Evaluation and Management of Infertility in Women: The Internists' Role

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Interventions for infertility have greatly increased in number and sophistication. Women with multiple medical problems and women near or beyond menopause are now able to conceive. The internist will be called on to assess the risk that infertility interventions pose and to counsel patients accordingly. Knowledge of the medical illnesses associated with infertility, the types of infertility treatments available, and the medical complications of these interventions are required to properly assess this risk. Medical complications of infertility interventions can be direct effects of related drugs and technologies and indirect consequences of the induced pregnancy, multiple gestation, or associated medical conditions. This article reviews the definitions and scope of infertility, the interventions used for treatment of infertility, the medical complications of these interventions, the potential risks of fertility treatment in women unable to conceive spontaneously, and important issues for preconception counseling.

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Medical and surgical services for infertility increased dramatically in number and sophistication during the last quarter of the 20th century (1). Social and scientific trends (such as delayed childbearing), increases in sexually transmitted diseases that can cause fallopian tube dysfunction, new drugs and techniques for treating infertile women and men, and an expanding cohort of physicians specializing in reproductive assistance have been the driving forces behind this remarkable extension of reproductive opportunities (2, 3). Internists and family physicians may be faced with questions and decisions about infertility evaluation and pregnancy management in older patients, patients with serious medical illness, and patients with heritable conditions that affect reproduction (4, 5).

Definitions and Scope

There is no standard definition of normal fertility. Biologically, inability to procreate can be classified as infertility (the inability of a couple to conceive) or infecundity (the inability of a couple to produce a live birth) (6). The word "barren" conveys the trying, potent emotional toll that failure to produce children exerts on a couple (7). The importance of male infertility should not be minimized; in fact, a male factor may be present in up to 40% of cases. This paper, however, focuses on the medical import of infertility treatments among women.

During their reproductive lives, 10% to 15% of couples are unable to achieve conception and deliver a living child after 1 year of unprotected coitus (2, 6). The proportion of women unable to bear children increases with age. Among the Hutterite Brethren of North America, contraception is discouraged and there is no incentive to limit family size. Although the fecundity of Hutterite women is legendary, Teitze (8) found that 11% bore no children after 34 years of age, 33% bore no children after 40 years of age, and 87% of women were infertile by the time they reached 45 years of age. Approximately one third of women who defer pregnancy until their mid- to late 30s and half of women who defer pregnancy until after 40 years of age will be unable to conceive (9–11). Advancing maternal age is associated with a higher risk for maternal illness, which may in turn be associated with infertility or increased obstetric risk.

Prevention of Infertility

The primary prevention of infertility should be a goal of all physicians caring for young women. Prevention should be aimed at lowering risk for sexually transmitted diseases by recommending use of condoms and limitation of number of sexual partners. It is imperative that sexually transmitted diseases and postpartum endometritis be promptly diagnosed and treated to avoid pelvic inflammatory disease and tubal dysfunction. Screening for sexually transmitted diseases in asymptomatic women may be indicated in certain high-risk groups, including patients with HIV infection; patients with previous pelvic inflammatory disease, preterm labor, or ectopic pregnancy; and patients with abnormal Papanicolaou smears. Progressive dysmenorrhea and pelvic pain should be aggressively evaluated to exclude endometriosis so that intervention can occur before

Table 1. Assisted Reproductive Technology

Assisted Reproductive Technique	Indication	Description
Gamete intrafallopian transfer (GIFT)	Unexplained infertility	Placement of oocytes and sperm into the fallopian tube
Zygote intrafallopian transfer (ZIFT)	Unexplained infertility	Placement of fertilized oocytes into the fallopian tube
Tubal embryo transfer (TET)	Unexplained infertility	Placement of cleaving embryos into the fallopian tube
Peritoneal oocyte and sperm transfer (POST)	Unexplained infertility	Placement of oocytes and sperm into the pelvic cavity
Intracytoplasmic sperm extraction (ICZI)	Male factor infertility	Injection of a single spermatozoon
Testicular sperm extraction (TESE)	Azoospermia	–
Microsurgical epididymal sperm aspiration (MESA)	Azoospermia	–

fertility is affected. Patients should be reminded that fertility rates decrease after 35 years of age and that they should modify their lifestyle to maximize chances of conception. Women should decrease smoking or recreational drug use and reduce vigorous exercise, especially when menses are abnormal. Men should minimize occupational exposures, avoid use of hot tubs and anabolic steroids, and avoid wearing tight briefs.

