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The latest advancements in fertility treatment include infertility's wide-scale validation as a high-burden disease, a reduction in multiple birth rates, and the challenging emergence of gene-editing technology

In this Update, we discuss several aspects of infertility and emerging technologic advances in treatment. We review an important infertility fact sheet recently issued by the World Health Organization (WHO) that provides a succinct overview of infertility causes, the rights of infertility patients, treatment challenges, and

advocacy efforts. In addition, we discuss what the infertility literature reveals about reducing multiple birth rates and the technologic, financial, and social factors involved. Finally, we look at the molecular progress made in germline-editing technology and the myriad complications involved in its potential future translation to clinical phenotyping.

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WHO recognizes the burden of infertility and addresses fertility care needs

World Health Organization (WHO). *Infertility fact sheet*. September 14, 2020. <https://www.who.int/news-room/fact-sheets/detail/infertility>. Accessed January 24, 2021.

why infertility is important, challenges, and the WHO response.

Factors in infertility

Infertility is caused by different factors in women and men, yet sometimes it is unexplained, and its relative importance can vary from country to country. For women, tubal disorders (for example, postinfectious), uterine problems (fibroids, congenital), endometriosis, ovarian disorders (polycystic ovary syndrome, ovulation disorders), and



WHAT THIS EVIDENCE MEANS FOR PRACTICE

Every person has the right to infertility and fertility care as endorsed by the recent WHO infertility fact sheet. To address this high-burden disease, all women's health care clinicians should be aware of, equitably diagnose and treat, refer as necessary, and advocate for infertile individuals.

endocrine imbalances are the most common factors.

For men, causes of infertility include obstruction of the reproductive tract (as after injuries or infection); hormonal disorders in the hypothalamus, pituitary, and/or testicles (for example, low testosterone); testicular failure to produce sperm (such as after cancer treatment); and abnormal sperm function and quality (low count, motility, or morphology).

Environmental and lifestyle factors—including smoking, obesity, alcohol, or toxins—can affect fertility.

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Addressing infertility is an important part of realizing the right of individuals and couples to found a family

Recognizing all individuals' fertility rights

The WHO infertility fact sheet makes strong statements, recognizing that individuals and couples have the right to decide the number, timing, and spacing of their children. Addressing infertility is therefore an important part of realizing the right of individuals and couples to found a family. This includes heterosexual couples, same-sex partners, older persons, individuals not in sexual relationships who might require infertility management and fertility care services, and notably marginalized populations.

Addressing infertility also can help mitigate gender inequality, which has significant negative social impacts on the lives of infertile individuals, especially women. Fertility education is important to reduce the fear of infertility and contraception use in those wanting pregnancy in the future.

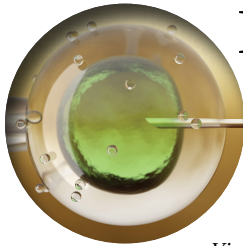
In most countries the biggest challenges are availability, access, and quality of interventions to address infertility. This includes the United States, where only 1 in 4 individuals receive the fertility care they need. Lack of prioritization, ineffective public health strategies, inadequate funding, and costs are barriers. Health policies need to recognize that infertility is a disease that often can be prevented, thereby reducing future costs. Comprehensive awareness and education programs, laws and policies that regulate and ensure access and the human rights of all involved, are essential.

Advocacy efforts

To address infertility and fertility care, the WHO is committed to:

- collaborate with partners on epidemiologic and etiologic research
- facilitate policy dialogue globally to frame infertility within a legal and policy framework
- support generation of data on the burden of infertility
- develop guidelines
- produce other documents of standards
- collaborate with all stakeholders to strengthen political commitment and health system capacity, and
- provide country-level technical support to develop or strengthen policies and services.

For your practice, this means that infertility is recognized as a disease that should receive its appropriate share of health care resources. Infertility and fertility care are the right of every individual according to their desires to found a family. Besides providing the best care you can to all your patients, including referring them when necessary, all health care clinicians should advocate on behalf of their patients to payors, policy makers, and the public the need to provide equitable laws, resources, and funding for infertility and fertility care.



Lessons learned in reducing multiple pregnancy rates in infertility treatment

Views and reviews section. Fertil Steril. 2020;114:671-672; 673-679; 680-689; 690-714; 715-721.

