Reproduction at an advanced maternal age and maternal health

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Advanced age is a risk factor for female infertility, pregnancy loss, fetal anomalies, stillbirth, and obstetric complications. These concerns are based on centuries-old observations, yet women are delaying childbearing to pursue educational and career goals in greater numbers than ever before. As a result, reproductive medicine specialists are treating more patients with age-related infertility and recurrent pregnancy loss, while obstetricians are faced with managing pregnancies often complicated by both age and comorbidities. The media portrayal of a youthful but older woman, able to schedule her reproductive needs and balance family and job, has fueled the myth that "you can have it all," rarely characterizing the perils inherent to advanced-age reproduction. Reproductive medicine specialists and obstetrician/gynecologists should promote more realistic views of the evidence-based realities of advanced maternal age pregnancy, including its high-risk nature and often compromised outcomes. Doctors should also actively educate both patients and the public that there is a real danger of childlessness if individuals choose to delay reproduction. (Fertil Steril® 2015;103:1136–43. ©2015 by American Society for Reproductive Medicine.)

Key Words: Advanced reproductive age, advanced maternal age, menopausal pregnancy, assisted reproduction, maternal health

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Sitting in the audience at our weekly obstetrics and gynecology Morbidity and Mortality Conference, I was recently surprised that neither the residents nor the faculty asked for the details of a 53-year-old twin pregnancy included in the postpartum statistics. I finally inquired, "Is there nothing to say about the menopausal twin pregnancy?" The resident seemed somewhat puzzled by the question and responded, "What is it that you wish to know about her?" Once again I was reminded of time passing. Certainly this pregnancy would have made headline news 25 years ago, yet now was seemingly mundane. In fairness, today's residents have grown up in a world in which women of almost any age give birth to children, and fairly regularly. Yet the risks of delayed childbearing are historically well known and relate to both natural fertility and pregnancy. With respect to these two important parameters little has really changed in my three decades of practicing medicine.

What drives the shifting paradigm of modern reproductive choices is indeed multifactorial. It likely began in the 1960s with the advent and use of safe, effective, affordable, and accessible oral contraceptive pills, providing women the opportunity to control their own reproductive destinies. Shortly thereafter, legalization and social acceptance of abortion allowed American women the option of terminating unwanted pregnancies, which in many cases would have ended their educational or vocational pursuits or perhaps in other cases led to unwanted marriages and compromised lives. Undoubtedly, lessening the risk of unintended pregnancy has resulted in more women completing their education and subsequently entering the workforce. Consequently pregnancy is postponed to a more optimal or convenient time.

Despite a fall in the birth rate of the general population of the United States over the past three decades, the birth rate for women aged 35–55 years has risen (1) (Fig. 1). An accelerated increase in births to older women, especially in their 40s and 50s, occurred after 1990 (Fig. 2). This trend followed the publication of several landmark articles published in the United States and Europe, which detailed successful pregnancies in women over the traditional age of reproduction using oocyte donation (2–4). The popular press coverage sensationalized the births and generally portrayed the small number of babies born favorably (5). However, at the time of these early medical publications meaningful data were lacking regarding the overall

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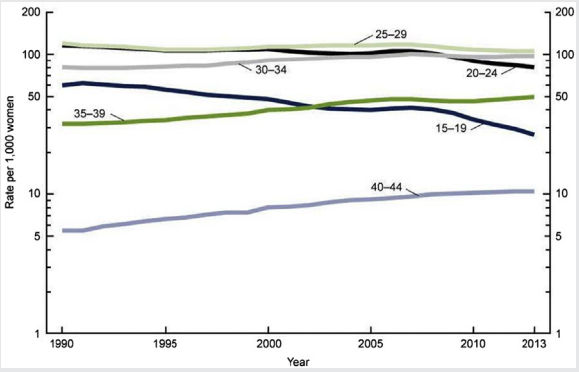
FIGURE 1



Birth rates by selected age of the mother: United States, 1990–2012. Source: CDC/*Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Vital Statistics System.

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safety of assisted reproduction in older mothers. With respect to the mass media characterization of "menopausal mothers," the favorable reporting bias generally continues to this day (6).

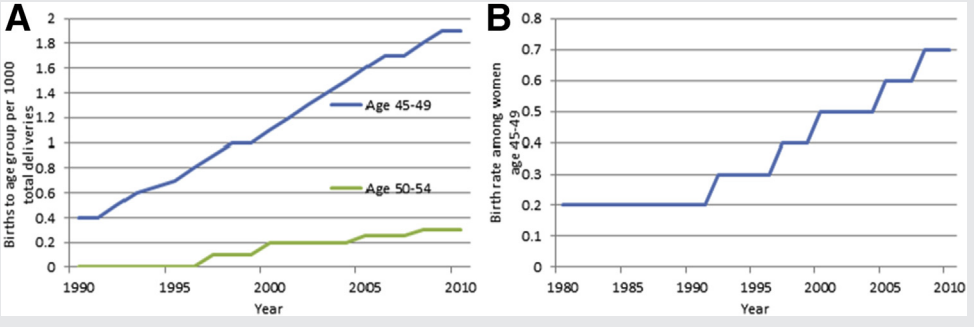
EVOLVING DEFINITION OF ADVANCED MATERNAL AGE

I was an obstetrics/gynecology resident during the early 1980s, and I remember that we openly described pregnant women over the age of 35 as "elderly." This remains the definition in medical dictionaries, although I rarely hear it spoken aloud today (7). We considered these patients at high risk for obstetric complications, including death, and triaged them accordingly (8). However, in that era elderly gravidas represented few of the women delivered in a busy urban labor room. It was uncommon to deliver a patient older than 40 years and rare to manage multiple births in this age group. Today it is not unusual to have women of "advanced maternal age" (AMA) on the schedule and, as mentioned earlier, even postmenopausal women with multiple gestations appear. The definition of AMA in the literature has been creeping upward from 40 to 45 years, and even older—often with the added descriptive of "very advanced," as if to better differentiate the *really* old patients from the less than old but still elderly patients (9).

Commonly older patients are suffering from a variety of medical disorders, accrued as age advances, which complicates their pregnancy and their medical management. The recent report of a 50-year-old mother giving birth after IVF with her own oocytes is a good case in point. It is true that she was apparently the oldest mother to successfully deliver under such circumstances, but she was also a hypertensive, insulin-dependent diabetic who was delivered preterm by cesarean section for impending eclampsia (10). A celebrated birth, perhaps, but it also represented a very risky medical scenario that could have ended tragically for both mother and child.

An ethical defense related to the "how old is too old" argument followed the initial reports of pregnancies in menopausal women and cited the relatively favorable obstetric experience of earlier series of older women offered treatment (11). Although the numbers were too small to harbor any statistical power, and certainly lacked analytical significance, the high-risk nature of pregnancies to elderly gravidas was actually apparent from the beginning. Despite the rigorous prenatal medical and reproductive screening required of the seven patients, aged 40–44 years, enrolled in our initial clinical trial at the University of Southern California (USC), all six who conceived had complicated obstetric courses: one miscarried, one had twins, four of five deliveries were by cesarean section, and the one vaginal birth was a 40-week fetal demise (2). However, because the high-risk gestations of women in their late 30s and early 40s were considered manageable, it was reasonably projected that such problems should occur in similar frequency and severity in women even older. This assumption further encouraged patients and their doctors to push the limits of "natural" reproduction, well beyond menopause.

FIGURE 2



Change in the **(A)** total number of births and **(B)** birth rate among women aged 45 and older in the United States. From reference (12).

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