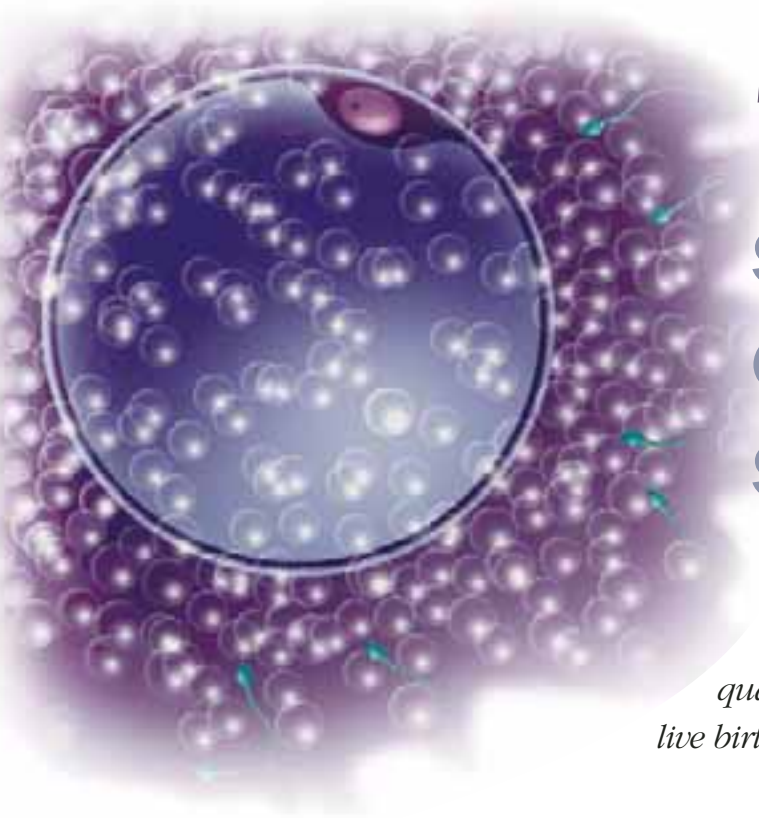

7 easy steps to evaluating subfertility

Before selecting a treatment strategy, the clinician should quantify a couple's potential for live birth. Two experts outline the steps.

BY IAN TUMMON, MD, and DANIEL A. DUMESIC, MD

A 35-year-old nullipara who has not conceived after 2 years of unprotected intercourse presents for treatment. Her primary desire—apart from becoming pregnant—is obtaining a truthful estimate of her prognosis. Obviously, that is our priority as well, since appropriate treatment can be determined only when the prognosis is clearly defined.

Of course, we informally estimate patients' prognoses every day based on their history, physical examination, and laboratory studies. But when it comes to fertility—particularly when the woman is over 30 years of age—a quantified estimate is vital. Here, we outline the steps involved in evaluating a couple for "subfertility" and offer a model for predicting prognosis as precisely

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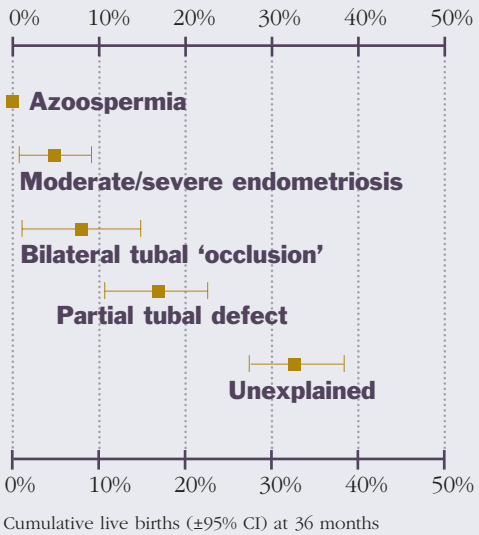
Chance of live birth by diagnostic category

FIGURE 1



Cumulative live births (±95% CI) at 36 months

as possible. We base our recommendations on guidelines from the American Society for Reproductive Medicine (ASRM) and the American Urologic Association (AUA).[1,2] We also searched Cochrane systematic reviews and MEDLINE English-language articles published between October 1, 1991, and October 1, 2001 (using the key words "infertility," "prognosis," and "diagnosis"), as well as the November 8, 2001, issue of the *New England Journal of Medicine*. The prediction model itself originated with Collins and colleagues and Snick et al.[3,4]

Diagnostic categories of subfertility include oligospermia; azoospermia; mild, moderate, or severe endometriosis; bilateral tubal occlusion; partial tubal defects; and unexplained subfertility. Of these, unexplained subfertility carries the best prognosis for spontaneous pregnancy and live birth, while oligospermia and mild endometriosis have an "intermediate" prognosis. The other categories have a poorer prognosis relative to unexplained subfertility (*Figure 1*). A failure to diagnose these problems will delay appropriate treatment.

