An Overview of the Effects of Age on Fertility in Women

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I. INTRODUCTION

For a variety of social and economic reasons, women (and couples) are putting off having babies until they are in their mid-thirties, or later. As shown in Figure 1, this trend is common to most industrialized countries. In the United States, the average maternal age at first birth increased from 21.4 to 24.9 years of age from 1970 to 2000. Overall, birth rates in the United States decreased from 1970 to 1980, but since then, the birth rates for women over 30 years of age have increased significantly (Figure 2).

Although some women can, and do, have babies into their forties and even fifties, in general, fertility decreases markedly with a woman’s age, particularly from 35 years onward. As shown in Figure 3, the chance of being infertile is approximately twice as great for women 40-44, compared with women 30-34. It is important to note that the onset of age-related infertility occurs approximately 10 years before menopause (te Velde and Pearson, 2002). The decrease of fertility with age, coupled with the tendency toward later child-bearing has led to the suggestion that “female ageing ... is now the main limiting factor in the treatment of infertility” (Ford et al. 2000).

This paper is intended as an overview of the information available on the relationships between age and fertility in women. It is by no means an extensive review of the literature, but rather, the data have been selected to illustrate general principles. Moreover, it is becoming increasingly evident that the fertility of a couple decreases with age of the male, as has been recently reviewed by Fisch (2005). The effect of male age is beyond the scope of this paper, but where relevant and whenever possible, studies have been chosen that have been controlled or adjusted for male age as well as frequency of intercourse and lifestyle factors.
II. THE EFFECT OF AGE ON NATURAL CONCEPTION

The birth of a normal healthy baby requires that a woman be able to ovulate a mature, normal oocyte (egg) at the appropriate time, that a fertile sperm be present within the oviduct (Fallopian tube) for fertilization, that the oviduct and uterus be capable of supporting the development of the embryo, and that the embryo (later the fetus) reside in uterus until fully developed and delivered without major complications. Many of these processes have been shown to be affected by the woman’s age.

The development of the oocytes and the follicles in which they reside begins when the woman is herself a fetus. Primordial germ cells develop into oogonia which divide and differentiate into primary oocytes. The primary oocytes are enclosed in a single layer of granulosa cells to form primordial follicles, numbering approximately 7,000,000 in both ovaries at 4-5 months of gestation. From there onward, the oogonia stop dividing, and the primary oocytes are arrested in development until puberty. Most of the primordial follicles are lost to atresia such that only approximately 1,000,000 are left at birth, 40,000 at the time of puberty and 1,000 at menopause. Throughout reproductive life, groups of the primordial follicles spontaneously grow and develop into early antral follicles. Most of these are also lost, except for (usually) one follicle per menstrual cycle that continues to develop into a large antral (dominant) follicle in response to gonadotrophic hormones (FSH and LH) secreted by the anterior pituitary gland. A surge of LH at mid-cycle induces the final maturation of the oocyte in the dominant follicle and its release (ovulation) into the oviduct where it can be fertilized. (See Piñón, 2002)

The ability to produce and ovulate that one oocyte is directly related to the number of antral follicles on the ovaries at that time. As shown in Figure 4, the number of antral follicles present on the ovaries declines with age.

In addition to the significant decline in the number of antral follicles, increasing age is also associated with chromosomal and functional aberrations in the oocytes. Most notably, as shown in Figure 5, the frequency of aneuploidy (abnormal numbers of chromosomes) in human oocytes increases exponentially after 35 years of age. Although the sperm can also contribute to chromosomal defects in the embryo, defects in the aged oocyte are thought to be the major cause of Downs Syndrome and other chromosomal abnormalities in newborns (Figure 6). Increased maternal age is also associated defects in oocyte mitochondria, a structure responsible for energy production and many other important functions. These include an increased rate of point mutations in oocyte mitochondrial DNA (Barritt et al. 2000), and with a decreased ability of the mitochondria to produce energy (Wilding et al. 2002).

As discussed in the following section on assisted reproduction, there is evidence that maternal age can have effects on fertilization and on development of the embryo. In natural conception, it is difficult to be certain whether problems of fertility arise from deficiencies in the embryo or deficiencies in the reproductive tract. However, it is very clear that the ability to get pregnant, to maintain the
pregnancy, and to deliver a healthy baby decreases with maternal age.

Figure 7 shows that the probability of establishing a clinical pregnancy following intercourse on the most fertile day of the cycle decreases steadily with increasing maternal age. Even for women who do eventually become pregnant, the likelihood of achieving conception within six months is dramatically reduced for women 35 years of age and older (Figure 8).

