rising infertility rates have prompted primary care NPs to begin the infertility work-up while patients are in the process of being referred to a specialist or awaiting an appointment. The initial primary care visit can serve as the first opportunity to address fertility concerns. Continuity of care in fertility treatment is key, especially in this vulnerable population that wants to feel supported and understood, which includes ongoing communication between patient and provider. NPs are in a position to support continuity of care for patients seeking fertility assistance and play an essential role in the health history, physical exams, and lab investigations of both partners. Primary care NPs can initiate timely pharmacologic infertility management. Assessment, diagnosis, and treatment of fertility issues within primary care can effectively reduce the emotional and financial burden on couples, helping some avoid lengthy wait times and achieve pregnancy sooner.

**Background**

Infertility is defined as the failure to conceive after 12 or more months of regular, unprotected sexual intercourse. The prevalence of infertility is steadily increasing due to delayed childbearing and rising rates of male infertility. Female age is one of the most important factors affecting fertility. Female fertility naturally declines with age, so women in their 20s and 30s should be counseled about the age-related risk of infertility. A full infertility workup is recommended for all women age 35 and older who have had consistent unprotected vaginal intercourse for 6 months and for all women who want to become pregnant.

**Keywords:** endometriosis, fertile period, fertility specialist, infertility, ovulation, polycystic ovary syndrome (PCOS), pregnancy, semen analysis
under age 35 who have had consistent unprotected vaginal intercourse for 12 months or more and have not achieved pregnancy. Investigations may still be warranted for women under age 35 who have not been trying to conceive for a full 12 months, when risk factors are present. Risk factors may include: the presence of only one ovary; known or suspected uterine/tubal/peritoneal disease or stage III–IV endometriosis; or recurrent pregnancy loss (two or more). Discussions about fertility should occur as part of a larger conversation about reproductive health issues, including contraception and sexual health practices prior to conception planning. One study found that the social and emotional impact of being unable to conceive can be devastating for patients, with high rates of anxiety (23.2%) and depression (17%) among women unable to conceive on their own. Even when eventually connected with a fertility specialist—20% of patients will wait 2 or more years for the referral—rates of self-discontinuation from care are high. In patients with health insurance that covered fertility treatments where finances were not the primary barrier, dropout rates were still staggeringly high between 46% and 58%. NPs can address and support patients with emotional or psychological hurdles who require counseling, coping strategies, and couple-based interventions, again illustrating the significance of continuity of care and close follow-up prior to and after referral to specialists.

**Sexual and gynecologic history**

Infertility can be a complex issue, so it is important to assess both partners, preferably together. A thorough menstrual history is needed, with details of the patient’s normal menstrual cycle, including length between cycles, duration and amount of bleeding, as well as age of menarche. An earlier age of menarche is associated with a higher risk of developing endometriosis. In addition, the presence or absence of subjective and objective signs of ovulation (also called molimina) throughout the cycle can help identify ovulatory versus nonovulatory states; molimina includes breast tenderness, food cravings, fatigue, and fluid retention. Lack of ovulation with certain conditions, including polycystic ovary syndrome (PCOS), often causes cycle irregularities such as amenorrhea or oligomenorrhea. Pelvic pain with chronic, cyclic, persistent, or progressive patterns may signify endometriosis. Women may also complain of dyspareunia, dyschezia, dysuria, or menorrhagia, all of which require further investigation.

Both partners should be assessed for a history of chlamydia or gonorrhea infections, which can lead to pelvic inflammatory disease (PID). Chlamydia and gonorrhea are important preventable causes of PID and infertility. Female patients should be assessed for any history of leiomyomas, also known as uterine fibroids, as these are the most common benign tumors in adult women. Leiomyomas can cause a wide array of symptoms, including menorrhagia, iron-deficiency anemia, pelvic pain and pressure, and subfertility.

Previous successful pregnancy followed by the development of infertility, known as secondary infertility, is a key component of the patient’s history, which should include information about the overall health of each pregnancy and the circumstances of the delivery. This history can reveal individual risk factors that may have contributed to secondary infertility including the presence of recurrent pregnancy loss (marked by greater than two early pregnancy losses), previous infertility treatments, and traumatic deliveries, which may have caused injury to or scarring of the female genital tract. If positive findings are noted during initial screening, the NP should treat or refer accordingly. If conditions are discovered that may warrant surgical intervention, such as the presence of leiomyomas, the NP should immediately refer the patient to the appropriate specialist.

