

Reproduction at an advanced maternal age and maternal health

Mark V. Sauer, M.D.

Division of Reproductive Endocrinology and Infertility, College of Physicians and Surgeons, Columbia University, New York, New York

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

Discuss: You can discuss this article with its authors and with other ASRM members at <http://fertilityforum.com/sauerm-advanced-maternal-age-reproduction/>



Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for “QR scanner” in your smartphone’s app store or app marketplace.

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

Received February 5, 2015; revised March 3, 2015; accepted March 5, 2015.

M.V.S. has nothing to disclose.

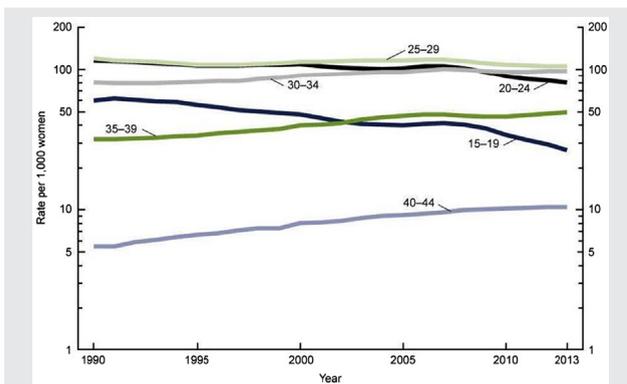
Reprint requests: Mark V. Sauer, M.D., Center for Women’s Reproductive Care at Columbia University, 5 Columbus Circle, 2nd Floor, New York, New York 10019 (E-mail: mvs9@columbia.edu).

Fertility and Sterility® Vol. 103, No. 5, May 2015 0015-0282/\$36.00

Copyright ©2015 American Society for Reproductive Medicine, Published by Elsevier Inc.

<http://dx.doi.org/10.1016/j.fertnstert.2015.03.004>

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.

Sauer. *Reproduction at advanced maternal age. Fertil Steril* 2015.

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

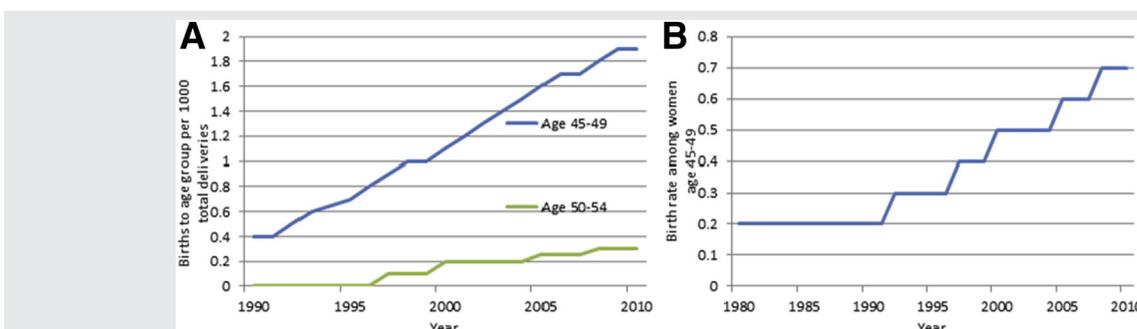
I was an obstetrics/gynecology resident during the early 1980s, and I remember that we openly described pregnant women over the age of 35 as “elderly.” This remains the definition in medical dictionaries, although I rarely hear it spoken aloud today (7). We considered these patients at high risk for 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).

Sauer. *Reproduction at advanced maternal age. Fertil Steril* 2015.

Reviewing AMA pregnancy outcomes 25 years downstream from the introduction of oocyte donation to menopausal women, it is striking that most of the early reports predicted the larger contemporary experience (12). Therefore, it should be with guarded optimism that we promote delayed childbearing to our patients, because risks to both mother and child are invariably present; and because many failed attempts also occur, the risk of life-long childlessness cannot be overstated.

SOCIETAL CHANGES DEFY BIOLOGIC REALITIES: WHY 40 IS NOT THE NEW 20

To attain personal autonomy, young women are urged to achieve their educational goals and establish a career path before marriage and family. Many have heard stories, often told by their mothers or grandmothers, of how a baby “derailed” their own aspirations. Yet achieving vocational objectives typically takes years to accomplish and coincides with the most fertile period of women’s lives. For example, young doctors or lawyers are likely to be in their mid-30s before they can reasonably afford time to have a baby without interfering with their career trajectory. Ideally pregnancy should also occur when they are settled with a life partner who will share the burden of raising offspring. Not surprisingly, this is commonly problematic or unrealistic, and this phenomenon is at least partially responsible for the epidemic of age-related infertility. Biologically speaking, women are most fertile between the ages of 15 and 30, a time in which many are unwilling or unable to start a family. From a career perspective, the years from age 35 to 45 would make the most sense; but these years represent the terminal decline in normal fecundity. Unfortunately, this conflict is not possible to resolve, and in my opinion offering egg freezing to older patients is not the remedy, especially knowing that the aneuploidy rate observed in the mature oocytes of women approaching age 40 years is nearly 75% (13).

