

# Evaluation of women with infertility

By Jordan Vaughan, MSN, WHNP-BC

## Faculty

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## Intended audience

This continuing education (CE) activity has been designed to meet the educational needs of women's health nurse practitioners (NPs), adult NPs, family NPs, certified nurse midwives (CNMs), and other healthcare providers (HCPs) who care for reproductive-aged women.

## CE approval period

Now through May 31, 2018

## Estimated time to complete this activity

1 hour

## CE approval hours

1.0 contact hour of CE credit

## Needs assessment

As many as 15% of couples trying to conceive a child are diagnosed with infertility, defined as the inability to conceive within 1 year despite unprotected intercourse. Because advancing maternal age is a driving force in the decline in fertility, the time span in the definition may reasonably be altered to 6 months for women older than 35. Although referral to a specialist in reproductive endocrinology and infertility (REI) is considered early in the assessment of infertility in women with endometriosis, tubal disease, a history of three or more spontaneous abortions, and the like, advanced practice nurses (APNs) can initiate the evaluation of women who do not have a complicated history and who have not previously tried ovulation induction medications, are anovulatory, or have polycystic ovary syndrome. If pregnancy is not achieved after 3-6 months under the APN's care, referral to an REI specialist is suggested.

## Goal statement

Advanced practice nurses will know how to conduct the evaluation of women who present with infertility, as well as when to refer to an REI specialist.

## Educational objectives

At the conclusion of this educational activity, participants should be able to:

1. Identify essential elements of the personal and family history and physical examination in the evaluation of a woman with infertility.
2. Describe the various types of diagnostic testing used to evaluate ovulatory function, ovarian reserve, and tubal patency.
3. Recognize when to seek referral to a specialist in REI.

## Accreditation statement

This activity has been evaluated and approved by the Continuing Education Approval Program of the National Association of Nurse Practitioners in Women's Health (NPWH), and has been approved for 1.0 contact hour of CE credit.

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**Jordan Vaughan, MSN, WHNP-BC**, states that she receives consulting fees from the Family Planning National Training Center and serves on the Speakers' Bureau for EMD Serono.

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Advanced practice nurses (APNs) may be the first point of contact in a woman's lengthy fertility journey. Although caring for a patient with infertility is within the scope of practice of APNs, this process can be intimidating and complex. APNs need to set realistic expectations, educate patients, and provide initial management. The author discusses the initial evaluation of a woman with infertility prior to a referral to a reproductive endocrinology and infertility specialist if necessary.

**KEY WORDS:** infertility, infertility evaluation, ovulatory dysfunction, ovarian reserve, tubal patency

As many as 15% of couples trying to conceive a child are diagnosed with infertility, defined as the inability to conceive within 1 year despite unprotected intercourse.<sup>1</sup> Because advancing maternal age is a driving force in the decline of fertility, the time span in the definition may reasonably be altered to 6 months for women older than 35 years. Overall fertility rates, which peak between the ages of 20 and 24 years, are 4%-8% lower in women aged 24-29, 15%-19% lower in those aged 30-34, 26%-46% lower in those aged 35-39, and as much as 95% lower in those aged 40-45.<sup>1</sup>

Infertility is a complex diagnosis that can greatly affect physical, mental, and financial aspects of a couple's life together.<sup>2</sup> In general,

infertility is considered a *couple's* diagnosis because 35%-40% of cases are due to male factors, 30%-40% to female factors, and up to 30% to a combination of male and female factors or unexplained factors.<sup>1</sup> Common causes of infertility in women are ovulatory dysfunction and tubal/peritoneal pathology, and a common cause of infertility in men is a sperm abnormality.<sup>3</sup>

Referral to a specialist in reproductive endocrinology and infertility (REI) is considered early in the assessment of infertility in a woman with endometriosis, tubal disease, a history of three or more spontaneous abortions, or previous ovulation induction, or in a case of male factor infertility. When known risk factors exist, or when a woman

is older than 35 years, APNs should not wait to initiate assessment and referral until a couple has tried to conceive for a full year. However, women who have not previously tried ovulation induction medications, are anovulatory, have polycystic ovary syndrome (PCOS), or have unexplained infertility may be treated by an APN for 3-6 months prior to referral.<sup>4</sup> Male factor infertility may be addressed with an intra-uterine insemination if an andrology laboratory is available. Knowing the appropriate components and timing of an infertility assessment is essential.

