FERTILITY

Too many women and men around the world are affected by infertility. Unfortunately, access to assisted reproduction therapies (ART) when necessary is not balanced. These experts address how natural fertility can be optimized and why efforts to address ART access barriers are needed.

›› G. David Adamson, MD
Dr. Adamson is Founder/CEO of Advanced Reproductive Care, Inc; Adjunct Clinical Professor at Stanford University; and Associate Clinical Professor at the University of California, San Francisco. He is also Medical Director, Assisted Reproductive Technologies Program, Palo Alto Medical Foundation Fertility Physicians of Northern California in Palo Alto and San Jose, California.

›› Mary E. Abusief, MD
Dr. Abusief is a Board-Certified Specialist in Reproductive Endocrinology and Infertility and Chair, Department of Reproductive Endocrine Fertility at Palo Alto Medical Foundation Fertility Physicians of Northern California.

Dr. Adamson reports that he is a consultant to Ferring and has other current financial arrangements with Advanced Reproductive Care, Inc (ARC Fertility) and Ziva. Dr. Abusief reports no financial relationships relevant to this article.

Patients seeking fertility care commonly ask the physician for advice regarding ways to optimize their conception attempts. While evidence from randomized controlled trials is not available, data from observational studies provide parameters that can inform patient decision making. Knowledge about the fertility window, the decline in fecundability with age, and lifestyle practices that promote conception may be helpful to clinicians and aid in their ability to guide patients.

For those patients who will not achieve conception naturally, assisted reproductive technologies (ART) offer a promising alternative. ART options have improved greatly in effectiveness and safety since Louise Brown was born in 1978. More than 5 million babies have been born globally.[1] However, even though the United States is wealthy, access to in vitro fertilization (IVF) is poor relative to many other countries, with not more than 1 in 3 people needing IVF actually receiving the treatment. Understanding the international experience enables physicians to take actions that help increase access for their patients who need IVF.

In this article we not only address ways in which your patients can optimize their natural fertility but also examine this country's ability to offer ART options when they are needed. Without such examination, fundamental changes in societal attitudes toward infertility and payor attitudes toward reproductive care will not occur, and it is these changes, among others, that can move this country to more equitable ART access.

IN THIS ARTICLE

CONTINUED ON PAGE 26

CONTINUED FROM PAGE 25

Optimizing natural fertility

The fertile window within a woman's menstrual cycle lasts approximately 6 days and includes the day of ovulation and the 5 days preceding ovulation. Conception rates are highest when intercourse takes place on the day of ovulation or within the 1 to 2 days preceding ovulation. Basal body temperature, changes in cervical mucus, and at-home kits designed to measure urinary luteinizing hormone (LH) can be used to predict ovulation and time intercourse appropriately.[2–4]

Factors affecting the probability of conception

Frequency of intercourse impacts the chance of conception. More frequent intercourse results in a higher chance for conception: Daily intercourse results in a 37% chance for conception within a cycle, and intercourse every other day results in a 33% chance for conception. Couples who have intercourse once per week have a 15% chance for conception.[4]

Frequent ejaculation is not associated with a decrease in male fertility. Results of a study of almost 10,000 semen specimens revealed that, in men with normal semen quality, sperm counts and motility remained normal even with daily ejaculations.[5] While abstinence intervals as short as 2 days are associated with normal sperm counts, longer abstinence intervals of 10 days or more may be associated with decreasing semen parameters. It is unclear, however, if this translates into impaired sperm function.[6,7]

Neither coital position nor postcoital practices (such as a woman remaining supine after intercourse) affect the chance of conception.

Lubricants that do not impair sperm motility, such as canola oil, mineral oil, and hydroxyethylcellulose-base (Pre-Seed) may be helpful for some couples.[8] Sexual dysfunction can be a cause of infertility or subfertility. Similarly, stress over lack of conception can impair sexual function; therefore, it is important to ask patients if they experience pain or difficulty with intercourse.

