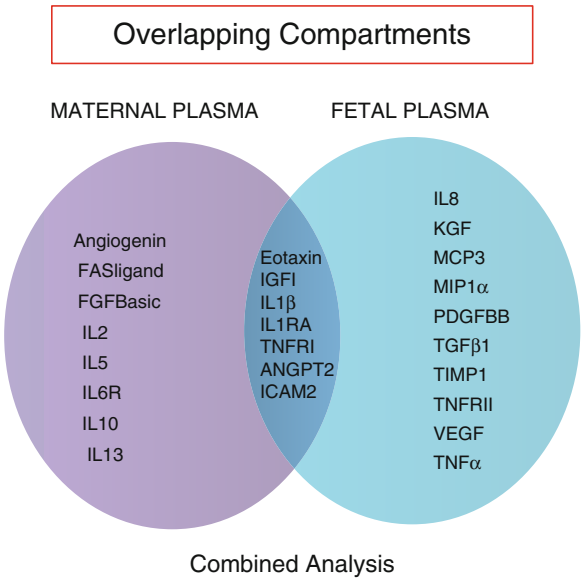

Fig. 12.1 Combined race analysis: Venn diagram of 36 biomarker analysis using maternal and fetal plasma from spontaneous preterm birth and normal term births. Maternal samples were collected at the time of diagnosis of preterm labor and fetal cord blood samples were collected right after placental delivery. Biomarkers that are up or down regulated in maternal and fetal compartments are shown specific to each compartment and that are common to both compartments

races? (3) Can biomarkers determine distinct biofunctions that predispose to preterm birth in different races?

In a retrospective cohort study, amniotic fluid (collected at the time of active labor prior to delivery), maternal plasma (collected at the time of admission due to preterm labor), and cord plasma (collected after placental delivery) from 105 cases (59 African American and 46 European American) and 86 controls (40 African American and 46 European American) were analyzed for 36 biomarkers from known preterm birth pathways. Figure 12.1 summarizes the dysregulated biomarkers in our combined and stratified (by race) analysis study, which addressed the questions that we proposed above [68]. A bioinformatics analysis using Ingenuity Pathway Analysis (IPA) was conducted to understand the role of these dysregulated biomarkers in promoting preterm birth in different races. IPA analysis revealed differences in combined (all races) analysis and in data stratified by race. Maternal–fetal and intra-amniotic contributions of biomarker functions also differed in each race. For combined race, the top biological function in the amniotic fluid was inflammatory response. The top function for the cord plasma compartment was cellular movement associated with early stages of antigen presentation and initiation of inflammation. The top biological function for the maternal plasma compartment was also cell-to-cell signaling and interaction associated with inflammatory changes.

For African Americans, the top biofunction for the amniotic fluid was immune cell trafficking associated with early-stage immune response (Fig. 12.2). There was no significant biological function found for cord plasma. The top biological function for the maternal plasma compartment was inflammation. For Caucasians, the top biological function was antigen presentation for amniotic fluid determined by dysregulation of pro-inflammatory chemokines and cytokines (Fig. 12.3). The top biological function for the fetal compartment was cellular growth and proliferation related to hematologic

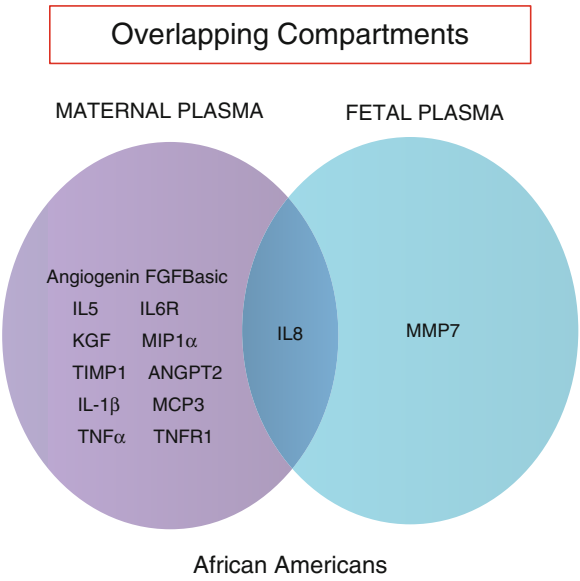

Fig. 12.2 African Americans: Venn diagram of 36 biomarker analysis using maternal and fetal plasma. Biomarkers that are up or down regulated in maternal and fetal compartments are shown specific to each compartment and that are common to both

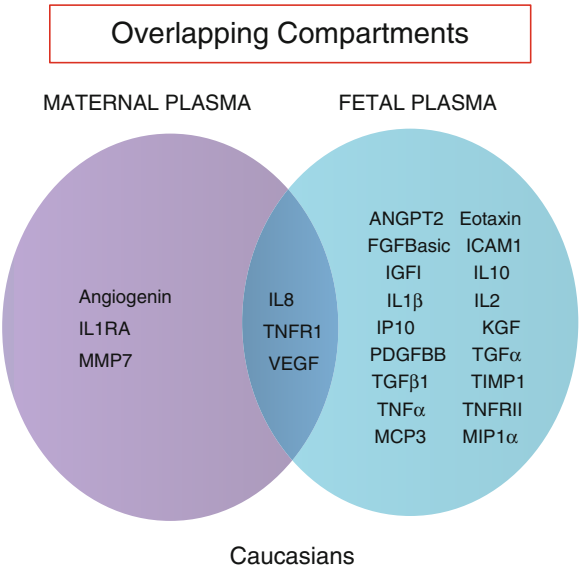

Fig. 12.3 Caucasian: Venn diagram of 36 biomarker analysis using maternal and fetal plasma. Biomarkers that are up or down regulated in maternal and fetal compartments are shown specific to each compartment and that are common to both

functions and inflammation. Increased presence of anti-inflammatory and matrix remodeling markers (inflammatory disease) provided the top biological function for the maternal compartment. This is indicative of differential response to mechanistic preterm labor by different compartments in different races [68].

We propose that preterm birth complexities are further enhanced with our recent findings on biomarkers where we see that even inflammation associated with preterm

birth is not a homogeneous phenomenon. Different pathogens and other risk factors produce inflammation but the stage of inflammation (acute vs. chronic), the biomarker initiating involved in different stages of inflammation, and the pathway initiated by biomarkers and their pathophysiologic manifestation (end phenotype) all differ.

Can Racial Disparity in Dynamic Biomarker Changes Associated with Preterm Birth Be Genetically Determined?

The difference in biomarker response in preterm birth is hard to explain based on one or few factors that are risk indicators (infection, socioeconomic, nutrition, BMI, etc.) in preterm birth. Some of the disparity observed in the biomarkers reported above in two different populations may have an underlying genetic predisposition. To support our approach, genetic epidemiologic studies have suggested that an individual's susceptibility to infectious diseases has a genetic basis [69]. This led us to examine genetic variants (single-nucleotide polymorphisms—SNPs) as potential contributors to the observed differences in biomarker response in PTB.

We summarize some key findings from our already published genetic association reports:

1. Genetic variants, SNPs, differ in their frequencies between different racial ethnic groups [70–75].
2. Genetic association between candidate gene variants and preterm birth differs between ethnic groups [70–75].
3. Gene–gene interactions (epistasis) are evident in preterm birth and these interactions differ based on primary genetic associations [73, 74, 76].
4. Gene variants are associated with changes in biomarker concentrations that can partially explain the observed differences in biomarker signature between various racial groups [75–79].
5. Unpublished data from our genome-wide association studies also reflect similar differences in genetic associations between races.
6. Population admixture also contributes to non-reproducibility of observed genetic associations between preterm birth and the studied population in other independent cohorts.

Reduction of Racial Disparity Needs a Thorough Understanding of Pathophysiologic Pathways in Different Racial Groups

So far the research focus has been on epidemiologic factors, but their pathophysiologic manifestations (pathways) were unclear. Epidemiologic and genetic risk factors of racial disparity are mostly non-modifiable. Although the understanding of such risks

is immensely important, prevention of racial disparity requires understanding of modifiable risk factors (both epidemiologic and pathophysiologic) and target intervention specifically to induced pathways in a given individual from a given race. Using our data from preterm birth we are showing that genetic, environmental (infection as a proxy), and gene x environmental factors contribute to racial disparity.

1. Gene *x* environmental interactions produce pathways that are unique to given racial groups, suggesting heterogeneity in pathways of preterm labor [76, 80].
2. Biomarker response to risk factors of preterm birth such as infection differs between races [81–85].
3. Pathophysiologic pathways that result in the initiation of preterm labor process differ between races [68]. For example, inflammation is a well-characterized underlying pathology but as mentioned above inflammation is not a homogeneous process. Similarly overwhelming oxidative stress is a major factor associated with adverse pregnancy outcome. None of these pathologies are homogeneous and biomarkers involved in inflammation and oxidative stress differ based on the type and stage of immune response or redox imbalance. As reported above, these factors differ between races.
4. Pathophysiologic pathways contributed by maternal–fetal compartments differ between races [68].

All this evidence from our laboratory and many others have confirmed that expression of risk-induced pathways differs between races. Currently our "universal" approaches of prevention of preterm birth using antibiotics, tocolytics, and corticosteroids have failed to reduce preterm birth risk or reduce the disparity in preterm birth. Prevention of preterm birth or any other pregnancy complications without considering race as a risk modifier or modifier of a risk-induced heterogeneous pathways is expected to fail as effectors of adverse pregnancy outcome are not the same in all races. Tailored intervention is required for prevention of adverse outcome, and such an approach requires a thorough understanding of not only epidemiologic risk factors but also their interaction with genes, individual's own unique environmental factors, epigenetic changes they can produce, and their influence in pathways.

We specifically address the following factors for consideration in any studies of racial disparities:

1. Definition of the phenotype: Heterogeneities in complex diseases such as preterm birth arise due to different clinical manifestations, differences in biological pathways leading to disease diagnosis, and differences in severity of symptoms. Appropriate definition and description of the phenotype studied can avoid this dilemma.
2. Population admixture and selection of appropriate population for studies: Poorly replicated genetic association studies have introduced the need for stringent population stratification to properly identify the correct "race/ethnicity" studied in a given population [28, 86]. Population stratification is the differences in allele frequencies between cases and controls due to ancestral contributions. This is a major source of spurious association even in the most well-designed studies.

It can arise because of population admixture, mating between persons with distinct ancestries, or because a sample consists of a mixture of subpopulations and/or distinct ancestral groups. This can greatly compromise the interpretation of results (e.g., analyzing data consisting of a combination of African American and Caucasian samples can remove or add association signals from either population). This can result in invalid associations of genes with disease and as shown above it can also contribute to differences in biomarker signature and the biofunctions or pathophysiology induced by these markers that can underlie a disease. For this reason, care must be taken in grouping individuals into racial groups. If self-reported ethnicity is used, it is advisable to only include individuals within a given group if they can trace their ethnicity back two generations to their parents. An alternative approach is to use ancestry-informative markers, markers that have established allele frequency differences between different geographic populations. Using a group of these highly differentiated ancestry informative markers across the genome will help to estimate an individual's geographic origin [87–91].

Racial disparity adds a new dimension of challenges to already complex adverse pregnancy phenotypes. A systematic approach is needed to understand the epidemiologic, biologic, physiologic, and clinical aspects of this complexity. What we have provided is an approach we have taken where race is used as a surrogate to understand complexities of spontaneous preterm birth. Similar models and approaches are needed to further understand racial disparity.

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Chapter 13
Racial Diversity and Uterine Leiomyoma

Mohamed Sabry and Ayman Al-Hendy

Introduction

Uterine leiomyomas (ULM, aka fibroids or myomas) represent the number one indication for hysterectomy in the USA [1], with estimated annual costs for the USA of $5.9–34.4 billion [2]. Black races are reported to have a higher incidence rate (threefold) as well as increased relative risk of clinical uterine fibroids in addition to earlier age of onset, plus more severe disease burden if compared with White races [3–6]. Increasing evidence suggests distinct gene expression patterns and unique genetic polymorphisms in Black races are contributing factors to the higher prevalence in women of color [7, 8].

Uterine Leiomyoma and Estrogen

The vast majority of clinical studies and research evidences support the traditional concept of the crucial role of estrogen in promoting the growth of ULM [9, 10]; with advancement of age the cumulative incidence of occurrence of ULM exponentially increase till the age of menopause at which they typically regress and/or become asymptomatic [11] Moreover, the use of gonadotropin releasing hormone agonists

M. Sabry, M.D., A.R.D.M.S.
Department of Obstetrics and Gynecology, Faculty of Medicine, IBN-SINA IVF/ICSI Center, Sohag University Hospitals, Naser City, Sohag 82524, Egypt
e-mail: mhsabry14@gmail.com

A. Al-Hendy, M.D., Ph.D. (✉)
Department of Obstetrics and Gynecology, Center for Women Health Research, George Hubbard Hospital, Meharry Medical College, 1005 Drive D.B. Todd Jr. Blvd., Nashville, TN, 37208, USA
e-mail: ahendy@mmc.edu

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leads to shrinkage of ULM may be through the suppression of ovarian estrogen production to postmenopausal levels [12, 13]. The ULM cells found to express estrogen receptors as well as progesterone receptors [14, 15] the findings that support the well-known concept. Leiomyoma cells derived from the Eker rat model for this disease proliferate in response to estrogen in culture, and this response can be inhibited by estrogen antagonists such as tamoxifen and raloxifene [16]. In addition, an elevated transcriptional response to estrogen in leiomyoma cells suggests that these tumors may have increased responsiveness or be hypersensitive to estrogen stimulation [17].

Epidemiology of Racial Differences in the Incidence of ULMs

ULMs are widely spread between African American women in comparison with other race, the prevalence of ULM is about four times higher in that ethnic group compared to Caucasians [18]. This may be related to "something in the blood of the dark-skinned people that considered to be a predisposing factor to fibroid number" [19].

Many epidemiological studies found a higher prevalence of ULM among black women compared with white women [20]. A case control study of women who received surgical or medical treatment of ULM have been demonstrated that black women had nine times the odds of clinically apparent ULM (OR, 9.4; 95 % CI, 5.7–1) 5.7 [21]. Another study randomly screened selected women their age were between 35 and 49 years old for leiomyoma tumors with ultrasound scans. After analyzing the data for body mass index (BMI) and parity, black women were about three times more likely to have fibroid tumors in comparison with white women (odds ratio 2.7; 95 % confidence interval) the result also demonstrated that the incidence of leiomyoma was 60 % among African-American women by 35 years of age, and the incidence increased to over 80 % by 50 years of age. Caucasian women had an incidence of 40 % by 35 years of age and almost 70 % by 50 years of age [3].

In addition to a higher prevalence of leiomyoma tumors among black women, many studies have identified that black women have been diagnosed with leiomyoma at a younger age, with rapidly growing, larger, and more numerous leiomyoma in comparison with white women. Huyck et al. demonstrated that the average age for leiomyoma tumor diagnosis is 31 years between black women and 37 years between white women ($P < 0.001$) [5]. More studies have confirmed this result; with black women have a diagnosis of leiomyoma tumors at younger age than white women [11, 22]. Another study demonstrated the difference in leiomyoma tumor growth by race; by 6 month the volume of the tumor increased with age in black women but decreased with age among white women ($P < 0.004$) [6].

Hysterectomy is the most common non-obstetric surgery among women in the USA, with about 600,000 surgeries performed every year [23]. Several studies identified higher rates of hysterectomy among black women [24, 25]. Black women are two times more to have hysterectomy for leiomyoma compared to Caucasian [18] and to have it at younger age [22, 26]. Many factor contributing to higher rate of

hysterectomy among African-American women compared with White women include heavier average uterine weight, larger mean size of largest leiomyoma, more numerous and symptomatic tumors, and a higher proportion of Black women reported severe symptoms in the form of anemia or severe pelvic pain than Caucasian women [3, 27].

Being a major health disparity issue, ULMs appear to further diminish the quality of life for AA women who also suffer from higher incidence of chronic diseases such as diabetes, heart disease, and obesity [28], and have higher mortality rates from breast and endometrial cancer than White women [29]. This is may be due to more frequent adverse features in African- American women, include advanced tumors, high-grade tumors and more aggressive histology which result in worse survival among black patient than white patients [30].

Genes Involved in Estrogen Synthesis and/or Metabolism CYP17

The CYP17 gene codes for the cytochrome P450C17α enzyme, the enzyme mediates steroid 17 α-hydroxlyase and 17, 20-lyase activities, and functions at key branch points in human steroidogenesis [31]. The 50 untranslated region of CYP17 contains a single base pair polymorphism, a T (designated as A1) to a C (designated as A2), 34 base pairs upstream from the initiation of translation and 27 base pairs downstream from the transcription start site [32]. The steady increase in serum estradiol and progesterone concentration among premenopausal women may depend on the number of A2 alleles that a woman carries, with the A2/A2 genotype corresponding to the highest concentrations [33]. Age, race and parity appeared to affect the incidence of ULMs in that model which included Caucasian and Black South African women. Logistic regression analysis in Caucasian women showed that oral contraceptives were protective against the development of ULMs regardless of CYP17 genotype. Logistic regression applied in Black South African women showed that age and CYP17 polymorphism were correlated positively with the presence of ULMs. Using categorical data analysis, the risk for ULM development among Black South African women with the CYP17 A2/A2 genotype was shown to be increased, whereas the risk in Black South African women with the CYP17 A1/A1 and A1/A2 genotypes was shown to be lower [34]. However, these findings can't be applied on neither Japanese nor Brazilian women [35, 36].

Catechol-O-Methyltransferase

Catechol-O-methyltransferase (COMT) gene plays an important role in the inactivation of catechol estrogens. COMT is a phase II enzyme involved in the inactivation of many endogenous catechol substrates by transferring a methyl group

from S-adenosyl-L-methionine (SAM) to the substrate and thus converting them into their methoxy derivatives. Regulation of COMT activity may indirectly modulate the biological effects of estrogen and play an etiological role in leiomyoma formation as it catalyzes the conversion of 2,4 hydroxy estradiol to 2,4 methoxy estradiol [37, 38].

A common genetic polymorphism, G to A transition at codon 158, resulting in a valine-to-methionine substitution, is associated with thermal instability and a fourfold decrease in enzymatic activity. The genotypes designated in relation to the predicated enzymatic activity of the protein are high (Val/Val), intermediate (Val/Met) and low (Met/Met) activity [39].

In recent work by the authors' group, COMT gene polymorphism was studied in 186 women with ULMs and 142 women without ULMs. All subjects had a hysterectomy, and the presence (study group) or absence (control group) of ULMs was documented at histological level. Genotyping was performed using DNA isolated from normal myometrium, and was confirmed with DNA isolated from peripheral blood cells. The Val/Val (high activity) genotype was highly represented in ULM patients (39 %) compared with the controls (21 %) from all ethnic groups. However, the homozygous Met/Met (low activity) genotype was less represented in ULM patients (12 %) compared with the controls (27 %). The heterozygous Val/Met genotype did not differ significantly between cases (49 %) and controls (52 %). Within each ethnic group, the Val/Val genotype was significantly more common in ULM cases than controls [40].

Using multiple logistic models, White women had the lowest occurrence of leiomyomas. African-American and Hispanic women were 5.3 and 2.1 times more likely to have ULMs than White women, respectively. Overall, women with the Val/Val genotype were 2.5 times more likely to have ULMs compared with women with the Met/Met genotype (controlling for ethnicity). Conversely, COMT Val/Met and Met/ Met did not mediate significantly different associations with ULMs.

The natural distribution of COMT genotypes in different racial groups was also addressed in the authors' study. African-American women had a high frequency of the Val/Val genotype (47 %) and a low frequency of the Met/Met genotype (5 %); heterozygous Val/Met was 49 %. In sharp contrast, White women had a low frequency of the Val/Val genotype (19 %) and a higher frequency of the Met/Met genotype (33 %); heterozygous Val/Met was 48 % [40]. These results could be replicated within Brazilian women, where de Oliveira et al. stated that COMT polymorphism is a risk factor for the development of large uterine fibroids in Brazilian women suffering from fibroids [41].

Overall, these data show that the high-activity COMT (Val/Val) genotype is associated with ULMs in all ethnicities. This genotype is more common in African-Americans race compared to others, and this may be associated with the higher incidence of ULMs in that ethnic group.

COMT converts 2-hydroxy estradiol to 2-methoxy estradiol. 2-hydroxy estradiol has been found to work as anti-estrogen in many tissues [42]. On the other hand, 2-methoxy estradiol has been demonstrated to possess a mitogenic effect on different cell types. Therefore, the most active COMT genotype (Val/Val) would derive

rapid and efficient conversion of the anti-estrogenic metabolite (2-hydroxy estradiol) into the more mitogenic counterpart (2-methoxy estradiol), thus creating a high estrogenic cellular milieu. Conversely, the low-activity COMT genotype (Met/Met) would lead to the accumulation of 2-hydroxy estradiol, creating a low estrogenic environment. This is the possible mechanism by which COMT gene polymorphism assess in pathogenesis of leiomyoma [43].

In vitro data have confirmed the effects of the COMT genotype on the phenotype of myometrial and ULM cells [40].

The Val/Val primary myometrial cells showed a significantly higher proliferation rate, greater transcriptional response to estrogen (as evidenced by higher luciferase reporter transactivation) and a gene expression profile expressive of high estrogenic milieu (increased expression of cyclo-oxygenase 2, cyclin D1, PR-A, PR-B, and Bcl2, and decreased expression of BAX) compared with their Met/Met comparable. This confirms the high estrogenic drive of myometrial cells of the COMT Val/Val genotype.

