



A hysterosalpingogram (HSG) with water-soluble contrast medium or sonohysterography is generally performed to evaluate tubal patency and uterine anatomy.²⁴ HSG can also have therapeutic benefits. Pregnancy levels have been shown to increase in the year following HSG, possibly due to straightening out tubes, clearing debris, and breaking adhesions.¹⁰ If laparoscopy is deemed necessary, based on previous findings (including the presence of adhesions or endometriosis), an evaluation by an REI should be considered.

Ovarian reserve should be tested in women aged ≥ 35 or those aged 30–35 with risk factors including: previous ovarian surgery, smoking, irregular cycles, or otherwise unexplained infertility. Ovarian reserve is tested using cycle day 3 follicle stimulating hormone (FSH) and estradiol—with the appearance of elevated FSH indicating a poor reserve—or with transvaginal ultrasound, showing low ovarian volume or few follicles.^{10,8} However, women of advanced maternal age have a poor prognosis despite normal ovarian reserve test findings.⁹

Men

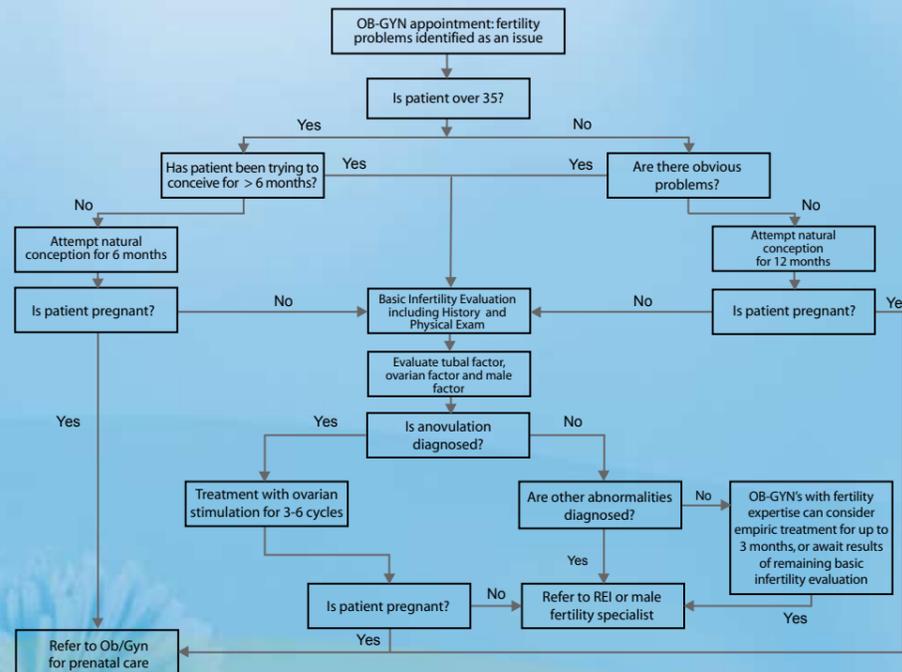
Male factor contributes to infertility or is the sole factor identified in 30–50% of couples seeking treatment.²² Initial evaluation of the man should include a reproductive history and semen analysis.²³ If abnormalities are detected in the initial evaluation, then more comprehensive evaluation by a male fertility expert should be done. For complete male evaluation, comprehensive history and physical examination are recommended.^{21–24}

During physical examination, consideration of secondary sexual characteristics (hair distribution, masculinization) and hormone-related abnormalities (gynecomastia) is needed.^{21,22} Special attention to the scrotal exam (position, size, and consistency of the testes), presence of associated structures (epididymis, vas deferens) and varicoceles should be provided.^{21,22} Semen analysis should include at least 2 tests separated by a month or more, with evaluation of semen volume, sperm concentration, motility and morphology.^{21,22,24} Morphology evaluation by strict criteria (Kruger [Tygerberg]) may be helpful to identify couples going through IVF at risk for fertilization failure (and therefore may benefit from intracytoplasmic sperm injection [ICSI]).²² Men with oligospermia (sperm concentration less than 20 million sperm/cc) may benefit from hormonal evaluation (FSH, testosterone) or other specialized testing (scrotal ultrasound, genetic testing, etc.)²¹ Treatment of specific male abnormalities should be offered.

