The evaluation of female infertility

Simon M Kelly MB ChB FRANZCOG, Togas Tulandi MD FRCSC FACOG

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There is considerable debate regarding the most appropriate method of investigating female infertility. Ideally, the process should be diagnostically accurate and prognostically useful. It should be performed within an acceptable timeframe and be as minimally invasive as possible. It should also conform to the couple's wishes. The present paper is a critical review of the investigative process as it pertains to ovarian, tubal and uterine factors. Advanced transvaginal ultrasound techniques play a pivotal role in the modern evaluation of female subfertility and may replace more traditional invasive procedures such as laparoscopy and hysteroscopy. A critical review of the essential components of female infertility investigation is presented.

Key Words: *Doppler ultrasound; Fecundability; Hysterosalpingocontrastsonography; Pivotal ultrasound; Subfertility*

Survol : Évaluation de l'infertilité chez la femme

RÉSUMÉ : Un débat fait rage actuellement au sujet de la méthode la plus appropriée pour vérifier les problèmes d'infertilité chez la femme. Idéalement, le processus devrait être précis sur le plan diagnostique et utile sur le plan pronostique. Il devrait être effectué à l'intérieur d'un échéancier acceptable et être aussi peu effractif que possible. Il devrait également se conformer aux souhaits du couple. Le présent article fait le point de façon critique sur le processus diagnostique associé aux facteurs ovariens, tubaires et utérins. Les techniques d'échographie transvaginale de pointe pourraient jouer un rôle déterminant dans l'évaluation de l'infertilité féminine de nos jours et être appelées à remplacer les interventions traditionnelles plus effractives, comme la laparoscopie et l'hystéroscopie. On présente ici, une vue d'ensemble critique sur les composantes essentielles de l'examen de la femme infertile.

The term 'infertility' can be broadly defined as a reduced ability for conception compared with the mean ability of the general population. In practical terms, clinicians generally use a more specific definition. Of most favour is a couple's inability to conceive after one year of unprotected intercourse. It is at this point that most couples are advised to seek the advice of a fertility specialist (1).

Although the present review is aimed at the optimal assessment of female infertility, it is a central dogma that, in most cases, appropriate assessment should involve the couple and should not be centred on an individual.

It is well recognized that a diagnosis of infertility has many potential psychological sequelae for a couple. Feelings of guilt, anger, frustration, grief and depression are common (2). The health care professional's approach in dealing with these couples is vital to minimizing these potentially detrimental sequelae. Indeed, the term 'infertile' is, in itself, often very emotive for couples.

A useful approach at the initial consultation is to discuss with the couple the meaning of the terms that are used by clinicians, and to discuss 'normal' fertility and what we mean by 'reduced' fertility. There are some very useful pieces of information that couples can be given to help them understand their individual situation.

For instance, the reason why the definition of infertility is set at 12 months of unprotected intercourse is that, in approximately 85% of couples, conception occurs within the first year. This figure increases to more than 90% with

Department of Obstetrics and Gynecology, McGill University, Montreal, Quebec
Correspondence: Dr Simon M Kelly, McGill Reproductive Centre, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, Quebec H3A 1A1.
Telephone 514-842-1231 ext 36861, fax 514-843-1496, e-mail simon.kelly@muhc.mcgill.ca

24 months of unprotected intercourse, but tends not to increase significantly thereafter. For couples attempting to conceive their first child, the average time to conception is approximately five to six months. For subsequent conceptions, the average duration is three to four months (3). For some couples, the investigation process may be initiated earlier – particularly in older female patients or in patients with a history of amenorrhea.

Fecundability is a term that is used commonly to describe the chance of conception in a given timeframe. Conventionally, monthly fecundability is used, and for a couple in whom the female is around the age of 30 years, the chance of conception is approximately 20% to 25% per month ('fecundity' is the term used to describe the monthly chance of achieving a live birth, which, by necessity, is lower). Couples are often surprised at this figure, but it is useful as a comparison when discussing the influences of female age on fertility or when explaining success rates of various fertility treatments.