Ian Tummon, MD

HSG provides a transient boost to pregnancy chances by flushing of the tubes.

1 Basics: the history and physical

A thorough history and physical are the starting point, with special attention focused on signs and symptoms that suggest "a specific cause for infertility and thereby help to direct subsequent diagnostic evaluation."[1] An example would be a woman with irregular menstrual cycles and findings of hirsutism. The history is critical and should emphasize the following questions:[3]

1. How long has the couple been subfertile?
2. Has the partnership produced a prior pregnancy?
3. How young is the female partner?

The answers to these questions form the basis of the couple's prognosis for live birth independent of treatment. The prognosis is poorer if the woman already has been treated by other physicians.[3,4] The baseline prognosis also declines with advancing maternal age and the duration of subfertility.[3,4]

The male partner also should be screened if the couple has failed to conceive after 1 year of unprotected intercourse.[2] An atypical reproductive history or semen analysis is sufficient reason to refer him to a urologist or other specialist for full evaluation.[2]

Interestingly, abnormalities detected during the physical had no effect on the probability of conceiving in one study of 960 couples.[5] On an individual basis, however, physical findings may be highly predictive of subfertility if disorders such as a congenital absence of the vas are discovered.

2 Assess ovulation

Ovulatory factors are a critical part of evaluation. If findings suggest ovulatory dysfunction, further testing will be necessary—possibly including an appraisal of ovarian reserve.[1] Interventions aimed at restoring or improving ovulation should be closely monitored. If the couple fails to conceive within 3 to 6 treatment cycles, further diagnostic evaluation is recommended or—if evaluation is complete—another conception strategy should be tried.[1]

The guidelines suggest assessing ovulatory function by using one or more of the following methods:[1]

- **Menstrual history**
- **Basal body temperature (BBT).** However, it cannot reliably define the time of ovulation
- **Serum progesterone.** Midluteal-phase values exceeding 3 ng/mL are presumptive evidence of ovulation.
- **Urinary luteinizing hormone (LH).** Results generally correlate well with the peak in serum LH, particularly in evening urine specimens. However, the accuracy, reliability, and ease of use vary among tests.
- **Endometrial biopsy.** Histologic examination can confirm secretory endometrial

development, although the accuracy of the criteria used to diagnose luteal-phase defects is questionable. In fact, the accurate assessment by endometrial biopsy of luteal-phase sufficiency may be impossible in some cases, owing to intercycle differences in progesterone production, variations in sampling sites, and interobserver differences in histologic assessment.[6]

- **Serial transvaginal sonography (TVS).** This detects evidence of ovulation by noting the disappearance of the dominant follicle.
- **Thyroid-stimulating hormone (TSH).** This is for women with oligo-ovulation and should be measured with prolactin.
- **Follicle-stimulating hormone (FSH).** This diagnoses premature ovarian failure or hypothalamic amenorrhea in amenorrheic women.
- **Cycle day 3 FSH.** Also known as the clomiphene-challenge test, this is for women over 35 or with previous oophorectomy. Screening for ovarian reserve will not predict fecundity in the general population of subfertile women with ovulatory menstrual cycles.[7] However, screening for ovarian reserve with a day 2-3 serum FSH level is useful for women such as our patient (age >35 years, history of poor ovarian response, or previous oophorectomy).[1]

3 Eliminate postcoital testing

In most cases, postcoital testing should be abandoned.[1] This recommendation is based on a good-quality trial that found that postcoital testing is unpredictive of cumulative pregnancy rates.[8]

Daniel A. Dumesic, MD

The reference standard for assessing tubal patency is laparoscopy.

4 Assess the uterine cavity

A thorough evaluation must include an appraisal of the uterine cavity, with the method tailored to the individual patient.[1] A hysterosalpingogram with water-soluble dye is suggested. The patient should be instructed to use doxycycline for prophylaxis against pelvic infection prior to the hysterosalpingogram and advised to expect the test to be mildly to moderately uncomfortable. In some cases, pain can be severe, especially with abnormal findings.