WHEN TO REFER TO REI/FERTILITY SPECIALIST

An algorithm for the management of infertility and appropriate referral to a reproductive endocrinologist or fertility specialist is given in Figure 2.

Figure 2. Algorithm



CONCLUSION

Patients who have expressed a desire to become parents, but who are in a high-risk group for infertility based on their age, should have a basic fertility evaluation and be referred to a specialist in a timely manner in order to maximize their fertility potential.



ROLE of the OB-GYN and Reproductive Endocrinologist in Evaluating Fertility

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ROLE of the OB-GYN and Reproductive Endocrinologist in Evaluating Fertility

OBJECTIVES:

- Understand the role and importance of male and female reproductive aging in the comprehensive evaluation and management of infertility
- Review the basic evaluation of the infertile women and men to expedite an appropriate course of action
- Encourage timely referral to a reproductive endocrinologist or fertility specialist

TARGET AUDIENCE:

The intended target audiences for this brochure are obstetrician-gynecologists and reproductive endocrinologists.

In 2002, 1.9 million women used fertility services within the preceding 12 months.¹ Physicians involved in women's healthcare have a responsibility to provide the best care for patients during their reproductive years, including acting in a timely and appropriate manner when a patient desires pregnancy. It is important for obstetricians, gynecologists, reproductive endocrinologists, and other fertility specialists to develop and maintain open communication toward the shared goal of increasing a patient's potential for a successful pregnancy.

I. IMPACT OF AGE ON FERTILITY

Infertility is an unpleasant reality for many patients wishing to conceive. Approximately 1 couple in 7, aged 30-34, will have difficulty conceiving, and this number increases as a function of parental age.^{2,3} The decline in female fertility with advancing maternal age has become an even more pertinent issue in recent years due to social trends. A greater number of women are joining the workforce and participating in higher education, which has led to later mean ages of first marriages. Consequently, more than 20% of women are delaying childbirth until after the age of 35.^{4,5}

THE IMPACT OF AGE ON MISCARRIAGE RATES

The rate of miscarriage increases with advancing age of women and men. The European Study of Infertility and Subfecundity reported that there was a significant risk of miscarriage in women 30-34 years old if their male partner was ≥ 40 years old. When the study cohort evaluated older women (aged 35-44), the risk of miscarriage was significantly increased regardless of the man's age. If the woman was ≥ 35 years old and her male partner was ≥ 40 years old, the miscarriage risk was significantly higher than all other age combinations.⁶

FERTILITY RATES IN THE NATURAL SETTING

According to results obtained from the classic study of the Hutterite population (an isolated community that does not practice contraception, therefore studied as a natural model for stable populations), 20%-30% of couples who are not using contraception

will conceive within 1 month.^{7,8} Moreover, by 1 year, approximately 85%-90% of these couples are expected to successfully conceive.^{7,8}

Unfortunately, the natural fertility rate begins to decline with age, particularly in women over the age of 35.^{9,10} According to Hutterite data, the incidence of infertility of women aged 34 was 11%, and this increased to 33% for women aged 40 and 87% for those aged 45.^{11,12} In these women, the average age of a last pregnancy was 40.9 years, which supports that the time a woman remains fertile enough for natural conception is finite.^{11,12}

More recent data have echoed the findings in the Hutterite population. In a study by Menken et al., women aged >35 years are twice as likely to remain childless than those younger than 35 years of age (Table 1).² For women who are 40 years of age or older, fertility can be expected to decrease rapidly with each year of advancing age.¹²

Table 1. Relationship of Remaining Childless and Age²

Age Group	% Chance of Remaining Childless*
20-24	6
25-29	9
30-34	15
35-39	30
40-44	64

*Historical data based on age at which a woman marries.