The significance of female age on fertility is often underemphasized. By way of example, the same couple described above, with fecundability of 20% to 25%, would have approximately 5% fecundability if the woman were approximately 40 years of age. There is a steady decline in fecundability from the age of 30 over the subsequent decade and this is accelerated from the age of 38 years. In addition, because miscarriage rates are also age related, there is a proportionally greater decline in fecundity, especially over the age of 35 years (4,5).

It is useful to subclassify the term infertility because it includes both men and women who are sterile and who have no possibility of conception, as well as those who are subfertile. In fact, while sterility may refer to either the man or the woman, subfertility is a term that pertains to the couple.

Above all, health professionals need to provide a service that not only meets the medical needs of couples with fertility problems, but also understands their unique emotional and educational situation. This is best provided by a team-based approach involving clinicians, nurses, scientists and psychologists, where appropriate (6).

THE INITIAL CONSULTATION

The primary aim of the investigation of infertility is to provide an accurate diagnosis in a manner that is rational and performed with a minimum of intervention within a limited timeframe. It is often not until a diagnosis is reached that the couple can be given an accurate prognosis. This prognosis may have far reaching implications for the couple, including emotional and financial issues.

The focus of the present review is on evaluating aspects of female fertility. In reality, it is ideal for both partners to be present at the initial consultation; hence, a more complete history can be obtained.

A detailed history of the female partner should commence with determining her age and the duration of infertility. A comprehensive reproductive history is essential and should include the following:

- Age at menarche;
- Menstrual cycle – length and regularity, duration of flow, dysmenorrhea;
- Gravidity and parity, including pregnancy outcome;
- Previous fertility investigations or treatment;
- Contraceptive use – methods and duration;
- Coital frequency – problems such as impotence, anorgasmia, dyspareunia;
- Gynecological history – surgery, sexually transmitted diseases, cervical smear history.

At this point, it is worth clarifying the presence or absence of particular symptoms that may suggest possible diagnoses. These include pelvic or abdominal pain, galactorrhea, hot flushes, hirsutism, weight gain or loss, and symptoms of thyroid dysfunction. It is also important to assess whether there are any extraordinary psychological stressors.

A medical and social history should include the following:

- Any major illnesses, injuries or surgical procedures;
- Current or past medications and allergies;
- Family history of medical problems, reproductive problems or congenital defects;
- Occupation, including potential toxin exposure, levels of stress;
- Tobacco, alcohol or recreational drug use.

A physical examination should also be performed at the initial consultation and should include the following:

- Weight and body mass index;
- Vital signs;
- Thyroid palpation;
- Evaluation of normal or abnormal hair distribution;
- Assessment of stigmata of endocrine disease, such as striae, buffalo hump, acanthosis nigricans (a marker of insulin resistance);
- Breast examination as indicated;
- Abdominal examination;

- Pelvic examination with an emphasis on detecting any vaginal or cervical abnormalities, uterine size and mobility, adnexal masses or tenderness, and any cul de sac tenderness or nodularity.

The pelvic examination is an opportune time to perform a Pap smear if one has not been performed within the previous 12 months. In addition, a culture swab for chlamydia may also be taken.

INVESTIGATIONS

Although the process of investigation is largely a standardized one, a thorough history and examination allow one to individualize. The extent and duration of the investigative process are tempered by the patient's age and duration of infertility, as well her and her partner's wishes.

Following a normal semen analysis, the investigative process should focus on the areas of female fertility in which problems most commonly arise. From a practical perspective, a simple method is to categorize the process into ovarian, tubal and uterine assessment.

Ovarian function

In approximately 20% of couples, the cause of infertility is ovulatory dysfunction. Often, women present with a history of irregular menses or secondary amenorrhea. In particular, when the menstrual cycle is either short or prolonged, it is often suggestive of disordered ovulation.