The differences in steroid receptor expression were one of the molecular mechanisms evaluated by researchers to explain the racial differences in ULMs. Several recent reports have attempted to expose leiomyomas to gene microarrays, and suggested no significant difference in OR expression in leiomyomas in comparison to adjacent normal myometrium [44]. Moreover, two studies failed to show significant differences in the expression of ORs and PRs in the myometrium between different races (Black and White) [45, 46].

Retinoic Acid Nuclear Receptors

Recently, Wei et al. [47] applied immunohistochemistry with high-density tissue microarray to identify the ethnic differences in the expression of selected gene products between Black, Asian, Hispanic and White women diagnosed with ULMs. Relative protein expression was controlled by the absolute immune-scores of the adjacent normal myometrium. The absolute expression value of OR-a in both normal myometrium and ULMs was higher in Black women compared with other ethnicities; however, when the relative OR-a expression was calculated, ULMs of Black women did not differ significantly from those of other ethnic groups. In ULMs of Black women, the relative expression of PR-A (up-regulated in relation to normal myometrium), retinoid acid receptor-a (RAR-a; down-regulated) and retinoid X receptor- a (RXR-a; no change from adjacent myometrium) differed significantly from other ethnic groups. About one-third of ULMs from Black women sub-clustered together in association with a group of up-regulated gene products. Many other gene products, including local growth factors, insulin-like growth factor signaling proteins and cell proliferation markers, were dysregulated in ULMs, but showed no significant differences between the ethnic groups. As ULMs are hormone dependent, the differential expression of steroid hormone receptors (OR and PR) among different races would be of crucial importance to explain the ethnic

differences in the incidence of these benign tumors. The down-regulation of retinoic acid receptors (RAR-a and RXR-a) in ULMs of Black women in comparison with their up-regulation in other ethnic groups indicates dysregulation of retinoic acid metabolism in ULMs of Black women. Other studies have shown abnormal expression of genes coding for enzymes involved in retinoic acid metabolism in ULMs [48, 49]. However, the exact role of retinoic acid and its nuclear receptors in the ethnical disparity of ULMs still needs to be elucidated.

Estrogen Receptor Genes Polymorphism

The question was whether the function or the expression of steroid receptors is the key behind the racial differences in the incidence of ULMs. The distribution of two common OR gene polymorphisms was assessed between Black, Hispanic and White women with or without ULMs. The polymorphisms tested were in the first intron of the OR gene and included a T/C polymorphism that is recognized by the restriction endonuclease PvuII, and an A/G polymorphism recognized by XbaI restriction enzyme. The T and C alleles correspond to the presence (p allele) or absence (P allele), respectively, of the restriction site. Similarly, the A and G alleles correspond to the presence (x allele) or absence (X allele), respectively, of the restriction site. Genotypes for PvuII and XbaI polymorphisms were termed PP, Pp, and pp, and XX, Xx, and xx, respectively [50].

According to the authors' results, the PP genotype was associated with significantly greater risk of ULMs among Black and White women, but not among Hispanic women. Using the logistic model, White women had the lowest incidence of leiomyomas. Black and Hispanic women were 9.7 and 2.4 times more likely, respectively, to have ULMs than White women. Overall, women with the PP genotype were 6.4 times more likely to have ULMs compared with women with the pp genotype. Furthermore, the PP genotype was significantly more common in cases with severe disease (uterine weight >400 g) and was associated with younger age at hysterectomy compared with the pp genotype.

The authors also addressed the distribution of different OR genotypes in various ethnic groups. Black women had a significantly high frequency of the PP genotype (35 %) compared with White women (13 %) and Hispanic women (16 %). In contrast, White and Hispanic women had a higher frequency of the pp genotype (38 and 40 %, respectively) compared with Black women (27 %). There was no significant difference in the Pp heterozygous genotype among the three ethnic groups.

The strong association between ULMs and the PP genotype of ORs, and the in vitro data of higher cellular proliferation in myometrial cells harboring the same genotype detected in the authors' study, together with the results of other studies that detected more ULM-related hysterectomies and higher bone mineral densities in women with the PP genotype [51, 52] indicate the higher prevalence of the P allele in more potent local estrogenic environments.

It is not fully understood how the polymorphism at the Pvu II locus, which is located in the first intron of the OR gene, alters the estrogenic response. There are a

number of possibilities; the first intron may contain a regulatory site (like an enhancer) to control the gene function, this polymorphism may lead to differential mRNA splicing with different functional proteins, or this polymorphism may serve as a marker in linkage with other, as yet unidentified, regulatory regions.

Aberrant Expression of Micro-RNAS

Micro-RNAs (miRNAs) are a class of small, noncoding RNAs, which are transcribed by RNA polymerase II. miRNAs regulate cell proliferation, differentiation and cell death during development [53]. It has been documented to have aberrant expression in some tumors [54, 55]. Many genes are dysregulated in ULMs, and some of this dysregulation may be due to abnormal expression of miRNAs [56].

It has been demonstrated that ULMs from Black women showed more than twofold overexpression in certain miRNAs, including miR-23a/b, let-7s, miR-145, miR-197, miR-411, and miR-412, when compared with tumors from White women; after matching 55 samples of ULMs with myometrium from 41 patients of different ethnic groups for microarray based global miRNA expression analysis [57]. The miRNA expression profile from Non Black, Non White racial groups (Asian and Hispanic) appears to be in between that of Black and White women. The tissue growth factor-b (TGFB)-induced factor) is considered as one of the predicted target genes of miR-23b; and it plays a considerable role in inhibiting retinoic-acid-dependent RXR-a transcription. ULMs in Black women exhibit minimal change of RXR-a expression compared with ULMs in other races, in which a higher level of overexpression of RXR-a is evident [50].

We can conclude that incidence of ULMs in Black women is much higher than in women of other races. The explanation based on the molecular background of this racial difference is not fully understood.

Possible mechanisms would be polymorphism of genes involved in estrogen synthesis and/or metabolism (COMT, CYP17), variation in the expression levels or function of steroid receptors (OR, PR) or retinoic acid nuclear receptors (RAR-a, RXR-a), or aberrant expression of miRNAs.

Future Directions

Beside various genetic factors described above, other contributing factors could be responsible for the remarkable ethnic disparity of this common global disease of female reproductive tract. These additional factors include nutritional aberrations such as vitamin D deficiency or other dietary habits such as high intake of high estrogen food. Epigenetics also might be a central playing factor especially exposure to various hormone disruptors early in embryonic or neonatal life which can conceivably lead to permanent developmental reprogramming of various estrogen-dependent genes eventually leading to the development of uterine fibroids.

Hopefully further understanding of the molecular pathogenesis of uterine fibroids will lead to the development of novel therapeutic and preventative options that can lead to effective management of this common disease and improvement of women health worldwide.

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Chapter 14
The Effect of Obesity on Fertility and ART Success Among Ethnic Groups

Diana P. Broomfield[†] and Torie Comeaux Plowden

Introduction

Obesity is becoming a serious public health concern in many developing and developed countries. Obesity and overweight have become an epidemic. Since 1980, worldwide obesity has more than doubled [1]. In 2008, the World Health Organization reported 1.5 billion adults, 20 years or older were overweight; almost 300 million women met criteria for obesity [1]. In 2009–2010, more than one-third of adults in the USA (35.7 %) were obese [2].

Definitions

Body mass index (BMI) is used as a proxy for determining total body fat and is calculated as weight in kilograms divided by height in squared meters. Normal weight individuals are defined as having a BMI of 18.5–24.9. Underweight is characterized by a BMI of <18.5, whereas overweight refers to a BMI of ≥25–29.9. Obesity is defined as a BMI of ≥30 but is actually divided into three subcategories [3]. See Table 14.1. Interestingly, many individuals who are overweight and even morbidly obese do not see themselves as overweight as classified by clinical definitions. Using data from the National Survey of Youth in 1997, Krauss and colleagues looked at adolescent females' weight misperception and noted that their misperceptions was a function of racial/ethnic disparities. "Compared to their white counterparts,

[†]D.P. Broomfield (Deceased)

T.C. Plowden, M.D., M.P.H.
Department of Obstetrics and Gynecology, Bayne-Jones Army Community Hospital,
1585 Third Street, Fort Polk, LA 71459, USA
e-mail: tcomeaux@gmail.com

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Table 14.1 Obesity categories

Obesity category	Parameters (BMI)
Class I	30–34.9
Class II	35–39.9
Class III	≥40

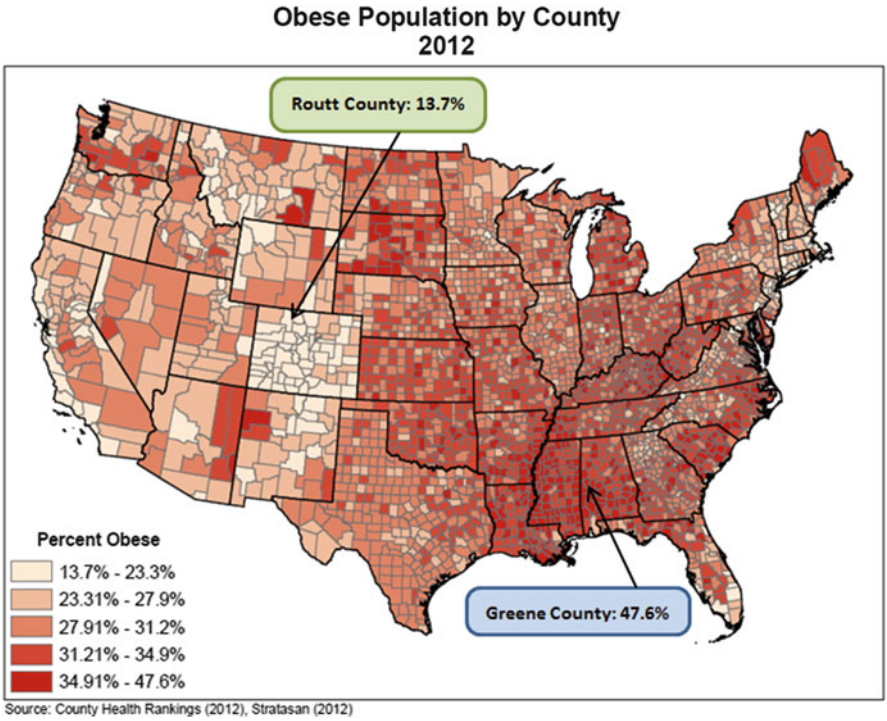

Fig. 14.1 US adult and child obesity prevalence by state

higher proportions of black and Hispanic adolescent females under perceived their weight status; that is, they misperceived themselves to have lower weight status compared to their clinically defined weight status. Compared to their black counterparts, higher proportions of white and Hispanic adolescent females misperceived themselves to be heavier than their clinical weight status [4]." As noted by the authors, this misperception may play a pivotal role in the incidence and reduction of obesity in this population.

Current Obesity Trends in America

Seventy-eight million adults in America are obese [2]. There is no significant difference in the prevalence of obesity among men and women [2]. Obesity prevalence ranges from 21 % in Colorado to 34 % in Mississippi (see Fig. 14.1). In 2000, 28

Table 14.2 States with obesity prevalence of ≥30 %

Alabama	Missouri
Arkansas	Oklahoma
Kentucky	South Carolina
Louisiana	Tennessee
Michigan	Texas
Mississippi	West Virginia

states had a prevalence of obesity of <20 % and there were not any states with >30 % prevalence [5]. Obesity has become a national public health issue that is progressively worsening. Shockingly, in 2010, no state had a prevalence of <20 % and 12 states had a prevalence of obesity of 30 % or more [6] (see Table 14.2). These states were also found to have at least 8.2 % of the adult population with diabetes [7]. An analysis of regions revealed that the South had a higher prevalence of obesity whereas the West had the lowest [8].

Obesity disproportionately affects minority women in America. In 2008, 49.6 % of non-Hispanic Black women were obese versus 33 % of their non-Hispanic white counterparts [9]. Mexican-Americans were also noted to have a higher prevalence of obesity (45.1 %) [9].

Overweight and obese people are known to have a significantly increased risk of multiple medical issues to include diabetes, cardiovascular problems, respiratory illnesses, and musculoskeletal diseases [10]. A causal relationship between obesity and some cancers of the colon, breast, endometrium, kidney, and esophagus has been documented [11]. The likelihood of developing these comorbidities increases with BMI as well as with increased waist-to-hip ratio (>0.85) in women and with increase waist circumference (≥80 cm) [12]. The healthcare costs associated with this increase in obesity prevalence will be astronomical. One study indicated that almost $40 billion were spent related to obesity and its complications through 2006 [13].

Obesity and Infertility

The female reproductive system involves a variety of complicated interactions. As such, disturbances anywhere along the hypothalamic–pituitary–ovarian (HPO) axis can lead to difficulties achieving and maintaining pregnancy. Obesity has an overall negative impact on reproductive health. Obesity is frequently associated with decrease fecundity as well as with menstrual irregularity and ovulatory dysfunction. Obese women are three times more likely to have irregular cycles [14]. Obesity in childhood or adolescence increases the likelihood of cycle irregularity in reproductive aged women [12]. Serum sex hormone-binding globulin (SHBG) is lower in obese women; subsequently, these women have higher levels of circulating testosterone and other androgens [14]. It is possible that this relative hyperandrogenemia may adversely affect ovarian function, contributing to oligomenorrhea [14]. There has been an observed decrease in LH pulse amplitude in obese women; although the etiology of this phenomenon has not been confirmed, it can lead to menstrual irregularity [15].

Despite regular menstruation accompanied by regular ovulatory cycles, women who are overweight or obese are more likely to be affected by reduced fecundity [16–18]. One study evaluated over 2000 infertile couples; exclusion criteria included anovulation, bilateral tubal dysfunction, and severe male factor infertility [17]. Using a primary endpoint of time to spontaneous ongoing pregnancy within 12 months, the authors concluded for every BMI unit above 29 kg/m^2, the probability of pregnancy decreased by approximately 5 % [17]. Another large study also observed a decrease in fecundity in overweight and obese women regardless of parity, tobacco use, age, and regularity of menses [18].

The reproductive milieu is an intricate balance of neuropeptides, hormones, proteins, and growth factors that modulate the activity of the hypothalamic–pituitary–gonadal axis and specifically the GnRH neuronal network. Leptin is a protein that is secreted by adipocytes that helps to regulate energy homeostasis, reproduction, fertility, and the immune system. Some studies have indicated that leptin plays a role in human pubertal development since girls with congenital leptin deficiency do not undergo puberty [14]. It has been shown to be elevated in obese women and, in high concentrations, seems to have inhibitory effects upon folliculogenesis and ovarian steroidogenesis [14, 19, 20]. In fact, elevated leptin has been associated with dysregulation of GnRH secretion, altered ovarian steroidogenesis, and dysregulation of perifollicular blood flow, all of which can cause chaos on the HPO axis [14]. Leptin has also been found in secretory endometrium and could possibly play a role in implantation or endometrial receptivity [14]. This could explain why obesity has been linked to impaired fecundity and increased spontaneous abortions.

Obesity and Pregnancy Complications

Obesity in pregnancy has been associated with increased morbidity in both the mother as well as in the fetus. Obese women have a higher incidence of spontaneous abortions [21, 22]. During pregnancy, these ladies are more frequently affected by hypertensive disorders, including gestational hypertension, preeclampsia, and chronic hypertension [23, 24]. These women also are at higher risk of developing gestational diabetes [23, 24].

Obesity is also associated with many obstetrical risks and complications. Specifically, obesity is associated with increased difficulties during labor and delivery including difficulty with monitoring the fetal heart tracing and contraction pattern [23]. These women experience an increased risk of labor induction, often requiring more oxytocin, as well as increased risk of operative delivery and increased need for cesarean section [23–25]. When obese women undergo cesarean section, they typically experience more complications including increased blood loss, longer operative time, endometritis, postoperative wound infections/wound breakdown, and thromboembolism [23, 24]. Anesthesia complications related to difficult or impossible placement of regional anesthesia and difficult intubation are common [23].

In addition to obstetrical complications, there are fetal and neonatal risks associated with maternal obesity. The fetuses of obese mothers are also at risk for health issues.

Several studies have demonstrated that obese women are twice as likely to have a child with a neural tube defect compared to women with normal weight [19, 26, 27]. One recent meta-analysis found that obese mothers had a significantly increased risk of pregnancy being complicated by neural tube defects, cardiovascular anomalies, cleft palate and/or cleft lip, limb reduction disorders, and anorectal atresia when compared to women with normal BMIs [28]. Unexplained stillbirth, fetal macrosomia, and shoulder dystocia also occur more frequently [23, 24]. Evidence also indicates that the children of obese women have a higher likelihood of suffering from childhood obesity [23]. Unfortunately, this could set the stage for development of a vicious cycle and can make obesity and its sequelae a continued problem in future generations.

Psychological Sequelae

The health consequences of obesity have been frequently documented. Some studies have implied that obesity can have a negative impact on quality of life [29–33]. Heavier women may be deemed less attractive by their partners [30]. Overweight women were less likely to have been married and were more frequently found to be less educated and have lower household incomes [31]. Obesity has also been linked to increased risk of depression [32, 33].

Obesity has also been correlated with sexual dysfunction. The female sexual functioning index (FSFI) is a 19-item questionnaire that was developed to assess sexual function in women in 6 different categories (desire, arousal, lubrication, orgasm, satisfaction, and pain) [34]. One study examined female patients preparing for bariatric surgery and after administering the FSFI questionnaire, found that 60 % reported sexual dysfunction [35]. Another study used the FSFI questionnaire and compared female candidates for bariatric surgery to normal controls that were matched by age, marital status, and education. Interestingly, the obese patients experienced sexual dysfunction in five of the six categories; no difference was found in the pain category [36].

Kolotkin et al. evaluated men and women about to undergo bariatric surgery and found that the women had lower self-esteem, greater rates of depression, were less likely to be married and had more dissatisfaction in their sex lives [37]. Another study also examined obese men and women and found an impairment of sexual function in both groups, but the dysfunction was more severe in women [29].

Obesity and Response to ART

Although there is significant data that suggests that obesity impairs fertility, effects on oocyte quality and the exact mechanism are still under much investigation. The literature from assisted reproductive technology studies has been inconsistent regarding obesity and reproductive outcomes. Some studies have reported that

oocyte quality and/or embryo quality is affected by obesity, while other studies have not substantiated this claim [25]. A recent study reviewed thousands of embryo transfers and concluded that obesity was indeed associated with a decrease in achieving a clinical pregnancy when autologous oocytes were used; however, no decrease was seen when donor oocytes were utilized [38]. This data is particularly interesting because it implies that there may not be any post-implantation events that negatively affect pregnancies in obese women. Additionally, this study also concluded that as BMI increased, the likelihood of achieving a live birth decreased [38].

As previously mentioned, obesity has been connected to poorer reproductive outcomes. Recent literature has observed a link between obesity and lower rates of implantation, pregnancy, and birth rates as well as a decrease in follicle development and number of oocytes produced [39]. Dessolle et al. evaluated 450 frozen-thawed embryo transfers using donor oocytes and concluded that obesity negatively impacted pregnancy rates [40].

Shah and colleagues specifically explored differences in pregnancy rates in obese and normal weight patients. The patient population had a 20 % prevalence of overweight women and 18 % prevalence of obese women; 5 % of the patients had class III obesity. Obese patients had lower estradiol levels and less normally fertilized oocytes as well as decreased rates of pregnancy and live birth rates. The odds of achieving a clinical pregnancy were 33, 44, and 50 % lower in women with class I, II, and III obesity [41]. This study supports the conclusion that obesity may negatively affect reproduction by influencing ovarian and extra-ovarian factors [41].

Given the growing body of evidence that overweight and obese women are more likely to experience adverse outcomes after undergoing assisted reproductive technology, there has been some speculation about whether or not obese women should be offered ART. A retrospective study conducted in the UK evaluated a group of patients undergoing in vitro fertilization. The study did find a higher incidence of anovulation, an increase in the total dose of gonadotropins used and increased incidence of early pregnancy loss as BMI increased. However, the study did not find a significantly increase in costs of ART for overweight or class I obese patients compared to normal weight women [42].

Koning et al. published a very interesting article that examined current literature to determine effects of obesity on spontaneous pregnancy, success of ART, and pregnancy outcomes while also constructing a theoretical model to evaluate costs associated with fertility care [43]. The study found that for a hypothetical cohort of women, the costs per live birth in ovulatory overweight and obese women was 44 and 70 % higher compared to normal weight women; surprisingly, the costs per live birth in anovulatory overweight and obese women were 54 and 100 % higher [43]. Given the associated risks of pregnancy and the decreased odds of success, it would be reasonable to encourage women to work toward achieving a normal BMI prior to attempting pregnancy or undergoing fertility treatments. This practice is especially prudent in young women because diminished ovarian reserve is not typically a concern in that patient population. Older women may not have the luxury of delaying pregnancy until their BMI is normalized.

