Helping patients through the pain of infertility

Abstract: While males and combined couple factors play a large part in infertility cases, women often carry the physical, social, and emotional burden of these diagnoses. Nurse practitioners are in a prime position to assess women at risk for infertility, initiate an investigation to identify potential etiologies, refer women to specialized centers, and provide them with ongoing care and support through this difficult period in their lives.

By Susan Kelly-Weeder, PhD, FNP-BC

Infertility is defined as the inability to conceive a pregnancy after 1 year of unprotected regular intercourse. Chandra and colleagues reported that infertility affects 7.4% of married women or more than 2 million couples in the United States alone. National estimates of infertility are based upon data from the National Survey of Family Growth (NSFG), which is couple-based and focuses exclusively on married women. Given this definition, it is likely that the current rates of infertility are underestimated, as single women may also be struggling with fertility problems.

Previous cycles from the NSFG have demonstrated increased rates of infertility among Black women. According to recent data, this trend is ongoing with 7% of White women, 7.7% of Hispanic women, and 11.5% of Black women identified as infertile. A number of sociodemographic factors including income, education, access to healthcare, and racial differences in the prevalence of sexually transmitted infections (STIs) and pelvic inflammatory diseases (PIDs) also contribute to these disparities.

Etiology
The American Society for Reproductive Medicine defines infertility as a disease and encourages medical evaluation after 12 months of unprotected intercourse that fails to achieve a pregnancy. However, if the female partner is 35 years of age or older, an evaluation is recommended after 6 months of unsuccessful pregnancy attempts. The major causes of infertility can be divided into three basic categories. Approximately one-third of the cases are due to a female
factor, another third are due to a male factor, and the remaining third are due to a combination of factors, of which 20% are unexplained.6

Female causes
A number of conditions have been identified as causes of infertility in women including ovulation disorders, blocked or incompetent fallopian tubes, endometriosis, reduced oocyte quality, as well as anomalies of the cervix and uterus.7 Ovulation disorders are the most common cause of female infertility, accounting for approximately 40% of the cases.7 These disorders may present with obvious menstrual irregularities such as amenorrhea, oligomenorrhea, or dysfunctional uterine bleeding, or more subtle changes such as a shortened luteal phase.7 A number of underlying conditions predispose women to ovulatory disorders including endocrine problems (thyroid disease, adrenal disease, hyperprolactinemia), polycystic ovary syndrome (PCOS), diminished ovarian reserve, premature ovarian failure, and excess body weight.7

PCOS is the most common cause of anovulatory infertility and affects more than 6% of childbearing-aged women.8 It is identified as a problem in up to 20% of infertile couples.9 PCOS is associated with menstrual irregularities and hyperandrogenism, and characterized by hirsutism, acne, and male pattern alopecia, as well as polycystic ovaries identified on ultrasound.10 Additional common manifestations of PCOS include obesity, impaired glucose tolerance, and insulin resistance.10

Age-related declines in oocyte quality and quantity have long been associated with the development of infertility in women. Changes in the oocyte have been linked to chromosomal abnormalities and an increase in spontaneous abortion in women over the age of 35.11 Ovarian function fluctuates prior to menopause, resulting in irregular menstrual cycles and subsequent fertility impairment.12 Premature ovarian failure is associated with amenorrhea, estrogen deficiency, and elevated follicle-stimulating hormone (FSH) prior to the age of 40.12 Premature ovarian failure has been identified in 1% to 5% of women and is significant in the development of female infertility.13 Age-related changes in the uterus, such as the development of fibroids and endometrial polyps, also impact a woman’s ability to conceive.14

Tubal factors have been implicated in 30% of female infertility cases.13 STIs and PIDs are associated with the development of tubal infertility, and chlamydial infections are particularly problematic. Chlamydia is asymptomatic in 75% of women and infections of the lower genital tract are known to ascend, causing intramural inflammation and tubal scarring.14-16 Research has indicated that if untreated, 20% to 40% of women with a previous Chlamydia infection will develop PID, 50% to 70% will develop tubal infertility, and 65% will have an ectopic pregnancy.17-18 Additional causes of tubal disease include a previous ectopic pregnancy as well as a history of abdominal or tubal surgery.13