There are a number of methods available to determine whether a patient is ovulating regularly. Despite the available tests, it is often said that the only proof of 'normal' ovulation is the development of a subsequent pregnancy.

There are both direct and indirect methods of investigation (7). Direct determination of ovulation requires the detection of follicle rupture, either via laparoscopy or ultrasound. The use of high resolution transvaginal ultrasound affords the visualization of the corpus luteum and/or the appearance of follicular fluid in the pouch of Douglas. However, from a practical perspective, these methods are invasive and are not cost effective. They are indicated only if the presence of luteinized unruptured follicle is suspected.

Indirect assessment of ovulation can be achieved by a number of methods.

Basal body temperature (BBT): An elevation in BBT taken early in the morning, and its persistence from days 11 to 16 of the menstrual cycle, provides retrospective evidence of ovulation. It is not a particularly concise method and cannot be used reliably to define the time of ovulation (8).

Urinary luteinizing hormone (LH): There are many commercially available kits to detect the LH surge before ovulation. Most patients commence testing around day 11 of their menstrual cycle, and an evening urine sample appears to correlate most strongly with serum LH levels. Ovulation occurs, on average, within 24 to 36 h of a positive test. It is a useful adjunct for timed intercourse or insemination treatment (9).

Luteal phase endometrial biopsy: Luteal phase endometrial biopsy can be performed one to four days before expected menstruation. The histological appearance of secretory endometrium implies progesterone production following ovulation. The endometrium can also be dated using established criteria (Noyes' Criteria) (10). Results are often reported in terms of being in or out of phase with the day of the menstrual cycle. It is not advocated routinely as a test for ovulation alone simply because of its invasive nature and the possibility that it may interfere with pregnancy. It may be advocated for the diagnosis of luteal phase defect (LPD), where a delay in maturation of longer than two days is the recognized diagnostic criteria. However, there is considerable debate about this and the existence of LPD itself (11).

Midluteal serum progesterone (MLP) level: MLP level is the most accepted method of ovulation determination. Progesterone rises significantly after ovulation. Although units may vary, it is generally accepted that a level of at least 3 ng/mL (10 nmol/L) taken on days 18 to 22 of the menstrual cycle is confirmation of ovulation. However, a level greater than 10 ng/mL (32 nmol/L) is correlated more strongly with a normal luteal phase (12).

In addition to determining ovulation, there are a number of other hormonal investigations that should be considered routinely.

Serum follicle stimulating hormone (±LH): Serum FSH should be performed on any patient when fertility treatment may be contemplated. A day 3 FSH level is a widely accepted measure of 'ovarian reserve'. It is particularly important in older women (older than 35 years of age), when there is a history of potential ovarian trauma from surgery, infection or endometriosis, or when there has been a previous poor response to fertility medications. From a practical point of view, most clinicians consider that a day 3 FSH level of greater than 10 mIU/mL is evidence of impaired ovarian reserve (13). These patients are likely to respond less well to fertility medications and have a lower fertility potential. The higher the FSH level, the stronger the correlation. In patients with amenorrhea, a serum FSH level differentiates patients with ovarian failure (high FSH level) from those with hypothalamic dysfunction (low FSH level).

A significant number of patients with polycystic ovarian syndrome have a typically elevated LH level in comparison with their FSH level. These patients are at risk of ovarian hyperstimulation during fertility treatment.

Serum thyroid stimulating hormone (TSH): Thyroid dysfunction is relatively common in women of reproductive age, and significant hyperthyroidism or hypothyroidism may interfere with reproductive function. There is also some evidence to suggest that even a subtle reduction in TSH may be associated with increased neurological problems in the offspring of these women (14). Many clinics now include TSH as a routine investigation.

Serum prolactin: Hyperprolactinemia may lead to amenorrhea and anovulation. Serum prolactin should be measured under basal conditions and the generally accepted normal range is 30 to 40 ng/mL (600 to 800 mIU/mL).