Reproductive predicaments and dilemmas are unintentionally created when women schedule childbearing. There is a presumption that pregnancy occurs relatively easily in young women and needs to be avoided unless desired. Beginning as early as middle school “health classes,” girls are taught the importance of responsible sexual behavior and contraception. However, rarely is there mention of childlessness as a result of aging and delayed reproduction. Until recently, even at the highest levels of graduate medical education, the dangers posed by postponing pregnancy were not incorporated into formal training or curriculum. Yet, the association of fertility and age has been known and well-evidenced for hundreds of years (14). Beginning as early as age 30 years, fertility potential within the population invariably declines. Fecundity progressively falls, reaching a nadir at approximately age 40 years, whereas spontaneous abortion rates increase logarithmically during this same decade. Graphs profiling the loss of fertility in 17th century women look remarkably similar to those for modern populations.

Although improvements in nutrition, hygiene, infection control, and modern medicine have had a beneficial impact

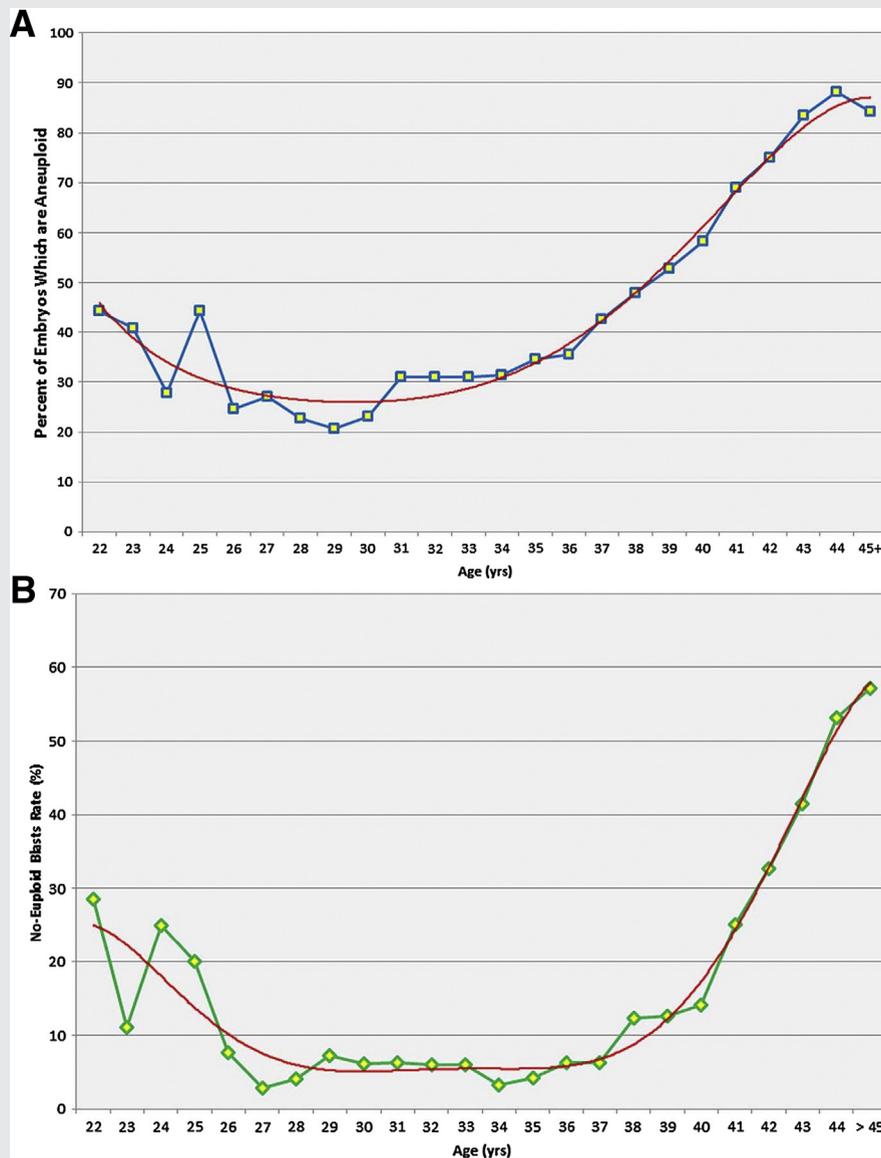
on obstetric morbidity and mortality, none of these factors has significantly altered the underlying reproductive biology responsible for normal conception. Natural populations are known to be relatively sterile by the middle of the fifth decade of life, an age concordant with the average age of death within the population a few hundred years ago but considered to be at the threshold of middle age today (14, 15). From an evolutionary point of view, female reproductive aging in humans is very similar to that seen in both monkeys and great apes and reflects the rate of follicular depletion known to accompany ovarian senescence (16, 17). Loss of ovarian function is not pathologic but rather an inevitable consequence of aging, and ultimately unavoidable (18).