Pregnancy is a chance occurrence with a cumulative pregnancy rate of 25% when female age is above 35, with this rate dropping the longer couples attempted pregnancy. In order to maximize the chances of conception, couples can be taught about the fertile period, which generally includes the 5 days prior to ovulation as well as the day of ovulation. Couples can engage in frequent sexual intercourse to ensure maximum coverage of the fertile period.

Male factors solely account for 20% of all cases of infertility and are considered contributory, along
with female factors, in another 30% of cases.\textsuperscript{13} It is therefore important to discuss any potential erectile or ejaculatory dysfunction and determine if the male partner previously fathered any children.\textsuperscript{14} Patients should refrain from using barriers for sperm such as over-the-counter products that contain spermicides. The uterotubal junction is also a barrier for sperm anatomically, physiologically, and/or as a mucus barrier to sperm passage; therefore, postcoital behaviors that affect anatomical passage, such as voiding or douching the vagina immediately after intercourse, should be discouraged for infertile couples.\textsuperscript{15} That is, consider the vagina immediately after intercourse, should be affect anatomical passage, such as voiding or douching to sperm passage; therefore, postcoital behaviors that affect anatomical passage, such as voiding or douching the vagina immediately after intercourse, should be discouraged for infertile couples.\textsuperscript{15} That is, consider the vagina immediately after intercourse, should be a
discouraged for infertile couples.\textsuperscript{15} That is, consider the vagina immediately after intercourse, should be a

**Surgical history.** The female patient’s history should also include any prior abdominal or pelvic surgery, such as dilation and curettage from an elective, spontaneous or therapeutic abortion, or fallopian tube surgery from a previous ectopic pregnancy. Patients need to be assessed for a history of any loop electro-surgical excision procedures, cryosurgery, cone biopsy, or laser vaporization subsequent to abnormal cervical cancer screening. Male patients need to be screened for previous genitourinary surgeries that may impact fertility, including vasectomy reversal, surgery for testicular cancer, or surgical repair of cryptorchidism.\textsuperscript{13} If a condition that may warrant surgical intervention is revealed, the NP should immediately refer the patient to the appropriate specialist.

**Past and present health status** 
Past and present health status should be assessed and documented in detail, highlighting any triggers or precipitating events that may contribute to infertility. It is well known that cancer and its treatments can impair male fertility.\textsuperscript{13,14} Conditions such as cystic fibrosis and mumps are well known to cause male sterility and need to be ruled out.\textsuperscript{13,16} Any type of surgical instrumentation near or in the reproductive tract can lead to scar tissue formation and adhesions, which can impact future fertility.\textsuperscript{12,17} Women with some autoimmune disorders are at an increased risk of infertility unrelated to direct effects of antibodies on fertilization and implantation.\textsuperscript{18}

**Mental and emotional health.** Couples’ emotional health is often overlooked in primary care settings and needs to be included in fertility assessments. Rates of sexual dissatisfaction, depression, anxiety, and marital discord are staggeringly high among couples faced with a diagnosis of infertility.\textsuperscript{1,19,20} Particularly, high rates of anxiety and depression among infertile women represent a significant barrier to achieving pregnancy.\textsuperscript{1} NPs can identify patients early who may require referrals to mental health professionals through the use of screening with the Hospital Anxiety and Depression Scale, the Beck Depression Inventory, or the Center for Epidemiologic Studies-Depression Scale.\textsuperscript{1} Current research supports the notion that psychological interventions can double the pregnancy rate in infertile women who participated as compared with the control group.\textsuperscript{1}

**Lifestyle associations.** It is important to explore the couples’ social history to identify possible risk factors for infertility and assist with preconception planning. Preconception planning should include the standard use of prenatal vitamins with folic acid for all women wanting to achieve pregnancy. Both partners should be encouraged to make healthy lifestyle choices that promote overall good health, including exploration of nutrition, and avoidance of any toxicities to the fetus.\textsuperscript{1,21} Females should be encouraged to take a prenatal vitamin with folic acid (400 to 800 mcg daily) to limit the risk of neural tube defects.\textsuperscript{21} Males should be aware that the use of hot tubs or saunas may elevate testicular temperatures and can lead to altered spermatogenesis.\textsuperscript{14}

**Family history.** A thorough family history may highlight a possible genetic predisposition to several conditions implicated in infertility. Genetic conditions known to affect fertility rates include: PCOS, Fragile X syndrome, premature ovarian insufficiency, endometriosis, and cystic fibrosis.\textsuperscript{7,8,18,22} A referral to a genetic counselor can be considered for patients with positive family histories of genetic conditions. This is ideally done in anticipation of childbearing years to determine overall risk.