Approximately 50% of patients with an elevated prolactin level have galactorrhea (15). TSH level should be measured to exclude hypothyroidism in patients with a high serum prolactin level. In addition, pituitary imaging should be considered to determine the presence of a microadenoma (smaller than 1 cm) or macroadenoma (larger than 1 cm).

Tubal function

Tubal disease occurs in 15% to 20% of patients presenting with infertility (16). There are a number of investigations available to assess tubal patency and, to some extent, their use depends on the available resources and expertise of individual fertility centres. The investigations are not necessarily independent of one another and accurate diagnosis may require more than one form of assessment.

Hysterosalpingogram (HSG): HSG is the most widely used method of assessing tubal patency. It is an outpatient x-ray procedure involving instillation of either water- or oil-based contrast media into the uterine cavity (17). It not only provides information about tubal patency, but also delineates the uterine cavity. It is performed during the first half of the menstrual cycle – after the end of menstruation and before ovulation (normally between days six and 10 of the cycle). It is advisable to screen for chlamydia before the procedure and to treat if necessary, or to routinely give antibiotic prophylaxis. There is a 1% to 2% risk of pelvic infection following HSG.

Laparoscopy with chromopertubation: This procedure is the 'gold standard' method of tubal assessment. Under laparascopic vision, a solution of methylene blue (or indigo carmine) is injected into the uterine cavity and, hence, the fallopian tubes. Laparoscopy with chromopertubation also demonstrates peritubal adhesions or endometriosis that cannot be detected with a more conventional HSG.

In most situations, laparoscopy is reserved as a second line investigation, if it is required. This is due to a number of factors, including the risks associated with an operative procedure, the excess cost above other simpler investigations and the possible waiting time required for patients to undergo this investigation (18).

In some conditions, including endometriosis, periadnexal adhesions or tubal blockage, laparascopic treatment is indicated. Instead of performing laparoscopy for diagnostic purposes only, it is preferable to combine both diagnosis and treatment in the same setting.

Hysterocontrastsonography (HyCoSy): High resolution transvaginal ultrasound can be used in combination with echo-sensitive contrast agents to assess tubal patency. It may be used to provide information regarding the uterine cavity and tubal patency on a par with traditional HSG (19). There is an additional benefit in that HyCoSy can be combined with a pelvic ultrasound assessment. Pain score studies have shown that it is more acceptable to patients than is HSG (20).

One of the difficulties with HyCoSy is that it is rarely possible to demonstrate the complete length of the fallopian tube in one scanning plane. The addition of power Doppler, which is sensitive to low flow, can be used to overcome this problem. If available, three-dimensional power Doppler imaging enables the operator to capture a volume of contrast along the entire tube length. Using surface rendering software, a three-dimensional image of the tube with intraperitoneal spill can be obtained (21).

The routine application of HyCoSy is dependent primarily on the availability of appropriate equipment and scanning expertise.

In most situations, HSG is the first line investigation of tubal patency.

Uterine assessment

Specific problems of the uterus are not common causes of female subfertility. However, an assessment should be performed, especially before commencing treatment.

During the course of an HSG, the uterine cavity is usually defined and most developmental abnormalities can be identified. Disorders such as polyps, submucous fibroids and intrauterine adhesions may also be seen.

At this point, it is worth mentioning the assessment of cervical factors in relation to subfertility. The postcoital test was designed to evaluate the interaction between sperm and cervical mucus. This has lost favour with many clinicians because the results were often inconsistent, with a significant degree of both intra- and interobserver variation (22). Many clinicians now treat unexplained subfertility directly with intrauterine insemination, thereby avoiding any cervical factor.

There are two predominant methods of assessing the uterus:

Transvaginal ultrasound: In most situations, transvaginal ultrasound is the investigation of choice for assessing uterine and associated pelvic anatomy. It appears to be as effective as, and, in many situations, superior to laparoscopy for identifying uterine lesions.

Three-dimensional ultrasound can be as effective as more traditional diagnostic methods with respect to congenital abnormalities of the genital tract.