Two benefits are expected with hysterosalpingography (HSG). One is a determination of whether the shape of the cavity appears normal, whether there is a suggestion of a congenital defect such as a double uterine cavity, or whether acquired abnormalities exist such as distortions of the cavity related to extrinsic compression from leiomyomata. The second is a transient boost to pregnancy chances by mechanical flushing of the tubes. Although hysteroscopy is the reference standard, sonohysterography using saline for visualization has the same diagnostic accuracy for detecting polyps or hyperplasia.[9]

5 Don't neglect tubal factors

Assessment of tubal patency is another key element in the subfertili-

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Key points

- Diagnostic categories of subfertility include oligospermia; azoospermia; minimal/mild or moderate/severe endometriosis; bilateral tubal occlusion; partial tubal defects; and unexplained subfertility.
- The duration of a couple's subfertility, the age of the female partner, and whether the partnership has produced a prior pregnancy form the basis of their prognosis for live birth independent of treatment.
- If a couple fails to conceive within 3 to 6 treatment cycles after ovulation induction, further diagnostic evaluation is recommended.
- The accurate assessment by endometrial biopsy of luteal-phase sufficiency may be impossible in some women.
- In most cases, postcoital testing should be abandoned.

ty investigation.[1] However, because each evaluation method has one or more technical limitations, a confirmatory test with a second method is recommended whenever results are abnormal. For example, HSG shows whether tubes are patent but not whether there are adhesions on the exterior of the tube. (Peritubal adhesions might compromise pick-up of the ovulated oocyte.)

The reference standard for assessing tubal patency is laparoscopy. In comparison, HSG has a sensitivity of 65% and a specificity of 83%. When it comes to evaluating peritubal adhesions, however, HSG is unreliable.[10]

HSG is used for both diagnosis and therapy. When it is used therapeutically, some experts believe the benefits of oil-based contrast media are superior to those of aqueous media. We at first were inclined to agree, since a Cochrane systematic review concluded that HSG with oil-based media enhanced pregnancy chances (compared with no HSG), and that chances of post-HSG pregnancy were greater with oil-based media (compared with aqueous media).[11]

However, most board-certified reproductive endocrinologists choose aqueous media, since it is safer, less expensive, and easier to use.[12] In fact, roughly 90% of reproductive endocrinologists use aqueous media, according to a 1994 survey.[12] In addition, a well-designed, prospective, multisite, randomized comparison of oil and aqueous media, with the power to detect a 10% difference, failed to confirm the superiority of oil-based media.[13] This trial was not included in the Cochrane review.

Comparative studies suggest 2 alternative methods for assessing tubal health. In areas with a high prevalence of chlamydia, the measurement of serum antibodies to chlamydia is as accurate as HSG in diagnosing tubal disease.[14] Contrast hysterosonography concurs with HSG in 70% of cases.[15]

6 Evaluate the peritoneum

When there is a strong suspicion of endometriosis or pelvic adhesions, laparoscopy is recommended, particularly if aggressive empirical therapy is planned that would entail greater than average risk or cost.[1]

Like HSG, laparoscopy is used both diagnostically and therapeutically. Although we consider it a prerequisite for diagnosing endometriosis, the ultrasonographic diagnosis of endometriomata is 90% accurate.[16]

The surgical reduction of dark endometriotic lesions in women with minimal/mild endometriosis appears to be modestly effective (*Figure 2*).[17-19]

7 Look for male defects

As we mentioned earlier, the male partner should be screened if no pregnancy has occurred after 1 year of unprotected intercourse.[2] If risk factors exist—or the male partner is uncertain of his fertility—earlier evaluation may be justified. A reproductive history and 2 semen analyses comprise the initial evaluation.

Unfortunately, we lack "true" reference figures for semen parameters.[2] Nevertheless, despite overlapping parameters between fertile and subfertile populations, subfertility should be suspected if the sperm concentration is less than 13.5 x 10^6/mL, if motility is less than 30%, or if normal morphology is less than 9% using strict criteria.[20]

Even so, the use of strict criteria to assess sperm morphology is not any more accurate than the criteria developed by the World Health Organization (WHO)[21] when it comes to discriminating between fertile and subfertile men.[22] Menkveld and colleagues used

Efficacy of surgical reduction in minimal/mild endometriosis FIGURE 2

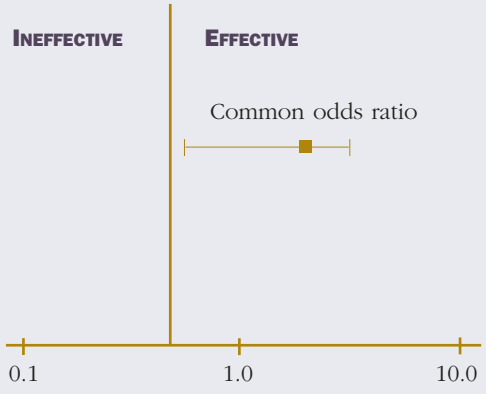

TABLE 1
The effect of historical factors on treatment-independent live birth

	Primary care	Secondary care
Baseline prognosis[a]	28%	14%
Modifying factors	**Relative chance[b]**	**Relative chance[b]**
Age of female partner ≤30 years	1.4 (1.0-1.8)	1.5 (1.1-2.2)
Adjustment factor for each additional year >30	—	0.95 (0.92-0.98)
Duration of subfertility • <24 months=primary care • 24-36 months=secondary care	1.5 (1.2-2.1)	1.7 (1.1-2.5)
Adjustment factor for each additional 12 months of subfertility >36 months	—	0.82 (0.76-0.88)
Previous pregnancy in partnership	1.5 (1.1-2.1)	1.8 (1.2-2.7)