Treatment of Infertility

Once infertility is diagnosed, patients are likely to ask their internists for referral to an infertility specialist or for information on the medical risks associated with various infertility interventions. Primary approaches include 1) ovulation induction with the antiestrogen clomiphene citrate for women with ovulatory dysfunction; 2) radiographic, endoscopic, or surgical procedures to alleviate tubal obstruction; 3) medical or surgical ablation of endometriosis; 4) artificial or intrauterine insemination with donor or partner sperm for male factor infertility; and 5) hormonal support of an inadequate luteal phase (defined as a lag of more than 2 days in histologic development of the endometrium compared with the day of the cycle) with clomiphene or progesterone derivatives. If the cause of infertility is unexplained or if conventional therapy is ineffective, controlled ovarian stimulation and assisted reproductive techniques may be used.

Ovulation Induction

After other reversible causes of anovulation have been excluded, clomiphene citrate is the first-line drug for induction of ovulation. It is a nonsteroidal medication that binds to the estrogen receptor and can initiate ovulation in women who still have some endogenous estrogen. It could be thought of as one of the first of the selective estrogen receptor modulators, similar to raloxifene. Approximately 80% of women will ovulate and 40% will conceive with clomiphene treatment alone. Multiple pregnancy rates are approximately 5%, most of which are twin gestations (12).

Controlled ovarian stimulation, or superovulation, is a method of ovulation induction resulting from administration of exogenous human gonadotropins (luteinizing hormone and follicle-stimulating hormone). The goal of superovulation is the recruitment of multiple ovarian follicles. The ovarian response to stimulation is monitored with sonographic imaging of ovarian follicles and assessment of serum estradiol concentrations. Human chorionic gonadotropin is then used to stimulate the final maturation or ovulation of the follicles. Controlled ovarian stimulation may be used for patients who do not respond to clomiphene citrate, but it is primarily used to treat unexplained infertility in conjunction with in vitro fertilization or other assisted reproductive techniques. The main risks of superovulation include multifetal pregnancies and the ovarian hyperstimulation syndrome.

Assisted Reproduction

Assisted reproductive technology involves the retrieval, manipulation, and replacement of oocytes or sperm to achieve fertilization and conception. In vitro fertilization was first introduced in the early 1980s for treatment of infertility secondary to tubal disease (13). It remains the most common assisted reproductive technique and is used for tubal disease as well as for other indications, such as unexplained infertility and endometriosis. Some of the other assisted reproductive techniques used for unexplained infertility are defined in **Table 1**. The basic protocol for performing in vitro fertilization includes controlled ovarian stimulation, ultrasound-guided transvaginal aspiration of oocytes, insemination and fertilization of oocytes in vitro, and transfer of the resultant embryos to the maternal uterus. Progesterone supplementation is commonly used during the first trimester if a successful pregnancy occurs.

Assisted reproductive techniques have revolutionized the treatment of infertility. Women previously unable to become pregnant because of medical disorders or premature ovarian failure are now able to "bear" children. Pregnancies are possible in postmenopausal women and have even been reported in women in their sixth and seventh decades of life (14, 15). Application of assisted reproductive tech-

nologies has raised troubling ethical dilemmas in some cases (16), and the economic considerations are enormous (17, 18).

Effect of Advanced Maternal Age on Infertility Interventions

Women seeking infertility treatment are often older than 35 years of age. This increases the likelihood of coexistent medical problems, such as hypertension and diabetes, and the likelihood that the woman will require pharmacologic therapy for underlying medical disorders, some of which may have adverse effects in pregnancy. Maternal disease, drugs, and the potential for chromosomal anomalies with advanced maternal age must be considered before initiating treatment and when determining maternal and fetal risk. Studies of conception and gestation in achieved pregnancies indicate that age has a greater effect on the gamete than on the capacity of a healthy uterus to support pregnancy (9–11). Women 50 years of age or older routinely have successful pregnancies with donated, fertilized oocytes (9, 11). In contrast, among women with pregnancies resulting from ovulation induction, the incidence of spontaneous abortion increases dramatically after 30 years of age, an epidemiologic pattern similar to that of unassisted conceptions in women in their 30s and 40s. The effect of aging on tubal function is unexplored, although the time between fertilization and implantation is an important determinant of the risk for spontaneous abortion (19).