In the October 2020 issue of *Fertility and Sterility*, the Views and Reviews section included 5 articles on avoiding multiple live birth rates (LBRs) in assisted reproductive technologies (ART).¹⁻⁵ International experts provided a comprehensive review of global multiple LBRs and their associated negative impact on maternal and perinatal outcomes, reasons for global variability, strategies to reduce multiples, single embryo transfer, and implications of funding and reporting. These international comparisons and recommendations are helpful and applicable to infertility care in the United States.³

elective single embryo transfer (eSET). However, numerous factors affect the decision to perform eSET or not, and this ideal is far from being achieved. Older women, those with longer duration of infertility and/or failed treatment, often feel a time pressure and want to transfer more embryos. Of course, biologically this is reasonable because the number and quality of their embryos is lower. While attempts have been made to assess embryo quality with preimplantation genetic testing for aneuploidy, evidence that this increases the LBR is controversial except possibly in women aged 35 to 38 years. This is especially true when the cumulative LBR, that is, the number of live births after transfer of all embryos from an egg retrieval cycle, is the measured outcome.

The major factor that determines the frequency of eSET is financial. Affordability is the out-of-pocket cost (after insurance or other subsidy) as a percentage of disposable income, and it is the most important factor that determines whether eSET is performed. Less affordable treatment creates a financial incentive to transfer more than one embryo to maximize the pregnancy rates in fewer cycles.⁵ Other factors include whether the effectiveness of treatment, that is, LBR, is emphasized over safety, that is, MBR. In the United States, the Society for Assisted Reproductive Technology now reports cumulative LBR, singleton and multiple LBR, and preterm births as outcomes, thereby increasing the emphasis on eSET.

Sociologic, cultural, and religious factors also can affect the frequency of eSET. Even within the United States, great variation exists in values and beliefs regarding infertility treatment. It can be challenging to determine who makes decisions: the patient alone, the physician, the payor, professional guidelines, or laws. In many countries, including the United States, it is an amalgam of these.

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The rise of multiple birth rates

During the first decade of in vitro fertilization (IVF), live birth rates were low, increasing to 14% in 1990. Multiple embryos needed to be transferred so that even these LBRs could be obtained. In the 1990s, however, laboratory technology improved rapidly, with increased implantation rates and subsequent rapid increases in LBR, but also with increased multiple birth rates (MBRs).

In the United States, clinic-specific reporting helped create competition among clinics for the best LBRs, and this led to MBRs of 30% and higher. Numerous studies documented the associated significantly increased morbidity and mortality of both mothers and babies. Similar situations occurred in many other countries while some, especially Nordic nations, Australia, New Zealand, and Japan, had twin rates of less than 10% or even 5% since the early 2000s. So why the difference?

The higher MBR is due largely to the transfer of more than one embryo. The immediate solution is therefore always to perform

Setting new goals

If the goal is to reduce the MBR, what should that rate be? In the past few years, the MBR in the United States has been reduced to approximately 10%. It is reasonable now to set a goal of 5% in the next several years. To do this, we can learn from countries that have been successful. The United States already has very high-quality clinical and laboratory services, knowledgeable physicians, and a reasonable regulatory environment. Improved technology, specifically embryo selection for transfer, and focus on adherence to established embryo transfer guidelines could help.

Many would argue that eSET essentially should be performed always in women younger than age 40 and in all women of any age with a known euploid embryo. The major problem that drives multiples is the lack of affordability, which can be addressed by increased subsidies from payors. Increased subsidies can result from legislative mandates or societal pressures on employers, either of

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The multiple birth rate in ART has been reduced to 10% in the United States through an increased understanding of the complex factors that affect embryo transfer practices globally. Further progress will depend primarily on increased subsidies that make ART more affordable.

which could be associated with requirements for eSET and/or reduced MBRs.

In your practice, you can now reassure your infertility patients that cumulative LBRs are excellent in the United States and that the risk of multiple pregnancy has been reduced dramatically. This should encourage more patients to accept and take advantage of this successful technology that has resulted in the birth of millions of babies globally. Further reduction of the MBR to 5% should be possible within a few years through education and advocacy by women's health care clinicians that results in increased subsidies and more affordable IVF.

Genetics and ART: Selection versus correction



FAST TRACK

Molecular progress has not been accompanied by an equivalent clinical progress because a defined and predictable clinical phenotype often cannot be attributed to a detected molecular genotype

Adashi EY, Cohen IG. The case for remedial germline editing—the long-term view. *JAMA*. 2020;323:1762-1763.

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Following the completion of the Human Genome Project in 2003 and major technologic advancements in the subsequent years, the field of human genetics became the focal point of convergence for several distinct but interrelated disciplines: bioinformatics, computational biology, and sequencing technologies. As the result, individual human genomes can now be sequenced at a single base pair level, and with higher fidelity, at a fraction of the original cost and at a much faster speed.

