

PREVENTION OF INFERTILITY SOURCE DOCUMENT

THE IMPACT OF AGE ON FEMALE FERTILITY

BACKGROUND

Over the past several decades, demographic and socioeconomic trends have resulted in an increase in the absolute number of women seeking pregnancy in their late 30's and early to mid-40's. In addition, a significant number of women in this age group are seeking evaluation and treatment for infertility. Although there is a very well demonstrated decline in female fertility as a function of age, this phenomenon has typically been under-recognized not only by the general population, but also by many health care providers. This is probably related to the fact that in previous decades women generally had completed childbearing by the late 30's and in fact many of the pregnancies that occurred in the later reproductive years were unplanned. An increased awareness of the effects of aging on fertility for patients and health care providers is critical to the prevention of age-related infertility.

Factors influencing the tendency for a woman to delay childbearing are reflected in recent socioeconomic trends, including: 1) later age at first marriage, 2) increased level of education, and 3) increased percentage of women employed outside the home. In addition, increased divorce rates have been associated with an increase in the number of second marriages. The "Baby Boom" period of increased birthrates observed between 1946 and 1964 has resulted in a large population of women currently in their late 30's and 40's. Women in this age group are much more likely to experience difficulty conceiving and to seek infertility treatment. Thus, the combined result of these phenomena has been a dramatic increase in the absolute numbers of infertile women. The National Survey of Family Growth (NSFG) conducted in 1973, 1976, 1982, 1988 and 1995, based on interviews of women between the ages of 15 and 44, focuses on a number of social and demographic variables surrounding female fecundity and pregnancy, illustrating these trends. According to the most recent survey (1995), the combination of increased absolute numbers of women comprising the older age group, as well an increased percentage of the older women who reported infertility, accounted for the recent increases in the overall number of women experiencing impaired fecundity (1).

EFFECT OF FEMALE AGE ON FERTILITY

Compared to other major organ systems, the female reproductive system ages to the point of failure at a relatively young age. Although the average age of menopause is 51, peak efficiency in the female reproductive system occurs in the early 20's with a steady decline thereafter. There is a gradual loss of fertility as a function of female age with the rate of decline in fertility becoming more dramatic after the age of 35. This decline in fertility occurs in spite of the fact that women generally maintain regular, ovulatory menstrual cycles well into the fifth decade. Menken, et al. provided compelling evidence for this trend in their report of the effects of age at marriage on fertility (2). Samples were examined from seven historical populations meeting the following criteria: 1) marriage later in life is relatively common, 2) contraception is rarely practiced, 3) premarital conceptions are rare, and 4) accurate birth records were maintained. This study demonstrated that the fecundity of the couple is much more dependent upon the age of the female than the male, with the percentage of married women remaining childless rising steadily

with age: 6% at age 20-24, 9% at age 25-29, 15% at age 30-34, 30% at age 35-39 and 64% at age 40-44. In such natural, non-contracepting populations, the average age of woman at the time of the last pregnancy ranges between 39 and 42. Further evidence of the effect of female age on fertility can be found in reports of donor insemination pregnancy rates (which control for the age and fertility of the male partner as well as coital frequency) (3-5). For example, French data examining pregnancy rates in 2193 donor insemination recipients married to azoospermic men demonstrated that cumulative conception rates declined significantly after the age of 30 (4).

The profound effects of female age on fertility are further illustrated in the outcome of advanced infertility therapies such as controlled ovarian hyperstimulation and in vitro fertilization (IVF). Older women are less responsive to gonadotropins, producing lower numbers of developing follicles and oocytes in spite of higher dose requirements of gonadotropins (6). Pregnancy rates following controlled ovarian hyperstimulation with gonadotropins in women over age 40 with otherwise unexplained infertility are reported to be 5% or less per treatment cycle (7-9). In a 1993 report from the French national IVF registry, clinical pregnancy rates per oocyte retrieval declined sharply beyond the age of 38 (N=63,400 oocyte recoveries) (10). This decline in IVF success rate occurred in spite of the fact that only women with adequate ovarian stimulation who progressed to egg recovery were included. Furthermore, this study did not take into account the impact of spontaneous abortion on delivery rates, since only very early clinical pregnancies were considered.