Women are clearly delaying childbearing. Natality data from the United States demonstrate a dramatic rise in births to mothers once considered “elderly” (1). This is particularly evident in women older than 40 years. The rise in both primary and secondary infertility, as well as higher rates of pregnancy loss by older women, has also driven the increased demand for fertility services. There were fewer than 200 ETs reported to women older than 40 years in the 1988 and 1989 Centers for Disease Control and Prevention (CDC) data, compared with more than 17,000 cycles in 2012 (19–21). However, a profound decrease in pregnancy success rates accompanies female aging, whether reproductive attempts are natural or assisted. Remarkably, little appreciable increases in ART success rates have been realized over the three decades of national data for women older than 40 years, unless donor oocytes are used (21).

Assisted reproduction and fertility treatments such as ovulation induction and IUI are commonly offered to enhance the chance of pregnancy while expediting the event. In the younger population evidence supports this presumption, at least with respect to monthly fecundability (22). However, success precipitously falls after medical interventions as women age. Loss of ovarian reserve and poor performance with fertility-enhancing medications are contributing factors, but even when normal-appearing blastocysts are obtained, trophoctoderm biopsies discover an alarming rate of aneuploidy in the embryos of older women (Fig. 3) (23). Few births occur after IVF in women older than 45 years (24). Generally speaking, significant improvements in IVF success rates have occurred as a result of enhancements in methodology, techniques and tools, training of personnel, and laboratory science and culture systems (25). However, for women older than 40 years, these gains have had minimal impact on improving live births per ET. Clearly, technology and medicine do not always trump underlying biology, and with respect to accepted definitions of “medical futility” within the general community, reproductive intervention in the form of conventional IVF within this age group might well be viewed as futile (26).

Accompanying the loss of fertility is the rising risk of aneuploidy in the conceptus of older women. Most losses are secondary to meiotic spindle abnormalities known to occur in older oocytes, leading to chromosomal nondisjunction and abnormal embryos that either fail to implant or end in spontaneous abortion (13, 27). Clinically, the

FIGURE 3



Prevalence of aneuploidy relative to age in (A) biopsied human preimplantation and (B) the percentage of cycles with no euploid embryos on biopsy. Reproduced with permission from Franasiak et al. (12).

Sauer. Reproduction at advanced maternal age. *Fertil Steril* 2015.

spontaneous abortion rates of young women (aged <30 years) are significantly lower (10%–15%) than for women older than 40 years (approaches 25%), and miscarriages occur in approximately 50% of diagnosed pregnancies in patients conceiving in their mid-40s (28). Aneuploidy is the most commonly discovered abnormality. The majority of aneuploidy conceptions are lost as early or late miscarriages, but not all are fatal, resulting in increasing numbers of affected offspring. Trisomy 21 risk is 1 in 1,000 in women aged ≤ 30 years, but rises to 1 in 30 by age 45 years (29).

Until 1990 the proverbial “chicken or the egg” comment was often debated to explain the rising loss of pregnancy potential in older women. Perhaps the uterus

was equally at fault by not allowing implantation, or on the other hand, being overly permissive in accepting the implantation of abnormal embryos, thus resulting in more losses (30, 31). These debates were largely settled by the dramatic reversal in implantation and ongoing pregnancy rates of women after oocyte donation (3–5). Generally speaking, age itself was no longer a natural barrier to pregnancy, and patients well beyond menopause were seeking fertility services in moderate numbers. For the first time in history, the question of whether it was wise to prolong reproductive longevity was germane to motherhood and being asked with increasing frequency, especially poignant when reports of 70-year-old mothers hit the internet and newspapers (32).