Racial and Ethnic Disparities in Obese Infertility Patients

Minorities in America have experienced healthcare disparities and limitations regarding access to care for a variety of medical issues [44–46]. This has also been true regarding treatment for infertility as well [47]. The National Survey of Family Growth noted that 7.4 % of American married women reported infertility [48]. Of this group, the highest rates of infertility were noted among African-American women (11.5 %) [48]. Wellons and colleagues conducted a study to determine racial differences in a cohort of black and white women specifically related to infertility and risk factors for infertility [49]. The population studied was composed of a large group of women from four major American cities: Birmingham, Chicago, Minneapolis, and Oakland. Black women were found to have a higher likelihood of experiencing infertility. If Black women do have a higher incidence of infertility, one might expect they would be more likely to seek out treatment for infertility. However, low-income women were significantly more likely to have never received any treatment for infertility [48]. Minority women also had a longer duration of infertility prior to seeking out care [50].

Minority women have been shown to have poorer outcomes when treated for infertility [47, 51–59]. One study reviewed outcomes of African-American and white women undergoing fertility treatment at a university-based program [56]. The women in the African-American group had a higher BMI and also had been suffering from infertility for longer prior to seeking out treatment when compared to Caucasian women. The Caucasian patients had higher implantation rates, clinical pregnancy rates and ongoing pregnancy rates even though both groups were similar in the number of oocytes retrieved and number of embryos transferred [56]. Feinberg et al. evaluated Department of Defense beneficiaries. Due to lower costs associated with ART treatment, this group has increased access to care. The findings noted a clinically significant decrease in live birth rate in African-American patients that did not actually reach statistical significance; additionally, the black patients were noted to have a statistically significant increase in spontaneous abortions [57]. Another study again compared black and white women and analyzed differences related to ART access and outcomes among military beneficiaries [51]. African-American women were noted to have lower clinical pregnancy rates as well as lower live birth rates than Caucasian women [51].

Contradictory information does exist. One retrospective cohort study did not find any difference in ectopic pregnancies, spontaneous abortions or live birth rate in African-Americans, Hispanics, and Asians [60]. A particularly interesting study examined a population of African-Americans and Caucasian women living in Washington, DC who sought infertility treatment [61]. Given that the District of Columbia has a large population of middle-class African-Americans, the authors speculated this would control for any socioeconomic differences that often confound results in this field. The study did not note any differences in implantation rate, pregnancy rate or live birth rate [61]. The above studies had various strengths but all were limited by the relatively small sample sizes.

Recently, large database studies have been conducted on this topic. Seifer and colleagues analyzed the SART database and reviewed more than 72,000 cycles. Ultimately, the findings discovered an overall live birth rate per cycle of 18.7 % in African-American women versus 26.3 % in white women undergoing fresh non-donor embryo cycles [55]. Once confounding factors were controlled for, Black race actually appears to be an independent risk factor for not achieving a live birth [55].

Poorer outcomes after ART are not specific to women of African descent. Purcell et al. also conducted a review of SART data as well as data from the University of California at San Francisco. The authors determined that Asian women had a decrease in clinical pregnancy and live birth rates compared to white women [59]. Indian women have also been found to have a significantly decreased live birth rate when compared to Caucasians, even though similar embryo quality was noted [54].

Recently, a large study examined ART outcomes in several different ethnic/racial groups [47]. When compared to white women, African-American, Asian, and Hispanic women had worse outcomes after ART including decreased live birth rates [47]. Another large study examined more than 220,000 fresh embryo transfer cycles. The data revealed that African-American, Asian, and Hispanic women were less likely to achieve a clinical pregnancy than white women [58]. Hispanic and Asians also were found to have a higher likelihood of pregnancy loss in the second and third trimesters; African-American women were more likely to suffer from pregnancy loss in all trimesters [58]. Although none of these studies can fully explain why these differences exist, these large studies certainly reinforce the presence of disparities and highlight the need for further research which would help decrease knowledge gaps.

As stated earlier, obesity is more prevalent among some minority groups, including non-Hispanic Blacks and Mexican-Americans [9]. There are a variety of factors that influence obesity including both cultural and economic issues. A recent study demonstrated that when examining black and white people living in similar socioeconomic disadvantaged environments, there was actually no difference in likelihood of obesity among the two groups [62].

Luke et al. recently conducted a study that examined racial/ethnic disparities in ART in the context of BMI categories. Failure to achieve a clinical pregnancy was more likely in obese women overall; overweight and obese Black women, normal weight and obese Asian women, and normal-weight Hispanic women were also less likely to have a clinical pregnancy [63]. Similarly, all overweight and obese women were less likely to achieve a live birth but this risk was also increased in minority groups [63].

The ASRM Health Disparities Special Interest Group notes that their mission is to "identify disparities in access and outcomes of women of color seeking reproductive health services and to identify strategies to address these disparities and other reproductive problems in women of color [64]." This group recently performed a systematic review of the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) data that specifically reported racial/ethnic disparities. The studies reporting live birth rates consistently saw lower live birth rates in minority women [64]. They found more than 35 % of cycles could not be used for analysis because the data on race/ethnicity was not completed and that

patients were frequently not asked about race/ethnicity. Self-reporting on race/ethnicity is certainly considered the gold standard [64]. Ultimately, the ASRM Health Disparities Special Interest Group has recommended providers obtain this information so that future studies can make more accurate comparisons when evaluating outcomes of ART [64].

Weight Loss

After weight loss, ovulation, pregnancy rates, and other reproductive parameters are improved [12, 65]. Studies have demonstrated that even modest weight loss results in improved fecundity parameters. Clark et al. demonstrated that with an average weight loss of only 10.2 kg/m^2 90 % of the anovulatory subjects resumed ovulation. There was also significant improvement in pregnancy and live birth rates as well as a decrease in the miscarriage rate, which improved from 75 to 18 % after weight loss [66]. The women in the treatment group also had improved self-esteem and less depression and anxiety [66]. Lifestyle modification and weight loss, through diet and exercise, should be considered a first-line treatment in overweight and obese women with infertility [12, 66]. Galletly and colleagues conducted a study of 24 women who were allowed to exercise and instructed on healthy diet and the importance of healthy lifestyle. After the study period, a significant number of women lost weight (5.2 ± 5.11 kg (<0.0001)) and interestingly there was a corresponding improvement in self-esteem and depression scores [67]. This led these investigators to postulate that it may be important that patients lose weight prior to fertility treatments to improve their fecundity and self-esteem.

Bariatric Surgery and Future Pregnancy

Bariatric surgery is a reliable means of achieving and sustaining significant weight loss in the morbidly obese population [68]. In recent years, the number of bariatric surgeries has increased dramatically in the entire population, but particularly among women of childbearing age [69]. Currently, more than 80 % of patients who undergo bariatric surgery between the ages of 18 and 45 are female [68]. Adolescents, especially girls, are increasingly likely to undergo this procedure [69, 70]. Obstetricians are going to be faced with caring for a growing number of patients with a history of bariatric surgery.

The National Institutes of Health consensus panel currently recommends bariatric surgery in people with a BMI of ≥ 40 or ≥ 35 with associated comorbidities or for those who have failed conservative therapies [71]. Two primary types of procedures for bariatric surgery are adjustable gastric banding and the Roux-en-Y gastric bypass [70]. Gastric banding is a restrictive procedure that places a band around the stomach, subsequently reducing its functional capacity; conversely, the Roux-en-Y

gastric bypass has a combination effect that is both restrictive and malabsorptive [70]. Other types of procedures exist but are less frequently used.

One major concern related specifically to gastric bypass and future pregnancy is malabsorption and its effect on the fetus/pregnancy. Nutrient deficiencies can occur even if patients have undergone a restrictive surgical procedure [70]. After surgery, patients can frequently have deficiencies in vitamins A, D, K, B12, calcium, and iron, which are often mild [68–70]. Several case reports have described poor fetal/neonatal outcomes including electrolyte imbalances, growth restriction, anemia, and even fetal death in cases of severe vitamin deficiencies [69]. A retrospective study reviewed pregnancy outcomes in 70 women who had a gastric bypass prior to pregnancy and found a significant reduction in the incidence of gestational diabetes; however, there was an increased risk of neonates that were small for gestational age [72]. Obviously, bariatric surgery is not without complications, including band migration or erosion, bowel obstructions, and anastomotic leaks [70]. Imaging studies or reoperation can be delayed in pregnancy; these delays could lead to significant morbidity and/or mortality. Therefore, any pregnant patient with a history of gastric bypass should be thoroughly evaluated when presenting with any abdominal complaints [69, 70].

There has been some debate regarding the issue of timing of pregnancy after bariatric surgery. There may be some issues with absorption of oral contraception in patients with a history of bariatric surgery; the pregnancy rate in adolescents has been show to be double the rate of the general population [70]. Currently, there is insufficient data to support recommendations, however, many have advocated avoiding pregnancy for 12–18 months after the procedure [68].

Obesity and Male Infertility

Studies on obesity and its effect on male fertility are emerging in the literature. Obese men have lower circulating levels of testosterone [12, 25]. High levels of leptin, which are elevated in obese people, have a negative effect on testosterone levels [25]. The incidence of both oligozoospermia and asthenospermia increases as BMI increases [73]. The scrotum in obese men is frequently in contact with surrounding tissue; subsequently, higher temperatures in the scrotum could affect semen quality [12]. Additionally, obese men frequently experience erectile dysfunction [25].

Weight loss may improve fertility in obese men [68]. There is some evidence that erectile dysfunction can be improved after weight loss [25]. One recent case series reported secondary azoospermia with complete cessation of production of sperm in a group of obese men who were status-post Roux-en-Y gastric bypass [74]. It is possible that nutrient deficiencies were so severe that spermatogenesis was no longer possible. The full extent of how obesity contributes to male infertility is not well understood and further research should be undertaken in this population.

Future Research

Recently, there has been new evidence in the literature regarding vitamin D deficiency and its subsequent consequences have been linked to obesity as well as race [63]. A link between maternal vitamin D deficiency and both preeclampsia and low infant birth weight has been demonstrated [75]. Ozkan et al. have found that higher serum and follicular fluid vitamin D levels were associated with increased clinical pregnancy rates in patients after IVF-embryo transfer [76]. Perhaps in the future, supplementation of vitamin D could be a viable treatment option, although additional studies are needed.

Clearly there needs to be more research investigating the impact of obesity, race, and ethnicity on infertility. As demonstrated in the Venn diagram (Fig. 14.2), there are many variables that have overlapping and additive consequences on reproductive health, obesity, and ethnicity. There are several studies which look at one or two of these variables, nevertheless, more studies combining all of these variables are necessary to ascertain the true impact these variations have on reproductive health.

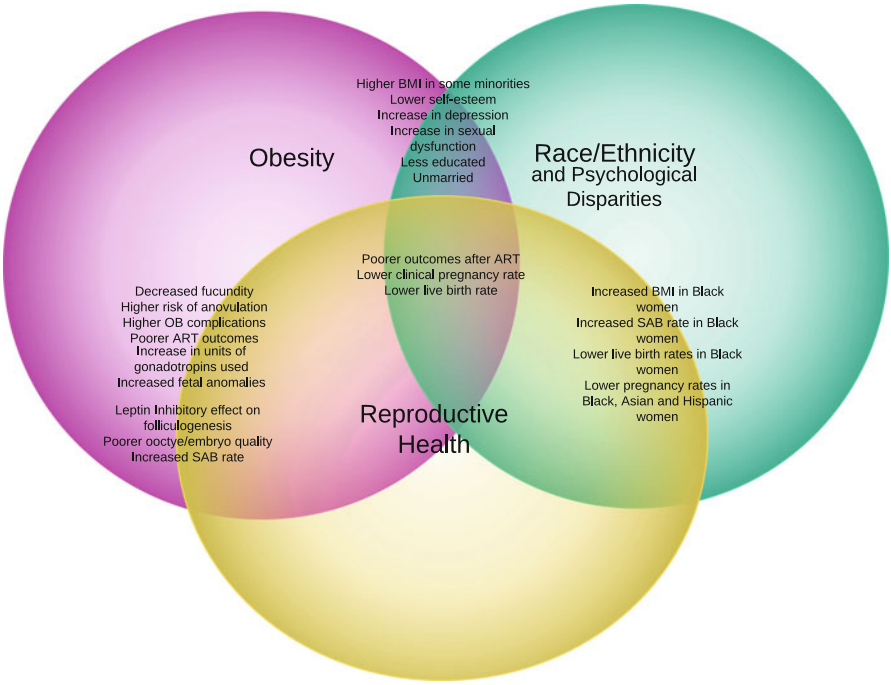

Fig. 14.2 Many variables have overlapping and additive consequences on reproductive health, obesity, and ethnicity

Conclusion

The effect of obesity on women's health, particularly related to reproduction is a complicated issue that is only partially understood. Further study is needed to eliminate disparities in obesity and reproductive health. Weight loss, weather with diet and exercise or medical or surgical intervention has been shown to improve multiple health parameters. Public health programs focusing on prevention of obesity and weight loss in American women, particularly in minority women, would certainly be beneficial. Cooper et al. found that interventions to reduce disparities including ensuring community involvement and improving cultural competence were very important when working to eliminate disparities related to race and ethnicity [77]. Public health programs that implemented these strategies could improve their impact. Once we understand the role of the multiple variables on reproductive health, we will have a more robust handle on the mechanism of disease and health care barriers that lead to or predispose women to health disparities.

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Chapter 15
Polycystic Ovary Syndrome Across Racial and Ethnic Groups

Lawrence Engmann and Richard Legro

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine abnormality affecting women of reproductive age consisting of oligo-anovulation and hyperandrogenism. It is associated with significant long-term health consequences including the metabolic syndrome, obesity, dyslipidemia, cardiovascular disorders, type 2 diabetes, and endometrial cancer [1–3]. The definition and diagnosis have evolved over the years from the initial 1990 National Institute of Health (NIH) criteria to the joint ESHRE/ASRM workshop resulting in the "Rotterdam criteria" [4] to the recent criteria proposed by the Androgen Excess Society (AES) [5]. These differences in criteria may influence the differences in prevalence of the syndrome and the metabolic consequences in different ethnic and racial groups and have created a broad and confusing spectrum of syndrome phenotypes.

Ethnic health disparities may arise from differences in socioeconomic, political, or environmental exposures that may result in differences in disease prevalence or differences in access to or quality of health care received [6]. The differences that may exist in women with PCOS amongst racial and ethnic groups may be due to intrinsic genetic differences or environmental factors such as cultural, lifestyle, accessibility to care, as well as acculturation. The differences in prevalence and manifestation of PCOS across ethnic and racial groups are of utmost importance

L. Engmann, M.D., M.R.C.O.G.
Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Connecticut Health Center, 263 Farmington Avenue, Farmington, CT 06032, USA
e-mail: lengmann@uchc.edu

R. Legro, M.D. (✉)
Department of Obstetrics and Gynecology, Hershey Medical Center, College of Medicine, Pennsylvania State University, 500 University Drive, Hershey, PA 17033-0850, USA
e-mail: rs11@psu.edu

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since the disorder is of significant public health concern and attempts at prevention and treatment of the long-term health consequences of the disease may allow appropriate targeting of the relevant population. However, reports regarding variability in presentation and metabolic consequences across ethnic and racial groups may be biased by differences in criteria used for the diagnosis of PCOS across racial and ethnic groups. Moreover, the differences in metabolic consequences in women with PCOS amongst different racial and ethnic groups may be influenced by genetic and environmental factors and may also be directly related to the differences that exist across racial and ethnic groups in the general population. In this chapter we try to address any racial and ethnic similarities and differences between women with PCOS and the general population.

Prevalence

The prevalence of PCOS in the general population may be between 6 and 10 % using the NIH criteria but as high as 15 % using the Rotterdam criteria which incorporates polycystic ovary size and/or morphology into the diagnostic criteria [7]. Any differences in prevalence amongst different racial and ethnic groups in various studies are highly variable and may be difficult to compare because of several factors. Selection of the relevant population is problematic because diagnosing the disease may be logistically challenging since there may be the need for physical evaluation including blood tests and/or ultrasounds depending on the diagnostic criteria used. Therefore, prevalence studies in different ethnic and racial groups have used samples that are more convenient including prospective university employees presenting for preemployment physical [8, 9], women presenting for routine annual physical examination [10], or blood donors [11]. Moreover, in view of the heterogeneity of the symptomatology, previous studies have used the different types of diagnostic criteria used to define the condition.

Taking into consideration these limitations, the prevalence of PCOS reported in the literature may vary in different ethnic groups and geographical areas. It has been estimated that the prevalence may range from 4 to 6.6 % among unselected women in the USA [8, 9] and 5 % in Spain [11], 6.8 % in Greece [12], 8 % in England [13], and 6.3 % in South Asia [14] to as low as 2.2 % in Southern China [10]. The low prevalence rate of 2 % noted in women from Southern China compared to other geographical areas may be due to differences in the selection population and the diagnostic criteria used as well as possible differences in environmental and intrinsic biologic factors. For example few Chinese women with PCOS have overt hirsutism by western standards.

However, the differences in population-based prevalence of PCOS in different racial groups have not previously been extensively evaluated. No differences have been seen in the prevalence of PCOS between blacks and whites [8, 9]. Knochenhauer and colleagues [8] evaluated 277 unselected women of reproductive age seeking a preemployment physical in the USA and found a prevalence of PCOS of 4.7 %

among white and 3.4 % among black women. This was subsequently expanded on by this same group of authors [9] who continued to show no significant difference in the prevalence of PCOS in blacks of 8.0 % and whites of 4.8 % in the USA. The prevalence of PCOS in Mexicans living in Mexico of 6 % [15] is similar to that reported for other racial groups [8, 9], although it is significantly lower than that reported for Mexican Americans living in the USA of 12.8 % [16]. This may be due to differences in study design and recruitment and the fact that these were not population-based comparative studies or it may be due to true differences in environmental exposures. Previous studies that have been cited in the literature suggesting a higher prevalence of PCOS in Caribbean Hispanic and South Asian women [17, 18], or lower prevalence in black women [19], were actually case-matched studies and not population-based studies and therefore these may be more likely to suffer from selection bias. Therefore, more population-based studies are needed to determine the prevalence of PCOS in different racial groups [7].

PCOS Symptomatology and Phenotype

Any differences in the prevalence of PCOS amongst ethnic and racial groups may be attributable to variability in phenotypic presentation and clinical symptomatology. Since different diagnostic criteria for PCOS have been used in various studies as well as possible sample population selection bias and self-reporting bias, the prevalence of these symptomatology of PCOS in different ethnic populations may vary. Oligo-anovulation is a common presentation of PCOS and the ethnic and racial prevalence has not been extensively studied. In the general population, the prevalence of oligomenorrhea has been reported as 4.4 % in a Swedish population-based study [20] whilst a much higher rate of 21 % has been reported in Pima Indians, a population known to have a high frequency of obesity [21]. No differences have been reported in the prevalence of menstrual dysfunction between black and white women with PCOS [8, 9].

PCO morphology is included in the Rotterdam criteria for the diagnosis of PCOS [4]. The highest prevalence of the presence of polycystic ovarian morphology in the general population has been reported in South Asian immigrants living in Britain of 52 % [22], compared with the prevalence in British female population of 22 % [23]. Legro and coworkers [24] in a large prospective multicenter trial found a lower prevalence of PCO morphology in white women with PCOS compared with other racial groups, though all racial groups exceeded 90 % prevalence of PCO morphology. However, previous studies have not found any differences in the prevalence of PCO morphology between NHB, Hispanic, or NHW women with PCOS [25].

Clinical hyperandrogenism is probably the most important phenotype in the various recommended diagnostic criteria for PCOS. However, defining racial and ethnic differences in the prevalence and severity of hirsutism may be problematic since terminal body hair growth has significant racial and ethnic variations. In view of this, different cutoff values for hirsutism score have been established for different

ethnic and racial groups [26]. Ethnic and racial variations in the prevalence of hirsutism may therefore be a reflection of differences in selection bias as well as differences in the use of appropriate cutoff levels for hirsutism scores. The prevalence of hirsutism in the general unselected population may range from 4.3 to 10.8 % in NHWs and NHBs and the prevalence may be lower in Asians [26]. No differences have also been reported in the prevalence of hirsutism between NHWs and NHBs in the general population [27]. An evaluation of 633 unselected NHW and NHB women in the general population presenting for preemployment physical examination found similar prevalence and degree of facial and terminal body hair in the two groups [27].

In women with PCOS, previous studies have also shown that the prevalence and severity of clinical hyperandrogenism is similar between NHW and NHB women with PCOS [8, 24, 25]. In an unselected population of 369 women with PCOS in Southeastern United States, Knochenhaeur and colleagues [8] showed no significant differences in the prevalence and severity of hirsutism between NHWs and NHBs. In a large prospective multicenter trial involving 626 infertile women with PCOS, no differences were found in the prevalence and severity of hirsutism between African Americans and Caucasians [24]. In the same study, it was shown that Latino women with PCOS may have a trend towards a higher prevalence of hirsutism compared to non-Latinos [24]. The prevalence of hirsutism in South Asian women with PCOS living in the United Kingdom has been shown to be higher than Caucasian women with PCOS [28]. However, women with PCOS of East Asian ethnicity such as Japanese [29] or Southern Chinese [10] have been shown to have lower prevalence of hirsutism.