Once an older woman becomes pregnant she also has a significantly increased risk of spontaneous abortion even after detection of fetal cardiac movement by transvaginal ultrasound (11). According to the 1997 report of Assisted Reproductive Technology Success rates, the percentage of clinical pregnancies that failed to result in a live birth rose according to the woman's age in non-donor cycles: 14% for patients under age 35, 16% at age 35-37, 26% at age 38-40 and 38.5% after age 40 (12). The live birth rate per initiated ART cycle was only 8% in women over 40 compared to 31% among women under 35, and deliveries resulted from fewer than 5% of initiated cycles in women over the age of 41 (12).

Studies examining the rate of implantation per embryo transfer indicate that, in addition to producing fewer eggs and embryos, older women produce embryos that are less likely to implant than those derived from the oocytes of younger women. Hull reported the effects of age on embryo implantation in 561 IVF patients, demonstrating that implantation rates decline as a function of female age: 18.2% at age 20-29, 16.1% at age 30-34, 15.3% at 35-39, and 6.1% at age 40-44 (13). A recent study of 431 cycles of in vitro fertilization in women 41 and older found no deliveries in women 44 and older, with delivery rates per oocyte retrieval among women 41-43 varying between 2% and 7% (14).

ETIOLOGY OF AGE-RELATED INFERTILITY

Age-related changes in the oocyte

There are several lines of evidence documenting abnormalities of the oocyte as the predominant cause of age associated infertility. For example, oocytes from normal women in their early 40's exhibit a high incidence of abnormalities in microtubule and chromosome placement at the metaphase stage of meiosis II (15, 16). Higher rates of single chromatid abnormalities have been

reported in oocytes derived from older infertility patients following ovarian hyperstimulation (17). The incidence of spontaneous abortions, the majority of which are due to chromosomal abnormalities, also increase significantly with advanced maternal age (18). Similarly, the rate of clinically significant cytogenetic abnormalities in live births rises from about 1/500 for women under 30, to 1/270 at age 30, 1/80 at age 35, 1/60 at age 40, and 1/20 at age 45 (19). Finally, and most convincingly, pregnancy and delivery rates after oocyte donation are almost solely correlated with the age of the donor rather than the recipient (20-22). According to the 1997 report by the Society for Assisted Reproductive Technology and Centers for Disease Control and Prevention, no significant age-related decrease in success rates was observed after oocyte donation (12). Therefore, replacing the defective oocyte with that of a younger woman appears to largely, if not completely, reverse the age-related decline in female fertility.

Age-related changes in the uterus

There is also some evidence of a decrease in the functional capacity of the human uterus in older reproductive age women. For example, there is an age-related increase in the number of spontaneous abortions in which the embryo is apparently chromosomally normal (18). There are well-documented increases in the incidence of placental previa (23, 24), dysfunctional labor (23-25), and uterine pathology (26, 27). Findings from diagnostic hysteroscopy revealed an age-related increase in the incidence of endometrial polyps and fibroids in reproductive aged women (27). Furthermore, the proportion of myometrial arteries containing sclerotic lesions in grossly normal uterine autopsy specimens increases with age: 11% at age 17-19, 37% at 20-29, 61% at age 30-39, and 83% after age 39 (28). While the impact of these lesions on fecundity is ill-defined and probably modest, they may be related to the observed increases in obstetrical complications in older women such as placental abruption (25), Cesarean delivery (23, 25, 29), operative vaginal delivery (23, 29-31), malpresentation (24, 29), and abnormal labor patterns (23-25).