MOTHERHOOD AT ANY AGE IS NEVER RISK FREE: OLDER GRAVIDITY IS ALWAYS HIGH RISK

Pregnancy outcomes and maternal morbidity and mortality have been well reported with respect to age, and older gravidity has always been associated with increased risk and compromise (33). Older patients are more prone to develop chronic illnesses, particularly obesity, hypertension, and diabetes mellitus. However, pre-existing disease does not fully explain all the adverse events associated with age and obstetric outcomes. Even after ART, in which patients are generally screened prenatally and known to be healthy, rates of complications are consistently increased, particularly related to cardiovascular events. Compounding the underlying risk is the high percentage of women experiencing multiple gestations as a result of ART, with the twin rate doubling in older American mothers in the decade of 1990–2000, and the triplet rate quadrupling (34, 35).

Maternal mortality rates are significantly increased in women older than 35 years, and even more pronounced after age 40 years (Fig. 4) (36). Deaths are mostly attributed to cardiovascular disease, diabetes, placental abruption, and complications from operative deliveries (37). Physiologic changes in pregnancy challenge aging organ systems that might be well compensated in a nonpregnant state but are ultimately overwhelmed by increases in blood volume, cardiac output, and insulin resistance that accompany pregnancy.

The medical and obstetric risks associated with advanced reproductive age were known to me 30 years ago as a resident and were well chronicled by Richard L. Naeye, M.D., in his review published in 1983 (38). Data from more than 44,000 deliveries profiled the increased perinatal mortality, stillbirths, anomalies, and malformations, as well as higher rates of gestational diabetes and hypertension, experienced by aging mothers. Interestingly, he somewhat apologetically questioned “the usefulness of the findings,” given the rarity of pregnancy in these far-advanced age ranges. However,

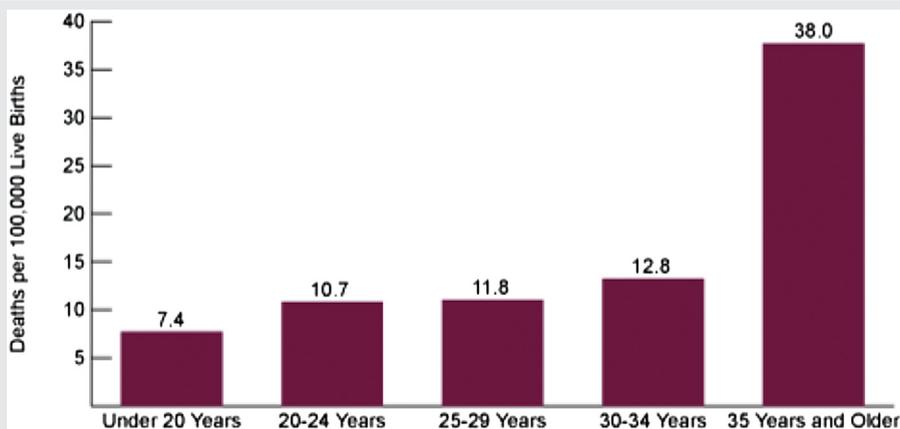
today no one would question the value of information gained from this review, and the data accurately predicted the problems that we increasingly encounter in our contemporary obstetric practices and delivery rooms.

Reviewing the Nationwide Inpatient Sample profiling American births for years 2008–2010, the associated risks, both medical and obstetric, are significant as women age, including the risk of death (Table 1) (12). Although the absolute risks are relatively low, the severity of the morbidity and the possibility of mortality remain important concerns. Pregnancies to women older than 45 years represented only 0.19% of all gestations yet accounted for up to 2% of the deaths or severe cardiac events.

A large meta-analysis by Schoen and Rosen (39) incorporated 16 studies and evaluated maternal and perinatal risks in women aged 45 years and older. Their findings were also in line with these more recent observations. The authors reported an increased incidence of pregnancy-induced hypertension (relative risk [RR] 2.8), diabetes (RR 14.2), cesarean delivery (RR 4.1), and perinatal mortality (RR 2.4), but in addition they noted that pregnancies resulting from assisted reproduction conferred further additional risk.