Fecundability refers to the probability of achieving pregnancy within a single menstrual cycle. Studies measuring fecundability reveal that 80% of couples attempting conception will achieve pregnancy within 6 months of attempting and 85% within 12 months. Another 7% to 8% will achieve conception over the next 3 years. The remaining couples will have a very low chance of achieving spontaneous conception.[9]

The probability of conception is inversely related to female age. Fecundability is decreased by approximately 50% in women who are in their late 30s compared with women in their early 20s.[10,11] The chance for conception significantly decreases for women after age 35 and, while the effects of advancing age are most striking for women, some decline in fertility also occurs in men, especially after age 50.[11,12]

The effects of diet and consumption habits

Folic acid supplementation, at least 400 μg per day, is recommended for all women attempting conception and is associated with a decreased risk of neural tube defects.[13] Obese women and thin women have decreased rates of fertility. While healthy dietary practices aimed at normalizing body mass index (BMI) to normal levels may improve reproductive outcomes, there is little evidence that a particular dietary practice or regimen improves conception rates.[8] Data are also lacking on the use of fertility supplements to improve ovarian reserve or aid in conception.

Smoking is unequivocally detrimental to female fertility. Women who smoke have been found to have increased rates of infertility and increased risk for miscarriage.[14–16] Menopause has been found to occur 1 to 4 years earlier in smoking versus nonsmoking women.[17,18]

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A lower or higher than normal BMI, smoking, and high alcohol and caffeine consumption can adversely affect fertility

The effect of alcohol on female fertility has not been clearly established, with some studies showing an adverse impact and others showing a possible favorable effect. Based on the available evidence, higher levels of alcohol consumption (>2 drinks/day with 1 drink = 10 g of ethanol) are probably best avoided when attempting conception, but more moderate consumption may be acceptable.[8] No safe level of alcohol consumption has been established during pregnancy, and alcohol consumption should be completely avoided during pregnancy.

Caffeine consumption at high levels (>500 mg or 5 cups/day) is associated with impaired fertility. While caffeine intake over 200 mg to 300 mg per day (2–3 cups per day) has been associated with a higher risk for miscarriage, moderate consumption (1–2 cups of coffee per day) has not been associated with a decrease in fertility or with adverse pregnancy outcomes.[8,19–22]

While the public has access to volumes of information on the Internet, it is important for patients to be educated through accurate information that is best found from professional sources, such as http://www.reproductivefacts.org, offered by the American Society for Reproductive Medicine (ASRM).

Increasing access to assisted reproductive technologies

Besides per capita income, the major factor affecting access to ART is the role of public funding of health care. However, effectiveness also matters. Globally, only 1 cycle in 5 results in a live birth.[23] In the United States, 1 in 3 cycles result in a live birth—even with a population of older patients than many other countries. For US patients aged 37 or younger, approximately 2 in 5 who undergo 1 ART cycle will have a baby.[23] However, these results also demonstrate that, even with the highest live-birth rates in the world, a large majority of US patients will require more than 1 cycle of IVF. Therefore, access remains critical to enable not only the first cycle but also more than 1 cycle to be attempted.

One of the reasons for the higher US pregnancy rate is that we, historically, have replaced more embryos than other countries. This is not the only, or even the major, reason for higher pregnancy rates; however, it is the major reason for a higher *multiple* pregnancy rate.

Physician and patient education programs to address this problem have resulted in fewer embryos being replaced, and a slight reduction in the multiple pregnancy rates, but much further progress is needed (**FIGURE 1,** page 28).[23]

The crux of the problem: Competition for a positive result

Importantly, the major reason more embryos are replaced in the United States is that poorer access is related to a higher number of embryos replaced in order to try to get patients pregnant with fewer cycles. This pressure is created both by patients and by physicians—especially because the United States is one of the few countries that mandates the publication of clinic-specific pregnancy rates.