Age-related changes in ovulation and hormone secretion

Other physiologic factors contributing to the age-related decline in fertility include decline in ovarian sensitivity to gonadotropins, evidenced by higher serum levels of follicle stimulating hormone (32-35). This limits the efficacy of many common fertility treatments aimed at increasing the number of available oocytes. The underlying mechanism of this phenomenon is almost certainly related to the progressive depletion of the ovarian follicle pool that occurs with age (36-38). There is a finite endowment of ovarian primordial follicles with the maximum number of ovarian primordial follicles occurring at approximately 5 months of fetal age. This number gradually declines from this point onward until the time of menopause when only few poorly responsive follicles remain. The wide range of age in menopause (mean 50 ± 8 years) implies that the initial endowment of primordial follicles and/or the rate of follicle loss is variable between individuals. In addition, a loss of significant number of functional ovarian follicles due to surgery, chemotherapy, severe endometriosis, or infection may accelerate the loss of ovarian reserve, and in severe cases, lower the age of onset of age-related changes in fecundity or menopause.

Interestingly, normal ovulatory cycles are preserved in women until well beyond the age of onset of significant decline in fertility (32, 35, 39, 40). Metcalf has demonstrated that ovulatory frequency remains high (95%) in menstruating women age 40-55 until the onset of

oligomenorrhea, when the percentage of ovulatory cycles drops significantly (40). Early changes such as shortening of the follicular phase length (time to ovulation) may be a clinical sign of decreased ovarian reserve and significant ovarian aging (32, 41). However, even when these clinical signs are present, studies in normal women indicate normal (32, 35, 42) and often supraphysiologic (39, 43) ovarian secretion of both estradiol and progesterone until significant menstrual irregularity associated with the perimenopause occurs. For this reason, many patients and practitioners may be falsely reassured by the continued presence of normal menstrual cyclicity and peripheral steroid concentrations.

EVALUATION AND TREATMENT OF AGE-RELATED INFERTILITY

Older patients seeking pregnancy as well as patients experiencing infertility beyond the age of 35 should seek early basic evaluation with assessment of ovarian reserve, ovulatory status, uterine and tubal anatomy, and semen parameters. In general, infertility examination is deferred until after at least one year of unprotected intercourse; however, in the older age group, it is appropriate to initiate this evaluation after as few as 6 months of attempted conception due to the rapid decline of treatment success over time. Therefore, abnormalities if present may be addressed as soon as possible, when such intervention would still allow a reasonable chance of pregnancy. Similarly, trials of infertility treatment should be concerted with fairly rapid progression to more advanced infertility treatments when indicated. It should be cautioned that normal testing for ovarian reserve (such as day 3 FSH and estradiol, and clomiphene citrate challenge test) do not negate the effects of chronologic age on oocyte quality, embryo implantation, and pregnancy rates (44).

Treatment of age-related infertility is somewhat limited, with no specific treatment available for oocyte abnormalities or decreased ovarian reserve. In general, empiric therapy for normal older women is directed toward increasing the number of available oocytes through controlled ovarian hyperstimulation and/or assisted reproductive technologies. However, due to the low implantation rates (in spite of increased egg production and normal fertilization), these treatments are associated with a disappointing success rates beyond the age of 40. Delivery rates per attempted cycle of in vitro fertilization are less than 5% by the age of 43 in spite of apparent improvements in implantation through modifications such as assisted hatching (12, 14). On the other hand, excellent success rates can be achieved through oocyte donation in women up to and beyond the age of 50 years (45). However, this therapy is not readily available due to its high cost (at least \$10,000 per attempt) and insufficient numbers of women who are willing and qualified to serve as oocyte donors. Other patients may find this treatment unacceptable due to the loss of a genetic relationship between the mother and potential child.

Other precautions and limitations to delayed childbearing beyond the age of 35 include increased rates of aneuploidy in liveborn children, and obstetrical issues such as increased rates of hypertension, gestational diabetes, placenta previa, Cesarean section, and dysfunctional labor. There is limited information regarding the potential psychosocial and developmental impacts of significantly advanced parental age.

SUMMARY

In summary, enhanced awareness in the health care setting as well as education of the general public will allow for consideration of the impact of age on fertility with regard to family and

career planning. Current areas of research in the treatment of age-related infertility include in vitro oocyte maturation, oocyte cryopreservation and oocyte nuclear transfer; however, currently these procedures are considered highly investigational and of unproven efficacy. In general, current fertility treatment of the normal older woman offers little advantage over expectant management in terms of cumulative pregnancy rates except when oocyte donation is utilized.

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