This molecular progress, however, has not been accompanied by an equivalent clinical progress, because in a significant number of cases a defined and predictable clinical phenotype cannot be attributed to a detected

molecular genotype. This has resulted in an overabundance of variants of uncertain significance. Variable expressivity, incomplete penetrance, epigenetics, mosaicism, and the polygenic nature of many human traits further complicate reliable interpretation and prognostication of the colossal amount of molecular genetic data that are being generated by the above-mentioned technologic advances.

Considering these limitations, at this juncture it is crucial to acknowledge that any attempts to prematurely commercialize these preclinical and research studies (such as polygenic risk scores for embryos) are perilous and have the potential to cause significant harm in terms of unnecessary stress and anxiety for intended parents as well as the potential for yet-unmapped societal and legal implications.

However, it is just a matter of time until more accurate clinical phenotyping catches up with molecular genotyping. As we get closer to this next historic milestone, precision medicine in the postnatal life (with regard to both diagnostics and therapeutics) and preimplantation genetic testing (PGT) at the prenatal stage for a much wider spectrum of conditions—including both monogenic and polygenic traits—may indeed become a reality.

The potential of germline editing

Specifically regarding PGT (which requires IVF), it is important to recognize that due to the limited and nonrenewable endowment of human oocytes (ovarian reserve), combined with the detrimental impact of advancing age on the quality of the remaining cohort as manifested by a higher risk of aneuploidy, the current clinical practice of trying to “select” a nonaffected embryo can be very inefficient. As a result, the intended parents pursuing such treatments may need to undergo multiple cycles of ovarian stimulation and oocyte retrieval.

A potential solution for genes associated with known diseases is the prospect of remedial germline editing by CRISPR-Cas9 technology or its future descendants. This would

take advantage of the existing embryos to try to “correct” the defective gene instead of trying to “select” a normal embryo. These technologies are still in the early stages of development and are remotely distant from clinical applications. On the other hand, although germline gene editing, if actualized, would be a monumental breakthrough in the history of genetics and medicine, we must be cognizant of its serious legal, societal, and ethical ramifications, which are currently unknown. Furthermore, even at the biologic and technical level, the technology still is not advanced enough to reliably rule out off-target modifications, and the unintended clinical consequences of the on-target corrections have not been studied either.

Regulation of genetic modifications

Due to these myriad concerns and the lack of an existing appropriate regulatory framework and oversight for such interventions, current US law (since December 2015, through provisions in annual federal appropriations laws passed by Congress and renewed annually thereafter) bars the US Food and Drug Administration from considering any clinical trial application “in which a human embryo is intentionally created or modified to include a heritable genetic modification.” Notably, this moratorium also prohibits mitochondrial replacement technology (MRT), which is a less controversial and relatively better-studied innovation.

Mitochondrial genetic disorders caused by the mutations in mitochondrial DNA (versus nuclear DNA) are amenable to a specific treatment strategy aimed at substituting the defective maternal mitochondrial genome with the mitochondrial genome of an unaffected donor oocyte. This can be achieved via either pronuclear transfer, which involves isolation and transfer of the male and female pronuclei from an affected embryo to an enucleated normal donor embryo, or maternal spindle transfer, which involves isolation and transfer of the metaphase II spindle complex of an affected oocyte to an

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enucleated disease-free donor egg. It is noteworthy that in 2015 in the United Kingdom, Parliament expanded the definition of “permitted eggs and embryos” to include those “where unhealthy mitochondrial DNA is replaced by healthy mitochondrial DNA from a donor.” This thereby allows the UK Human Fertilisation and Embryology Authority to formally direct and oversee clinical trials in MRT.

Summing up

Although the future of assisted human reproduction cannot be clearly outlined at this time, it is likely to be radically different from the current state given these emerging applications at the intersection of ART and diagnostic and therapeutic genetics. To ensure

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The field of human genetics has already transformed medicine. However, the convergence of the interrelated disciplines of bioinformatics, computational biology, sequencing technologies, and CRISPR–Cas9 technology is creating incredible new advances that will bring great benefits but also major societal challenges.

that exploring this uncharted territory will ultimately be in the interest of humankind and civilization, proper regulatory oversight—after careful consideration of all ethical, societal, and legal implications—needs to be developed for all preclinical and clinical research in this field. Participatory public engagement must be an integrated part of this process. ●

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