Nevertheless, any potential racial or ethnic differences in biochemical evidence of hyperandrogenism are less clear. In the large prospective multicenter PCOS trial, serum testosterone (T) levels were found to be comparable between African Americans and Caucasians although lower levels were found in Asians, Hispanics, and Native Americans [24]. However, other studies have not shown any differences in serum T levels between Caribbean-Hispanic [17], Mexican American [30, 31], or South Asian [28] women with PCOS compared with white women with PCOS. Moreover, Welt et al. [25] did not show any differences in serum T levels between blacks, Hispanics, and whites. The apparent disparity in racial differences in serum T levels in various studies may be due to the variability of circulating T levels [32] as well as the inter-assay variability of serum T which may not be universally accepted [33]. No differences have been found in serum sex hormone-binding globulin (SHBG) levels between different racial groups [24, 25, 34], although lower levels were seen in South Asian women with PCOS compared with white women with PCOS [28]. Moreover, no differences have been found in serum DHEAS levels in Mexican American [30], Hispanic [25], South Asian [28], or NHB [25, 34] women with PCOS compared with NHW women with PCOS. African American and Caribbean-Hispanic adolescent girls with premature adrenarche have been shown to have marked hyperandrogenism and reduced insulin sensitivity [35] and therefore may be at increased risk of having PCOS since premature adrenarche has been shown to be a risk factor for PCOS [36, 37].

Metabolic Syndrome

The metabolic syndrome is a clustering of specific risk factors in an individual and considered to be an antecedent to cardiovascular disease (CVD) and type 2 diabetes. The diagnosis requires three of the five factors, each of which are closely linked to insulin resistance and comprising central obesity, low high-density lipoprotein cholesterol (HDL-C), hypertriglyceridemia, hypertension, and fasting hyperglycemia [38]. It is expected that early diagnosis and treatment of the syndrome might delay or prevent the onset of type 2 diabetes and ultimately CVD.

The prevalence of metabolic syndrome in the general population as well as in women with PCOS may vary in different racial and ethnic groups. In the general US population, as high as 15 % has been reported in women aged 20–29 and 17.5 % in women aged 30–39 years [39]. In women with PCOS, the prevalence has been estimated to be 33.4 % [40] and it may vary in different ethnic groups. It has also been reported in women with PCOS to be as high as 43–47 % in America [41–43], 46 % in the Indian subcontinent [44], 35 % in Thailand [45], 33 % in Germany [46], 28 % in Brazil [47], 16 % in China [48], 14 % in Korea [49], and the lowest of 8 % reported in Italy [50].

There may also be differences in the prevalence across racial groups in the general population and it has been reported to be higher in NHBs, Mexican Americans, and Asian Americans compared with NHW [39, 51, 52]. Although in women with PCOS previous studies have not shown any significant differences in the prevalence of the metabolic syndrome, there have been differences reported in the prevalence of individual components of the syndrome across racial groups [25, 40].

The high prevalence of the metabolic syndrome and individual components of the syndrome in NHBs and Hispanics in the general population is attributable mostly to the disproportionate occurrence of obesity, hypertension, and diabetes in NHBs and the high prevalence of obesity and diabetes in Hispanics [53]. However, the predictive value of the metabolic syndrome in identifying high-risk individuals for the development of CVD and type 2 diabetes in NHBs and Asian Americans has been questioned [54, 55]. It has been shown that the prevalence of CVD is much higher than the prevalence of metabolic syndrome in NHBs [53]. This is because the cutoff level used to define some of the criteria for the diagnosis of the syndrome such as elevated waist circumference and obesity as well as hypertriglyceridemia may not accurately detect CVD risk in NHBs and Asian Americans [52, 56, 57]. These factors are important when considering the prevalence of the syndrome as well as identifying high-risk individuals for the development of CVD and type 2 diabetes. These individual risk factors may be more important in risk prevention in both the general population and in women with PCOS.

Diabetes and Prediabetes

The prevalence of diagnosed diabetes in adults over 18 years of age in the general population is highest among blacks and Hispanics compared to whites Asian

Americans [58]. The racial predilection for type 2 diabetes has been partly attributed to the higher incidence of obesity and insulin resistance which have been found in certain racial groups. In women with PCOS, there is increased risk of developing metabolic abnormalities including impaired glucose tolerance (IGT) and type 2 diabetes [59, 60]. In contrast to the general population, it has been shown that Asian and Hispanic women with PCOS have an increased prevalence of diabetes compared to white and black women with PCOS independent of BMI [19], and the prevalence was similar between blacks and whites. Other studies have not shown any differences in the prevalence of diabetes amongst racial groups [25].

Obesity and Fat Distribution

Obesity is one of the strongest risk factors for the development of type 2 diabetes. It has been previously shown that in the USA, the prevalence of obesity in the general population varies by race. Recent National Health and Nutrition Examination Survey (NHANES) data have shown that the age-adjusted prevalence of obesity in adults 20 years of age and older was highest in NHBs followed by Mexican Americans [61]. Moreover, the prevalence of extreme obesity was highest amongst NHBs compared with NHWs and Mexican Americans [61]. Therefore racial/ethnic differences in obesity may contribute to the highest risk of type 2 diabetes in NHBs and Mexican Americans.

In the PCOS population, similar findings have been found and a higher prevalence of obesity exists in blacks compared with Caucasians [9, 19] although other studies have not confirmed this [24]. Moreover, a higher prevalence has been found in Mexican Americans compared with whites [30]. Lo and coworkers [19] found that blacks and Hispanics had the highest prevalence of obesity compared with whites but this study may be limited by selection bias. The prevalence of obesity in an unselected PCOS population was found to be higher in blacks compared with whites [9] although the study was limited by its small sample size. In a prospective multicenter study with a larger sample size, no differences were found in BMI and weight distributions as well as abdominal obesity between Caucasians and African Americans and although Asians had a lower BMI this may be due to the small number of women in that racial group [24].

Thus, body weight alone may not explain the differences in the prevalence of type 2 diabetes and in fact although South Asian Indians in the general USA population have one of the highest prevalence of type 2 diabetes they have a low prevalence of obesity but a high prevalence of being overweight [62]. It has also been shown that visceral adiposity may be an important factor that may explain some of the differences [62]. Therefore, any difference in insulin resistance amongst racial groups in women with PCOS is unlikely to be due to obesity.

Waist Circumference and the Metabolic Syndrome

Waist circumference is included in the criteria of the metabolic syndrome because visceral adipose tissue (VAT) is the fat depot that has an important association with insulin resistance [56]. It has been suggested that the waist circumference threshold that may predict the risk of developing adverse metabolic events may be higher in NHB [63, 64] and lower in Asian Americans [52, 57] than NHW women in the general population. In women with PCOS, no differences in waist circumference have been found between NHBs or NHWs [24, 34], although another study found a higher waist circumference in blacks compared with Asians and whites [25]. Moreover, waist circumference was found to be lower in Asians compared with NHWs although the sample size was small [24].

Glucose Metabolism and Insulin Resistance

In the general population, the high prevalence of type 2 diabetes in NHB and Mexican Americans compared with NHW have been attributed to differences in glucose metabolism and homeostasis [65]. NHBs have a greater hyperinsulinemia [66–68] and insulin resistance [66, 69–72] compared with NHW which is independent of obesity. Several of these studies have also shown that NHBs augment insulin secretion to compensate for the insulin resistance [66, 69–71, 73, 74]. Similar findings have also been shown in Mexican Americans [66, 71, 73]. In women with PCOS, several population-based studies have also confirmed similar findings of differences in glucose metabolism and homeostasis in different ethnic group [17, 28, 30, 34], although the sample size in these studies was small. Ehrmann and colleagues [34] showed that controlling for BMI, black women with PCOS had greater hyperinsulinemia and insulin resistance than white women. These findings have also been corroborated in other ethnic groups and Mexican American [30], Caribbean-Hispanic [17], and South Asian [28] women with PCOS tend to have higher insulin levels and greater insulin resistance compared with white women of similar weight and BMI. However, this finding is in contradiction with a much larger prospective multicenter trial by Legro and coworkers [24] which showed comparable fasting insulin and insulin resistance in blacks compared with whites. Moreover, although Welt and colleagues [25] showed greater hyperinsulinemia and insulin resistance in African Americans compared with Asian and Caucasian women with PCOS, the differences were entirely accounted for by BMI.

Hypertriglyceridemia

Fasting triglyceride (TG) is currently used as one of the components of the metabolic syndrome because it has a strong positive correlation with insulin resistance [75].

Elevated TG is not one of the commonest presentations of the metabolic syndrome in NHBs and West Africans compared to NHWs in the general population, in whom elevated TG is one of the common features of the syndrome [76]. Moreover, TG levels are lower in NHBs although it is most often normal in insulin-resistant NHBs [77]. It has therefore been argued that the use of elevated fasting TG as one of the criteria for diagnosing the metabolic syndrome may lead to underdiagnosis of the metabolic risk in NHBs [78]. It has been suggested that the lower TG levels seen in NHBs may be due to low VAT, low hepatic fat high lipoprotein lipase, and low apolipoprotein CIII levels [79–81].

African American women with PCOS have significantly lower serum TG levels compared with Caucasians after controlling for age, BMI, and insulin resistance [82]. Moreover, although BMI positively correlated with TG levels and Mexican American women with PCOS were more insulin resistant than NHWs, there were no significant differences in TG levels between the two racial groups [31]. Other studies have also shown comparable TG levels in blacks, Hispanics, Asians, and whites [25].

Low HDL-C

Low HDL-C is another criterion for identifying metabolic syndrome and HDL-C has been shown to be higher in NHBs than NHWs in the general population [76]. On the contrary, the HDL-C level is lower in NHBs who are insulin resistant regardless of normal TG levels [76]. Therefore it has been suggested that low HDL-C levels, rather than elevated TG, may be an important risk factor for development of type 2 diabetes or CVD in NHBs. In women with PCOS, Koval and colleagues [82] showed higher HDL-C levels in overweight or obese African American women compared with Caucasians. However, the study did not evaluate the HDL-C levels only in insulin-resistant women with PCOS in different racial groups. No differences have been found in HDL-C levels in Mexican Americans [31], NHBs, or Asians [25] compared with NHWs.

Hypertension

The prevalence of hypertension in the general population is higher in NHBs and Mexican Americans than NHWs [83]. Moreover, the prevalence of hypertension in Native Americans and Alaska Natives is lower compared with NHBs and NHWs [83]. However, black women with PCOS were more likely and Hispanics less likely to have hypertension [19], although no differences in the prevalence of hypertension amongst racial groups was shown in other studies [25]. Asians were found to have lower blood pressures compared with blacks and whites and there were no differences in blood pressure between whites and blacks [24].

Potential Reasons for Ethnic and Racial Differences in Metabolic Syndrome

Although there has been some previous studies that have attempted to determine potential reasons for the ethnic and racial differences in glucose metabolism and metabolic syndrome in the general population studies are lacking in women with PCOS. It is however possible that the reasons for the racial disparities can be extrapolated to women with PCOS but future studies are needed to explore this further. Beck and colleagues [84] described the phenomenon of "metabolic inflexibility" in NHB women who failed to increase fat oxidation or decrease carbohydrate metabolism despite increases in their insulin levels after being fed a high-fat diet compared with NHW women. This may contribute to the higher risk of obesity and insulin resistance seen in NHB women. It has also been shown that compared with NHW women, NHBs have lower levels of 25-hydroxyvitamin D which may explain the ethnic/racial differences in insulin sensitivity [85–87]. Moreover, Asian Americans have been shown to have reduced β-cell function which may explain their high risk of diabetes at lower BMI levels [74].

It is possible that ethnic differences may exist in susceptibility genetic loci for type 2 diabetes; however, it is unlikely that ethnic/racial differences may be explained by genetic variation since such loci have not been currently identified [78]. Several SNPs and microsatellite regions have been identified and associated with the PCOS phenotype [88]; however no clear gene has been identified nor is there a genetic test for PCOS [89]. A Chinese multicenter group led by Dr. Chen has identified several SNPs of interest in a large genome-wide association study (GWAS) conducted in women with PCOS [90]. Some of these SNPs have been individually replicated in Caucasian cohorts [91, 92]. Ongoing GWAS in Caucasians should be insightful for those genetic sequences unique to PCOS independent of race and ethnicity. Identification of such genes may help explain any ethnic/racial differences in PCOS phenotype.

Adiponectin is an adipokine produced exclusively by adipocytes [93] and may play a role in the pathogenesis of obesity-related disorders including hypertension [94] and lower levels may be risk factors for type 2 diabetes [95] and coronary artery disease [96] in the general population. Adiponectin levels have been found to be lower in African Americans compared with Caucasians in the general population [97], which may explain differences in the risk of hypertension.

It is known that the level of physical activity is an important risk factor for diabetes [98] and so differences in physical activity in different ethnic groups may account for the differences in metabolic disorders. It has been shown that NHBs, Mexican Americans, Native Americans, and Alaska Natives report less leisure-time physical activity than NHWs [83]. Although such studies have not been performed specifically in women with PCOS, it is likely that lower physical activity levels in these groups may contribute to the elevated risk of obesity, insulin resistance, and diabetes. It has also been shown that smoking is a risk factor for type 2 diabetes in the general population [99] and Alaska Natives and Native Americans have a higher

prevalence whilst Mexican Americans have lower prevalence of smoking compared with NHWs [83]. However, the prevalence of smoking is similar in NHBs and NHWs [83].

Conclusions

Differences in study design, diagnostic criteria, recruitment of the relevant population, and small sample size may not allow a definitive identification of any ethnic or racial differences in the prevalence, symptomatology, and the metabolic consequences of PCOS. Large prospective comparative well-designed studies are therefore needed to identify any differences that may exist since appropriate targeting of the relevant and vulnerable population may help prevention and treatment of long-term consequences. Such studies are therefore needed in women with PCOS to determine if ethnic differences in fat oxidation, serum 25-hydroxyvitamin D and adiponectin levels, physical activity, and prevalence of smoking may explain any racial/ethnic differences seen in various metabolic disorders.

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Chapter 16
Ethnicity and Ovarian Response: The Role of FSH Receptor Genotype

Botros R.M.B. Rizk and Dmitris Loutradis

Introduction

Ovarian response depends on the age of the patient, antral follicle number, and follicle-stimulating hormone receptor genotype. FSH receptor genotype might possibly vary between different ethnic groups, and, therefore, explain the variation in response among women of different ethnic origins (Figs. 16.1–16.4). In this chapter, we have analyzed the FSH receptor genotype among women of different ethnic groups and their relation to ovarian response.

Follicle-Stimulating Hormone

The follicle-stimulating hormone is the key hormone of human reproduction that is essential for gonadal development, as well as gamete production [1]. Follicle-stimulating hormone, luteinizing hormone, and human chorionic gonadotropin consist of a common alpha subunit and a receptor-specific beta subunit. FSH stimulates the growth of follicles in the ovary (Figs. 16.1 and 16.2) by a specific FSH receptor in the cell membranes of granulosa cells. FSH is responsible for the proliferation of granulosa cells and the synthesis of aromatase enzyme. This enzyme, in turn, is responsible for estradiol formation. FSH is also responsible for the selection of the dominant follicle [2].

B.R.M.B. Rizk, M.D., M.A., FRCOG, FRCS, HCLD, FACOG, FACS.
Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of South Alabama, 251 Cox Street, Suite 100, Mobile, AL 36604, USA
e-mail: botros4@gmail.com; botros3@aol.com

D. Loutradis, M.D.
Department of Obstetrics & Gynecology, 'Alexander' Maternity Hospital, V. Sofias 80, Athens, Attiki 11528, Greece
e-mail: loutradi@otenet.gr

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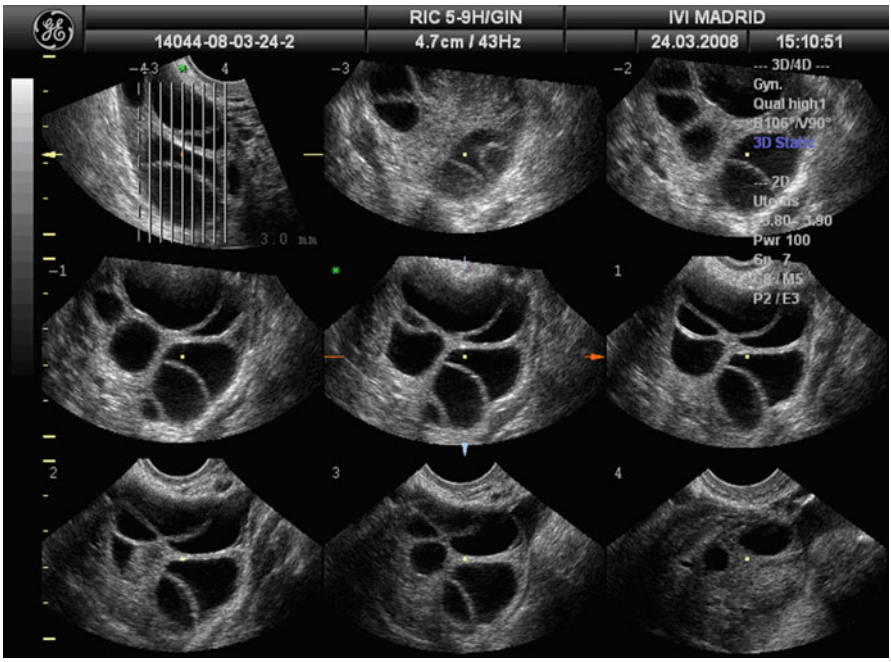

Fig. 16.1 Hyperstimulated ovary. TUI mode allows obtaining millimetric images of the selected structure. Reproduced with permission, from Puente and Garcia-Velasco. In: Rizk B (ed). Ultrasonography in Reproductive Medicine and Infertility. Cambridge University Press 2010, chapter 8, 68

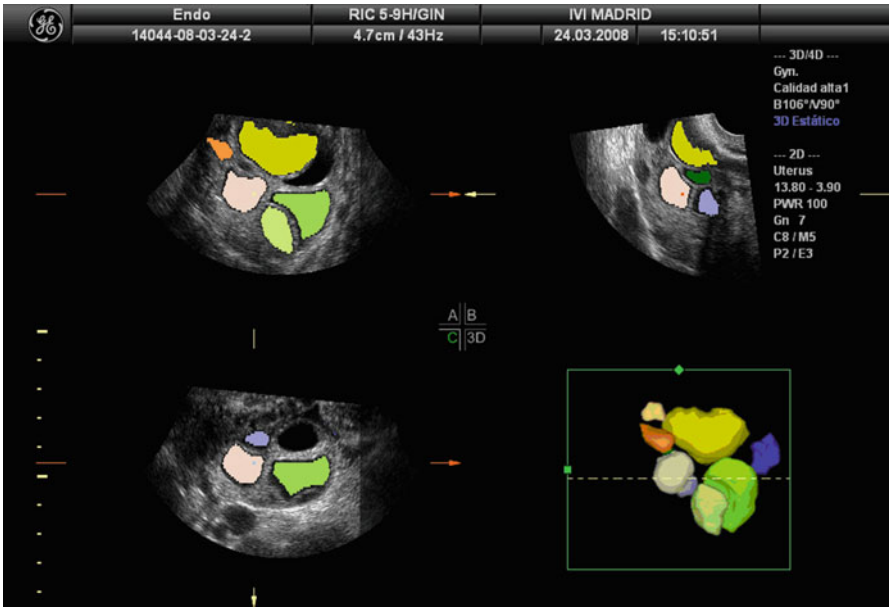

Fig. 16.2 SonoAVC software permits both follicular diameter and volume calculation (automated volume calculation). The operator just needs to capture ovarian volume and the application analyzes and determines diameter as well as volume of the sonolucent areas found. Reproduced with permission, from Puente and Garcia-Velasco. In: Rizk B (ed). Ultrasonography in Reproductive Medicine and Infertility. Cambridge University Press 2010, chapter 8, 70

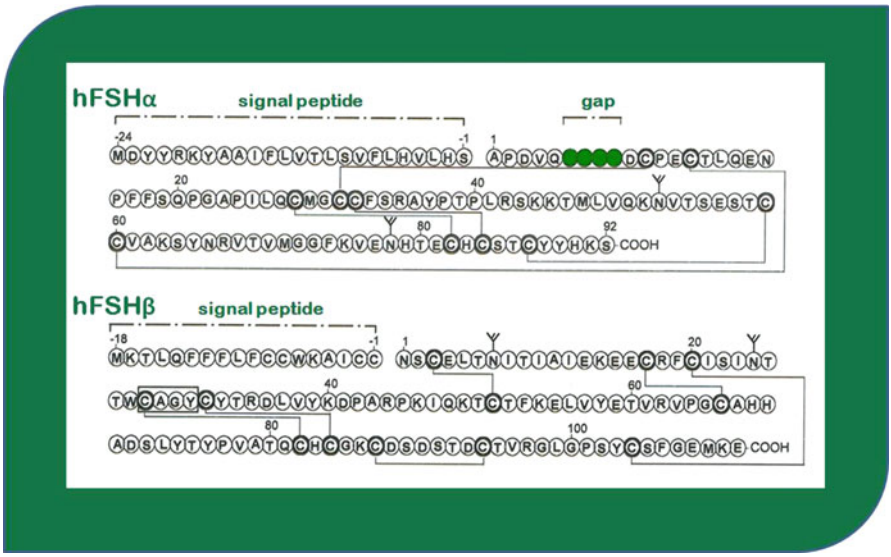

Fig. 16.3 The sequence of the common human α-subunit (hFSHα; *upper panel* and human FSHβ; *lower panel*). Modified, with permission, from Ulloa-Aguirre A, Timossi C. Biochemical and functional aspects of gonadotropin-releasing hormone and gonadotropins. *Reproductive BioMedicine Online* 2000; 1(2):48–62

Follicle-Stimulating Hormone Receptor

Follicle-stimulating hormone receptor belongs to the family of G-protein coupled receptors. The FSH receptor could be divided into three regions: the extracellular domain, a transmembrane region, and an intracellular domain [3, 4]. The FSH receptor is characterized by seven hydrophobic helices inserted in the plasma membrane (Figs. 16.3 and 16.4) and in the intracellular and extracellular domains. Binding between the FSH and the FSH receptor occurs through a hand-clasp binding model [4]. It resembles the appearance of two hands clasped together. The FSH molecule fits into a notch in the curve of the receptor and the receptor itself wraps around the FSH molecule. The intracellular portion of the FSH receptor is coupled to a G protein, and, upon receptor activation by the hormonal interaction with the extracellular domain initiates a cascade of events that finally leads to the specific biological effects of the gonadotropin [5] (Fig. 16.5).