This government mandate changes clinical practice toward maximizing pregnancy rates because IVF clinics cannot afford, for competitive reasons, to have lower pregnancy rates than other clinics. This is unfortunate, because it has been shown that when elective single embryo transfer (eSET) is implemented, pregnancy rates do not decrease significantly but, in fact, multiple pregnancy rates drop dramatically (**FIGURE 2,** page 28).[23]

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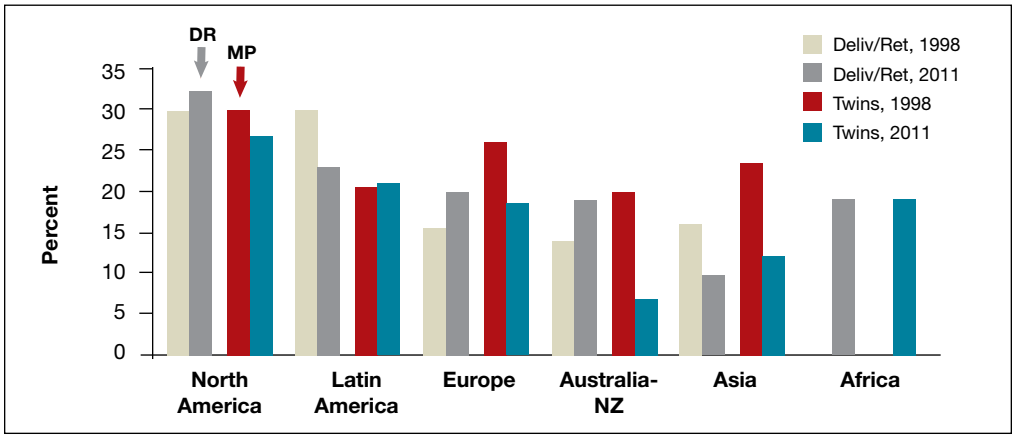
Competition within the marketplace can result in IVF clinics attempting to maximize pregnancy rates by practicing multiple, versus single, embryo transfer

CONTINUED ON PAGE 28

CONTINUED FROM PAGE 27

FIGURE 1. Delivery rate (fresh) and twin pregnancies per region, 1998–2011[23]



Abbreviations: Deliv/Ret, delivery per retrieval; DR, delivery rate; MP, multiple pregnancy rate.

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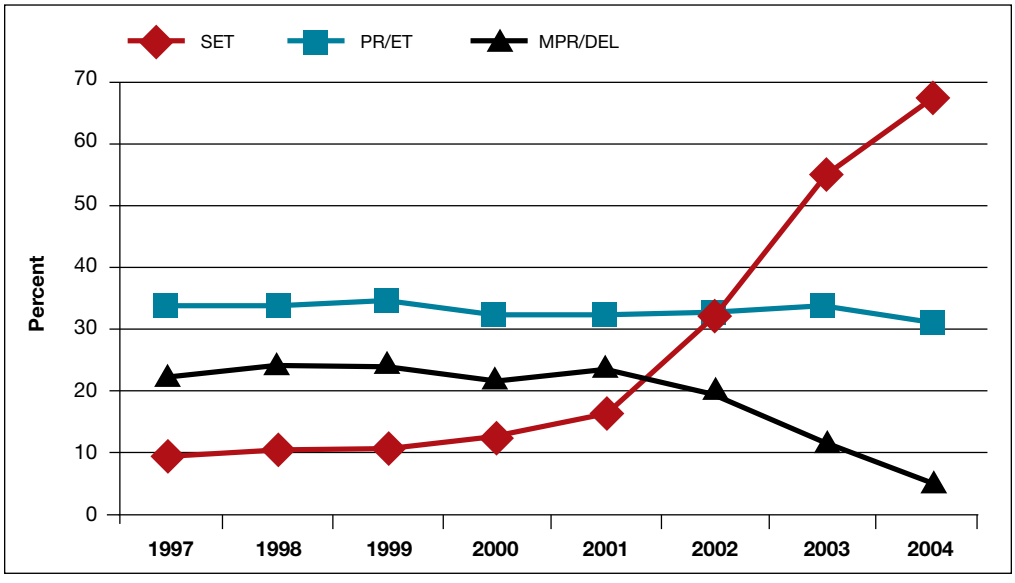
IVF costs in the United States are among the least affordable in the world

The cost of IVF obviously impacts access, but the issue is more complex than it appears. IVF in the United States costs about 30% to 50% more than in other countries. But general US health care costs are also relatively even higher than that, and IVF is not expensive relative to other medical services.[24,25] Nevertheless, compared with other countries, the average US cost of a standard fresh IVF cycle is the highest as a percentage of gross national income per capita, at about 25%.[26] However, because of higher live birth rates, the cost-effectiveness of ART (which is the cost per live birth) in the United States is not unfavorable relative to other countries.[26]