In the two published series focused on mothers older than 50 years the same obstetric problems emerged. The USC experience profiled a decade of work and noted that one-third of patients developed mild or severe pre-eclampsia; 20% experienced gestational diabetes; and 78% required cesarean delivery, one of which was accompanied by hysterectomy (40). Our experience at Columbia University with 101 women (aged 50–59 years) noted hypertensive disorders in roughly one-quarter of the patients; diabetes in 4%; 87% required cesarean delivery, one of which was accompanied by hysterectomy; and one first-trimester death likely secondary to myocardial infarction (41). A death was also previously reported in a 50-year-old woman from The Netherlands who suffered an eclamptic seizure after the cesarean delivery of twins and died from cerebral hemorrhage (42). Both the

FIGURE 4



Maternal mortality rates by age in the United States as reported to the CDC and Prevention 2005. Source: US Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau. Women's Health USA 2008.

Sauer. Reproduction at advanced maternal age. *Fertil Steril* 2015.

TABLE 1

Medical and obstetric events present at the time of delivery among women aged 35–44 y (n = 1,836,403) and aged ≥45 y (n = 23,807) compared with women aged < 35 y (n = 10,768,536), Nationwide Inpatient Sample, years 2008–2010.

Condition/event	Age 35–44 y	Age ≥45 y
Medical condition		
Maternal death	2.07 (1.78–2.40)	9.90 (5.60–15.98)
Transfusion	1.21 (1.20–1.23)	2.46 (2.27–2.68)
Myocardial infarction	4.05 (3.29–4.98)	21.38 (11.46–39.88)
Cardiac arrest	2.07 (1.80–2.42)	10.84 (6.48–18.14)
Pulmonary embolism	1.83 (1.69–1.98)	5.01 (3.47–7.23)
Deep vein thrombosis	2.02 (1.91–2.14)	4.38 (3.26–5.89)
Acute renal failure	1.86 (1.76–1.97)	6.38 (5.06–8.04)
Obstetric event		
Cesarean delivery	1.62 (1.61–1.62)	2.51 (2.44–2.57)
Gestational diabetes	2.42 (2.41–2.44)	3.5 (3.37–3.62)
Gestational hypertension	1.11 (1.10–1.12)	2.17 (2.09–2.25)
Preterm labor	1.16 (1.15–1.17)	1.91 (1.84–1.98)
Fetal growth restriction	0.92 (0.91–0.93)	1.53 (1.42–1.64)
Fetal demise	1.30 (1.27–1.33)	2.53 (2.22–2.89)
Premature rupture of membranes	1.10 (1.09–1.11)	1.38 (1.30–1.46)

Note: Values are odds ratio (95% confidence interval). Modified from reference (12). All *P* values < .001 compared with women aged <35 y.

Sauer. Reproduction at advanced maternal age. *Fertil Steril* 2015.

USC and Columbia authors concluded that pregnancy in this very advanced maternal age group was at high risk for hypertensive disorders and operative delivery, but similar to complication risks known to exist in older women spontaneously conceiving even at somewhat younger ages. Thus, given proper informed consent and appropriate screening, care should be extended to them regardless of age. However, this is not to suggest that these individuals are minimal- or no-risk patients; rather, that they should be considered acceptable high-risk pregnancies.

REPRODUCTIVE MYTHOLOGY AS PERPETUATED BY THE MEDIA

A recent article from the United Kingdom spoke directly to the false premise of risk-free delayed reproduction (43). Analyzing thematic portrayals of pregnancy and births in women older than 35 years by British newspapers, magazines, and television programs, consistent patterns of representation were evident. First, delayed childbearing was viewed in a positive light. Second, the media did not acknowledge age as an obstacle to pregnancy and endorsed assisted reproduction as a means for solving any and all reproductive problems when and if encountered. Finally, images and descriptions of postpartum fitness reinforced the message that a youthful beautiful body can be regained after the delivery of a baby. These same themes are clearly prevalent in viewing the American mass media as well, and are equally misleading.

Reports of sensational births that have occurred at extreme reproductive age, as well as the focused celebrations of births to prominent older women, usually fail to describe the attendant risk to health and well-being of the larger

population. In the British review one-quarter of childbirth articles focused on celebrities, and in articles containing specific reference to older mothers, nearly half focused entirely on celebrities. Poor outcomes, including infertility and perinatal loss, were seldom mentioned.

The flip side to this view was also disturbing: that early motherhood and career advancement are fundamentally incompatible. Childbearing was represented as inevitably leading to workplace absence, reduced productivity, and barriers to career progress. Interviews with older celebrity mothers further reinforced the benefits of delayed childbearing as life-experience, maturity, and financial stability enabled them to better adapt to the lifestyle changes demanded of parenting. This is particularly evident to young single mothers who commonly lack fiscal and physical resources available in two-parent households.