FSH Receptor Gene

The FSH receptor gene is located on chromosome 2p21-p16 [1, 6, 7]. The LH receptor gene can be mapped to the same chromosomal location. The FSH receptor gene is a single-copy gene that consists of ten exons and nine introns. The extracellular domain

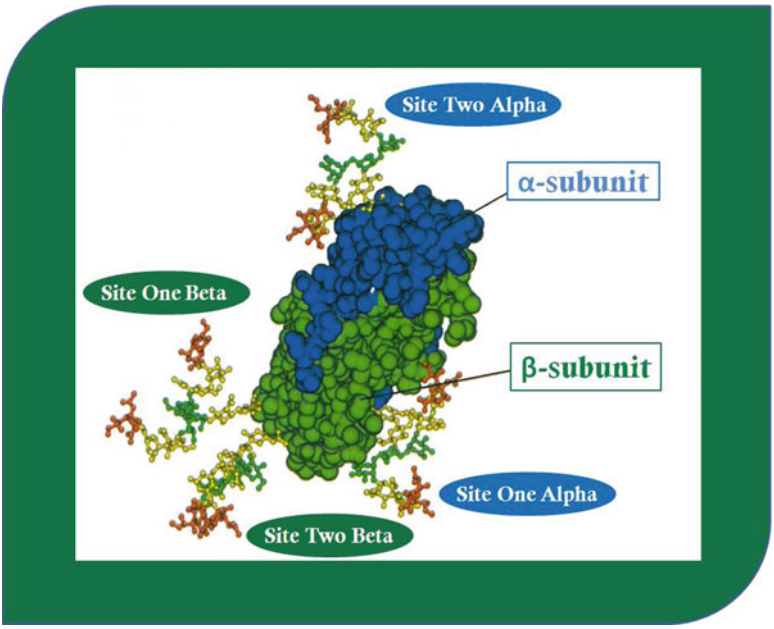

Fig. 16.4 Model of a fully glycosylated and sialylated human FSH molecule. Modified, with permission, from Ulloa-Aguirre A, Timossi C. Biochemical and functional aspects of gonadotropin-releasing hormone and gonadotropins. *Reproductive BioMedicine Online* 2000; 1(2):48–62

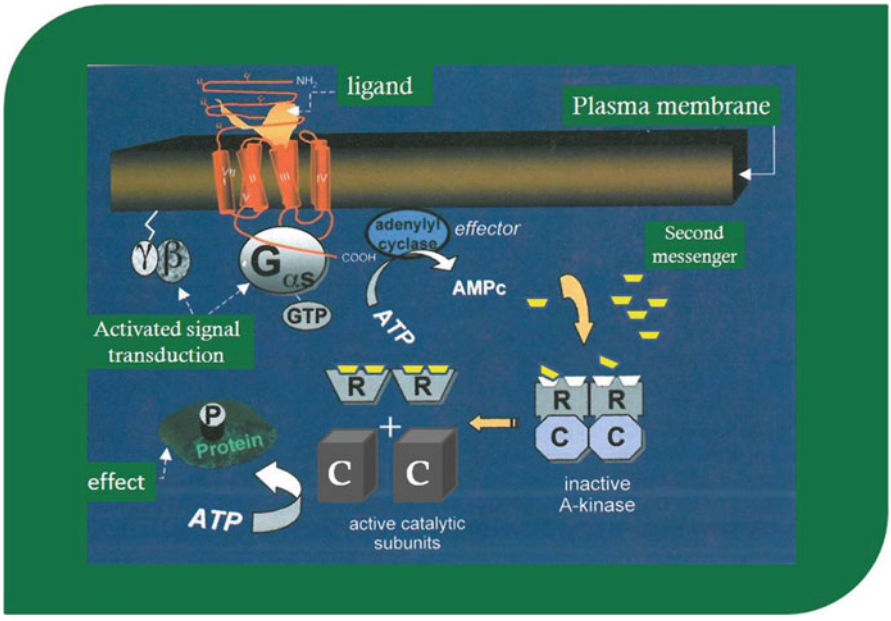

Fig. 16.5 Interaction between FSH and FSH receptor. Modified with permission from Ulloa-Aguirre A, Timossi C. Biochemical and functional aspects of gonadotropin-releasing hormone and gonadotropins. *Reproductive BioMedicine Online* 2000; 1(2):48–62

of the human FSH receptor is encoded by nine exons. The C-terminal part of the extracellular domain, the transmembrane portion, and the intracellular domains are encoded by exon 10. The FSH receptor gene encodes 695 amino acids, including a single peptide with 17 amino acids. The FSH receptor gene has been carefully studied by detecting point mutations and their functional consequences at the protein level [2, 7]. The presence and frequency in a given population of allelic variants at known or suspected polymorphic sites have also been studied, and more than 700 single nucleotide polymorphisms and mutations of the FSH receptor gene have been found [7].

FSH Receptor and Ovarian Response

The portion of chromosome 2 including the gene codifying the receptor for FSH can display point mutations that cause variations in the amino acid sequence of the receptor protein. Some of these structural changes affect the receptor's functional properties, which may be enhanced or impaired [8]. The resulting mutations have been classified as activating, inactivating, or neutral, according to the FSH receptor activity level [7, 9]. Activating mutations confer to FSH receptor a higher responsiveness to FSH, making it constitutively active, even in the absence of the ligand. It may even make it able to nonspecifically respond to other hormones, such as thyroid-stimulating hormone [7]. These mutations predispose to ovarian hyperstimulation syndrome (OHSS) [10]. Inactivating mutations reduce the receptor's function up to a total block. These mutations may either alter the formation of the receptor–ligand complex or FSH signal transduction. These inactivating mutations may cause amenorrhea, infertility, or premature ovarian failure.

Polymorphisms of the FSH receptor are changes at the nucleotide level of the gene itself. These polymorphisms result in allelic variations. Finally, the sequence of amino acids on the receptor protein may be altered. The polymorphisms are distinct from the point mutations that are very rarely observed. The proportion of different polymorphisms in any given population is variable according to ethnic origin [4, 7] (Table 16.1).

Ethnicity and FSH Receptor Polymorphisms

FSH receptor gene polymorphisms at specific sites would influence FSH receptor protein responsiveness to exogenous FSH. Polymorphisms at codons 307 and 680 are of specific interest (Table 16.2). The clinical interest in these polymorphisms is significant because they affect the effectiveness of in vitro fertilization as well as the possibility of developing severe OHSS [2, 4, 7, 11, 12].

Two common single nucleotide polymorphisms (SNP) within exon 10 of the human FSH receptor gene result in two almost equally common allelic variants, exhibiting threonine (Thr) or alanine (Ala) at position 307 in the hinge region,

Table 16.1 Frequency distribution of FSHR genotypes at position 680 in different study groups

Study	Asn/Asn (%)	Asn/Ser (%)	Ser/Ser (%)	Subjects (type)	Subjects (No)	Origin	Gender
Conway (1999)	25	52	23	PCOS	93	UK	Females
Perez Mayorga (2000)	29	45	26	IVF patients	161	Germany	Females
Sudo (2002)	41	47	12	Ovulatory and anovulatory	522	Japan	Females
De Castro (2003)	31	50	19	IVF patients	102	Spain	Females
Laven (2003)	16	44	40	Normogonadotropic anovulatory infertile	148	Germany	Females
Sundblad (2004)	32	45	23	Ovulatory	44	Argentine	Females
Daelemans (2004)	25	51	24	IVF patients	130	Belgium	Females
Falconer (2005)	35	24	41	Infertile women	68	Sweden	Females
Greb (2005)	34	49	18	Ovulatory	125	Germany	Females
De Koning (2006)	21	58	21	FSH>10 IU/L	38	Netherlands	Females
	45	42.5	12.5	FSH<10 IU/L	40		
Jun (2006)	42	46	12	IVF patients	263	Korean	Females
Klinkert (2006)	38	45	17	IVF patients	105	Dutch	Females
Loutradis (2006)	27	39	34	IVF patients	125	Greece	Females
Livshyts (2009)	18.6	53.9	27.5	Ovarian dysfunction	102	Ukraine	Females
	12.8	51.3	37.9	Poor responders	39		
	30.0	57.5	12.5	Good responders	40		
Achrekar (2009)	31	56	13	Controls	100	India	Females
	42	46	12	IVF patients	50		

Table 16.2 Activating mutations of FSH receptor (FSHR) and ovarian hyperstimulation syndrome (OHSS)

Asp567 → Asn	FSHR increased sensibility to FSH or HCG Spontaneous or iatrogenic OHSS
Thr449 → Ile	FSHR increased sensibility to FSH, HCG or TSH
Thr449 → Ala	Spontaneous or iatrogenic OHSS even due to hypothyroidism
Ile545 → Thr	FSHR increased sensitivity to FSH, HCG, or TSH Spontaneous or iatrogenic OHSS even due to hypothyroidism

HCG human chorionic gonadotropin, *TSH* thyroid stimulating hormone

asparagine (Asn) or serine (Ser) at codon 680 in the intracellular domain. Pugni and Simoni [13] note that there are a total of five single nucleotide polymorphisms in exon 10, occurring at codons 307, 329, 524, 665, and 680, but only four of these SNPs cause a change in the amino acid sequence. The two codons responsible for amino acids 307 and 680 are, they note, in "linkage disequilibrium" [13]. They are linked to each other in a noncasual pattern during recombination, and four different allelic variants are generated with a specific frequency in a given population. If one polymorphism occurs at one site, the second site is typically found to be exchanged as well. The two most common allelic variants are Ala^{307}/Ser^{680} and Thr^{307}/Asn^{680}, which represent 55 % of the alleles in the Caucasian population [6, 13]. Each allelic variant can be found in homozygous and heterozygous forms, and, as a result, nine different allelic combinations are possible [7]. They found that there are no fertility differences between the Ala^{307}/Ser^{680} and Thr^{307}/Asn^{680} groups, but the different genotypes do influence the different aspects of the normal ovarian cycle [13].

Perez-Mayorga et al. [14] and de Castro et al. [15] have demonstrated that p.N680S determines the ovarian response to FSH stimulation in patients undergoing in vitro fertilization. Patients with Ser^{680} allele need more exogenous follicle-stimulating hormone during the controlled ovarian stimulation to reach the same estradiol concentrations of Asn^{680}. Women with normal menstrual cycles that have Ser^{680}/Ser^{680} tend to have higher FSH serum concentrations and prolonged cycles. They also found that Asn at position 680 may be important in post-translational receptor processing and cell surface expression due to introduction of a sequence for glycosylation. Ser at position 680 appears to be involved in receptor turnover via a phosphorylation mechanism [14].

Greb et al. [16] found that, in women with the Ser/Ser genotype, estradiol concentrations were significantly lower and FSH levels started to rise earlier, compared to women with the Asn/Asn genotype. FSH concentrations were steadily and significantly higher during the follicular phase in the Ser/Ser genotype group. Estradiol and velocity of growth of the dominant follicle showed no difference between the groups. Higher concentrations of endogenous FSH are therefore necessary to achieve ovulation in carriers of the Ser/Ser genotype, with the difference of about 2 days between these women and those women with the Asn/Asn genotype.

Perez-Mayorga et al. [14] evaluated the impact of the FSH receptor genotypes at position 680 on the ovarian response to FSH stimulation in 161 European patients

undergoing IVF-embryo transfer in Munster, Germany. There was no difference in the number of oocytes retrieved and no difference in serum estradiol concentration on the day of HCG administration. Basal FSH concentrations and number of gonadotropin ampules were higher in the Ser/Ser group. The presence of a Ser in position 680 is associated with high FSH basal concentrations and higher requirements of exogenous FSH for ovarian stimulation. FSH receptor with a Ser in position 680 is less efficient than FSH receptor with Asn in position 680 [14, 17]. The presence of Ser in position 680 is associated with poor response to gonadotropin therapy in in vitro fertilization [15].

In 2002, Sudo et al. [17] analyzed different FSH receptor polymorphisms in a group of 522 Japanese women, where 168 of the women had either conceived spontaneously or had confirmed spontaneous ovulation, 96 suffered from amenorrhea (hypothalamic–pituitary amenorrhea, secondary amenorrhea, hyperprolactinemia, or PCOS), and 258 with regular menstrual cycles and none of the aforementioned gynecologic problems. They found complete linkage between 307 and 680 amino acid transition, showing three genotypes: Thr^{307}–Asn^{680}/Thr^{307}–Asn^{680} (TN/TN), Thr^{307}–Asn^{680}/Ala^{307}–Ser^{680} (TN/AS), and Ala^{307}–Ser^{680}/Ala^{307}–Ser^{680} (AS/AS). The frequencies of these genotypes in the entire population of the study were 41.0 % TN/TN, 46.9 % TN/AS, and 12.1 % AS/AS; the frequencies in the spontaneous ovulation group were 43.5 % TN/TN, 43.5 % TN/AS, and 13.0 % AS/AS. When comparing the frequency of genotypes with the different diseases in the amenorrheic group, no associations were found between any of the genotypes with hypothalamic primary amenorrhea, secondary amenorrhea, or premature ovarian failure. They did find, however, that the number of TN/AS patients was significantly larger in patients with PCOS compared to patients with spontaneous ovulation (66.7 % versus 43.5 %). Upon measurement of serum FSH levels, they noted that the AS/AS group demonstrated a significantly higher basal FSH level (mean 13.0) compared to the TN/AS group (mean 8.9). There was also a difference between the AS/AS and the TN/TN groups, but it was not found to be statistically significant. The investigators also found a difference in the ovarian responses among FSH receptor genotypes. Patients in the TN/AS group required lower doses of hMG to reach adequate follicular growth, compared to the AS/AS group. Ultimately, the TN/TN group and the TN/AS groups showed higher serum estradiol levels than the AS/AS group on the day of hCG administration. There was also comparison of receptor bioactivity via cyclic AMP responses among the different polymorphisms, but no significant differences in in vitro bioactivity were demonstrated [17]. Sudo et al. [17] compared their findings to that of Perez-Mayorga et al. [14], who found that the distribution of the different genotypes to be 29 % TN/TN, 45 % TN/AS, and 26 % AS/AS in European women, as opposed to 43.5 % TN/TN, 43.5 % TN/AS, and 12.1 % AS/AS distribution seen in their population of Japanese patients. This led the authors to suggest that Japanese women have an increased incidence of the TN allele when compared to Caucasian women. Both studies demonstrated that basal serum FSH levels tend to be higher in the AS/AS genotype. Perez-Mayorga et al. [14] showed that serum FSH levels were significantly higher in both the TN/AS and AS/AS groups when compared to the TN/TN group. Sudo et al. [17], on the other hand, showed that the AS/AS patients

had a higher basal FSH level compared with the TN/AS group but that the levels of the TN/TN group did not different significantly from either group.

Jun et al. [11] investigated FSH receptor gene polymorphisms and ovarian response to controlled ovarian hyperstimulation (COH) in a group of 263 Korean women, all of which were under 40 years of age and were undergoing in vitro fertilization for tubal, male, or unexplained infertility. Patients with a history of polycystic ovarian syndrome, endometriosis, or prior ovarian surgery were excluded. Genomic DNA was extracted and FSH receptor polymorphisms at position 680 were determined by PCR analysis. They found that distribution of allelic variants at position 680 among the subjects were 41.8 % Asn/Asn, 45.6 % Asn/Ser, and 12.5 % Ser/Ser. There were no significant differences among the patients in terms of distribution of infertility factors or stimulation protocols. It was noted that day 3 basal FSH levels were significantly higher in the Ser/Ser group (mean 8.2 IU/L) compared to the Asn/Ser and Asn/Asn groups (means 6.0 IU/L and 5.7 IU/L, respectively). They found no significant difference in the levels of serum estradiol on the hCG administration after receiving similar doses of gonadotropins. There was a difference noted in the number of oocytes retrieved among the different groups. Patients in the Asn/Ser group had a greater number of oocytes retrieved (mean 9.6) compared to the Ser/Ser group (mean 7.9). Also, the clinical pregnancy rate per embryo transfer was higher in the Asn/Asn group (45.7 %) versus the Ser/Ser group (28.1 %) and the Asn/Ser group (31.1 %). The researchers, however, found no differences among the groups in terms of fertilization rate, number of embryos transferred, quality of embryos transferred, or endometrial thickness on day of hCG administration. Interestingly, there was a marked difference in the number of oocytes retrieved versus the differences in the dose of gonadotropins used when GnRH agonist was used. Patients in the Asn/Asn group demonstrated a higher pregnancy rate when using a GnRH agonist, but the rate was significantly higher when GnRH antagonist was used. Ultimately, the study showed decreased estradiol levels, decreased numbers of oocytes, and decreased clinical pregnancy rates in the Ser/Ser group compared to the Asn/Ser and Asn/Asn groups. The authors concluded that there is a difference in the pregnancy rate among the different follicle-stimulating hormone receptor genotypes of infertile Asian women, without any association to polycystic ovarian syndrome [11].

Jun et al. [11] also compare their findings to that of Perez-Mayorga et al. [14], who evaluated FSH receptor genotypes at position 680 and their effect on ovarian response in a population of 161 European women. Perez-Mayorga et al. [14] found no differences in the number of oocytes retrieved or in the serum estradiol concentration on the day of hCG administration among different genotypes, but they did demonstrate that the number of gonadotropin ampules and basal FSH levels were both increased in the Ser/Ser group, leading that team of researchers to conclude that FSH polymorphisms can aid in the prognosis of COH cycles in normo-ovulatory, infertile women. Jun et al. found the genetic polymorphisms in the population of Asian women that they studied differed from that of the German women in Perez-Mayorga et al.'s study, stating that the frequency of the Ser/Ser genotype was lower in the Korean population versus the previously studied German population [11, 15].

On the other hand Klinkert, published in 2006 the role of FSH receptor gene polymorphisms in ovarian response to controlled ovarian stimulation, in a Dutch population. They presented results that were contrary to the work of previous researchers: women carrying the Asn/Asn genotype presented lower pregnancy rates in comparison with women carrying the Ser/Ser and Asn/Ser genotypes [18]. They postulate that these differences are due to ethnicity.

Loutradis et al. [19] studied 125 Greek women to assess how polymorphisms at the 680 position affected response to ovarian stimulation prior to IVF. They divided the patients into three different groups: "good responders (GR)," "poor responders (PR)," and "ovarian dysfunction (OD)," based on a number of factors, including number of follicles developed, serum estradiol concentrations at the hCG administration, FSH levels on day 3 of the menstrual cycles, among other factors. The frequencies of the allelic variants were evenly distributed in both the OD group (45.5 % Ser/Ser, 22.7 % Asn/Ser, and 31.8 % Asn/Asn). They are also equally distributed in the PR group, but, of note, there was a statistically significant tendency for patients in the GR group to display Asn/Ser genotype. Upon hormone testing, they found statistically significant differences among the groups in the FSH concentration on day 3 of the menstrual cycle. The patients in the OD and GR groups with either the Ser/Ser variant or the Asn/Asn variant had significantly higher levels of FSH, compared to the Asn/Ser subgroup. It was also noted that patients in the Asn/Ser subgroup had significantly higher levels of estrogen on the day of hCG administration, higher numbers of preovulatory follicles and collected oocytes, and required significantly lower doses of recombinant gonadotropin for ovulation induction. Of the follicles and oocytes collected from the patients, it also appeared that Asn/Ser subgroup produced better quality embryos compared to the Ser/Ser subgroup. Pregnancy rates, however, were similar among the three subgroups (3/49 in the Asn/Ser subgroup, 3/42 in the Ser/Ser subgroup, and Asn/Asn 2/34). Most of the pregnancies, six out of eight, occurred in the GR group. This study led the authors to postulate that the Asn/Ser genotype may confer greater FSH sensitivity to these patients. Conversely, they hypothesize that the Ser/Ser and Asn/Asn genotypes may confer some level of relative resistance to the action of FSH [19].

The Prediction of OHSS Severity by FSH Receptor Polymorphism

The proportion of different polymorphisms in a population may vary according to their ethnic origin [7]. The association of S^{680} allele with poor response to ovarian stimulation led to the hypothesis that Asn^{680} allele could be associated with excessive response. This means that patients are at higher risk for iatrogenic OHSS. Daelemans et al. [20] observed no statistically significant difference in allelic frequency in OHSS patients and the IVF control population. However, a significant enrichment in allele 680 was noted as the severity of OHSS increased. The genotype

in position 680 cannot predict which patients will develop OHSS, but could be a predictor of severity of symptoms among the subset of patients who do develop OHSS.