Medical Conditions Associated with Infertility

The many causes of infertility include tubal or pelvic pathologic conditions, hypothalamic–pituitary disorders, ovulatory dysfunction, and unexplained infertility. It is best to consider and review associated medical conditions according to the cause of the infertility.

Tubal or Pelvic Pathologic Conditions

Disorders that interfere with normal endometrial function include the Asherman syndrome, uterine scarring and synechiae from previous dilation and curettage, and endometriosis. Tubal infertility is caused by ascending pelvic infections (for example, *Chlamydia trachomatis*), adhesions from previous pelvic surgery, and pelvic inflammation (for example, inflammatory bowel disease and endometriosis). Sexually transmitted diseases tend to occur together and in women with more sexual partners. Women with tubal infertility should be screened for multiple sexually transmitted diseases, particularly HIV infection, syphilis, and viral hepatitis.

Pelvic tuberculosis has also been associated with endometrial impairment and tubal infertility. In one retrospective study in India, tuberculosis was the underlying cause of tubal infertility in 117 of 300 women (20). As the worldwide incidence of tuberculosis increases, it must be considered as a cause of infertility and treated accordingly.

Ovulatory Disorders

Anovulation or ovulatory dysfunction is a frequent cause of infertility that may be associated with many important medical conditions, including hypothalamic–pituitary disorders and ovarian failure. Polycystic ovarian disorders, although often associated with abnormal ovaries, are classified by the World Health Organization under hypothalamic–pituitary dysfunction and are discussed below.

Hypothalamic–Pituitary Disorders

Disruption of the hypothalamic–pituitary axis (hypogonadotropic hypogonadism) may be secondary to physical injury to the hypothalamus or pituitary gland (neoplasm, ischemia, infiltration, or granulomatous) or disturbed regulation (anorexia nervosa, long-term oral contraceptive use, excessive exercise, chronic renal failure, cirrhosis, and hyperprolactinemia). The resulting deficiency in levels of gonadotropin-releasing hormone or decrease in luteinizing hormone or follicle-stimulating hormone levels necessitates assisted reproduction for fertility. Hyperprolactinemia, adrenocorticotropic hormone deficiency, central hypothyroidism, and central diabetes insipidus are all commonly associated with pituitary infertility. There may also be continued overproduction from a secreting pituitary neoplasm (for example, prolactinoma), which may increase in size with pregnancy or oral contraceptive use.

To treat hypopituitarism, the deficient hormones must be replaced. Cortisol replacement does not usually need to be altered during pregnancy; however, parenteral stress doses are required for hyperemesis, intercurrent illness, and the stress of labor. Excessive glucocorticoid replacement can cause glucose intolerance, hypertension, excess maternal weight gain, and more pronounced striae. Because a slight physiologic decrease is seen in serum thyroxine levels during the second and third trimesters, it is unclear whether doses of thyroxine need to be increased in pregnancy (21).

Central diabetes insipidus worsens in approximately 60% of pregnant women because of increased clearance of endogenous vasopressin by the placental production of vasopressinase (22). Subclinical diabetes insipidus may manifest for the first

time in pregnancy. Desmopressin acetate, the standard treatment for diabetes insipidus, is not degraded by vasopressinase and is the treatment of choice in pregnancy. Desmopressin acetate poses no significant risks to the fetus (23).

Polycystic Ovary Disease

Polycystic ovary disease, the most common cause of anovulatory infertility, is a heterogeneous condition characterized by chronic anovulation with a spectrum of clinical manifestations (24). It is most frequently associated with hyperandrogenism, obesity, and an increased ratio of luteinizing hormone to follicle-stimulating hormone. Infertility is the presenting problem in 40% of women (25). Although 40% to 50% of women with polycystic ovary disease can achieve ovulation with clomiphene treatment, some will require more advanced ovulation induction and are at high risk for ovarian hyperstimulation (26).