### History

The APN takes a thorough history from each partner. The APN needs to learn how long the couple has been trying to conceive and the results of any previous evaluation to ensure that testing is not repeated unnecessarily.

### The woman

A full menstrual history is obtained, including age at menarche, cycle length, characteristics of bleeding, and presence or absence of moliminal symptoms (e.g., bloating, breast tenderness). Absence of moliminal symptoms may suggest anovulation.<sup>1</sup> The woman is asked about prior contraception use; her obstet-

ric history, including pregnancy outcomes and complications (e.g., ectopic pregnancy, cesarean delivery, dilation and curettage procedures); past surgeries; current medications; recent weight changes; signs and symptoms of thyroid disease; pelvic or abdominal pain; galactorrhea; hirsutism; and dyspareunia. A history of chlamydia, gonorrhea, or pelvic inflammatory disease (PID) increases the potential for tubal damage and raises suspicion of tubal infertility disease.<sup>1,5</sup>

A thorough family history includes a discussion of reproductive outcomes and the existence of birth defects, mental retardation, early menopause, and/or genetic abnormalities.<sup>1</sup> The American Congress of Obstetricians and Gynecologists recommends taking a detailed family history and, depending on a woman's ethnicity, performing preconception carrier screening for cystic fibrosis, sickle cell disease, Tay-Sachs disease, thalassemia, familial dysautonomia, and Canavan disease.<sup>6</sup>

### The man

Male infertility may be influenced by lifestyle factors (e.g., obesity; use of certain medications, alcohol, or tobacco) or a genetic condition (e.g., cystic fibrosis) or it may be idiopathic. Evaluation begins with a thorough reproductive history to assess for coital frequency and timing, duration of infertility, results of any past evaluations, childhood illnesses (e.g., mumps), systemic illness (e.g., diabetes mellitus, hypertension), past genitourinary surgery (e.g., orchiectomy, hernia repair), sexual history (e.g., erectile dysfunction, history of sexually transmitted infections), and exposure to environmental toxins.<sup>7</sup> The history entails a thorough review of systems, a complete family reproductive history, and a social history, including use of rec-

reational drugs, steroids, tobacco, or alcohol (these substances can affect semen parameters).

## Physical examination

### The woman

The APN performs a targeted physical examination to explore causes of infertility. Weight and body mass index (BMI) are calculated. Ovulatory dysfunction may occur at any BMI level but is more common when it falls outside the healthy range (20-24 kg/m<sup>2</sup>).<sup>1</sup> The thyroid is assessed for enlargement, presence of nodules, or tenderness. Signs of androgen excess (e.g., hirsutism, acne) are noted, as are characteristics of any breast/nipple discharge. Abdominal and bimanual exams are performed to assess for tenderness, organ enlargement, and masses. Pelvic tenderness in the posterior cul-de-sac or uterosacral ligaments may indicate endometriosis. The uterus is palpated for enlargement or immobility, which may indicate fibroids, uterine anomaly, endometriosis, or pelvic adhesions.<sup>8</sup> A speculum exam is done to assess the cervix for the presence of abnormalities, secretions, or discharge, which may suggest a pelvic infection.