When pregnancy is established, increasing maternal age has severely detrimental effects on the outcome. Many of these effects probably result from the effects of maternal age on the oocyte/embryo/fetus or the embryonic contribution to the placenta. Both the miscarriage rate (Figure 9) and the frequency of preterm delivery (Figure 10) increase with increased maternal age. The risks of a wide variety of perinatal complications in the mother and the baby are significantly greater in women older than 35 years of age compared with women from 18-34 years of age (Figure 11). For example, compared with women 18-34 years old, the risk of an emergency Caesarian section was 1.5 times as great for women 35-40 years old and more than twice as great for women older than 40. Based on historic data and on animal studies, Tarin et al. (2005) have suggested that delayed motherhood may also have long-term effects on the health of the children, including impaired fertility and reduced lifespan.
Inferfertility can result from lack of ovulation, poor quality oocytes, blocked oviducts (Fallopian tubes), impotence in the man, inadequate sperm numbers, poor quality sperm, or a poor interaction between the sperm and the cervical mucus. Many of these problems (and infertility due to unknown causes) can be treated, or at least circumvented, by assisted reproductive technologies (ART). However, although ART procedures can improve the chances of having a baby, the success rate decreases markedly with increasing age of the woman.

1. Intrauterine Insemination and Donor Insemination

Intrauterine insemination (IUI) is the simplest form of ART. Semen is collected from the male partner by masturbation and then the sperm are usually washed to remove dead cells and other possible deleterious components of the seminal plasma. The washed sperm are then placed directly into the uterus via a catheter which has been passed through the cervix. This serves to avoid any problems of passage of sperm through the cervix or cervical mucus, and provides a greater number of sperm within the uterus to increase the chances of fertilization. Intrauterine insemination is also commonly used in conjunction with ovulation induction, in order to ensure optimal timing of insemination.

Figure 12 shows that the age of the man can have a significant effect on the clinical pregnancy rate following IUI, but for any given age of the man, the clinical pregnancy rate decreases markedly with increasing age of the woman. Similarly, the pregnancy rate resulting from IUI with sperm from fertile donors is also significantly reduced with increasing age of the woman (Figure 13).

2. In-Vitro Fertilization

In-vitro fertilization (IVF) was originally developed to overcome the problem of blocked oviducts but is now also used to treat male-factor infertility (low numbers or quality of sperm) and infertility for which there is no apparent cause. In general, the woman is treated with gonadotrophins to increase the number of antral follicles that fully develop. It is important to note that gonadotrophin treatment has no effect on the numbers of primordial follicles that develop to the antral stage – it only acts to rescue the follicles that have already developed to the antral stage and would normally be lost to atresia. When the follicles have reached the appropriate size, the woman is given human chorionic gonadotrophin to mimic the normal ovulatory LH surge, and induce final oocyte maturation. A needle is used to recover the oocytes from the mature antral follicles. For standard IVF, the oocytes are placed together with sperm from the partner or a donor and the sperm penetrate the oocyte naturally. In cases where only small numbers or immotile sperm are available, fertilization can be achieved by injection of a single sperm into each oocyte (ICSI). After fertilization, the resultant embryos are cultured for 2 to 6 days and then transferred back into the uterus of the woman.

As shown in Figure 4, the number of antral follicles present on a woman’s ovaries decreases with age and this results in a decreased number of oocytes that can be retrieved for following gonadotrophin treatment for IVF (Figure 14a). Moreover, the quality of the oocytes also decreases with increasing age (Figure 14b), resulting in a decreasing proportion of the oocytes that can be successfully fertilized in vitro (Figure 14c).

Embryo development in culture is also affected by the age of the woman. In the example shown in Figure 15,
the proportion of fertilized oocytes that developed to the blastocyst stage by Day 5 was significantly reduced with increasing age of the woman.

Overall the reduced implantation rate and increased fetal loss rate in older women resulted in only 5% of embryos transferred developing to a live baby in women 41-42 years old compared with 23% in women younger than 35 (Figure 16d). For women 41-42 years old, only 11% of cycles started yielded a live birth compared with 37% for women younger than 35 (Figure 16e). This would mean that on average, a woman 41-42 years old would need 12 IVF treatment cycles to have a 75% chance of one live birth, compared with only 3 treatment cycles for a woman younger than 35.

In addition to the decrease in live-birth rate with increasing age, pregnancies and babies resulting from ART in older women using their own oocytes are subject to the same problems of pre-term delivery, perinatal complications and chromosomal abnormalities seen with natural conception.