Increasing evidence shows a relation between polycystic ovary disease and insulin resistance (27). Although many women with polycystic ovary disease are obese, both lean and obese women with polycystic ovary disease demonstrate insulin resistance more frequently than weight-matched controls (28). This is an important pathophysiologic association given the risks of type 2 diabetes mellitus and hypertension. The degree of insulin resistance may negatively affect the success of ovulation induction (29). Insulin sensitizers, such as metformin and troglitazone, have helped restore ovulation in some women (30). In a study of 254 women with polycystic ovary disease, 31% had impaired glucose tolerance and 7.5% had type 2 diabetes mellitus, as defined by World Health Organization criteria (31). This incidence of diabetes is sevenfold higher than that seen among women 20 to 44 years of age in the general population. Several studies have reported that the incidence of gestational diabetes (diabetes not present before conception) in women with polycystic ovary disease is 10% to 40%, compared with the background incidence of 3% (32).

Obesity, in particular abdominal obesity, is present in 50% to 60% of women with polycystic ovary disease (33). Compared with the general population, risk for hypertension increases threefold with advancing age in women who have polycystic ovary disease (34). Because women undergoing infertility treatment are often older, hypertension may be a frequent complicating factor.

In pregnancy, the insulin resistance associated with polycystic ovary disease, gestational diabetes, and obesity carries an increased risk for macrosomia, hypertension, and preeclampsia. Hyperglycemia is a frequent cause of congenital anomalies (35). Because each of these conditions is an independent risk factor for coronary artery disease, such risk must be assessed. We have seen postpartum myocardial infarction in a patient with polycystic ovary disease who did not receive counseling before undergoing assisted reproduction.

Ovarian Failure (Primary Hypogonadism)

Premature ovarian failure resulting from the early depletion of ovarian follicles is defined as primary or secondary amenorrhea associated with elevated gonadotropin levels and infertility in women younger than 40 years of age. It accounts for 10% to 28% of primary amenorrhea and 4% to 18% of secondary amenorrhea (36). Although intermittent ovulation may occur, many women with this condition require oocyte donation to conceive. Ovarian failure has various causes, some of which are associated with other important medical conditions that must be addressed and treated appropriately before and during pregnancy.

Autoimmune-Associated Premature Ovarian Failure

Autoimmune premature ovarian failure may occur as an isolated event, be associated with other autoimmune diseases, or be part of a genetic syndrome, such as the polyglandular autoimmune syndrome type I. Patients with autoimmune-associated premature ovarian failure may or may not have a history of other autoimmune disease when infertility treatment is initiated. In a study of 119 karyotypically normal women with ovarian failure, 27% had associated autoimmune hypothyroidism, 2.5% had adrenal insufficiency, and 2.5% had type 1 diabetes mellitus (37). Screening tests revealed 12 previously undiagnosed cases of hypothyroidism and 2 new cases of diabetes mellitus. In the absence of symptoms suggesting adrenocortical insufficiency, screening for other autoimmune conditions should include complete blood count; measurement of thyroid-stimulating hormone, glucose, calcium, sodium, and potassium levels; and liver function tests. If any features suggest Addison disease, an adrenocorticotropic hormone stimulation test should be done before pregnancy.

Gonadal Dysgenesis

Gonadal dysgenesis has been demonstrated in persons with 45X, 46XX, and 45XY chromosomes (38). The Turner syndrome, characterized by monosomy X chromosome (which may be mosaic), is associated with accelerated follicular atresia presenting with streak gonads, female phenotype, delayed puberty, and characteristic physical findings (short stature, webbed neck, and cubitus valgus). It is the most common cause of primary amenorrhea. Physicians may fail to screen for other complica-

tions of the Turner syndrome before initiation of oocyte donation (14).