### The man

In the absence of a history of trauma, surgery, genital abnormality, or sexual dysfunction, the physical exam of the man may be deferred pending a semen analysis. An abnormal history or semen analysis finding warrants a physical exam by a urologist or an REI specialist. If a physical exam by the APN is deemed appropriate in a given case, it consists of an inspection of the penis, noting the location of the urethral meatus and the presence of hypospadias; palpation of the testes; ascertainment of the presence and consistency of the vas deferens and

the epididymis; and determination of the presence of a varicocele. The APN notes the presence of secondary sex characteristics such as stature, hair distribution, and breast tissue distribution. A digital rectal exam may be considered to evaluate the prostate.<sup>1</sup>

## Diagnostic testing

### Ovulatory function

In order for a woman to conceive, several components are necessary: ovulation, patent Fallopian tubes, a suitable uterine environment, and motile sperm capable of fertilization. Ovulatory dysfunction accounts for up to 40% of female infertility cases and is identified in about 15% of couples.<sup>1</sup> Ovulation may be assessed by a mid-luteal progesterone level, an ovulation predictor kit, basal body temperature (BBT) measurements, or mid-cycle ultrasound. In some cases, a menstrual history may be sufficient. If a woman does not have regular and predictable menstrual cycles occurring every 21-35 days, further evaluation is necessary.

A mid-luteal progesterone level is assessed 7 days before expected menses; for a woman with a regular 28-day cycle, progesterone is assessed on cycle day 21.<sup>8</sup> For a woman with irregular cycles, this assessment may occur later in the menstrual cycle. A progesterone level greater than 3 ng/mL provides evidence of recent ovulation, although levels greater than 10 ng/mL better reflect good luteal function.<sup>9</sup> If the progesterone level is less than 3 ng/mL, the level is rechecked 5-7 days later. If the level remains low, the woman is further evaluated for anovulation.

A woman may choose to use an ovulation predictor kit, also known as a urine luteinizing hormone (LH) kit, to track her ovulation. A woman begins using daily test strips several



days before anticipated ovulation to identify the mid-cycle LH surge that precedes ovulation by about 36 hours. The test kit identifies peak fertility as the day of the surge and the following day. The kit is not reliable for all women, particularly those with premature ovarian failure or PCOS, because LH levels may already be elevated.

Although not widely recommended, another option for ovulation detection is the BBT method, an inexpensive way to look retrospectively at the ovulation time frame. An oral temperature is taken at the same time every morning before rising. About 2 days following ovulation, a woman's temperature rises roughly 0.5° F. Charting this temperature shift can help a woman better identify her ovulation pattern and peak fertility in subsequent months. Of note, evaluating an increase in cervical mucus or using an ovulation predictor kit has been found to be more reliable than BBT in terms of attempting to achieve a pregnancy in the current cycle.<sup>10</sup>

### Ovarian reserve

Oocytes decrease in quantity and quality as women age and are incapable of regenerating. The number of human oocytes peaks at 6-7 million at 20 weeks' gestation; by the time a female reaches puberty, only 300,000-500,000 oocytes remain. During her lifetime, a woman will ovulate 400-500 eggs. To assess a woman's fertility potential and determine a treatment plan, the APN must first assess ovarian reserve, which is done by measuring basal follicle-stimulating hormone (FSH), estradiol, and anti-Müllerian hormone (AMH) levels and performing ovarian imaging early in the follicular phase to evaluate the antral follicle count (AFC).

There is debate regarding the age at which to begin ovarian reserve testing. Current thinking is to recommend such testing for women older than 35 years who have not conceived after 6 months of regular unprotected intercourse.<sup>11</sup> The APN may consider testing a woman at an earlier age if certain risk factors are present: anovulation, family history of early menopause, certain genetic conditions such as fragile X or Turner syndrome, history of endometriosis or pelvic infection, previous ovarian surgery, history of cancer treated by gonadotoxic therapy or pelvic radiation, and tobacco use.