Endometriosis has also been linked to impaired fertility; however, controversy persists regarding its etiologic role. It has been proposed that endometriosis compromises fertility by causing pelvic adhesions, ovarian and tubal damage, impaired implantation, and endocrine and ovulatory disorders.19 Early research indicated a higher prevalence of endometriosis in fertile women when compared to their fertile peers; more recent research has not found improvements in fertility following removal of endometrial lesions.19

Cervical and uterine abnormalities also impact the development of female infertility. Abnormalities of the cervix, cervical mucus production, and sperm/mucus interaction may be involved but are rarely the only cause of an infertility problem.7 It has been estimated that uterine fibroids or myomas are associated with infertility in 2% to 3% of cases.20 Researchers suspect that fibroids impair fertility by altering the uterine contour consequently interfering with implantation, sperm movement, and sperm transport.20

In addition to delaying childbirth, a number of lifestyle choices affect the development of infertility issues.21-22 Tobacco use and its association with fertility impairment has been well studied and the deleterious effects are well documented.22 Cigarette smoking by women has been linked to conception delay, ovarian follicular depletion, chromosomal damage, an increase in miscarriage, as well as reduced success from assisted reproductive technologies (ARTs).23 Male fertility is also impacted by exposure to tobacco as researchers have demonstrated reductions in sperm quality in smokers.23 Caffeine and alcohol use have also been implicated in the development of female infertility. However, the researchers investigating these associations have not found conclusive evidence to link these behaviors with infertility.24

Weight is another contributing factor in the development of infertility. Overweight and obese women are at increased risk for anovulation, menstrual irregularities, reduced conception rates, and a decreased response to fertility treatments.25-26 To further support this association reductions in body weight, especially reduction in abdominal obesity, have been linked to improved outcomes.25 There is increasing evidence that obesity in men can also negatively affect fertility.26 The processes are not fully understood, but researchers have postulated that genetic, thermal, and endocrine mechanisms are involved.26

Women at the opposite end of the weight spectrum are also more likely to develop fertility impairment. Women with eating disorders are at risk for menstrual dysfunction, low bone density, sexual dysfunction, miscarriage, preterm delivery, and low-birth-weight newborns.27 Delays in conception have been reported in women with a body mass index less
than 20. In a recent study of infertile women undergoing fertility treatment, greater than 20% of the women met the criteria for a past or current eating disorder, which exceeds the U.S. average lifetime prevalence of eating disorders.

A number of occupational and environmental exposures have also been connected to the development of infertility, and an extensive literature base regarding these exposures has been accumulating. Although a number of compounds have been implicated, inconsistencies have been noted. To date, the strongest evidence available suggests that exposures to heavy metals, especially lead, may be problematic for childbearing-aged women.

**Male causes**
Male factor infertility is primarily related to sperm abnormalities and any condition that predisposes the male partner to impaired sperm quality or quantity can lead to infertility. Testicular dysfunction is the most common problem and can be due to androgen insensitivity, orchitis, cryptorchidism, congenital or developmental testicular disorder (Klinefelter syndrome), testicular trauma, radiation, systemic disorder, or a Y chromosome defect. Male factor infertility has also been linked to altered sperm transport due to an absent or obstructed vas deferens or epididymis, erectile dysfunction, or retrograde ejaculation. A third category includes problems with hypothalamic-pituitary axis and can be due to a state of androgen or estrogen excess (a tumor), a pituitary adenoma, or a multisystem genetic disorder such as Prader-Willi syndrome.

**Assessment and evaluation**
The extent of the clinical investigation for women with difficulty in conceiving is dependent upon the practice setting and parameters or guidelines in place for initial workup, testing, and referral. For example, in a family practice setting, the nurse practitioner (NP) may initiate the investigation into possible etiologies for both the male and female partners and refer for definitive treatment once a diagnosis is determined. However, in a women’s health site, where many women receive both primary and gynecologic care, the NP may begin the investigation and treatment protocols independently or in collaboration with a fertility consultant, while the male partner is referred to a urologist or other specialist. Regardless of the practice site, both male and female partners need to be evaluated simultaneously and many of the preliminary steps in the infertility investigation can be initiated by the NP caring for the woman and/or infertile couple.