The Turner syndrome is associated with several somatic abnormalities that must be documented and treated appropriately before pregnancy. Cardiovascular anomalies, which are the leading cause of death in such patients (39), include bicuspid aortic valve disease, coarctation of the aorta, ventricular septal defects, aortic stenosis, hypertension, and aortic aneurysms. Birdsall and Kennedy (40) reported dissection in a woman with the Turner syndrome who underwent assisted reproduction. The main risk factor for dissection is hypertension, and it is imperative that brachial hypertension be controlled without compromising uterine flow.

Renal anomalies, which occur in 33% to 60% of cases, include abnormal positioning (for example, horseshoe kidney), abnormal collecting systems (for example, duplication of ureters), and abnormal renal vasculature. Any women with the Turner syndrome who is considering assisted pregnancy must be fully evaluated for cardiovascular, renal, and endocrine abnormalities before conception and must be followed carefully throughout gestation (41).

Ovarian Destruction

Chemotherapy and radiation are both associated with ovarian failure. Prevalence depends on the age of the woman when she received the treatment, the dose of the drugs, and the type of drugs given (36). Because unfertilized ova do not usually survive, egg retrieval in the absence of fertilization is rarely done before treatment. Before oocyte donation is considered, physicians should assess the type of malignant condition, the risk for recurrence during pregnancy, the effect of ongoing medical therapy on pregnancy, and risk for other organ damage from therapy (for example, cardiomyopathy). Women who become pregnant after having pelvic irradiation may be at increased risk for fetal loss secondary to endometrial effect; the pregnancy success rate seems to be lower in this population (42).

Medical Complications of Infertility Treatment

The medical complications of infertility interventions can be direct or indirect (**Table 2**). In addition, there is some concern about a possible association between fertility medications and cancer. It should also be noted that the psychological effects of infertility on the individual person and the couple and the mood disturbances associated with hormonal manipulation are as important as medical complications.

Direct complications include the antiestrogen side effects of clomiphene citrate and the adverse effects of superovulation and assisted reproductive technology, such as the ovarian hyperstimulation syndrome, pelvic infection, intraperitoneal bleeding, and adnexal torsion (43). Of these, the ovarian hyperstimulation syndrome occurs most frequently; the most severe form occurs in 1.8% to 10% of cases, and milder forms occur in 10% to 30% of cases (44). Indirect complications are related to multiple gestation and associated problems and include preterm labor and prematurity.

Table 2. Medical Complications of Assisted Reproductive Technologies

Variable	Complication
Treatment	
Clomiphene citrate (antiestrogen)	Vasomotor instability
	Mood changes
	Headaches
	Visual disturbances
	Ovarian enlargement
Ovarian stimulation	Ovarian hyperstimulation syndrome
	Thromboembolism
	Acute respiratory distress syndrome
Egg retrieval and replacement	Intraperitoneal bleeding
	Pelvic infection
	Adnexal torsion
Indirect effects of treatment	
Multiple gestation	Prematurity
	Preterm labor
	Gestational diabetes
	Preeclampsia
	Fetal growth disorders
Preterm labor	Tocolytic-induced pulmonary edema

Clomiphene Citrate

The side effects of clomiphene citrate are not dose-related and may be most common at a dose of 50 mg, suggesting that patients who require high doses may have a relative insensitivity to the drug. The most common side effects are vasomotor flushing (10%); abdominal distention, bloating, pain, or soreness (5.5%); nausea and vomiting (2.2%); breast discomfort (2%); visual symptoms (1.5%); headache (1.3%); and dryness or loss of hair (0.3%). Basal body temperature increases during clomiphene treatment. Visual symptoms, which include blurring, scotomata, or abnormal perception, are self-limited and resolve with discontinuation of treatment. In the first few days after treatment, painful ovarian enlargement can occur.

Other Medications

Bromocriptine is used in the presence of hyperprolactinemia or galactorrhea and ovulatory dysfunction. Elevated prolactin levels interfere with normal menstrual function by suppressing pulsatile secretion of gonadotropin-releasing hormone. Bromocriptine is a dopamine agonist that directly inhibits pituitary secretion of prolactin. Side effects of bromocriptine, which are a result of its dopaminer-

gic effects, include nausea, diarrhea, headache, and fatigue.