Trivializing the physical and emotional demands inherent to older pregnancy misrepresents the reality of childbearing as well as the risks. “Mommy makeovers” are advertised to restore youthful appearance in women fortunate enough to successfully deliver. Vaginal “rejuvenation” is promoted to restore genital anatomy to a predelivery state. Egg freezing cocktail parties are spotlighted on nightly news segments in which subspecialists in reproductive medicine mingle with successful young, typically single women in their 30s and 40s intent on “putting their eggs on ice” so they can prioritize and advance their career and “stop the biological clock.”

COMBATING IGNORANCE WITH EDUCATION AND PREVENTIVE MEDICINE

The strength of the published evidence should compel medical professionals to increase educational efforts directed at alerting women to the danger of delayed childbearing. Past efforts have been modest and largely supported by the American Society for Reproductive Medicine through subspecialty focused programs aimed at earlier access to hormonal testing and referral for treatment when results are deemed substandard (44). However, such campaigns are typically short-lived and go unnoticed in the age of social media and Internet-driven medical advertising. What is required is a true preventive medicine approach. This begins with frank discussions on the biology of female reproduction and how age profoundly affects it. The topic needs to be introduced early in life, perhaps at the same time that discussions regarding menstruation and pregnancy occur. Aging should not be presented as an undesired endpoint or as pathologic; negative approaches create fear and the illusion that medicine can “cure the problem.”

Improved access to affordable options must also be considered. Today insurance will commonly cover the costs of testing, but much less often fertility treatment or oocyte cryopreservation. It is paradoxical that physicians should be able to identify a problem but not be able to introduce a remedy to confront it. This is particularly true for subgroups at risk of diminished ovarian reserve, in which “time is of the essence.”

Appealing to the mass media to accurately portray the realities of advanced reproductive age would also be helpful.

Too often patients have unrealistic expectations that a baby will solve problems in their life and serve as an enhancement. The reality of childbearing for older mothers is different from their younger counterparts and more complex. The pregnancy is often complicated, and more importantly the dynamic of raising a family during retirement years is challenging. Physical, psychological, financial, and social resources will be taxed by efforts to have a baby and will continue to be under siege as children are raised. Many patients of AMA are first-time mothers; they have lived adult lives without the encumbrances of children and now must undergo a radical transformation in lifestyle to accommodate the many needs of a baby.

Physicians trained in the tradition of Western medicine focus on identifying disease and eradicating it through medicine or surgery. It is difficult to tackle problems that invariably challenge us all as aging human beings. We live in an era of “replacement therapy” for body parts that simply wear out. Lasix and cataract extraction; knee and hip replacement surgery; dental implants; Botox and face lifts, breast, abdomen, and gluteal reconstruction are but some of the many enhancements that promise to reverse age-related effects on the body. The illusion of youth is celebrated, and the effects of age are feared or hidden. Even age-related pharmaceutical ads portray younger, healthier people than the patients that they are actually trying to attract.

It is easier to wait until the problem of advanced reproductive age (ARA) or AMA walks into the office, order a battery of tests, interpret the problem as age-related, and then offer treatments that we know are grossly complicated by the very problem that brought the patient to our office. By then it is obviously too late to be effective. Furthermore, patients are full of denial when seeking advice on reproduction. They see themselves as older but not too old; not as agile but still fit; overweight but not obese; borderline hypertensive but not hypertensive. Frank discussions on all of the problems that might be encountered when considering pregnancy take time. In the era of managed care, most physicians have but 5–10 minutes to discuss any and all of these issues and thus choose to forgo the discussion and simply refer to a “specialist.” However, in doing so they are inviting the same metric of testing and compromised treatment.

It is likely that more and more women will continue to delay childbearing and will therefore be seeking services of reproductive medicine specialists. Furthermore, as the technology of assisted reproduction evolves and is perfected, more treatment options will be discussed and offered to women intent on delaying pregnancy. The armamentarium will include the traditional paradigms of IVF, donor oocytes and embryos, and autologous cryopreserved eggs, embryos, and ovarian tissue. Obstetricians will ultimately be expected to manage the women who successfully navigate the assisted methods and find themselves pregnant, but also much older and at risk for maternal and perinatal morbidity and mortality. Therefore, as reproductive specialists advocating for the introduction and widespread application of these treatments, we also must remain vigilant not to overestimate their benefits and underestimate the associated risks.