**Medications and other substances.** There are a vast number of prescription medications and illicit drugs involved in male and female infertility. These substances contribute to infertility through both primary and secondary pathways. (See Medications and other substances affecting fertility.) Many medications and substances affect male spermatogenesis, including marijuana, anabolic steroids, and nicotine.\textsuperscript{13,14} Medications used in the treatment and maintenance of benign prostatic hypertrophy and lower urinary tract symptoms can severely affect male fertility, and
include alpha-adrenergic blockers (such as tamsulosin or doxazosin) and 5-alpha reductase inhibitors (finasteride, dutasteride). These types of medications can cause retrograde ejaculation, impotence, diminished libido, and an overall decrease in ejaculate volume. When appropriate, these medications should be discontinued or replaced with an alternate agent, but would likely require consultation with a urologist for collaborative management.

Medications commonly used to treat hypertension and congestive heart failure can have detrimental effects on male fertility; however, more research in this area is needed. For instance, propranolol can cause low libido through lower testosterone levels and erectile dysfunction. When appropriate, safer agents should be substituted, which may include amlodipine or hydrochlorothiazide that cause fewer male fertility related adverse reactions than beta-blockers, angiotensin-converting enzyme inhibitors, or other types of calcium channel blockers.

The most widely recognized and extensively researched medications known to significantly impact both male and female fertility belong to the psychotherapeutic, antipsychotic, and tricyclic antidepressant drug classes. Although antidepressant treatment can effectively improve the manifestation of major depression, it may induce or exacerbate symptoms of sexual dysfunction. Symptons of sexual dysfunction can significantly affect quality of life and may include decreased libido, anorgasmia, delayed ejaculation, erectile dysfunction, and dyspareunia. These adverse reactions often lead to nonadherence and subsequent relapses in depressive symptoms. Serotonergic antidepressants are frequently associated with the onset of sexual dysfunction, affecting more than 70% of sexually active patients. The risks and benefits of these medications should be addressed on an individual basis prior to discontinuation.

Since alcohol is the most widely used recreational substance, it is crucial to understand its implications on female and male fertility. Recent studies suggest that heavy alcohol consumption, defined as more than eight standard drinks per week for women, may diminish ovarian reserves and fecundability. Heavy alcohol consumption in males, defined as more than 15 standard drinks per week, can also negatively affect fertility by reducing the quality of semen, with occasional cases of azoospermia. Further, it has been well documented that alcohol use disorder and acute alcohol intoxication are associated with sexual dysfunction, including low libido and erectile/ejaculatory dysfunction. The impact of light to moderate alcohol consumption on male and female fertility is not fully understood, but does not appear to be statistically significant. Alcohol use disorder is often not discussed within the primary care setting in relation to potential causes of infertility and should be explored with all patients.

In addition, female fertility can be adversely affected by opiate use, regardless of whether these medications are being used recreationally or for chronic pain disorders. Although research is ongoing, it appears that opiate use can negatively affect the hypothalamic-pituitary-ovarian axis system. Therefore, a comprehensive medication history is important and counseling regarding recreational use of opioids should be addressed at the preconception stage when possible.

Over-the-counter medications are sold to millions of patients all over the world every day. Aspirin, ibuprofen, and naproxen are nonsteroidal anti-inflammatory drugs (NSAIDs) that prevent pain by inhibiting the enzymes involved in prostaglandin synthesis. Prostaglandins are essential for female reproduction; preovulatory levels of prostaglandins increase to facilitate ovulation and implantation. The inhibition of prostaglandin synthesis can vary by the type of NSAID, with aspirin being the least likely to cause issues and naproxen the most likely. The use of daily low-dose aspirin in seemingly healthy women is not recommended when trying to conceive. Only women diagnosed with antiphospholipid antibody syndrome may benefit from daily low-dose aspirin in addition to low-molecular-weight heparin and should be managed by an obstetrician.
Physical exam
The specific causes of couples’ fertility issues are unlikely to be revealed on physical exam. However, a few common causes of infertility are detectable on physical exam, particularly those related to PCOS or endometriosis. Female patients with elevated androgen levels often have a high body mass index (BMI), excessive hair growth on the face, acne, and alopecia, all of which are strong indicators of PCOS. It is important to note that older women with PCOS may have lower rates of hyperandrogenic symptoms and may have regained their regular menstrual cycles. In addition, high and low BMIs can impact overall fertility and should be documented.