Gonadotropin-releasing hormone agonists suppress gonadotropin secretion in infertile patients who retain endogenous production. Patients with normogonadotropic anovulation take gonadotropin-releasing hormone agonists to achieve hypogonadotropic anovulation, which is associated with a higher treatment success rate and a decreased risk for miscarriage. Gonadotropin-releasing hormone agonists can also be used to downregulate the pituitary gland, preventing premature ovulation in human menopausal gonadotropin–controlled ovarian hyperstimulation during stimulation for in vitro fertilization.

Ovarian Hyperstimulation Syndrome

The ovarian hyperstimulation syndrome, the most serious medical complication of superovulation with the stimulation protocols, is characterized by cystic enlargement of the ovaries and a marked increase in vascular permeability. This leads to extravasation of protein-rich fluid from the vascular compartment, which results in hemoconcentration and third spacing of fluids. In its most severe form, the marked fluid shifts may cause ascites, pleural and pericardial effusions, hypotension, hypovolemia, electrolyte and hepatic abnormalities, and renal insufficiency.

Patients initially present with abdominal distention, nausea, vomiting, and dyspnea. Later, the hepatorenal syndrome is present and is differentiated by a history of infertility interventions or ovulation induction and marked cystic ovarian enlargement on ultrasonography. Hemodynamically unstable patients may require hospitalization, intensive care support, and, in rare cases, termination of pregnancy. The ovarian hyperstimulation syndrome is a significant hypercoagulable state; venous and arterial thrombosis can occur and can present at unusual sites (45). There have been numerous reports of associated subclavian and internal jugular venous thrombosis and less frequent reports of involvement of the cerebral, vertebral, mesenteric, internal carotid, and femoral arteries (46, 47). The factor V Leiden mutation has been identified in some cases, but the frequency of thrombophilia in thrombosis associated with the ovarian hyperstimulation syndrome has not been systematically studied. Deaths have resulted from thromboembolism, the acute respiratory distress syndrome, and acute renal failure.

The cause of the ovarian hyperstimulation syndrome is not known and is an area of active investigation (48). It is thought that the ovarian renin–angiotensin system may play an important role. Ovaries are a major source of prorenin in women, and both prorenin levels and plasma renin activity increase substantially in patients with the ovarian hyperstimulation syndrome (49). In addition, vascular endothelial growth factor, which is present in ovarian follicular fluid, is thought to be a primary etiologic agent of increased vascular permeability and has been observed in the ascitic fluid of these patients (50, 51).

Maintenance of intravascular volume is the cornerstone of management, and treatment is largely supportive because the cause is still unclear. Often, paracenteis is necessary for relief of severe abdominal distention and prevention of pulmonary compromise. Short-term prophylaxis against venous thromboembolism is advised in all patients with the ovarian hyperstimulation syndrome.

At this time, prevention continues to be the best treatment strategy. Physicians should identify patients at risk, alter infertility regimens, and use sonography to carefully monitor ovarian size and number of follicles. Pregnancies complicated by the ovarian hyperstimulation syndrome are more likely to result in miscarriage, prematurity, low birthweight, gestational diabetes, and placental abruption (52).

Fertility Medications and Cancer

In the past two decades, various reports and studies have suggested an association between exposure to fertility medications (clomiphene citrate and human menopausal gonadotropins) and epithelial ovarian cancer (53, 54). It has been hypothesized that this type of cancer may result from malignant transformation of epithelial inclusion cysts that occurs with ovulation and with gonadotropin stimulation (55).

A causal relation has been difficult to confirm because of serious methodologic difficulties. Infertility and nulliparity, which are important characteristics of patients who are exposed to fertility medications, are also independent risk factors for ovarian cancer (56). Conversely, pregnancy, use of oral contraceptives, and lactation protect against ovarian cancer. Because more recent studies have not identified a significant association between the use of fertility medications and ovarian cancer (57), no specific recommendations for ovarian cancer screening in women exposed to these medications are available.