It is difficult to publically challenge convention, and it seems that these days it is politically correct to portray women enjoying the best of both worlds when it comes to family and work. However, if this is achieved by delaying pregnancy then the risk of complicated pregnancy, infertility, and childlessness must also be understood and accepted. The goal should be to promote earlier efforts at procreation, while condemning myths suggesting “you can have it all” by delaying reproduction until a time that it is convenient. Starting a family is never convenient and it never has been. A social re-engineering back to a more conventional time may be difficult, if not impossible to do, but a failure to do so will result in increasing numbers of women left childless and without adequate medical interventions to reconcile their needs. To succeed in this endeavor doctors will need to enlist the support of partners in all aspects of life: educators, employers, lawyers, theologians, and legislators. Finally, accurately portraying the difficulties faced by both older patients attempting pregnancy and those who are experiencing it is long overdue. Realistic characterization should not scare patients away from trying to have children but rather serve as a warning of the perils of postponement and be sobering reminders that all stages of life are fleeting and pregnancy is still best accomplished while young.

REFERENCES

1. Martin JA, Hamilton BE, Osterman MJ, Curtin SC, Matthews TJ. Births: final data for 2012. *Natl Vital Stat Rep* 2013;62:1–68.
2. Sauer MV, Paulson RJ, Lobo RA. A preliminary report on oocyte donation extending reproductive potential to women over 40. *N Engl J Med* 1990;323:1157–60.
3. Sauer MV, Paulson RJ, Lobo RA. Reversing the natural decline in human fertility: an extended clinical trial of oocyte donation to women of advanced reproductive age. *JAMA* 1992;268:1275–9.
4. Sauer MV, Paulson RJ, Lobo RA. Pregnancy after age 50: application of oocyte donation to women after natural menopause. *Lancet* 1993;341:321–3.
5. Rosen M. Turning back the biological clock, Barbara Strong gives birth after menopause with a donated egg. *People Magazine* 1990;34:115–8.
6. Saraceno J. Last chance babies. *AARP Bull* 2015;56:22–4.
7. Mosby's medical dictionary. 8th ed. Maryland Heights, MO: Elsevier; 2009.
8. Buehler JW, Kaunitz AM, Hogue CJR, Hughes JM, Smith JC, Rochat RW. Maternal mortality in women aged 35 years or older: United States. *JAMA* 1986;255:53–7.
9. Jackson S, Hong C, Wang ET, Alexander C, Gregory KD, Pisarska MD. Pregnancy outcomes in very advanced maternal age pregnancies: the impact of assisted reproductive technology. *Fertil Steril* 2015;103:76–80.
10. Rani G, Goswami S, Chattopadhyay R, Ghosh S, Chakravarty B, Ganesh A. Live birth in a 50-year old woman following in vitro fertilization-embryo transfer with autologous oocytes: a rare case report. *Fertil Steril* 2015;103:414–6.
11. Paulson RJ, Sauer MV. Pregnancies in post-menopausal women. Oocyte donation to women of advanced reproductive age: “How old is too old?”. *Hum Reprod* 1994;9:571–2.
12. Grotegut CA, Chisholm CA, Johnson LN, Brown HL, Heine RP, James AH. Medical and obstetrical complications among pregnant women aged 45 and older. *PLoS One* 2014;9:e96237.
13. Fragouli E, Alfarawati S, Spath K, Jaroudi S, Sarasa J, Enciso M, et al. The origin and impact of embryonic aneuploidy. *Hum Genet* 2013;132:1001–13.
14. Menken J, Trussell J, Larsen U. Age and infertility. *Science* 1986;233:1389–94.