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Chapter 17
Ethnic Differences in Fertility and Assisted Reproduction: Ethnic Disparity in Stem Cell Availability and Research

Chi-Wei Lu, Yasunari Seita, Nathan Treff, and Monica J. Roth

Underrepresentation of Non-Caucasian Genotypes in All Stem Cell Sources

Racial disparities in health care and biomedical research is now being realized. The underrepresentation for African-American, Asian, Hispanic and other non-Caucasian populations in medicine generally has resulted in a bias in the availability of stem cells for transplantation and for research. This includes stem cells of hematopoietic lineages (from both bone marrow and cord blood) and pluripotent stem cells, which are multipotent to differentiation into other lineages. Disparities in access to health care resulted in the lack of donor populations and consequently, the lack of awareness to donate tissues to expand stem cells banks. Because hematopoietic stem cells have limited expansion and life in tissue culture, an active and continuously

C.-W. Lu, Ph.D. (✉)
Department of Obstetrics, Gynecology and Reproductive Sciences, UMDNJ-Robert Wood Johnson Medical School, 89 French St. Room 3276, New Brunswick, NJ 08901, USA
e-mail: luch@umdnj.edu

Y. Seita, Ph.D.
Department of Obstetrics, Gynecology and Reproductive Sciences, UMDNJ-Robert Wood Johnson Medical School, 89 French St. Room 3276, New Brunswick, NJ 08901, USA

Department of Obstetrics & Gynecology, Child Health Institute of New Jersey, UMDNJ-RWJMS, New Brunswick, NJ, USA

N. Treff, Ph.D.
Department of Obstetrics, Gynecology and Reproductive Sciences, UMDNJ-Robert Wood Johnson Medical School, 89 French St. Room 3276, New Brunswick, NJ 08901, USA

Reproductive Medicine Associates of New Jersey, 140 Allen Rd, Basking Ridge, NJ 07920, USA

M.J. Roth, Ph.D.
Department of Pharmacology, UMDNJ-Robert Wood Johnson Medical School, 675 Hoes Lane, Rm. 636, Piscataway, NJ 08854, USA

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enrolling registry of donors is needed. In contrast, since pluripotent stem cells can be indefinitely cultured, they are ideal sources for banking and addressing the shortage of the representation of minority genotypes.

Ethnic Disparities in the Availability of Hematopoietic Stem Cells and Transplantations

Hematopoietic stem cells (HSCs) and their functional equivalents are the only stem cell types currently in clinical use. Transplantation of hematopoietic stem cells, from either bone marrow (direct collection or peripheral blood mobilization) or cord blood, is being actively engaged as therapeutic options. Most of HSC transplantations are used to repopulate blood lineages following bone marrow ablation treatments for leukemia and lymphoma patients (88.3 % of the total transplants), in addition to treatment of nonmalignant blood disorders (5.1 %) and solid tumors (5.8 %) [1]. HSC transplantations are also useful to treat diseases with genetic mutations affecting hematological functions including sickle cell anemia and thalassemia, both of which are known to show higher prevalence in specific ethnic populations. It was estimated that more than 50,000 HSC transplantations were conducted worldwide in 71 countries surveyed in the year of 2006. HSC transplantation is most frequently conducted in Europe and the United States, with only 2 % and 0.1 % of total worldwide transplantation procedures being done in eastern Mediterranean and African areas, respectively [1].

While most of the HSC transplantation were autologous (from preserved HSCs isolated from the same patient, 57.9 %), HSCs from allogeneic and unrelated donors are necessary for conditions with defects in HSC number and function, including myelodysplasia and severe combined immunodeficiencies. About half of patients received grafts from unrelated donors with matched tissue types. While the total annual number of HSC transplants performed is comparable to kidney transplants [17,875 HSCs in 2006 and 16,517 kidney transplantation in 2008 (http://optn.transplant.hrsa.gov/data/annualReport.asp)], HSC transplantation requires more donors than other organ types. Human leukocyte antigen (HLA) tissue typing for solid organ only requires matching for type I, whereas matching for HLA type II is also need for HSC transplantation to minimize the risk of the graft-versus-host disease. HLA matching between the donor and the recipient, particularly for the HLA-DRB1 loci, is the major contributing factor for the success of the hematopoietic transplantation [2]. The frequencies of HLA subtypes vary among different racial groups, with many alleles unique to African, Hispanic, Native American and Asian populations. This presents the need for a larger number of representative donors to generate a pool of tissue donors within minority populations compared to that of the Caucasian population [3, 4]. However, tissue donors for minority populations are disproportionate to their population. Therefore, the variety of tissue types, especially for rare HLA alleles that are enriched in the minority populations, cannot be fully represented. This presents a challenge for the

supply of tissues for HSC transplantations. In particular, African genotypes are the most underrepresented in all types of tissue donations, due to the religious beliefs of their older population and the distrust in the fair distribution of medical care in the younger population [5]. Similarly, all other non-Caucasian race groups have significantly lower numbers of registered bone marrow donors (over 6.5 million for white and less than 700,000 for Black/African Americans, 2012 National Marrow Donor Program data http://marrow.org/News/Media/Facts_and_Figures_(PDF).aspx). The underrepresentation for African and Hispanic American resulted in a lower chance of finding a matched bone marrow donor (30 % chance compared with 80 % chance in white population) [6].

The causes of underrepresentation for African- and Hispanic-Americans are attributed to lower awareness and opportunities for donation [7]. In addition, a survey for transfusion eligibility reflected an issue of the quality of tissue sources, showing high prevalence of exclusionary factors in African American blood donors, including medicinal use, virus infection, and low hemoglobin [8].

Umbilical Cord Blood Stem Cells

Umbilical cord blood (UCB) is being increasingly used as an alternative source of HSC for transplant procedures. Despite the higher birth rates in African and Hispanic American populations, of the cord blood donation reported in 2012, only 7 % were identified as black and 10 % Hispanics, compared to 71 % Whites (http://marrow.org/News/Media/Facts_and_Figures_(PDF).aspx), causing a racial disproportion worse than that of bone marrow [9]. The availability of HLA-matching cord blood for patients with non-European origins are significantly lower: in a single center study, only 21 % of African patients are matched ten out of ten HLA type from unrelated donors versus 53 % of white patients can find a similar match from the same pool of unrelated donors [10]. Unlike blood donation, the major factor for the low UCB donation rate is the lack of basic information available to patients, which is likely to be improved with better physician education [11]. In addition to limited availability of donor tissue, the quality of cord blood also biases the outcome of UCB transplantation to African American patients. For treating leukemia with UCBs, it was reported that fewer black patients received matched UCBs (21 %) compared with whites (40 %) and Hispanics (46 %). African Americans receiving UCBs also showed poorer post-transplantation survival (34 %, compared with 44 % for white and 46 % for Hispanic) [9]. Since UCB are from newborn donors and the cells are therefore less likely to be affected by infections and other lifestyle implicated conditions, they are more likely to be qualified as tissue source than BM HSCs. This can be helpful in addressing the need of donor HSCs for minority populations. From a recent report, more than 50 % of non-European patients receiving cord blood from donors of European ancestry [12]. Similarly, ethnic diversity of major UCB banks in Australia is reported to be greater than that of the Australian bone marrow registry [13]. This supports the use of UCB as an alternative source to compensate for the present ethnic disparities in current HSC sources.

Pluripotent Stem Cells: A Promising Source for Tissue Replacement Therapy

Embryonic stem (ES) cells are the result of artificial expansion of the inner cell mass of blastocysts into proliferative cultures that are immortal and are capable of differentiation into all somatic tissue types. Since their isolation from mouse [14, 15] and human [16], extensive investigations identified a number of characteristics of pluripotency, including a collection of transcription factors specific to the ES cell fate. Based on the collective knowledge of the phenotypes of ES cells, induced pluripotent stem (iPS) cells were generated, by ectopic expression of four transcription factors into primary fibroblasts of mouse and human [17–20]. Both ES and iPS cells were shown capable of forming wide varieties of human tissues in culture, through differentiation induced by growth factors, small molecule chemicals, co-culturing with growth-factor secreting feeder cells (reviewed in [21]), or forced through ectopic expression of growth factors (review in [22]). Through the combination of various differentiation inductive conditions, ES cells are capable of forming functional tissues. Their robust proliferation in culture allows extensive quality controls, ideal for tissue banking and ES cells are considered ideal sources for tissue replacement therapy. Due to the highly stringent criteria for federal funding and the limited availability of human embryos, ES cell research in the United States is outnumbered compared to that of other countries in recent years [23]. While a phase I clinical trial was approved and initiated for the use of ES cells derived oligodendrocytes in acute spinal cord injury, it was unfortunately terminated for economic considerations (Andrew Pollack, the New York Times Nov. 14, 2011).

The Lack of Pluripotent Stem Cells with Genetic Representation of Minority Populations

Another important issue of ES research and development is the lack of genetic diversity in ES cell lines as well as sources of IVF embryos for ES cell derivation. The predominance of Caucasian genotypes in available embryonic stem cells is a consequence of the ethnic differences in the patient population seeking fertility and assisted reproduction treatments. Since Caucasian women with advanced ages and high income remain the majority of the IVF patient population [24], genotypes of ES cells derived in the United States are limited to preferentially represent this population. African genotypes in IVF patients are extremely low, even less than the disparity seen in HSC sources. From clinically collected data, African- Americans account for only 1.8 % of the total patient population seeking IVF treatment in New Jersey (RMANJ in 2008 Nathan Treff, Personal Communication). Genetic screening analyzing 48,3304 genome-wide single nucleotide polymorphisms from 47 frequently used human ES cell lines in the US, with the exception of two Asian cell lines. The rest were of European or the Middle-Eastern genotypes. There were no

African genotype represented [25]. To date there are nearly 1,200 hES cell lines generated (International Stem Cell Registry, http://www.iscr-admin.com/), with 178 cell lines eligible for NIH funding listed in the NIH ES cell registry (http://grants.nih.gov/stem_cells/registry/current.htm). Outside the Unites States, most of the hES cell lines are derived from Asia (China and Korea), Europe (Spain, Sweden and Finland), and Australia. These new sources of ES cells, while improving ethnic diversity of stem cells, are unlikely to solve the underrepresentation of the African genotypes.

iPS cells can be derived from primary tissues of affected individuals to provide tissues that matched identically to the recipient. However, generating clinical grade tissues with this personalized approach is costly and time consuming, which is unlikely to be a solution for improving the health care of minorities. In order to make iPS cell-derived tissues available to the general public, banks of ES and iPS cells with arrays of HLA-haplotypes are proposed to be established. These will serve as a donor program, in a similar manner to the bone marrow registry. It was estimated that an ES cell bank with a panel of only ten ES lines with genotypes homozygous for common HLA types including HLA-A, HLA-B and HLA-DR would provide a complete match for 37.7 %, and partial match for 67.4 % of the population in the UK [26]. Similarly, a bank of only 30 iPS cell lines will be able to match 82 %, and a bank of 50 iPS lines can match 91 % of the Japanese population [27]. The limited number of cell lines required to build a bank is optimistic only for populations with limited genetic diversity. A recent report comparing haplotype frequency identifies that a bank of 20 lines with most frequent haplotypes provide matches for more than 50 % of European Americans but only 22 % of African Americans. Expansion of the bank to 100 iPS cell lines will leave 22 % of European American without a match, versus 55 % of African Americans that cannot find matching iPS cell lines [28]. Collectively, haplotype matching iPS cells will not be a resource to equally benefit minority populations without an effort to proactively establish a collection of iPS cells from tissue donors with, for example, African American genotypes.

The Use of ES and iPS Cells in Disease Modeling

Banking ES or iPS cells with sufficient variety of HLA subtypes is important for utilizing iPS cells as tissue sources for transplantation. Another important application of pluripotent stem cell research is to serve as disease models. In vitro differentiation of pluripotent stem cells uniquely simulates tissue formation processes, providing systems to look into changes in cellular and molecular phenotypes associated with disease progressions. Pluripotent cells with genetic mutations have been generated from a wide variety of conditions. Disease specific ES cell models are mostly derived from IVF embryos which have been diagnosed with genetic mutations through preimplantation genetic diagnosis with monogenic disorders and karyotypic abnormalities. These include diseases with high prevalence in specific race

populations, such as cystic fibrosis that preferentially affects patients with European ancestry, and sickle cell anemia that affects more African descendents.

There are increasing efforts to produce disease specific iPS cells as in vitro models for biomarker discovery and drug development. Since the initial report on the creation of disease specific iPS cells [29], a recent review has cited at least 44 different disease types now represented by iPS cells [30]. Some of these diseases are caused by genes that affect the development of specific tissue types, while others are derived from conditions without clearly defined genetic factors, including autism spectrum disorders and diabetes (both type I and II). For diseases with specific genotypes, tissues derived from iPS cells have been actively engaged in drug discoveries, especially for cardiomyocytes and neurological disorders [30]. Multifactor disease conditions are more complicated, in which genetic factors only contribute to a part of the disease developmental process. Phenotypes of disease conditions may not be directly revealed in iPS derived cell cultures and need to be induced by environmental stress. It may also require multiple iPS cell lines from different individuals in order to observe a common phenotype in tissue culture specific to the disease condition.

Both ES and iPS cells have their limitations for disease modeling. While embryo availability limits the number of ES cells being derived, they are irreplaceable for investigating conditions affecting prenatal development, including implantation failures and other conditions leading to early fetal demise. iPS cells rely on the expression of exogenous transcription factors to change cell fate. A common problem for iPS generation using non-integrating viral vectors or DNA free methods is the low efficiency and relative high cost. Integrating viral vectors have been widely used to generate most of the available cell lines. However, genomic integration of retroviral vectors used to deliver the reprogramming may result in variation of the genetic background and thus mask the disease phenotypes in culture [31]. In order to ensure the culture phenotypes observed faithfully reflect the genotype of the iPS cells, it would be important to use iPS cells derived from factors delivered by non-integration methods, or to reduce the phenotypes biased by viral integration through analyzing more than one clone of iPS cells generated from the same patient.

iPS Cells for Modeling Diseases Without Clear Genetic Association

The use of iPS cells in modeling multifactorial disease conditions with strong evidence of genetic predispositions is not yet explored. Observing developmental changes during differentiation of iPS cells generated from affected individual can shed lights into disease etiology and thus lead to better diagnosis and treatments. This can address some racially biased disease conditions including the high prevalence of preterm births in African populations. With recent advancements in genome sequencing and high throughput genotyping, more genetic variations are found to strongly associate with disease phenotypes. As an example, while the causes of diabetes are complex, recent reports have identified five SNP loci associated with

type II diabetes in African-Americans [32], and another independent report identified another group of SNP markers linked to increased risk of diabetes in African, Asian and Hispanic Americans [33]. While these SNP genotypes are of high values to serve as diagnostic markers for identifying susceptible patients, little is known about how these genotypes actually cause the disease phenotypes. It is also unknown whether phenotypes of disease can be reflected in cell culture or animal models. These would serve as platforms for drug and toxicology screening, in order to identify new treatment options. A rare but successful example is the discovery of ectodysplasin receptor (EDAR). A single nucleotide variation in the EDAR coding sequence was found as the most common human genetic variation and is associated with phenotype variations in ectodermal appendages including scalp hair thickness, changes in tooth morphology and sweat gland numbers. Therefore, the predominance of SNP at EDARV307A in the East Asia population was proposed to serve as a factor for adaptive selection [34]. Phenotypes observed in mice with the same mutations introduced in the *edar* coding sequence recapitulated dermal features of East Asian, including thicker hair, and higher density sweat glands, providing a proof of the genetic contribution to the phenotype observed [35]. Unlike this unique study, most of the human SNPs identified associated with multifactorial diseases are intergenic, and therefore cannot to be introduced into mice to observe their corresponding phenotypes.

Tissues isolated from patients with multifactorial diseases may transiently reflect the disease phenotypes at the time of diagnosis. However, this tissue is the endpoint of years of development in the presence of the disease state. Due to the short lived nature of most primary cultures, and the difficulty for simultaneous collection of large cohorts, it is difficult to establish the link between the genotype and disease with primary tissues. The disease phenotype of a tissue is the sum of the effects accumulated factors over time. For this reason, when a genetic predisposition of disease is suspected, observing tissue formation from the origin to the maturity of affected tissues in iPS models would provide a robust unparalleled tool in investigating the etiology of diseases. Defined culture conditions can be modified to simulate environmental stresses for analyzing combinatorial mechanisms of disease formation. The multipotent potential of iPS cells allows for the generation of all possible tissues associated with a particular disease. This can be closely monitored to redefine markers from the earliest time point of diagnosis. The inexhaustible nature of iPS cell cultures is also ideal for drug and toxicology studies to identify novel treatments. Currently, disease specific iPS cells are actively being used in drug discovery for studies of multifactorial disease including arrhythmia [36], schizophrenia [37], Alzheimer's disease [38], and Rett syndrome [39].

We envision that the systemic identification of the causative genotypes and establishment of disease models will soon be routinely applied for disease conditions with racially biased genetic predispositions (Fig. 17.1). Tissues isolated from individuals with disease phenotypes at time of diagnosis will be analyzed for disease presentations by gene expression or exon sequencing and be processed to establish iPS cultures. iPS cells can then be directed to differentiate into cell types of interest and compared with other iPS cells to determine the genetic contribution and serve as platform for drug and toxicology screening.

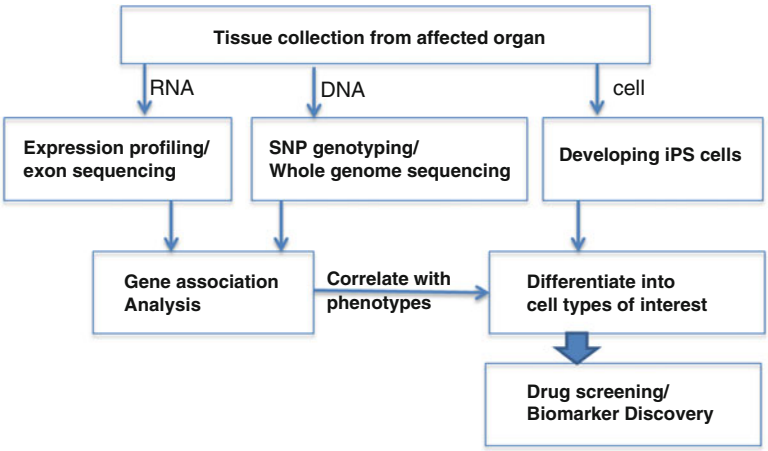

Fig. 17.1 Procedures of a retrospective iPS-based model of disease development. iPS cells derived from affected patients can be re-differentiated into all types of tissues that maybe involved in disease progression, providing a cell-culture system for biomarker and drug screening

Perinatal Diseases with Racial Disparities Without Known Genetic Factors

It is well recognized that African American populations are more susceptible to prenatal maternal-fetal health issues. Some of these conditions are well recognized and are being actively solicited for research efforts, including preterm birth, stillbirth and infant mortality (review in [40]). The calls for proactive research into these disease disparities are to address the need for the improvement in the identification of risk factors, biomarkers and therapeutic options. Although limited access to healthcare and socioeconomic status were considered as a major cause of this disparity, evidence is accumulating that suggests genetic variations as contributing factors to high risk preterm births in African-Americans [41]. Epidemiology studies from large cohorts also revealed high risk preterm births are linked to paternal African genes [42]. In addition, spontaneous preterm births were also linked to ethnic differences in single nucleotide polymorphisms (SNPs) nearby some susceptible genes, including IL6 and its receptors [43, 44], TNF-α promoter [45] and catechol-O-methlytransferase [46]. Genotype association analysis revealed putative genetic loci conferring other maternal-fetal disease predisposition in African American populations. Low infant birth weight was mapped to maternal vitamin D receptor [47]. Preterm membrane rupture was reported to associate with SNP variations within SERPINH1, MMP9 and MMP1 [48, 49]. Even in settings with comparable social economical levels (in the military service population), high prevalence

in preterm birth and low birth weight are observed in the African population, likely attributed to a higher rate of uterine leimyoma [50]. Similarly, even after adjusting potential predictors and confounders, pregnancy related maternal mortality is two- to fourfolds higher in African women, compared with Caucasian population [51]. Altogether, these studies provide evidence of a genetic predisposition for reproductive dysfunction in the African population. Since most of the genotyping were performed from maternal subjects, it remains largely unknown what tissue at the maternal/fetal interface is influenced by the genotype to cause these pregnancy complications. While these findings holds high value to develop the implicated SNP loci as a screening tools for high risk pregnancies, experimental proof is required to establish the pathophysiological mechanism of their action.

Direct differentiation of iPS cells into tissues, provides an experimental system to evaluate the mechanism that specific genotypes contribute to preterm birth. Of high interest is the differentiation of iPS cells into trophoblasts. Situated at the maternal-fetal interface, trophoblasts provide the structural connection for blood exchange and secrete hormones to accommodate the rapid fetal growth within the maternal body. It is likely that trophoblasts at least participate, if not directly trigger preterm labor. Consistently, IL-6 and TNFα, whose genes contain preterm labor-associated SNPs, are secreted by trophoblasts. It is therefore rational to hypothesize that iPS-derived trophoblasts could display altered phenotypes associated with preterm birth. Two differentiation systems have resulted in trophoblast differentiation from human ES cells. Trophoblasts have been observed as a component of mixed lineage differentiation within embryoid bodies [52] or after direct induction with BMP4 [53]. In our studies, we examined human ES cell differentiation toward trophoblasts for additional features and compared it with two commonly used trophoblast cell lines, HTR8 (immortalized first trimester cytotrophoblast) and JEG3 (choriocarinoma derived cells). In addition to expressing typical trophoblast markers, BMP4 induced differentiation of the human ES cell line H9 also expresses a subset of trophoblast hormones, and upon prolonged culture forms syncytiatrophoblasts marked by multinuclear foci expressing hCGβ (Fig. 17.2). These observations support the feasibility of human pluripotent stem cell models of trophoblast dysfunction.