Multiple Gestation

Medically, multiple gestation is the most important indirect consequence of assisted reproductive technology. The incidence of multifetal pregnancies after assisted reproductive technology is approximately 35%; of these pregnancies, 85% yield twins and 15% yield triplets or higher-order multifetal gestations (12, 17). The risks associated with multifetal pregnancies include prematurity with neona-

tal morbidity and death, fetal growth disturbances, increased incidence of preeclampsia, gestational diabetes, and anemia. The increased need for operative delivery is associated with risks for infection, bleeding, and thromboembolism. Preterm labor may be treated with fluids and tocolytics (agents used to inhibit labor), such as terbutaline and magnesium sulfate. Tocolytics are a frequent cause of noncardiogenic pulmonary edema, which is treated by discontinuing therapy with the medication, restricting fluids, and administering small doses of intravenous furosemide. Because the risk for previable preterm delivery is very high in multifetal gestations, a sonographically directed procedure can be used to eliminate one or more fetuses.

Counseling Women Who Are Considering Fertility Interventions

The internist's role in preparing the patient for pregnancy has become more prominent as more women with medical illness are able to bear children. It is estimated that 15% of all women beginning prenatal care have a medical illness. Patients seeking assisted reproductive technology are likely to be older and to have concomitant medical conditions, which may have originally contributed to the infertility. Other underlying medical illnesses, such as thrombophilia, may be exacerbated or unmasked by the complications of the drugs used for assisted reproductive technology. Because more than 50% of spontaneous pregnancies in the general population are unplanned, most patients do not present for prenatal care until organogenesis is complete (8 weeks after conception). Because patients undergoing infertility evaluations are aware of their menstrual cycle and the timing of conception, they are a unique population in which physicians can intervene early to maximize maternal and fetal outcome. All women should be counseled on the benefits of smoking cessation and the importance of folic acid for reduction of neural tube defects. They should also be screened for rubella and questioned about family history of genetic disorders and thrombophilia. Diabetic women should be told of the importance of normalizing hemoglobin A_{1c} levels before conception to prevent congenital anomalies. Preconception counseling should address the potential effects of both the assisted reproductive technology and its success (that is, pregnancy). How will pregnancy affect maternal disease, and how may the associated medical condition and its treatment affect the pregnancy and the developing fetus?

All patients contemplating assisted reproductive technology should be carefully evaluated (**Table 3**), and information from this evaluation should be shared with the patients' gynecologists. However, because no outcome data have been stratified by preprocedure risk assessment, recommendations must be extrapolated from preoperative literature and preconception counseling guidelines (58–60). The patient's psychosocial status should also be evaluated, and her ability to care for a child and to withstand the hormonal and emotional effects associated with assisted reproductive technology should

Table 3. Evaluation before Treatment with Assisted Reproductive Technology*

- History
  - Family
    - Obstetric
    - Thrombosis, myocardial infarction, or stroke before 50 years of age or, in women, before menopause
    - Malignant conditions
    - Diabetes
    - Hypertension
  - Obstetric
    - Risk evaluation for thrombosis
      - Recurrent pregnancy loss
      - Small or premature babies
      - Preeclampsia, especially before 28 weeks
    - Gestational diabetes
    - Cause of infertility
    - History of sexually transmitted diseases
  - Medical
    - Risk for coronary artery disease
      - Family history, hypertension, diabetes, smoking, lipid levels
    - Renal disease
    - Thromboembolic disease
    - Cardiopulmonary disease
  - Psychosocial
    - Previous treatment or diagnosis of psychiatric illness or substance abuse
- Medications
  - If possible, eliminate all potentially teratogenic medications or substitute safer ones
  - Encourage continuation of therapy with essential medication (for example, for asthma or epilepsy)
  - Plan to modify the regimen at the first missed period, if indicated (angiotensin-converting enzyme inhibitors, warfarin)†
  - Review use of over-the-counter and herbal preparations
- Laboratory evaluation‡
  - All patients
    - Complete blood count
    - Electrolytes
    - Blood urea nitrogen and creatinine levels
    - Liver function tests
    - Thyroid-stimulating hormone level
    - Prolactin level
    - Glucose level
    - Serologic examination for hepatitis
    - Thrombophilia evaluation
      - Consider factor V Leiden mutation
      - Perform complete evaluation if patient has a family, personal, or obstetric history compatible with thrombophilia
    - Offer HIV testing
  - Patients who are ≥45 years of age or have multiple risks for coronary artery disease
    - Electrocardiography
    - Lipid profile
    - Stress testing if indicated
  - Patients with known cardiopulmonary disease
    - Chest radiography
    - Echocardiography
    - Pulmonary function tests
  - Patients with tubal infertility
    - Screen for HIV, syphilis, hepatitis
    - Test for tuberculosis
    - Test for inflammatory bowel disease