NOTE: Numbers in parenthesis are 95% confidence intervals
[a] After 12 months of unprotected intercourse
[b] Versus entire untreated subfertility population
SOURCE: Collins JA, et al. The prognosis for live birth among untreated infertile couples. *Fertil Steril.* 1995;64:22-28.

receiver operator characteristic (ROC) curves—which relate true-positive results to false-positive results—to study the feasibility of discriminating between fertile and subfertile men using semen parameters.[22] WHO criteria had a marginally greater area under the curve than did strict criteria, with the 95% confidence intervals of the 2 sets of criteria overlapping. (Minimum values for in vivo conception are estimated as 20% normal morphology according to WHO criteria and 3% normal morphology according to strict criteria.[22])

In a population-based study, the probability of pregnancy positively correlated with increasing sperm density up to 40 x 10^6/mL, with no further correlation above this concentration.[23] The proportion of morphologically normal sperm, as measured using WHO criteria, strongly correlated to pregnancy, independent of sperm concentration.[23]

Combined semen parameters also were useful.[24] Using ROC curves and strict criteria for normal morphology, the thresholds (ejaculate) distinguishing fertile from subfertile men were 36 million total motile sperm, 6 million total normal sperm, and 5 million total normal motile sperm.[24]

TABLE 2
Effect of diagnostic factors on treatment-independent live birth

Diagnosis	Relative chance of live birth*
Male defect (sperm density <20 x 10^6 or motility <40%)	0.5 (0.3-0.8)
Endometriosis (aggregate figure for all stages)	0.4 (0.2-0.9)
Tubal defect (aggregate figure for any defect, either bilateral/unilateral or partial/complete)	0.5 (0.4-0.6)

* Versus entire untreated subfertility population.
SOURCE: Collins JA, et al. The prognosis for live birth among untreated infertile couples. *Fertil Steril.* 1995;64:22-28.

Calculating prognosis

How do we quantify our estimate of a couple's prognosis for treatment-independent live birth? Using the patient described at the beginning of this article as an example, we first estimate the chance of spontaneous conception within 12 months leading to live birth. In this case, as Table 1 shows, it would be 28%, since the patient has not been treated by other physicians.[3] (If she had, the chance of treatment-independent live birth would be 14%.) Subsequent steps include:

- **Adjust maternal age.** For a patient such as ours, who is seeking treatment for the first time, no adjustment is necessary. (For secondary care, however, the chance of treatment-independent live birth would decrease by a factor of 0.95 for each year beyond 30, as Table 1 indicates. Thus, we would adjust our estimate for our 35-year-old patient using the following formula: 14% x 0.95^5 = 10.8%.)

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- **Adjust for the duration of subfertility.** For the same patient who is seeking primary care for 24 months of subfertility, the formula would be: 28% x 1.5 = 42%. (The formula for a similar patient undergoing secondary care would be: 10.8% x 1.7 = 18.3%.) (See Table 1.)
- **Consider prior pregnancy in the partnership.** Since there has been none in the patient seeking primary care, our estimate remains at 42%. However, if the couple had previously conceived a child, the formula would be: 42% x 1.5 = 63%. (For the patient seeking secondary care, the formula is as follows: 18.3% x 1.8 = 33%.) (See Table 1.)

Table 2 shows additional adjustment factors in the event that a male defect, endometriosis, or a tubal defect is diagnosed. For example, if tubal disease is diagnosed, the formula for our patient would be: 42% x 0.5 = 21%. (The formula for a patient undergoing secondary care would be: 18.3% x 0.5 = 9.1%.) If more than one of these conditions is diagnosed, the clinician would use only 1 adjustment factor.

A few caveats

Even after a thorough diagnostic workup, a number of elements essential to successful reproduction will remain unknown. Thus, the estimate of treatment-independent live birth has only limited accuracy, since our assessments do not determine whether spermatozoa ascend the fallopian tube, the oocyte is released into the tubal ampulla, fertilization of the oocyte occurs, or whether the developing embryo enters the uterine cavity for implantation. Nevertheless, our model is useful in establishing a couple's baseline fertility by giving an objective estimate of fertility prognosis during diagnostic investigation. It also serves as an important benchmark for determining which therapeutic options are most appropriate and cost-effective. ■

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