Derivation of iPS Cell Lines with African-American Genotypes

Generation of iPS banks representing African genotypes can address multiple needs. First, generation of common variations provide baselines for studies. These can then be used to define disease implicated SNPs and to study single gene disorders. Additionally it proactively addresses the need for sources for tissue transplantation and for models for racially disproportional disease conditions. With the need for iPS cells representing African American genotypes being recognized, our group initiated an effort to generate iPS cell lines from African American populations.

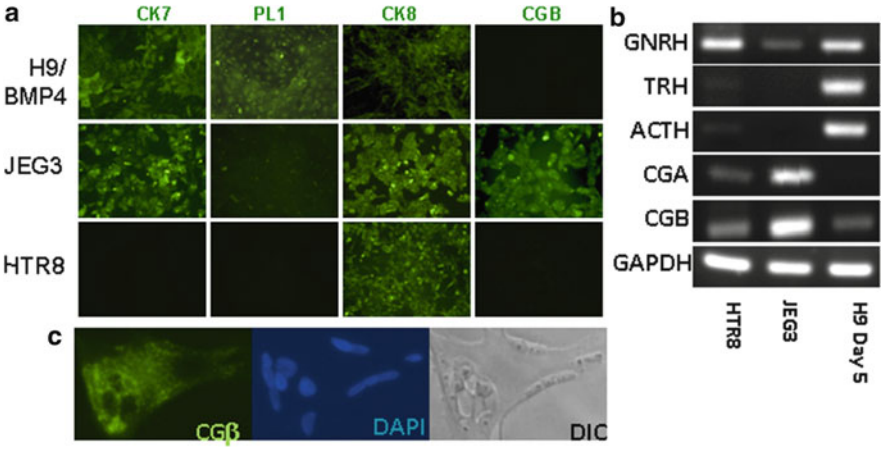

Fig. 17.2 Phenotypes of trophoblasts formed by BMP4 induction of hES cells. (**a**) Fluorescent micrograph showing immunostaining of H9 cells which have undergone 20 ng BMP4 treatment for 5 days. Markers examined include cytokeratins (CK) 7&8, placenta lactogen 1(PL1), and chorionic gonadotropin beta (CGB). Conventionally used trophoblast cell lines JEG3 and HTR8 are analyzed for comparison. (**b**) RT-PCR analysis of gene expression for trophoblast secreting hormones. (**c**) hCG beta expressing syncytia foci in BMP4-treated H9 cells after 10 days in culture

Primary tissues from self-identified African-American patients were obtained through the Cooperative Human Tissue Network, a service of National Cancer Institute. Collected skin tissues were pathologically defined as normal tissues from patients receiving cosmetic dermatology surgeries. Skin tissues were procured and cultured into fibroblasts, which were reprogrammed into iPS cells using retroviral [18] or lentiviral [54] vectors. After selecting in media conditions promoting the outgrowth of human pluripotent stem cells (FGF containing media on mouse embryonic fibroblast feeders), cell colonies with morphologies typical for pluripotent stem cells emerged and were propagated as cell lines (Fig. 17.3), denoted AG for African Genotypes. To date, iPS cell lines from 12 AG patients are established and banked. These newly formed cell lines possess the phenotypes of pluripotent stem cells, including expression of human ES cell markers TRA-1-60, SSEA-4, and pluripotency transcription factors OCT4 and NANOG. Teratomas from some of these cell lines showed evidence of multi-lineage differentiation, indicative of their identities as pluripotent stem cells. Genome wide single nucleotide polymorphism analysis validated normal karyotype of AG1 iPS cells. Most importantly, iPS cells from AG1 showed the identical genotype of its parental fibroblasts, which clustered within African American genotypes, and are distinct from two control ES and iPS cell lines used in our laboratory, iPS5/Daley and H9. This bank of iPS cell lines are still expanding and have wide applications ranging from research of disease mechanisms to high-throughput drug screening for drug and toxicity studies in biotech and pharmaceutical industries.

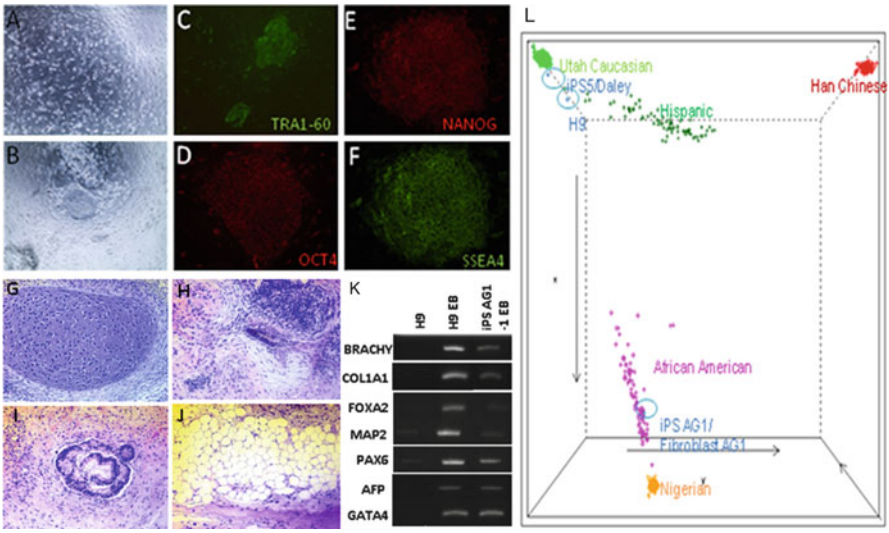

Fig. 17.3 Generation of iPS cell lines with African American genotype. (**a**) Fibroblast culture (**b**) ES-like colony formed after 14 days in culture (**c**–**f**): Expression of pluripotency markers in AG1 iPS line. (**g**–**k**) Teratoma formed from a AG iPS cell line showing structure of (**g**) Cartilage (mesoderm) (**h**) Pigmented epithelium (ectoderm) (**i**) Gut epithelium with mucosal goblets (endoderm) and (**j**) Fat (mesoderm). (**k**) Evidence of multi-lineage differentiation into three lineages from embryoid body formed from iPS AG1: Brachyury and Col 1A1for mesoderm, FOXA2 and MAP2 for ectoderm, PAX6 and AFP for endoderm. (**l**) principle component analysis of genome-wide SNP analysis showing the genotype of iPS line AG1 is identical to its parental fibroblast, which cluster in African American genotype and apart from routinely used control ES (H9) and iPS (iPS5/Daley) cell lines which showed closer association with Caucasian genotypes. iPS cell lines already established from 12 African American patients to date. At least three lines from each patient were banked

Conclusion and Future Direction

There is a clear need for specifically expanding the minority genotype representation in stem cells banks to justify their fair usage and population benefits. Additional efforts should be implemented to proactively solicit tissue donation and creation of HSC, ES, and iPS cell banks for depositing genotypes in excess to the ratio of minority population, in order to compensate for the wide range of genetic variations in the minority population. Since pluripotent stem cells can be grown and expanded indefinitely, they provide tissue sources for transplantation, as well as research models for studying disease mechanism and drug discoveries. With the initial success in creating and characterizing iPS cells for the African American population, more iPS lines derived from individuals affected by racially biased disease conditions, such as preterm birth and low infant birth weight, can accelerate the discovery for factors to early diagnose and treat these conditions.

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Chapter 18
How Can We Bridge the Gap? Role of Insurance Mandate

Kim Thornton, Karenne N. Fru, and Yetunde Ibrahim

Often the disparities in the ways men and women are treated are subtle; there are not these clear barriers that you have to break down

Eleanor Clift

Introduction

The National Institute of Health (NIH) defines health disparities as "differences in the incidence, prevalence, mortality, and burden of diseases and other adverse health conditions that exist amongst specific population groups in the United States" [1].

According to the Institute of Medicine (IOM), health care disparities have been documented in many aspects of medicine such as cardiovascular disease, HIV infection and AIDS, mental health services, cancer care, renal disease and renal transplantation [2]. These disparities are thought to occur as a result of a myriad of factors. However, the end result is the same—minority populations have less access to care through real or perceived barriers and suffer finite adverse health outcomes.

K. Thornton, M.D. (✉)
Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, USA
e-mail: kim.thornton@bostonivf.com

K.N. Fru, M.D., Ph.D.
Reproductive Endocrinology and Infertility, Program in Reproductive and Adult Endocrinology, 10 CRC, Room 1E-3140, 10 Center Drive, MSC 1109, Bethesda, MD 20892-1109, USA
e-mail: fruster@gmail.com

Y. Ibrahim, M.D.
Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215, USA
e-mail: yibrahim@bidmc.harvard.edu

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In a national effort to eliminate health care disparities, Congress passed the Healthcare Research and Quality act of 1999 tasking the Agency for Healthcare Research and Quality (AHRQ) with tracking disparities in health care and providing a National Healthcare Quality report (NHQR) and a National Healthcare Disparity report (NHDR) [3]. In response to this, the AHRQ in a combined effort with the IOM released their first National Healthcare Disparity report in July 2003, which demonstrated that "racial, ethnic and socioeconomic disparities are national problems that affect healthcare at all points in the process, at all sites of care, and for all medical conditions—in fact, disparities are pervasive in our healthcare system" [4]. Our objective is therefore to examine the spectrum of assisted reproductive technologies for areas in which disparities have been shown to exist and assess if efforts to bridge the gap are sufficient. The insurance mandate for the provision of reproductive care with insurance support has been used by some states and offers a forum to begin to address lapses in health care equality.

What epidemiologic data exist, estimate that approximately 12 % of reproductive aged women are infertile and many of these women require assisted reproductive technology to conceive [5]. These data suggest that the rates of primary infertility are similar across all racial groups. However, Hispanic and African American women had slightly higher rates of secondary infertility compared with Caucasian women (12 % and 13 % vs. 9 %) [5]. Further compounding this issue is the overrepresentation of minorities among the lower socioeconomic stratum of society, and the fact that they are less likely in general to report receiving fertility treatment [2]. Finally, there is overwhelming evidence that the three major minority groups, Blacks, Asians and Hispanics, have reduced clinical pregnancy and live birth rates compared to their white counterparts [6–9] undergoing in vitro fertilization. In addition, they are also more likely to give birth to small for gestational age (SGA) infants compared with white women [7] hence a disparity in outcome from treatment.

In an attempt to provide a vision of how to bridge the gap, we will discuss the evolution of in vitro fertilization and provide a historical perspective behind the current arguments for and against the drive to mandate insurance coverage for in vitro fertilization. We will discuss the pain and the politics involved in addressing the issue of inequity in infertility treatment and address how mandates have possibly impacted racial and ethnic disparities in infertility treatment. Finally, we will attempt to provide a glimpse into the future of how current mandates can possibly improve overall health outcomes for minority populations.

Historical Perspective

On July 25 1978, Louise Joy Brown was born in Great Britain as a result of in vitro fertilization (IVF) [10]. Initially, the future of in vitro fertilization was uncertain as a mainstream medical procedure and was considered purely experimental. However, in 2009, data collected from the Center for Disease Control and Prevention from IVF clinics in the USA showed that more than 146,244 IVF cycles were performed annually resulting in 45,870 pregnancies and 60,190 live births [11]. Ever since

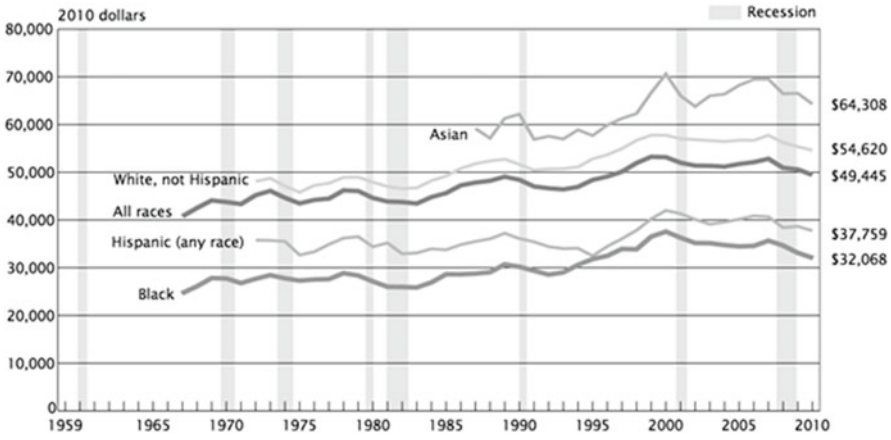

Fig. 18.1 Real Median Household Income by Race and Hispanic Origin: 1967–2010 [14]. *Note*: Median household income data are not available prior to 1967. *Source*: US Census Bureau, current population survey, 1968–2011 Annual social and economic supplements

inception, the growth of assisted reproductive technology (ART) has been rapid and there have been an estimated over three million children born worldwide after treatment with ART [12]. Its evolution has included the utilization of complex ovarian stimulation protocols, intracytoplasmic sperm injection (ICSI), extended embryo culture, cryopreservation of oocytes and embryos, and preimplantation genetic testing. ART is now widely accepted as being effective in treating multiple forms of infertility. The increase in services worldwide should have, in principle, leveled the playing field with regard to dealing with the medical challenges as they affect different ethnicities.

It would be an oversimplification, however, to ignore the role of economics in the evolution of this field. The unbridled expansion of ART services due to great strides in science and technology has come at great economic cost. It is estimated that the average cost of a standard IVF cycle in the US is $12,513 and the average cost per live birth is $41,132 [13]. These costs already comprise a very high percentage of the median income per household [14], and are likely prohibitive to many particularly to those who fall into lower median earning capacity (Fig. 18.1), not to mention those belonging to low-income and uninsured groups.

In a review of selected developed countries and the economic impact of ART, several interesting conclusions were reached [13]. In an effort to better characterize this, the societal perspective was defined as the relative affordability of treatment, which was the cost of a standard IVF cycle as a percentage of gross national income (GNI) per capita as defined by the world bank group (Fig. 18.2) [13]. From a patient perspective, the relative affordability was calculated as the cost of a standard IVF cycle as a percentage of disposable income for a single worker without children, earning 100 % of average earnings (Fig. 18.3) [13]. They concluded that ART is expensive from a patient perspective but not from a societal perspective in their selected developed countries [11].

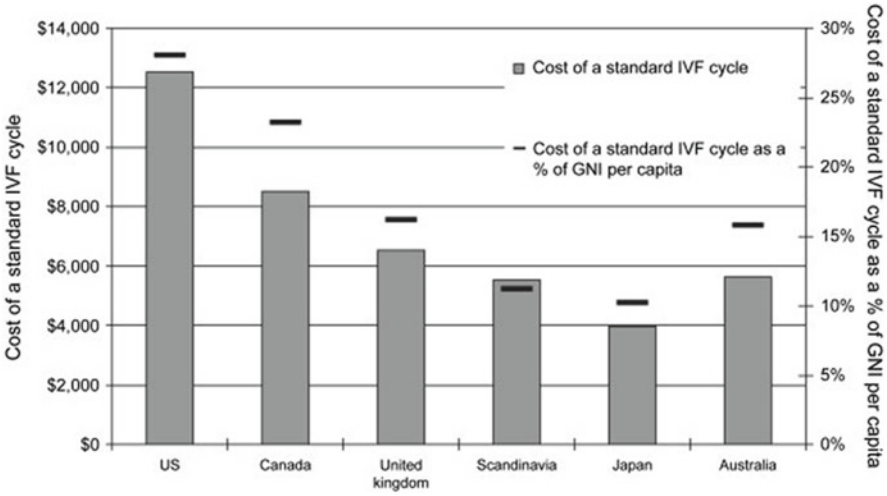

Fig. 18.2 Average cost of a standard fresh IVF cycle, and as a percentage of GNI per capital (USD 2006) [13]. *Note*: GNI per capita sourced from The World Bank Group, World Development Indicators database. *Source*: Chambers, International economic review of ART. Fertil Steril (2009)

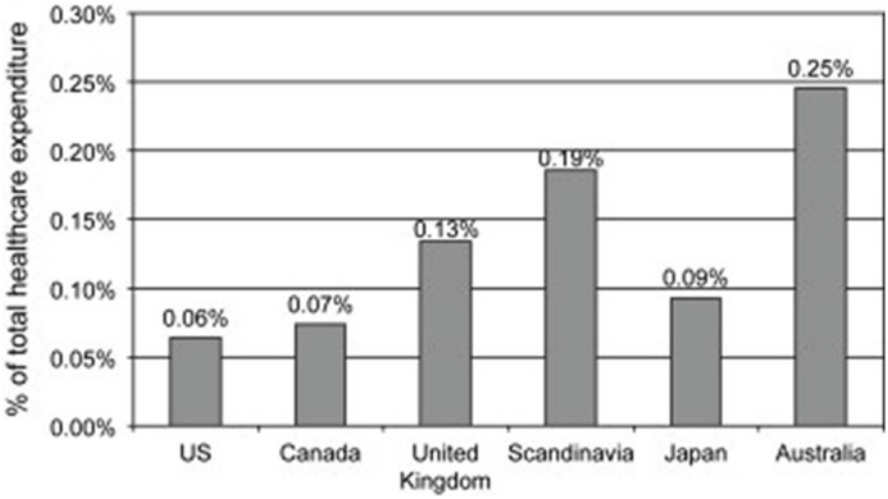

Fig. 18.3 Total ART treatment costs as a percentage of total health care expenditure (USD 2003). *Note*: Total health care expenditure was sourced from The World Bank, World Development Indicators database. *Source*: Chambers. International economic review of ART. Fertil Steril (2009)

The implication of the study above is not surprising. The USA has the most expensive health care system in the world and its higher cost of IVF treatment compared to other countries reviewed is a reflection of this. The cost of IVF is not an economic burden on the society as a whole in developed countries (Fig. 18.3) [13].

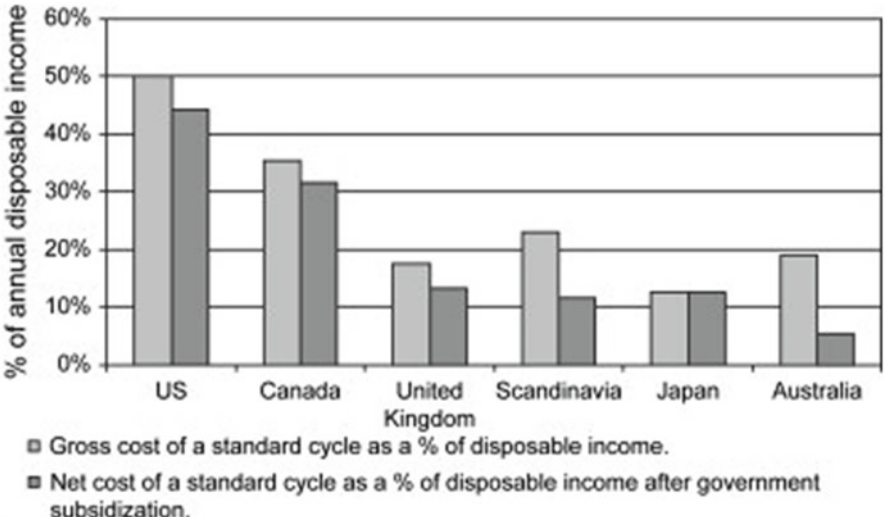

Fig. 18.4 Average cost of a standard IVF cycle as a percentage of annual disposable income (USD 2006) [14]. *Notes*: (1) Annual disposable income is based on a single person at 100 % of average earnings with no dependents. (2) The estimated percentage reduction in the average price of a standard IVF cycle due to government subsidization was 11 % for Canada, 25 % for the UK, 50 % for Scandinavia, 0 % for Japan, and 71 % for Australia. (3) In the USA, there is negligible government subsidization for ART; however, the central role of private insurance in the USA was included in the analysis, reducing the average price of a standard cycle by 12 %. *Source*: Chambers. International economic review of ART. Fertil Steril (2009)

However, when the burden is placed on an individual, there is a disparity in government subsidization of this cost amongst the developed countries [13]. What is most evident from this study is that the US insurance infrastructure places a great financial burden on individuals seeking ART services when compared to other developed countries (Fig. 18.4).

One argument that has been presented as a form of resistance to funding for IVF is that infertility is a social problem and not a medical problem. Hence, treatment via IVF is not medically indicated [15]. The tides may now be turning in popular opinion since the World Health Organization joined The American Society of Reproductive Medicine in classifying "infertility" as a disease in 2008 [16]. Another argument that has been made is that IVF is strictly experimental and that its effectiveness has not been proven [15]. While there are no randomized controlled trials that have been completed to demonstrate in vitro fertilization's effectiveness, data collected over the years by the Center for Disease control and Prevention and the SART database is sufficient to support its use. In spite of this, fertility treatment continues to remain predominantly a privately funded treatment making it not readily accessible to all who need it.