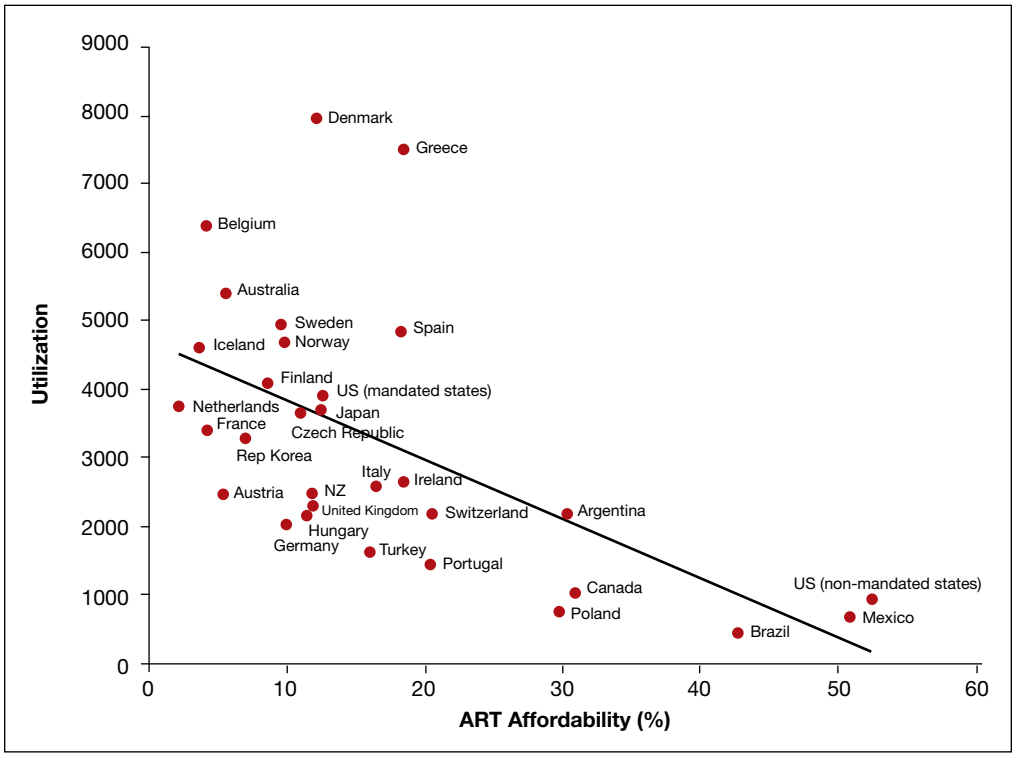
What matters to patients, however, is affordability, which is the net cost to patients after all subsidies relative to disposable income. US out-of-pocket costs for IVF as a percent of annual disposable income make

FIGURE 2. Elective single embryo transfer: The Swedish experience IVF/ICSI, 1997–2004[23]



Abbreviations: ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; MPR/DEL, multiple pregnancy rate per delivery; PR/ET, pregnancy rate per embryo transfer; SET, single-embryo transfer.

FIGURE 3. Assisted reproductive technology affordability and utilization, 2006/2007[28]



ART affordability is expressed as the net cost of a fresh IVF cycle as a percentage of annual disposable income of a single person earning 100% of average wages with no dependent children. Disposable income is calculated according to Organisation for Economic Co-operation and Development (OECD) methods. Utilization is expressed as the number of fresh autologous cycles per 1 million women of reproductive age (15–49 years).[28]

IVF costs in the United States among the least affordable in the world. Affordability predicts utilization, as well as number of embryos transferred.[24] It is clear that less affordable IVF cycles result in more embryos being transferred. Broad insurance mandates result in large increases in treatment access but also significantly less aggressive treatment. More limited insurance mandates generally have little effect on IVF markets, which is why there is only a slight difference in practice behavior in mandated states because, nationally, coverage is poor (**FIGURE 3**).[24,27,28]