The initial visit should include obtaining an in-depth medical history from each partner (see History required for males and females with infertility). The female partner requires:

<table>
<thead>
<tr>
<th>Infertile women</th>
<th>Infertile men</th>
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<tbody>
<tr>
<td>History of genetic disorders</td>
<td>History of genetic disorders, chronic illnesses, genital trauma, mumps</td>
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<tr>
<td>Surgical history including any gynecologic or genitourinary procedures</td>
<td>Surgical history including any genitourinary procedures</td>
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<td>History of endocrine disorders</td>
<td>Sexual development</td>
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<td>History of an STI or PID; or possible STI exposure; that is episodes of vaginal discharge, dysuria, fever, abdominal pain</td>
<td>History of STI; or possible STI exposure including urethral discharge, dysuria</td>
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<td>Previous fertility history; previous pregnancies and outcomes; history of ectopic pregnancy</td>
<td>Previous fertility history</td>
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<td>Detailed menstrual history; age at menarche</td>
<td>N/A</td>
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<td>Sexual history and current sexual practices including coital frequency and use of lubricants</td>
<td>Sexual history and current sexual practices including coital frequency and use of lubricants</td>
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<td>Smoking history</td>
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<td>Substance use including caffeine, alcohol, recreational drugs</td>
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<td>Medication history including oral contraceptive pills, and hormonal preparations</td>
<td>Medications including, sulfasalazine (Azulfidine), methotrexate, colchicine, cimetidine (Tagamet), spironolactone (Aldactone)</td>
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<td>Potential occupational and/or environmental exposures</td>
<td>Toxin exposure</td>
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a complete physical exam with particular emphasis on the breast and pelvic exam. Evidence of nipple discharge should alert the NP to the possibility of a prolactinoma, while signs of hirsutism, acne, and obesity may indicate PCOS. Vaginal discharge, cervical motion tenderness, or palpable masses on pelvic exam should raise the NP’s suspicion of an STI or PID. For the male partner, the exam should include a complete genital exam to rule out the presence of a hernia, testicular mass, and/or varicocele. The NP also needs to assess for evidence of androgen deficiency including increased body fat, decreased muscle mass, decreased facial and body hair, small testicles, and Tanner staging less than 5.13

Following the history and physical exam, a semen analysis is required. Typically, a minimum of two semen samples, separated by a 1 month period, are obtained before conclusions can be drawn regarding sperm quality or quantity. Additional tests may also include postejaculation urinalysis if retrograde ejaculation is suspected, as well as ultrasounds and specialized semen analyses. Their accurate results are indicated by an FSH less than 10 mIU/mL and an estradiol level of less than 80 pg/mL. Ovarian reserve can also be evaluated with a clomiphene citrate challenge test, a transvaginal ultrasound to obtain an antral follicle count, or an endometrial biopsy. A clomiphene challenge test consists of measuring FSH on day 3 of the cycle followed by the administration of clomiphene citrate for days 5 to 9 and then a repeat FSH on day 10. The test is abnormal if either the day 3 or day 10 FSH is above the accepted reference range established by the lab. Women over 40 who report amenorrhea may be experiencing ovarian failure, which can be determined by an elevated FSH.

Tubal causes of infertility are common and need to be evaluated. A hysterosalpingogram is the traditional method used to evaluate the fallopian tubes for patency. In addition to the information on tubal patency, this imaging exam, conducted with a water- or lipid-soluble contrast media, can provide information on the contour of the uterine cavity. An ultrasound and/or laparoscopy may be utilized to further evaluate uterine and pelvic pathology including the presence of endometriosis, endometriomas, or fibroid tumors.

Cervical factors impacting fertility can be evaluated during the pelvic exam. The postcoital test, once a mainstay of the infertility investigation, has been eliminated from the workup of infertile women. This procedure focused on examining the cervical mucus and identifying evidence of motile sperm in the vaginal vault following intercourse. Controversy has surrounded this procedure due to inconsistencies in technique, timing, and interpretation of the results.

Management

Management of female infertility should be individualized and focused on the findings obtained from the clinical investigation of potential etiologies. The role of the NP in the management of the infertile woman or couple is again likely to be practice-site specific. In a woman’s health site, the NP may initiate a number of different treatment protocols; however, in other sites, the NP role at this juncture may be to refer to an infertility specialist or an in-vitro fertilization (IVF)/ART specialized site.

Regardless of the practice site, all infertile women and couples should receive counseling and education regarding optimal intercourse frequency and scheduling. Instructions should be given indicating that conception is most likely to occur in the 3 days prior to ovulation and that every other day coital frequency is recommended. Women should also be advised to avoid douching and using lubricants during intercourse as these may interfere with conception. NP’s should also offer suggestions on how to eliminate any
potential risk factors. Women should be advised to decrease or stop smoking and reduce or eliminate caffeine and alcohol use. Additionally, women who are overweight or obese should be advised to lose weight and referred to a weight reduction program. Underweight women should be assessed for their eating and exercise habits and, if an eating disorder is suspected, appropriate referral should be initiated.