The focused female physical exam should include palpation of the thyroid gland for size and the presence of any nodules. A pelvic exam should be completed to assess patency of the cervical os; the presence of cervical polyps; potential deformities of the cervix or vagina; vaginal discharge or lesions suggesting the presence of an active infection; cervical motion tenderness; and any adnexal masses or tenderness. The general size, shape, and mobility of the uterus should be assessed as nodularity and thickened pelvic anatomy, particularly of the uterosacral ligaments, vagina, rectovaginal space, pouch of Douglas, and adnexa, are possible findings in endometriosis.

Physical exam of the male partner is generally not required, unless risk factors have been identified in the health history, which would then prompt a focused physical exam that is beyond the scope of this article.

Lab investigations
Female. Lab investigations allow the detection of hormonal imbalances. (See Normal hormone-based lab values.) Initial investigations for female patients should include measurement of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol levels during day 2 to 4 of the menstrual cycle. Ovulation can be confirmed by measuring progesterone levels on day 21 of the menstrual cycle. Women who perform basal body temperature monitoring, and know their day of ovulation, can have progesterone levels measured 7 days postovulation. All other lab investigations can be done at any time in the menstrual cycle and should include the following: thyroid stimulating hormone (TSH); prolactin levels; serology for hepatitis B, hepatitis C, HIV, and syphilis; rubella and varicella titers; and urine or cervical swab for chlamydia and gonorrhea.

Additional lab tests should be considered based on patients’ risk factors and physical exam results. These tests may include a complete blood cell count, comprehensive metabolic panel, hemoglobin A1C, lipid panel, and an antimüllerian hormone (AMH) level. AMH is expressed by preantral and early antral follicles and reflects the remaining primordial follicle pool or egg reserve. It is the best biochemical marker of ovarian function, even when compared with FSH, which has more cycle-to-cycle variability. Results of AMH tests are age-specific because levels normally decline with age, along with reproductive health and capability. Abnormal serum hormone results should prompt an immediate referral to a fertility specialist for further evaluation and treatment.

If PCOS is suspected, testosterone levels should also be measured. A pelvic ultrasound can aid in assessing for multiple follicles/cysts, which are typically evident in patients with PCOS, and can also detect other uterine abnormalities. It is important to note that pelvic ultrasound is not solely required to diagnose PCOS, as per the Rotterdam criteria.

Male. Despite being a poor predictor of overall male fertility, a semen analysis (SA) remains the cornerstone test when assessing male fertility. As outlined by the WHO, the most recently updated normal reference range for semen analysis is:

- volume ≥1.5 mL
- sperm concentration ≥15 x 10⁶/mL
- total sperm number ≥39 x 10⁹
- total motility ≥40%
- vitality (% live) ≥58%
- sperm morphology (% normal) ≥4%.

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**Normal hormone-based lab values**

| CD 2-4 FSH | <10 mIU/mL |
| CD 2-4 LH | 2-13 mIU/mL |
| CD 2-4 Estradiol | <60-80 pg/mL |
| AMH* | ≤1.0 ng/mL** |
| CD 21 Progesterone | >5 ng/mL or >15.9 nmol/L |
| TSH*** | 0.4-2.5 mIU/mL |
| Prolactin | 4-23 ng/mL |

**Abbreviation:** CD, cycle day

All assays are lab-dependent.

*age-dependent assay

**<1 ng/mL indicates very low levels

***TSH range for subclinical hypothyroidism
In order to achieve the most accurate results, the specimen should be collected after a period of abstinence (2 to 7 days), kept warm, and appropriately transported to a testing facility within 60 minutes of ejaculation.\textsuperscript{2,33} If an abnormal result is found, a repeat SA should be done within 3 months. Any abnormal SA indicators should prompt immediate referral to a urologist and a fertility specialist. In addition to SA, male partners should also be tested for serology of hepatitis B, hepatitis C, HIV, and syphilis.