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Ovarian reserve testing is not infallible and it does not determine the end of a woman's reproductive capability, nor does it predict the rate in which reproductive potential will diminish. The purpose is to assess the quality and quantity of the remaining oocytes to predict reproductive potential and, for the APN, the time to refer to a specialist. When results fall outside the normal range, the APN can encourage the patient to pursue more aggressive treatment options, which often include referral to an infertility special-

ist. Ovarian reserve can be assessed by measuring/doing the following:

### Basal follicle-stimulating hormone/estradiol

Low estradiol levels early in each menstrual cycle trigger increased secretion of gonadotropin-releasing hormone, leading to increased release of FSH. Then, as the developing cohort of follicles produces estradiol and inhibin B, the increased FSH is suppressed by negative feedback. As a woman ages, a smaller cohort of follicles is available to produce estradiol and inhibin B, which increases secretion of FSH. The robust secretion of FSH stimulates rapid follicular growth and higher estradiol levels, resulting in a shorter follicular phase.<sup>11</sup>

Estradiol and FSH levels are measured on menstrual cycle days 2-4. FSH values greater than 10 mIU/mL are associated with diminished ovarian reserve and poor response to ovarian stimulation. Because each menstrual cycle can vary, a single elevated FSH level does not predict an inability to conceive and, therefore, has limited reliability.<sup>12</sup> During follicular development, estradiol is released from the developing follicles. In the early follicular phase (typically, cycle day 2-4), the estrogen level is usually less than 50 pg/mL. An elevated value (>60-80 pg/mL) may indicate oocyte depletion.<sup>13</sup> For measurements to be meaningful, *both* FSH *and* estradiol levels are drawn on menstrual cycle days 2-4.

### Clomiphene citrate challenge test

The CCCT may be considered for ovarian reserve testing, although it does not clearly improve FSH and estradiol test accuracy for predicting poor ovarian response or pregnancy after *in vitro* fertilization (IVF).<sup>14</sup> The test requires measurement of cycle day 3 FSH and estradiol levels,



## Box. Patient education resources on infertility

American Society for Reproductive Medicine:

- **Infertility: An Overview. A Guide for Patients<sup>B</sup>**
- **Diagnostic Testing for Female Infertility<sup>C</sup>**

American College of Obstetricians and Gynecologists:  
**Evaluating Infertility<sup>D</sup>**

Brigham and Women's Hospital:  
**Patient Education, Support and Consent Forms<sup>E</sup>**

American Family Physician: **Infertility: What Women Should Know<sup>F</sup>**

CDC: **Infertility FAQs<sup>G</sup>**

followed by administration of clomiphene citrate 100 mg on cycle days 5-9. An FSH level is drawn again on cycle day 10; it should remain below 10 mIU/mL. If either the FSH or the estradiol level on day 3 or the FSH on day 10 is elevated, the patient likely has impaired ovarian function and a referral is warranted. Use of the CCCT has declined because newer tests such as AMH and AFC are simpler and have high predictive values.<sup>11</sup>

### Serum anti-Müllerian hormone

Anti-Müllerian hormone is secreted by the granulosa cells of the pre-antral follicles and is reflective of the primordial oocyte pool.<sup>15</sup> As women age and the number of oocytes decreases, the AMH level drops as well. The AMH level may be an earlier predictor of decreased ovarian reserve than FSH levels; it begins to decline early in the ovarian aging process, whereas elevated serum FSH levels are not found until cycles are already irregular.<sup>16</sup> The advantage of determining the AMH level is that it remains constant throughout the menstrual cycle and may be drawn at any time.<sup>11</sup> Evidence suggests that AMH levels may be diminished with oral contraceptive use and in women with obesity.<sup>17</sup> By contrast, women with PCOS have been noted to have AMH levels 2-3 times higher than unaffected women. Overall, an AMH value of 1.0 mg/mL predicts an

FSH value of 10.0 mIU/mL. Higher AMH levels suggest normal ovarian function, whereas lower levels have been associated with poor ovarian stimulation and poor pregnancy outcomes.<sup>18</sup> Women whose levels fall outside the normal range should be referred to an REI specialist.

### Antral follicle count

Ultrasound, although expensive, is another useful tool in evaluating ovarian reserve. AFC is the sum of the antral follicles in both ovaries early in the follicular phase (cycle days 1-4). Antral follicles have been defined as measuring 2-10 mm in diameter. A total of 3-6 antral follicles is considered low, and is associated with poor response in IVF. However, a low value is not predictive of a patient's ability to conceive.<sup>19</sup> No single test has 100% specificity and sensitivity; biochemical assays and imaging should be used in combination to most accurately evaluate ovarian reserve.