Ultrasound has the advantage of being able to assess not only the uterus, but also the endometrium and the ovaries. The concept of a 'pivotal pelvic ultrasound' (Table 1) is now commonplace (23).

Depending on the expertise and resources available, a number of investigations can be performed during this scan.

Apart from an anatomical assessment of the uterus and endometrium, an evaluation of the ovaries can be performed. The appearance of the ovary is important, ie, normal versus polycystic or multicystic, which may not only be diagnostic, but may have significant implications for treatment (24). An assessment of ovarian volume and, in particular, the antral follicle count, has gained acceptance as a highly useful measure of ovarian reserve, particularly in an in vitro fertilization (IVF) program. If Doppler capability is available, an assessment of ovarian stromal flow is also a predictor of ovarian response during IVF (25). Similarly,

TABLE 1
The pivotal pelvic ultrasound assessment

Ideally performed between days 10 and 12 of menstrual cycle
Uterus and uterine cavity
Dimensions
Anomalies or tumours
Endometrium
Thickness
Appearance
Saline contrast sonohysterography
Uterine artery blood flow parameters
Peak systolic velocity (PSV)
Pulsatility index (PI)
Ovarian morphology
Normal, polycystic or multicystic
Position and mobility
Volume and antral follicle count
Follicular size
Ovarian stromal and perifollicular blood flow parameters
PSV
PI
Tubal patency
Hysterocontrastsonography
Presence or absence of free fluid or masses within the pelvis

TABLE 2
Investigations for female infertility

First line investigations
Midluteal serum progesterone level
Day 3 follicle stimulating hormone level
Thyroid stimulating hormone*
Prolactin*
Hysterosalpingogram or hysterocontrastsonography
Pivotal pelvic ultrasound scan (transvaginal)
Chlamydia culture or antibody screen
Cervical Pap smear, if required
Rubella immunity
Second line investigations†
Laparoscopy
Hysteroscopy

**Clinicians should have a low threshold for these investigations; †When diagnosis requires further evaluation or when surgical treatment is indicated*

assessing uterine artery resistance can be useful. Where the pulsatility index is greater than 3.0 (implying elevated resistance), there may be reduced endometrial receptivity (especially if endometrial thickness is less than 7 mm) (26).

The addition of saline contrast helps to delineate endometrial lesions such as polyps or fibroids. Finally, the pivotal scan can be combined with HyCoSy to assess tubal patency.

Hysteroscopy: Hysteroscopy is the definitive method of assessing the uterine cavity. However, it is more invasive than transvaginal ultrasound and is generally reserved for further assessment and possible treatment of abnormalities detected by the above investigations. When patients require laparoscopy, it is prudent to perform simultaneous hysteroscopy.

In general, transvaginal ultrasound is becoming central to the evaluation of female fertility.

Miscellaneous investigations

When performing an initial assessment of a woman with subfertility, there are a number of nonfertility-specific investigations that need consideration.

Cervical Pap smear: This should be done if one has not been performed within the last year.

Chlamydia culture or antibody screen: *Chlamydia trachomatis* is the most common sexually transmitted infection leading to tubal damage and should be screened for in patients with fertility problems. In fact, the combination of a chlamydia antibody titre that is negative and a normal hysterosalpingogram predicts the absence of any major pelvic abnormality in 95% of patients (27).

Rubella immunity: Immunity from rubella should be ascertained in all women in whom pregnancy is a possible outcome. If there is low or no immunity, vaccination should be performed as soon as possible. The rubella vaccine is a live attenuated vaccine and it is recommended that pregnancy be avoided for six to eight weeks after vaccination.

CONCLUSION

There is still much debate concerning the most appropriate investigations for female infertility. Ideally, in the best interests of the couple, an optimal process is one that provides a reliable diagnosis within a reasonable timeframe and affords a useful prediction regarding treatment options and prognosis. Table 2 summarizes the first and second line investigations that are most likely to conform to this ideal.

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