* All patients considering assisted reproductive technology should have a complete history and physical examination.
† Reference 18.
‡ Needed to assess risk for and baseline presence of the ovarian hyperstimulation syndrome.

Table 4. Preconception Interventions for Medical Conditions Associated with Infertility

Illness	Intervention
Autoimmune disorders	Evaluate associated renal, cardiopulmonary, and thromboembolic disease Measure antiphospholipids and other autoantibodies Discuss relative safety of most immunosuppressants (with the exception of methotrexate)
Cardiac disease	Perform echocardiography to assess extent of lesion, document stenosis, and assess pulmonary pressure Evaluate for coronary artery disease if multiple risk factors are present Consider prophylaxis against subacute bacterial endocarditis for valvular disease
Chronic renal disease	Discuss risk for preeclampsia and fetal growth disorders; if risk is moderate to severe, discuss 50% perinatal mortality rate Discontinue therapy with angiotensin-converting enzyme inhibitors* Control hypertension Avoid infection
Coarctation of the aorta	Control brachial hypertension (without compromising uterine flow) Advise patient of increased risk for aortic dissection
Epilepsy	Note that risk for malformations is two to three times higher Aim for monotherapy Use supplemental folate If patient is seizure-free for 2 years, consider withdrawal of antiepileptic drugs†
Hypertension	Modify drugs as needed Discuss risk for superimposed preeclampsia, abruption, fetal growth disorder, and premature birth
Malignant conditions	Assess risk for recurrence and the effect of pregnancy on this risk Determine the effect of therapy on fetus and pregnancy Assess organ damage (for example, cardiomyopathy) Advise patient of increased pregnancy loss in the case of pelvic irradiation Discuss maternal longevity
Obesity	Advise weight loss before conception if possible Discuss risk for macrosomia, hypertension, cesarean delivery, infection, and thrombosis
Pituitary disorders	For diabetes insipidus, desmopressin acetate is the treatment of choice Continue cortisol replacement unchanged except in the case of illness, stress, or labor Continue treatment for macroadenoma (size increased by estrogen)
Thromboembolic disease	Consider thrombophilia evaluation, especially for factor V Leiden mutation Discuss need for heparin prophylaxis or treatment Discontinue warfarin therapy by 4 weeks because of teratogenic effects
Turner syndrome	Assess cardiac echocardiography Determine fasting glucose level Determine thyroid-stimulating hormone level Assess for genitourinary anomalies
Type 1 or 2 diabetes	Normalize hemoglobin A_{1c} level before conception to decrease risk for congenital anomalies‡ Obtain remission of proliferative retinopathy, which may worsen during pregnancy Assess renal and vascular disease After missed period, discontinue angiotensin-converting enzyme inhibitor therapy, which causes fetal renal failure and oliguria*

* Reference 58.
† Reference 59.
‡ Reference 60.

be considered. Many centers require a psychological evaluation, which may be of great assistance to the internist and the patient. After the initial evaluation is complete, the emphasis should shift to preconception counseling for any specific medical or psychosocial conditions. The effects of assisted reproductive technology and pregnancy on any underlying medical illness should be discussed. Possible preconception interventions for the more common medical illnesses are outlined in **Table 4**. For further discussion of prepregnancy counseling, which is beyond the scope of this article, the reader is referred to the excellent reviews listed in the references (58–60).

Summary and Conclusion

Internists can and should contribute to the care of all medically compromised pregnant women. The internist is also likely to see the patient before pregnancy or infertility interventions begin. A full knowledge of the effects of such interventions on medical illness and the impact of medical conditions on pregnancy will help clinicians counsel women considering assisted reproductive technology and will provide an opportunity for early intervention.

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