### Tubal patency

Impaired tubal patency is another common cause of infertility. When tubal disease is suspected by patient history (e.g., chlamydia, gonorrhea, PID, previous ectopic pregnancy, tubal surgery), a hysterosalpingogram (HSG) is considered.<sup>8</sup> An HSG can evaluate tubal patency and may have some therapeutic benefit. HSG is typically performed in the late

follicular phase, or 2-5 days after the end of menstruation. An HSG can document tubal patency and uterine abnormalities, including filling defects (polyps and fibroids) and uterine malformations (e.g., septum, bicornuate uterus). If an abnormality is noted, a referral is warranted.

### Semen analysis

For the male partner, a semen analysis is considered early in the evaluation. This analysis is the most accurate evaluation of male fertility and can be used as a cost-effective way to quickly exclude male factors as the cause of a couple's infertility. If the semen analysis yields normal results, attention is then focused on the female partner.

Prior to semen collection, the male partner should have an abstinence window of 2-5 days (2-3 days is preferred).<sup>20</sup> The analysis may be performed in a fertility center or a urology office where an andrology lab is available. The semen sample is collected in a sterile container provided by the lab. If the man chooses to collect the sample outside the lab, it must be kept warm and delivered within 1 hour of collecting. Normal results for a semen analysis include a volume of 1.5 mL or greater, more than 39 million sperm per ejaculate, total motility of 40%, progressive motility (linear movement) of 32%, and 4% normal forms. If the analysis

yields abnormal findings, efforts are made to identify modifiable factors to improve the natural ability of the man's sperm to fertilize an ovum. Because semen samples can fluctuate, the semen analysis is repeated in 4-6 weeks. If results remain abnormal on repeat evaluation, referral to an infertility specialist is advised.<sup>7</sup>

## Conclusion

A diagnosis of infertility is life altering for many couples, with lasting psychological impact. The cause of infertility is often multifactorial and complex, leading to frustration in both providers and patients. Because of the substantial emotional, financial, and physical burden to patients, providers must practice with a holistic and therapeutic approach. APNs are in an excellent position to provide this holistic care for their patients, addressing aspects of both physical and emotional well-being. Resources for patients are listed in the *Box*.

Much of fertility testing is cycle dependent and cannot be completed at a single visit. Therefore, a month or more may be spent completing diagnostic testing before treatment takes place. The APN must assess patient expectations and explain that the evaluation takes time. Once test results are received, the APN may decide to treat with ovulation induction medication (e.g., clomiphene citrate) and timed intercourse for several months or refer to an REI specialist. Because of the length and intimacy of the evaluation, patients may feel more comfortable working with an APN with whom they have already established a trusting relationship before referral to a specialist. ●

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## Web resources

- A. [npwh.org/courses/home/details/832](http://npwh.org/courses/home/details/832)
- B. [reproductivefacts.org/Booklet\\_Infertility\\_An\\_Overview/](http://reproductivefacts.org/Booklet_Infertility_An_Overview/)
- C. [reproductivefacts.org/FACTSHEET\\_Diagnostic\\_Testing\\_for\\_Female\\_Infertility/](http://reproductivefacts.org/FACTSHEET_Diagnostic_Testing_for_Female_Infertility/)
- D. [acog.org/Patients/FAQs/Evaluating-Infertility](http://acog.org/Patients/FAQs/Evaluating-Infertility)
- E. [brighamandwomens.org/Departments\\_and\\_Services/obgyn/Services/infertility-reproductive-surgery/infertility-services/education-consent-forms.aspx](http://brighamandwomens.org/Departments_and_Services/obgyn/Services/infertility-reproductive-surgery/infertility-services/education-consent-forms.aspx)
- F. [aafp.org/afp/2015/0301/p308-s1.html](http://aafp.org/afp/2015/0301/p308-s1.html)
- G. [cdc.gov/reproductivehealth/Infertility/](http://cdc.gov/reproductivehealth/Infertility/)