We must increase access to ART by increasing funding

In summary, the economic factors that affect affordability are the cost of treatment, socioeconomic status, disposable income, government coverage, insurance coverage, and access to financing/loan programs. Access is affected by many factors, but only countries with funding arrangements that minimize out-of-pocket expenses meet expected demand of infertile patients. ART is expensive from a patient perspective, but not from a societal perspective. To increase subsidies we must:

- change societal attitudes toward infertility
- change payor attitudes toward reproductive care
- convince payers of cost-effectiveness
- develop effective payment plans and programs
- improve protocols (eg, eSET)
- educate patients and professionals
- use technology appropriately
- standardize treatments through research
- innovate new technologies to reduce costs
- develop patient criteria for inclusion in subsidization.

The ASRM has taken the lead in this respect in the United States by having an

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Minimizing out-of-pocket costs to patients by increasing subsidies for ART technologies is essential to increasing ART access

Access to Care Summit in September 2015, as well as an Advocacy Forum, and will continue to advocate for better coverage for infertility care. Internationally, FIGO (the International Federation of Gynecology and Obstetrics) has taken the initiative to increase ART access, with the Committee on Reproductive Medicine distributing The FIGO Fertility Toolbox (http://www.fertilitytool.com).

World Health Organization Infertility Initiative

The World Health Organization (WHO) has, over the past 5 years, made a major initiative to increase global access to infertility diagnosis and treatment. This effort was effected through 3 major activities:

- rapid assessment task force
- reproductive medicine glossary
- fertility guidelines.

The Rapid Assessment Task Force. This Task Force developed a comprehensive questionnaire for the 195 governments that belong to and adhere to WHO guidelines. This questionnaire, which is to be completed by government health departments, requires the government to document the breadth and depth of their infertility services and identify deficiencies or gaps. It is expected that the questionnaire will be distributed to all governments of the world in 2016, including the United States. The information that is received by the Task Force will be analyzed by the WHO to help develop plans for improved national infertility services globally.

The Reproductive Medicine glossary. This glossary being developed is a revision and major update of The International Committee Monitoring ART (ICMART)/WHO Glossary.[29] The number of definitions in the glossary is being increased 4-fold to about 300 definitions to include not only ART but also sections on clinical definitions, outcomes, laboratory/embryology, epidemiology/public health, and andrology. While easy to overlook, definitions are essential to the accurate documentation of disease, communication among professionals, research comparisons, insurance coverage, billing and coding, and other issues.

For example, because the definition of infertility must include not only couples but also single persons, be flexible to deal with clinical versus epidemiologic and public health requirements, account for pre-existing conditions and age, and identify it as both a disease and a disability. Abortion definitions are complicated by the desire of many to call spontaneous abortion "miscarriage" and by the duration of pregnancy necessary before "delivery" of a fetus occurs. There is a desire to remove conception as a term (although it is widely used) because it is not a biological event. Pregnancy has its own complexities, including when it is initiated, which is now considered to be at the time of implantation. The glossary is expected to be published by mid-2016.

The WHO infertility guidelines. These have been an exhaustively-developed set of guidelines based on a comprehensive review and assessment of the entire literature by approximately 60 international experts working in teams with other assistants and experts using a standardized PICO (Population, Intervention, Comparators, and Outcomes of interest) system. This was a truly herculean effort. Guidelines are being finalized in the following areas: female infertility, unexplained infertility, polycystic ovary syndrome, ovarian stimulation, intrauterine insemination, ovarian hyperstimulation syndrome, IVF, and male infertility. After thorough review by the WHO, these guidelines will be published in hard copy and electronically in mid-2016.

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Global efforts to increase ART access include comprehensive infertility guidelines, developed and disseminated by WHO

Watch for access tools available this year

The plans are for the Task Force recommendations, the glossary, and the fertility guidelines, including The FIGO Fertility Toolbox to be presented as a comprehensive package to all of the governments of the world in 2016. This will give them the tools and encouragement to assess their fertility services and to use the WHO fertility package to improve access, effectiveness, and safety of infertility services in their respective countries.

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