This inequity in infertility treatment was recognized as early as the 1980s when advocates began lobbying their state legislatures to mandate private health

Table 18.1 States with mandated insurance coverage [15]

State	Year law enacted	Mandate to cover/offer to cover	IVF covered
Arkansas	1987[a]	Cover	Yes
California	1989	Offer	No
Connecticut	1989[b]	Offer	Yes
Hawaii	1987	Cover	Yes
Illinois	1991	Cover	Yes
Louisiana	2001	Cover	No
Maryland	1985	Cover	Yes
Massachusetts	1987	Cover	Yes
Montana	1987	Cover	Yes
New Jersey	2001	Cover	Yes
New York	1990[c]	Cover	No
Ohio	1990[d]	Cover	Yes
Rhode Island	1989	Cover	Yes
Texas	1987	Offer	Yes
West Virginia	1977[e]	Cover	No

Source: M. Bitler, L. Schmidt. Utilization of Infertility Treatments: The Effects of Insurance Mandates. Demography (2012)

[a]Some coverage for IVF was first required in 1987. The law was revised in 1991 to set maximum and minimum benefit levels and to establish standards for determining whether a policy or certificate must include coverage

[b]In 2005, Connecticut changed their offer mandate to a cover mandate

[c]In 2002, New York passed a revised law that clarified the 1990 legislation and appropriated $10 million to a pilot project to help pay for IVF for a small number of individuals

[d]The original 1991 law did not specifically exclude IVF. But in 1997, the state superintendent of insurance stated that IVF, GIFT, and ZIFT were not essential for the protection of an individual's health and were therefore not subject to mandated coverage. We code Ohio as an IVF state through 1997

[e]In 2001, the law was amended to mandate that HMO's must cover infertility treatment only as a "preventative service" benefit (thus excluding IVF)

insurance to cover the cost of infertility services [17]. The goal was to affect utilization of infertility services thereby narrowing the gap in access to infertility treatment and ultimately affect health outcomes. The measure has been successful in 15 states which now have laws mandating some form of coverage for infertility treatments as depicted in Table 18.1 [18]. Even while designed to ease the economic burden on individual citizens, it is clear from the coverage patterns that some states have more comprehensive plans that include IVF coverage. Ideally, this would be the universal model for erasing the gaps that occur in access to care secondary to limitations in personal finances (see Table 18.1).

Eliminating the Economic Divide

The burden of cost as a major cause of disparity in access to infertility treatment cannot be overlooked. However, it is not the only barrier to infertility treatment access amongst minority groups. As previously discussed, African American and

Hispanic women fall below the average median income per household and studies have supported the fact that this could limit their ability to afford infertility treatment [19–21]. However, the barriers to access amongst this group may be way beyond the impact of cost alone [6, 19, 22].

The question of what happens when the cost of treatment is eliminated can be closely scrutinized in examining a system such as the federal health care system. Within the US federal system, infertility services are available to active duty service members and their spouses at a lower cost than what is provided by the private sector [6]. The military health care system therefore should be one in which factors such as race and socioeconomic status are not barriers to health care provision. Therefore, it provides a unique opportunity to examine ART use by minority populations in an equal access to care setting. It has been demonstrated in a previous study that racial disparities in obstetric outcomes were reduced in the military because of increased access to care [23]. A similar question was posed with regards to infertility services.

By comparing the racial demographics of the study population at the Walter Reed Army Medical Center (WRAMC), it was established that the proportion of Caucasian and African American women seeking infertility services were representative of the racial distribution of the department of defense population [6, 22]. Hispanic women, on the other hand, were underrepresented and Asian women were disproportionately high [6]. What is most glaring from their findings is that African American women in their study utilized ART services at a rate that was fourfold greater than those in the US ART population [6]. Hispanic women still underutilized ART services even in this low-cost setting [6, 22]. This finding suggests that while decreasing cost may improve access to care in African American women who are in the military, there may be other factors that influence the lower utilization of these services in the general public.

However, a similar conclusion cannot be reached with respect to Hispanic women in the military. Despite the low-cost setting, Hispanic women underutilized infertility services. Education has been suggested to be a potential cause of disparity with the NSFG showing that the highest use of infertility services were among older and educated Caucasian women [5]. For Hispanic women, it may be a matter of values or cultural beliefs that are as yet poorly understood and therefore not properly addressed in order to improve use of such services.

One study identified a difference in approach to infertility treatment between Latino women raised in the USA and those who immigrated as adults. They found that women who were raised in the USA considered health care to be a basic human right and were thus more assertive in seeking it. Women who immigrated were more thankful for the care they received; however, they were less likely to seek out more expansive services [21]. Another qualitative interview study of a low-income immigrant Latino population identified major challenges in providing infertility services to this population. These challenges were related to communication barriers, lack of comprehension in the patient population, accessibility, availability, and affordability [19]. This study recommended that availability of translators and an improvement

in both patient and physician cultural orientation may be necessary to overcome these barriers in access [19].

Interestingly, in the military system, Hispanic patients who were more highly educated and had a good command of the English language still did not utilize ART services [22] so more work may need to be done to understand the limitations.

The Scope of the Mandate

So far, we have targeted three major influences on the disparity in access to infertility services and they include; cost, cultural/family values and possibly education. The federal health care system has suggested that if we provide an equal access to care setting, thereby eliminating economics as a factor, we may improve utilization of infertility services among African American women [7, 22]. Now that we have states mandating comprehensive coverage of infertility treatment, how has that helped to bridge the gap and eliminate the disparity in access to infertility treatment?

Fifteen states currently have mandates regarding insurance coverage for infertility treatment. There are four important factors that should be taken into consideration when examining the mandates. First and foremost is the year that the mandate was enacted. The earliest is documented in 1977 and the most recent, being enacted in 2001. Second is that some states completely exclude IVF from insurance coverage in their mandate. Thirdly, the regulations between states differ in whether they simply "offer" or "cover" ART services. A mandate "to cover" requires that health insurance companies provide coverage of infertility treatment as a benefit included in every policy bought by businesses. A mandate "to offer" requires that insurance companies make available for purchase, a policy that offers coverage of infertility treatments. Finally, the mandates vary in whether they provide universal coverage or are more restrictive in the scope of coverage that is offered [24].

The reason for examining the scope of the mandates across the different states is that it raises several concerns. The exclusion of IVF from insurance coverage suggests that these particular mandates are subjecting the insured to lower technology treatments, which may not be as effective as IVF [24]. Therefore for every patient for whom IVF is the optimal treatment, all payments are out-of-pocket. Similarly, the mandate to simply "offer" ART services compared to that which "covers" can be inadequate especially if one considers that the insurance provider could "offer" the coverage at a very high price to the insured [24]. These circumstances create doubts that such restricted coverage can effectively reduce the financial pressure on the patients who require infertility treatment but have limited access to it. Moreover, restricted mandates may not improve outcomes by subjecting individuals to services, which may not be as effective as IVF. It suggests that universal coverage may be the only effective option when attempting to bridge the gap and eliminate the disparities in infertility treatment.

The Effect of Instituting a Mandate

As predicted by previous studies, mandated health insurance coverage has been associated with overall increased utilization of ART services [24–26]. However, comprehensive insurance mandates play a major role in this increase in utilization while other types of mandates do not have as large of an effect [24]. An analysis performed using National IVF data from 1998 revealed a nearly threefold higher use of IVF services in states with comprehensive coverage [25]. Furthermore, older and more educated women may have increased use of infertility treatment as a result of state mandates [26, 27]. Unfortunately no evidence has been found that the state level mandate has eliminated the racial or ethnic disparities [26, 27].

In a study performed to determine whether patients accessing infertility treatments in a state with comprehensive coverage closely mirrored the demographics of the general population of that state, they found that significant disparities continued to exist [27]. African American women and Hispanic women were still underrepresented. The difference in the Hispanic/Latino women reached statistical

Table 18.2 Demographic characteristic of infertility patients presenting to Brigham and Women's Hospital, Boston, compared with the Massachusetts general population [24]

	Infertility patients ($n=561$)	Massachusetts Census 2000 data	P value
Ethnicity			
Caucasian	454 (80.9)	5,367,286 (84.5)	0.057
African American	25 (4.5)	343,454 (5.4)	0.385
American Indian	3 (0.5)	15,015 (0.2)	0.303
Chinese	24 (4.3)	84,392 (1.3)	<0.001
East Indian	6 (1.1)	43,801 (0.7)	0.397
Hispanic/Latino	22 (3.9)	428,729 (6.8)	0.011
Other Asian/Pacific Islander	27 (4.8)	109,931 (1.7)	<0.001
Education (highest level)[a]			
<High school	0 (0)	342,421 (15.1)	<0.001
High school	36 (6.4)	1,027,337 (45.3)	<0.001
2-year college	49 (8.7)	187,483 (8.3)	0.130
4-year college	198 (35.3)	431,070 (19.0)	<0.001
Master's degree	166 (29.6)	211,040 (9.3)	<0.001
Professional/doctorate degree	112 (20.0)	70,404 (3.1)	<0.001
Annual household income (gross)			
<$50,000	33 (5.9)	1,208,415 (49.4)	<0.001
$50,000–$100,000	189 (33.7)	803,739 (32.9)	0.716
$100,001–$150,000	166 (29.6)	267,300 (10.9)	<0.001
$150,001–$200,000	83 (14.8)	80,640 (3.3)	<0.001
>$200,000	90 (16.0)	84,494 (3.5)	<0.001

Source: Jain. Disparities in access in infertility services. Fertil Steril (2005)
Note: Values in parenthesis are percentages
[a]Massachusetts Census 2000 data represent the female population 25 years and older

significance. They also found that none of the infertility patients had less than a high school diploma and over 60 % of the infertility patients had an annual household income over $100,000 compared to only 17.7 % in the state (Table 18.2) [27]. This study showed that in Massachusetts, where broad insurance coverage for infertility treatments is provided, patients who accessed this service were predominantly Caucasian, highly educated and wealthy. This suggests that despite mandated universal coverage in the state of Massachusetts, access to infertility services may not be equal. Factors that may contribute to this disparity include but are not limited to, lack of education about the availability of treatment options, failure of the individual to seek medical assistance, failure of physician referral for advanced fertility treatment, logistical issues such as transportation and having the ability to take time off from work to pursue treatment It is also possible that a large population of patients was not captured as this study was conducted largely by survey which may have biased the results. In addition, we cannot ignore the fact that despite a broad insurance mandate and employers who are privately insured in Massachusetts, the state offered health plans (Massachusetts Health) for patients who are publicly funded and federal insurance plans are excluded from the requirement to adhere to state mandates (see Table 18.2).

Looking Ahead

It is safe to conclude that the burden of cost is a major influence on the disparity in access to infertility services. This one aspect can be targeted for improvement. What's more, the current mandates that do exist need to be scrutinized to see if they can be successful in narrowing the gap in infertility treatment especially when all services receive insurance support. It becomes more apparent that the reasons for the disparities are likely multifactorial and further studies are required to better understand them with the goal of providing equal and high quality infertility treatments.

From what data exists, it appears that we are yet to see the benefits of comprehensive insurance coverage in bridging the gap in ethnic differences in treatment access and or outcome. It may be that no prospective study thus far has analyzed the effect of mandated comprehensive coverage on newly diagnosed infertile women and the timing of infertility visits. What may also be helpful is looking at a sample of newly diagnosed infertile women who have received treatment in a sample year after a mandate was enacted and compare the racial distribution of patients who access care pre and post mandate. In addition, we know that there are disparities in the causes of infertility among the different racial and ethnic groups and that these differences may be related to differences in outcome [7]. Studies are needed to investigate the effect of mandates on diagnoses of the causes of infertility and their treatment. Of concern is that mandated coverage may be further widening the gap in disparity with the findings that utilization of infertility services is most improved among Caucasian, wealthy and highly educated women. This correlates directly to

the fact that they are most likely to have private insurance and most often seeking treatment due to delayed childbearing. A great push needs to be made to fully educate minority populations of the services that they may benefit from in states with an insurance mandate. Concurrently studies need to establish how willing minority populations are to use ART in order to better provide targeted culturally sensitive services assuming an optimistic future where all states provide comprehensive coverage.

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Chapter 19
Toward a Better Understanding of Racial Disparities in Utilization and Outcomes of IVF Treatment in the USA

David B. Seifer, Fady I. Sharara, and Tarun Jain

Introduction

Infertility is a major public health problem in the USA, affecting millions of women. Over the past three decades, the acceptance, advancement, and growth of assisted reproductive technologies (ART) to treat infertility has been significant [1, 2]. Despite such advances, and unlike other disciplines in medicine, racial and ethnic disparities in infertility have attracted only limited attention. Since the initial report of racial differences in ART outcomes [3], there has been a mounting body of evidence identifying racial disparities related to ART access and outcomes in the USA [4].

Survey data from the National Center of Health Statistics shows that infertility affects women of all race, ethnicities, and level of education, with Black (10.5 %), Hispanic (7 %), and other minority women (13.6 %) reporting infertility more often than White women [5]. Unfortunately, those most likely to be infertile are those least likely to seek medical help. There is evidence that infertility is increasing among women of color, particularly black women, while concomitantly decreasing among white women [6]. This is particularly concerning since the utilization and outcomes of ART treatment are generally less favorable for Black, Hispanic, and

D.B. Seifer, M.D. (✉)
Genesis Fertility and Reproductive Medicine, Maimonides Medical Center, 1355 84th Street, Brooklyn, NY 11228, USA

New York University School of Medicine, New York, NY, USA
e-mail: drseifer@genesisfertility.com

F.I. Sharara, M.D., F.A.C.O.G
Virginia Center for Reproductive Medicine, 11150 Sunset Hills Road, Suite 100, Reston, VA 20190, USA

Department of Obstetrics and Gynecology, George Washington University, Washington, DC, USA

T. Jain, M.D.
IVF, 28375 Davis Parkway, Warrenville, IL 60555, USA

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Asian women compared to White women [7–9]. This situation requires attention as such disparities appear to be widening over time [8].

Utilization of fertility treatments differ between Black, Hispanic, Asian and White women. Furthermore, ART is expensive (which may be cost-prohibitive to many families). State-mandated insurance coverage for ART was initially thought to be the solution to this financial barrier [10]. However, even in states such as Massachusetts and Illinois which have had mandatory insurance coverage for IVF since 1987 and 1991 respectively, there remain marked differences in utilization based on race and ethnicity and possible socioeconomic status [11–13]. Even in states with a mandate, couples who seek medical care for infertility tend to be highly educated, of upper socioeconomic status, and white [11]. To date, there is no evidence that insurance mandates improve utilization among women from non-white ethnic groups [10, 12, 13]. In another system of equal-access-to-care, namely, the Department of Defense (DoD) ART program at Walter Reed Army Medical Center, Hispanic women had low use of infertility services compared to white and black women [14]. Even those Hispanic women who were more highly educated and who spoke English still did not use ART services to the same extent as black women. A more recent publication from 3 programs in the DoD network showed similar findings, and noted that improved access may not translate into improved outcomes in some ethnic groups [15]. Thus, mandated coverage may be necessary to allow affordability and therefore access, but it is not sufficient to result in equal utilization. Racial disparities continue to exist despite the availability of mandated coverage, and therefore access to ART services may not be primarily economic in origin, but other factors such as social and cultural influences may represent significant barriers to care. This begs the question: why do those with the greatest need for infertility services not seek them out even when they are available as in insurance-mandated states?

More subtle and yet to be defined factors impact this issue. Cultural factors and value systems are suspected to influence women's and couple's behaviors and choices in pursuing medical care. Several studies have found that Black and Hispanic women with infertility wait more than a year longer to seek care compared to White women [3, 7, 11, 16]. More recent data, however, suggests a more complex situation [16, 17]. Survey data from an infertility population in Illinois found that Black and Hispanic women found it more difficult to find a physician with whom they felt comfortable, to get an appointment with a physician, and to take time off from work [16]. Interestingly, compared to White women, Hispanic women were four times as likely to have been referred to a fertility clinic by a friend or family member, whereas Black women were five times more likely to be self-referred. Furthermore, Black women were three to four times more likely to be concerned about the social stigma of infertility, "failure" to conceive, using science to conceive, and disappointing their spouse. Compared to white women, Black and Hispanic women were more concerned about their friends and family finding out about their infertility, treatment side effects, and poor pregnancy outcomes such as multiple births, miscarriages, ectopic pregnancies, and birth defects.

Differences in treatment outcomes recapitulate what is noted in disparities in utilization but have additional factors that may be better defined and may allow for more focused approaches. These factors include biological factors that contribute to

differences between women of different races and ethnicities [7–9, 18]. There is also a poor record of race and ethnicity being reported to national registries, with only about 52–60 % of IVF cycles having the race/ethnicity field completed [7, 8]. A recent survey noted that >35 % of ART programs reporting to SART have incomplete/missing ethnicities [19], which we find easily correctable. We believe this underreporting of race and ethnicity is bound to improve as there is increasing awareness regarding the impact that race/ethnicity has on utilization and outcomes for fertility treatment.

The importance of race in IVF success is understood by comparing race to age, an accepted prognostic metric of outcome. It is highlighted in one large national registry study that being 35–37 years old compared to being younger than 35 years old increases risk of not achieving a live birth by the same relative risk as black race, i.e., an adjusted RR of 1.21 for age 35–37 years old and an adjusted RR of 1.24 for black women [7]. Black women also have more pathology that relates to less favorable outcomes, such as having more tubal (i.e., hydrosalpinx) and uterine (i.e., leiomyomas) pathology. Furthermore, studies suggest that they tend to be older, have a higher BMI, and have approximately 25 % less ovarian reserve than their white counterparts matched for age [20, 21].

Given the above preliminary data, it seems that there are numerous cultural and social barriers confronting many ethnic minority populations, in addition to perceived financial constraints. Education of whole communities and increased cultural competency on part of the health care system are likely to be part of the solution. Possible strategies to improve outcomes may include more aggressive treatment of pathology and education of communities regarding causes of infertility, with an emphasis upon seeking care early. Educating community members that seeking fertility care should not be embarrassing and not associated with a social stigma will require thoughtful effort.

Future studies need to consider some of the following avenues of inquiry if we are to better understand the undefined parameters that impact on this crucial topic: What are the challenges of reporting accurate race/ethnicity of patients presenting for infertility care? Do we need to address the issues of self-reporting versus sight recognition by health care provider versus strict CDC definitions? How do we address confounders including socioeconomic and cultural status which are difficult and challenging to examine and may serve as a surrogate or proxy for class? Do partner's influence and exacerbate the impact of cultural and social reasons to delay medical assessment and treatment of their female partner and if so, why? Are there other race-related biologic differences to account for poorer outcomes? For example, why do ethnic minorities also have poorer obstetric outcomes?

Acknowledging there are many unanswered questions remaining ahead of us to investigate [22], we propose a preliminary model (Fig. 19.1) that may begin to assimilate and integrate some of the concepts that impact upon one another. We believe that many of these factors in Fig. 19.1 may result in a systemic bias. These biases lead to a delay in treatment, and ultimately to disparities in utilization and outcomes of ART between white women and women of color in the USA. However, as noted before, improved access may not necessarily translate into improved outcome. Some possible solutions towards improving access, utilization, and outcome

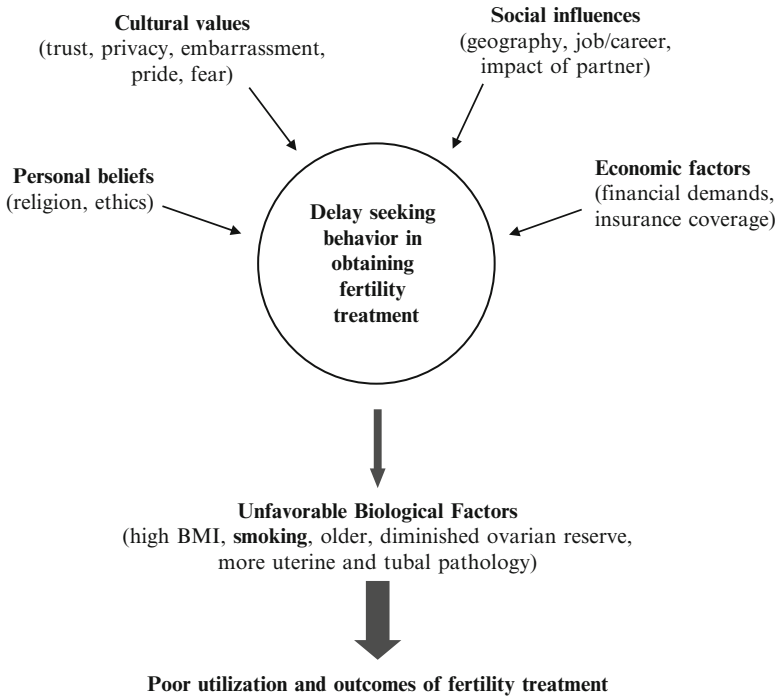

Fig. 19.1 Disparities in ART (DART) Hypothesis for explaining racial disparities in utilization and outcomes of ART in the USA

Table 19.1 Suggested solutions for moving toward improving racial disparities in access and utilization of ART

Problem	Suggested solution
Incomplete/missing race/ethnicity data in SART/CORS database	Encouragement of full compliance of SART clinics to record race/ethnicity into ART databases
Cultural and social barriers to infertility treatment	Increase funding from public and private agencies for community-based programs to access and educate women of color and their partners regarding their perceptions of seeking infertility care and its treatment
Insufficient public awareness and support for ethnic disparities in infertility	Raising the priority of private and public funding agencies to raise awareness and support more research directed at access and utilization of ART
Inadequate research funding into ethnic disparities in infertility	Funding research studies addressing solutions to identified challenges for women of color seeking infertility care and its treatment
Inferior ART outcome in ethnic minorities	Early identification and correction of factors that may cause worsening outcomes in ethnic minorities

of ART for ethnic minorities are summarized in Table 19.1. Future studies on how to improve access to care in minorities, and more importantly, improve outcomes, are sorely needed.

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