The NP should also allow time for the woman to express her concerns and feelings regarding the evaluation and treatment of her fertility-related problem. Infertility diagnoses and treatments can cause increased stress for the woman or the couple, so information on available support groups should be provided as well. RESOLVE: The National Infertility Association is a nonprofit organization devoted to the care and support of infertile couples and offers a wide range of information, resources, and support (http://www.resolve.org/).

**Treatment options**

Ovulatory problems are the most commonly noted etiologies of infertility in women and are the most amenable to treatment. Women with an underlying cause of ovulatory dysfunction (such as thyroid disease) should have treatment directed at these causes. For women with an elevated prolactin level, dopamine receptor agonist medications such as bromocriptine (Parlodel) may be successful in restoring normal ovulatory cycles. Women with PCOS have benefited from the administration of metformin with an increase in ovulation and conception rates noted.

For women without an obvious underlying etiology, improved rates of ovulatory cycles have been noted in response to an ovulation-stimulating agent such as clomiphene citrate (Clomid) or human menopausal gonadotropins (Pergonal). The major adverse reactions of these medications include ovarian hyperstimulation syndrome and multiple gestations. For women with limited ovarian reserve, oocyte donation has shown the greatest success.

Surgical options are available for women with tubal infertility and uterine and pelvic abnormalities including fibroid tumors and endometriosis. However, tubal surgery is rarely successful and can be associated with the development of subsequent ectopic pregnancies. Women with these problems often benefit from ovulation induction with or without intrauterine insemination (IUI) as well as advanced procedures including IVF/ART.

Varicocele repair has been shown to improve semen quality in men; however, it has not been shown to increase success with conception. Abnormalities identified in semen analysis should be referred to an infertility specialist and couples with these problems typically benefit from IUI and IVF procedures.

**IVF and ART**

In-vitro fertilization (IVF) is a method of assisted reproduction that involves combining oocyte and sperm cells in a lab setting and then transferring the resulting embryo into the uterus. Because this process bypasses the fallopian tubes, IVF is often the treatment of choice for women with tubal disease, as well as those with unexplained infertility. IVF procedures are expensive and are not covered by medical insurance in many states. This requires couples to pay “out of pocket” and therefore, these procedures become inaccessible. While IVF/ART procedures can be beneficial, the most current data indicates that only 35.4% of cycles result in a clinical pregnancy and 29% result in a live birth. While this does reflect significant progress for infertile couples, the vast majority of IVF/ART cycles (63.9%) still do not result in clinical pregnancies.

**Complementary and alternative methods**

A variety of complementary and alternative treatments are reported to improve fertility in women. It has been suggested that the use of botanicals with antioxidant properties, particularly vitamins A, C, and E may reduce oxidative stress associated with infertility; however, there have been few clinical trials investigating this phenomenon. Relaxation techniques have also been studied in groups of infertile women. In an often cited study by Barbieri and associates, 110 infertile women were placed in three different treatment options: an infertility support group, a relaxation group that included yoga and meditation exercises, and a control group which only received fertility medications. One year later, approximately 50% of the women in the support and relaxation groups had become pregnant, compared to only 20% of the women in the medication-only group. Acupuncture and its role in improving female fertility has also been widely studied. Acupuncture has been postulated to improve ovarian and uterine blood flow through the ovarian sympathetic nerves via the supraspinal pathways. The presumption is that if acupuncture can improve uterine blood flow, it can also improve the endometrial environment for embryo implantation. Acupuncture has been noted to improve relaxation in women undergoing fertility treatment. Specifically, 86% women reported increased feelings of relaxation following acupuncture treatments.

**Conclusion**

As primary care providers, NPs will encounter numerous women who are struggling with their fertility. By utilizing thorough assessment techniques, focused diagnostic procedures, and appropriate referrals, NPs can provide women with the resources they need to make decisions regarding.
available treatment options. NPs can also provide women with support and counseling to assist them in coping with infertility-related stress. For the 50% of infertile women who will not conceive a pregnancy even with advanced treatments, NPs can provide information and support as they make decisions regarding seeking adoption services or living child-free.

REFERENCES


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