Although there is no defined age limit for men to father a child, men can also expect to experience a decline in their fertility. Although age-related male infertility has not received the same degree of study compared with female infertility, studies have shown that male fertility rates drop after the age of 40, although at a slower rate than that observed in females.^{9,13}

DEFINING INFERTILITY

The classic definition of infertility is the failure to conceive after regular unprotected sexual intercourse for 1 year. However, it may be necessary to evaluate a couple's fertility potential earlier if certain conditions are met, including:

- **Maternal age over 35 years.** Evaluation after 6 months of trying to conceive is warranted because infertility becomes more pronounced in this age group⁹
- **Presence of an obvious medical problem.** Early evaluation is warranted at any age in the presence of obvious medical problems, including a history of pelvic infection, irregular menses, pelvic surgery or trauma, or genital pathology, or testicular trauma in men

II. THE IMPORTANCE OF TIMELY REFERRAL TO SPECIALIST CARE

It is imperative that obstetrician-gynecologist (OB-GYN) physicians discuss infertility concerns with their patients in a timely manner, in order to optimize their patients' ability to conceive.¹⁴ Important discussion topics include whether the patient desires pregnancy, what prior methods they have used to become pregnant, and whether or not they are interested in pursuing assisted reproductive techniques (ART) in order to achieve pregnancy, if infertility is confirmed.

In order to facilitate timely referral, the American Society for Reproductive Medicine (ASRM) has created infertility

referral guidelines. The guidelines are broken into 3 levels. According to these guidelines, if a woman is 35 years of age or older, or if ART is being considered, Level III care is appropriate. Level III care is defined as a practitioner with certification or documented experience in ART, reproductive endocrinology, or urology/andrology who offers infertility counseling services and is able to manage complicated female and male infertility and provide direct access to male and female microsurgical services, ART, and other related services.

POTENTIAL CONSEQUENCES OF LATE REFERRAL

Potential consequences of delayed, later-age referral to a reproductive endocrinology and infertility (REI) specialist include reduced natural conception rates, reduced success for intrauterine insemination (IUI) and ART, and an increased risk of miscarriage following ART. Based on the current understanding, it is clear that any significant delay in referral to specialist care could result in a couple never becoming pregnant.

Reduced natural conception rates

Age-related decreases in natural maternal fertility are due to a decline in egg number and quality and increasing ovarian senescence.¹⁰ The decrease in natural paternal fertility due to age is less defined, but may be due to endocrine abnormalities, genetic abnormalities, or poor sperm quality.¹⁵ Early evaluation and referral to a specialist can limit the effect that age has on a couple's fertility.

Reduced IUI success rates

The success rate for IUI also declines with female age. A study that included 1,117 IUI cycles reported that the live birth rate in women younger than 25 years of age was 26.7% per insemination; and this number declined to 14.2% in women aged 25-29, 12.5% for women aged 30-35, 9.5% for women aged 36-39, and 8.5% for women ≥ 40 years old.¹⁶ The gradual reduction in the live birth rate as women age was reportedly due to an increase in the number of miscarriages rather than reduced pregnancy rates.¹⁶

Reduced ART success rates

Female age is also a significant factor in achieving pregnancy through ART. The success rate for ART declines every year in women who receive nondonor fresh eggs and embryos (Figure 1). This decline is seen most prominently in women aged 40 and over.¹⁷ Moreover, a 2005 study by the Society for Assisted Reproductive Technology (SART) reported a similar age-related trend in the percentage of in vitro fertilization (IVF) cycles resulting in live births (from fresh embryos from non-donor oocytes; total cycles -122,815; Table 2)¹⁸

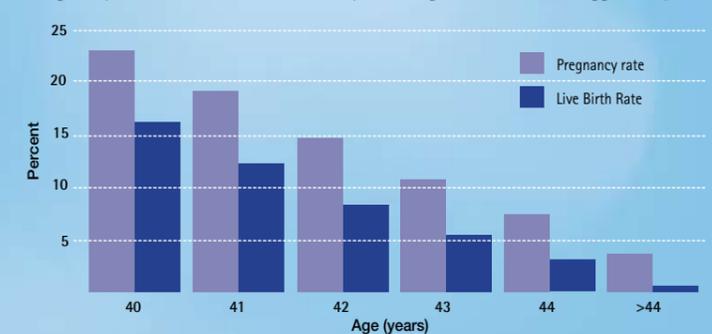
Table 2. Age-Related Trend in the Percentage of IVF Cycles Resulting in Live Births