3. The Use of Donor Oocytes

In cases where a woman has no ovaries or is otherwise unable to produce her own viable oocytes, oocytes may be obtained from other women. The donors are most often anonymous fertile, young women but may be a relative or friend of the patient. The donor is treated with gonadotrophins and oocytes collected as described in the preceding section. Sperm from the patient’s male partner is usually used for fertilization and the resulting embryos cultured and then transferred into the patient. Interestingly, it appears that the patient’s age has no appreciable effect on the ability to support a pregnancy. The live-birth rate for women receiving embryos created from donor oocytes is approximately 50% at all ages from 25 to 45 (U.S. Department of Health and Human Services – Centers for Disease Control and Prevention 2004). Of course, the babies born from donated oocytes have no direct genetic relationship to the patient.

Clearly, common ART procedures can improve the chances of pregnancy but cannot overcome the deleterious effects of aging on numbers and quality of the oocytes. Based on a computer model, Leridon (2004) has calculated that ART can make up for only half of the births lost by postponing an attempt to become pregnant from 30 to 35 years, and less than 30% of the births lost by postponing from 35 to 40 years. Based on a literature review and their own data, Broekmans and Klinkert (2004) conclude that the prognosis for a successful pregnancy with IUI or IVF for women 44 or older “is flat zero.”

There are, however, two specialized ART procedures, pre-implantation genetic diagnosis and oocyte cryopreservation, that can, or have the potential to, circumvent the effects of aging on fertility.
IV. APPROACHES TO CIRCUMVENTING THE EFFECT OF AGE ON FERTILITY

1. Pre-Implantation Genetic Diagnosis

As noted above, the frequency of chromosomal abnormalities in oocytes increases with age in women, and this results in increased frequencies of chromosomal abnormalities in the embryos, fetuses, and babies born. An early approach to this was to obtain cells from the fetus by amniocentesis or chorionic villus sampling for evaluation of the chromosomes. Fetuses with abnormal numbers of chromosomes were then aborted, in order to prevent the birth of chromosomally abnormal babies. More recently, it has become possible to determine the chromosome status of early embryos produced by ART, before they are transferred back into the patient (preimplantation genetic diagnosis, PGD). In this case, only embryos with normal chromosome numbers are transferred.

A positive side effect of embryo selection following PGD is that the implantation and birth rates are increased because chromosomally abnormal embryos are often also developmentally compromised. An example is shown in Figure 17, where the implantation rate for embryos that had been tested and judged to chromosomally normal was 17.6% compared with 10.6% for embryos that had not been tested (and presumed to be a mixture of normal and abnormal embryos). Pre-implantation genetic diagnosis is usually used for couples with some history of chromosomal or other genetic defects, recurrent miscarriage, or in older women. Based on the improved rates of development following PGD, it has been suggested that all embryos should be tested.

Figure 16. The effect of a woman’s age on the a) cancellation rate, b) implantation rate, c) fetal loss, d) approximate babies born per embryo transferred, and e) live birth rate with in-vitro fertilization of non-donor oocytes in the United States in 2002. (Taken or derived from: U.S. Department of Health and Human Services – Centers for Disease Control and Prevention 2004).

Figure 17. Implantation rates for unselected embryos and for embryos judged as chromosomally normal by pre-implantation genetic diagnosis (Munné et al. 2003).

2. Oocyte Cryopreservation

When living tissues are deep-frozen (cryopreserved) under the appropriate conditions, all biological processes are arrested and aging of the tissue stops until it is thawed. This approach has been long used for the storage of sperm and embryos, and has recently been extended to oocytes. A major interest in oocyte cryopreservation is to preserve the possibility of fertility for young women that are due to
undergo radiotherapy and chemotherapy for the treatment of cancer. Such treatments can have severely deleterious effects on the oocytes. By removing and freezing the oocytes, they are not exposed to the cancer treatments. After the patient has recovered from the cancer treatments and wants to start a family, the oocytes can be thawed and fertilized, and the embryos transferred back into her uterus.

In the same way that cryopreservation can protect oocytes from cancer treatments, it could also be used to protect oocytes from natural loss and degeneration due to aging. Stachecki and Cohen (2004) have suggested that this may offer an approach to preserving fertility for women wishing to delay reproduction. Oocytes would be collected from young women and then cryopreserved until they are ready to begin their families. Although as yet largely experimental, the pregnancy rates from cryopreserved oocytes are improving.

V. CONCLUSIONS

There is a tendency for women in industrialized countries to delay having babies until their mid-thirties or later. There are important social and economic reasons for doing so, but it is imperative that women be aware that fertility decreases significantly with age, particularly after 35 years of age. From a purely biological perspective, the best approach to ensuring fertility is for women to have their babies before they have reached their mid-thirties, but for many women, this is not a desirable or even practical option. At any given age, assisted reproduction techniques may improve the chances of becoming pregnant, but cannot make up for the loss of fertility due to the effects of aging on the numbers and quality of oocytes.

References