15. Tietze C. Reproductive span and rate of reproduction among Hutterite women. *Fertil Steril* 1957;8:89–97.
16. Jones KP, Walker LC, Anderson D, Lacreuse A, Robson SL, Hawkes K. Depletion of ovarian follicles with age in chimpanzees: similarities to humans. *Biol Reprod* 2007;77:247–51.
17. Miller PB, Charleston JS, Battaglia DE, Klein NA, Soules MR. Morphometric analysis of primordial follicle number in pigtailed monkey ovaries: symmetry and relationship with age. *Biol Reprod* 1999;61:553–6.
18. Lobo RA. Potential options for preservation of fertility in women. *N Engl J Med* 2005;353:64–73.
19. Medical Research International. The American Fertility Society Special Interest Group. In vitro fertilization/embryo transfer in the United States: 1985 and 1986 results from the National IVF/ET Registry. *Fertil Steril* 1988;49:212–5.
20. Medical Research International. The American Fertility Society Special Interest Group. In vitro fertilization/embryo transfer in the United States: 1987 results from the National IVF/ET Registry. *Fertil Steril* 1989;51:13–9.
21. Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. 2012 Assisted reproductive technology national summary report. Atlanta, GA: US Department of Health and Human Services; 2014.
22. Reindollar RH, Regan MM, Neumann PJ, Levine BS, Thornton KL, Alper MM, et al. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. *Fertil Steril* 2010;94:888–99.
23. Klipstein S, Regan M, Ryley DA, Goldman MB, Alper MM, Reindollar RH. One last chance for pregnancy: a review of 2,705 in vitro fertilization cycles initiated in women age 40 years and above. *Fertil Steril* 2005;84:435–45.
24. Franasiak JM, Forman EJ, Hong KH, Werner MD, Upham KM, Treff NR, et al. The nature of aneuploidy with increasing age of the female partner: a review of 15,169 consecutive trophoctoderm biopsies evaluated with comprehensive chromosomal screening. *Fertil Steril* 2014;101:656–63.
25. Wang J, Sauer MV. In vitro fertilization (IVF): a review of 3 decades of clinical innovation and technological advancement. *Ther Clin Risk Manag* 2006;2:355–64.
26. Schneiderman LJ, Jecker NS, Jonsen AR. Medical futility: its meaning and ethical implications. *Ann Intern Med* 1990;112:949–54.
27. Warburton D. Biological aging and the etiology of aneuploidy. *Cytogenet Genome Res* 2005;111:266–72.
28. Osborn JF, Cattaruzza MS, Spinelli A. Risk of spontaneous abortion in Italy, 1978–1995, and the effect of maternal age, gravidity, marital status and education. *Am J Epidemiol* 2000;151:981–5.
29. Snijders RJM, Sundberg K, Holzgreve W, Nicolaides KH. Maternal age- and gestation-specific risk for trisomy 21. *Ultrasound Obstet Gynecol* 1999;13:167–70.
30. Paulson RJ, Hatch IE, Lobo RA, Sauer MV. Cumulative conception and live birth rates after oocyte donation: implications regarding endometrial receptivity. *Hum Reprod* 1997;12:835–9.
31. Macklon NS, Brosens JJ. The human endometrium as a sensor of embryo quality. *Biol Reprod* 2014;91:98.
32. Daily Mail Foreign Service. World's oldest mother gives birth to twins at 70. Available at: <http://www.dailymail.co.uk/news/article-1031722/Worlds-oldest-mother-gives-birth-twins-70.html>. Accessed February 3, 2015.
33. Usta IM, Nassar AH. Advanced maternal age: part 1: obstetric complications. *Am J Perinatol* 2008;25:521–34.
34. Martin JA, Hamilton BE, Ventura SJ, Menacker F, Park MM, Sutton PD. Births: final data for 2001. *Natl Vital Stat Rep* 2002;51:1–102.
35. Oleszczuk JJ, Keith LG, Oleszczuk AK. The paradox of old maternal age in multiple pregnancies. *Obstet Gynecol Clin North Am* 2005;32:69–80.
36. US Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau. Women's Health USA 2008. Rockville, MD: US Department of Health and Human Services; 2008.
37. Jacobsson B, Ladfors L, Milsom I. Advanced maternal age and adverse perinatal outcome. *Obstet Gynecol* 2004;104:727–33.
38. Naeye RL. Maternal age, obstetric complications, and the outcome of pregnancy. *Obstet Gynecol* 1983;61:210–6.
39. Schoen C, Rosen T. Maternal and perinatal risks for women over 44. A review. *Maturitas* 2009;64:109–13.
40. Paulson RJ, Boostanfar R, Saadat P, Mor E, Tourgeman DE, Slater CC, et al. Pregnancy in the sixth decade of life. Obstetric outcomes in women of advanced reproductive age. *JAMA* 2002;288:2320–3.
41. Kort DH, Gosselin J, Choi JM, Thornton MH, Cleary-Goldman J, Sauer MV. Pregnancy after age 50: defining risks for mother and child. *Am J Perinatol* 2012;29:245–50.
42. Schutte JM, Schuitemaker NW, Steegers EA, van Roosmalen J. Maternal death after oocyte donation at high maternal age: case report. *Reprod Health* 2008;5:12.
43. Mills TA, Lavender R, Lavender T. "Forty is the new twenty": an analysis of British media portrayals of older mothers. *Sexual Reprod Healthcare*. 29 October 2014. <http://dx.doi.org/10.1016/j.srhc.2014.10.005>.
44. The Practice Committee of the American Society for Reproductive Medicine. Female age-related fertility decline. Committee opinion no. 589. *Fertil Steril* 2014;101:633–4.