Age Group	Percentage of cycles resulting in live births
<35	37.1%
35-37	29.2%
38-40	19.7%
41-42	10.5%
43-44	3.5%



Figure 1. Pregnancy Rates, Live Birth Rates for ART Cycles by Female Age (2004 Data)¹⁷

Pregnancy and Live Birth Rates for ART Cycles Using Fresh Non-Donor Eggs Embryos*



*All rates based on cycles started
Adapted from www.cdc.gov/ART/ART2004. Accessed January 26, 2007.

In the largest study to date, Klipstein et al. studied 1,263 women of older maternal age (40 to 48.8 years) who were undergoing ART (2,705 IVF cycles).¹² The live birth rate in women who were 40 years of age was 13.9%. There was a significant decline in the live birth rate to 9.7%, 9.2%, and 7.6% in women aged 41, 42, and 43, respectively ($P < .02$ for age 40 compared with 41, 42, and 43; $P = NS$ for 41, 42, and 43 compared with each other). In women who were 44 years old, the live birth rate fell to 2.6% ($P < .01$ for each comparison).¹² Of the 69 IVF cycles performed in women aged 45 and older ($n = 31$), there was only 1 live birth.¹²

Male age is also a precipitating factor in achieving a successful pregnancy through ART. A study of 221 couples undergoing ART evaluated the impact of male age on sperm parameters, fertilization rates, and pregnancy and live birth rates.¹⁹ In men who were ≤ 35 years old, the pregnancy rate was 53%. This dropped to 35% in men aged 36-40, and 13% in men ≥ 40 years of age. The live birth rates in these age groups were 38%, 17%, and 7%, respectively.¹⁹ This corresponded to a 5% increased risk of not achieving pregnancy with each year of advancing paternal age during the first ART cycle.¹⁹

Increased risk of miscarriage following ART

Miscarriage rates are also increased in older women undergoing ART for infertility. In the aforementioned study of women of older maternal age by Klipstein et al, the miscarriage rate was 23.9% in women who were 40 years of age and this percentage increased with each subsequent year, to a miscarriage rate of 66.7% in women aged 45.¹²

EVALUATING THE INFERTILE PATIENT

Infertility should be managed using an age-based approach because natural fertility and fertility achieved with ART declines with advancing age. Treatment for infertility should also be evaluated as early as possible if there is evidence of obvious medical problems.

The basic infertility evaluation

The evaluation of a patient for infertility should begin with a comprehensive medical history and physical examination. A review of past medical and surgical history, congenital abnormalities, medications, sexual, family, and menstrual history, history of sexually transmitted diseases, previous conception, environmental exposure, history of dyspareunia, history of smoking and other substance use, prior use of contraception (including IUD), and history of gonadal toxicity should be obtained in order to facilitate the diagnosis and guide laboratory and imaging choices.²⁰⁻²²

Women

The physical evaluation for women includes notation of body habitus (extremes of body weight including BMI, virilization, hirsutism), thyroid abnormalities, galactorrhea, tenderness or mass of the abdomen, adnexa, or cul-de-sac, genital anatomy, and uterine size, shape, position, and mobility.¹⁰

Following the history and physical examination, the basic infertility evaluation should include a confirmation of ovulation and patency of fallopian tubes.²³

Appropriate laboratory tests used to evaluate an infertile woman include an assessment of ovulation, as up to 40% of infertility in women is caused by ovulatory dysfunction.¹⁰ Basal body temperature, urine or serum leuteinizing hormone (LH) kits, or luteal phase serum progesterone levels can be measured to document ovulation. If an abnormality is found with ovulation, this should be the point of first intervention prior to attempting more invasive procedures.²⁴