\textbf{Initial pharmacotherapy options}

In North America, wait times for fertility specialists are highly variable due to the number of fertility clinics available, the number of fertility specialists employed per clinic, and the overall size of the population. For patients exhibiting an anovulatory clinical picture, ovulation induction medications can be safely and effectively initiated in primary care settings. Currently, clomiphene is the only oral agent approved for ovulation induction in North America; however, letrozole is fast becoming a preferred agent, however, it is being used off label. Initial manufacturer concerns expressed for the use of letrozole included concerns over fetal toxicity and malformation; however, further studies have demonstrated safety and the Canadian Fertility and Andrology Society (CFAS) supports the use of letrozole for the treatment of ovulatory dysfunction and unexplained infertility.\textsuperscript{34}

**Clomiphene.** Clomiphene citrate (Clomid or Serophene) is a well-known and trusted medication used in the management of ovulatory disorders, including PCOS.\textsuperscript{34} Ovulation induction agents can increase the risk of multiple pregnancy, ovarian hyperstimulation syndrome, and thrombosis, and may increase the risk of ovarian cancer in women who remain nulliparous; therefore, patients should be counseled about these risks.\textsuperscript{31} Patients who present with PCOS and amenorrhea will often require synthetic progesterone, such as medroxyprogesterone to induce menses before starting an ovulation induction cycle. After administration of the synthetic progesterone and ovulation induction agent, ovulation needs to be confirmed by a serum progesterone lab on menstrual cycle day 21, or 7 days before expected menses.\textsuperscript{31} If ovulation has not occurred (progesterone <5 ng/mL), the clomiphene dose can be increased.\textsuperscript{31-36}

**Letrozole.** Research has shown that letrozole (Femara) is a superior ovulation induction agent when compared with clomiphene and is often used as first-line treatment.\textsuperscript{34,35} Both letrozole and clomiphene have the ability to affect the recruitment of multiple follicles, which can increase the risk of a multiple gestation pregnancy. As such, starting to middle range dosages are recommended in primary care settings.\textsuperscript{35,36} For patients with higher-than-average risk of pregnancy complications, including those with previous pregnancy-induced preeclampsia, an increased risk of multiple gestation pregnancy may not be ideal. Therefore, ovulation induction may not be advisable within the primary care setting for these patients. It is important to note that dosing within the higher range of either induction medication should always be accompanied by ultrasound monitoring. Ultrasound can help ensure that two or fewer follicles have been recruited. Unfortunately, ultrasound technology is often not available within primary care settings; therefore, patients requiring higher doses of ovulation induction medications should await specialist referral.

**Metformin.** Metformin has historically been used to treat women with PCOS by increasing levels of sex hormone binding globulin, which may then reduce levels of insulin, free testosterone, and LH.\textsuperscript{36} However, metformin is no longer supported in the literature as monotherapy for ovulation induction, unless the patient has diabetes or displays signs of metabolic syndrome.\textsuperscript{36} When metformin was used in combination with clomiphene, only slight improvements in ovulation rates were observed, falling just barely within the statistically significant threshold.\textsuperscript{36} In addition, metformin is known to cause a variety of untoward adverse reactions, including abdominal bloating, nausea, cramps, and diarrhea, and should always be started at the lowest possible dose, with slow titration upward.

\textbf{Referrals}

When treating patients in primary care who meet criteria for infertility, obtain all required lab results including SA while initiating a referral to a fertility specialist. Due to long wait times, it is important to start the referral process early, as it can always be cancelled if pregnancy is achieved while being managed in primary care. Referral to other specialists should be initiated when positive subjective and objective findings are discovered, as previously mentioned.

\textbf{Conclusion}

Although infertility rates are steadily increasing, timely diagnosis and management of fertility issues within
primary care settings is lacking. A thorough health history is the first critical step in diagnosing infertility, allowing NPs to identify possible etiologies or comorbidities and guiding further investigations and treatment options. Emotional and psychological hurdles can be identified early through screening tools, as they represent a significant barrier to achieving pregnancy.

NPs provide continuity of care within the primary care model allowing ongoing patient communication and timely follow-up, which were identified as barriers in the literature when accessing specialist care. Assessments and treatments within the primary care setting should not negate a referral to a fertility specialist, who can offer more comprehensive consultation and treatment options. Primary care NPs are in an ideal position to identify clients at risk and initiate early investigations and treatments with the goal of optimizing patients’ fertility outcomes and quality of life.

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