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# Problems in Family Practice

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## Female Infertility

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Physicians can play an important role in the prevention of infertility through aggressive treatment of pelvic infections and improved surgical techniques. The cause of infertility can be diagnosed 90 percent of the time. Ovulation, tubal, peritoneal, uterine, and cervical factors should be evaluated. Sperm-cervical mucus interaction should be assessed. Basal body temperature charts are simple and reliable. An endometrial biopsy should be timed for 8 to 10 days after ovulation, histologically dated, and compared with basal body temperatures. Tubal factors are best assessed by hysterosalpingogram and treated by microsurgery. The incidence of pelvic factors increases with age, prior infection, previous surgery, and pelvic pain. Cervical mucus can be studied and changes quantitated by using a simple scoring system. Uterine anomalies increase pregnancy risk but do not usually cause infertility. Clomiphene therapy should be limited to women who ovulate infrequently or not at all. Estrogen improves cervical mucus production; progesterone treats luteal phase defects. Infertile patients are often angry, anxious, and depressed, and additional time should be set aside during an office visit for optimum communication.

There has been a tremendous increase in recent years in knowledge and understanding in the area of reproductive medicine. Excellent references are now available to aid the clinician in the evaluation

and management of the childless couple.<sup>1,2</sup> Still, it is alarming to recall that the human reproductive process is relatively inefficient. Approximately 16 percent of couples experience infertility. The incidence of documented spontaneous abortions, predominantly associated with chromosomal abnormalities, is 16 to 19 percent; the actual incidence is probably slightly higher. Perinatal loss in 1980 nationally was 12.0 per 1,000 births. The incidence of prematurity was approximately 7.1 percent. Of those infants born alive, the incidence of birth defects has been reported as ranging from 0.6 to 13.4

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percent, with an average incidence of significant anomalies being 2.9 percent.<sup>3</sup> Finally, when infertile couples do achieve pregnancy, they experience a higher incidence of spontaneous abortions, ectopic pregnancies, and perinatal deaths when compared with a control study group.<sup>4</sup>

It is imperative that physicians evaluating and treating patients with infertility keep abreast of advances in this field. Certain common practices should be discarded, such as using clomiphene therapy in the patient already ovulating regularly, telling the couple to just "relax," or explaining to a woman with a longstanding menstrual irregularity that she will probably "outgrow" it. Greater emphasis needs to be placed on accurate diagnosis; a cause for the infertility can be diagnosed 90 percent of the time.

### Prevention of Infertility

Although accurate incidence figures of infertility are difficult to obtain, most professionals dealing with reproductive problems believe that the incidence of infertility is increasing. Demographic studies indicate that optimum age for female reproduction is about 24 years.<sup>2</sup> However, in the United States during 1979, the number of first births in women aged 30 to 34 years increased 12.1 percent, and second births increased in the same group 6.7 percent.<sup>5</sup> The incidence of pelvic inflammatory disease is increasing, and its resultant tubal damage is well documented. It has been estimated that following a single clinically apparent episode of pelvic inflammatory disease, the incidence of infertility secondary to tubal destruction is 21 percent.<sup>6</sup> Strong effort must be directed toward making an early diagnosis, using aggressive therapy with appropriate antibiotics, and informing patients about the potential infertility problems associated with pelvic inflammatory disease.

Several investigators have also described reduced fertility in women undergoing appendectomy for perforated and nonperforated appendicitis and ovarian wedge resections.<sup>7,8</sup> The earlier diagnosis of appendicitis, perhaps utilizing laparoscopy in young female patients, and the application of microsurgical principles could potentially

improve fertility outcome. Pelvic adhesions following wedge resection of the ovaries in laboratory animals were significantly reduced when microsurgical techniques were utilized.<sup>9</sup> There is also convincing experimental evidence in animals that high molecular-weight dextran is useful in preventing postoperative adhesions.<sup>10</sup> Surgeons should still concentrate on improving their techniques, paying meticulous attention to hemostasis, using a fine-caliber, minimally reactive suture and considering some adhesion-prevention regimen as part of their armamentarium, particularly when performing surgery on a young female patient.

### Factors Requiring Investigation

There are specific prerequisites for conception. Predictable cyclic production of an ovum, physiologically competent and patent fallopian tubes, appropriate preparation of the endometrium, preovulatory alteration of the cervical mucus, repeated availability of large numbers of motile sperm deposited in the vagina around ovulation, and successful interaction of the sperm with the cervical mucus constitute the factors that need evaluation. When assessing these parameters, one needs to think, not in terms of what is "normal," but in terms of what findings are compatible with conception. It is appropriate to consider the ability of a couple to reproduce as their fertility index even if it cannot be numerically defined. If all the prerequisites for fertility are adequately met, it may be quite simple for a couple to achieve pregnancy. On the other hand, a woman who ovulates infrequently, has periovulatory cervical mucus changes that last only a few hours, and who has coitus only one to two times a week with a partner whose sperm count is consistently 20,000,000/mL with 50 percent motility could fall into the category of "normal" but has a reduced chance of pregnancy. The concept of a fertility index deserves further consideration and study.

It is impossible, given current clinical tools, to assess fully each factor relating to fertility. For example, it is easy to assess tubal patency, utilizing hysterosalpingography complimented by diagnostic laparoscopy, but it is difficult to assess

physiological competence of the tube: Similarly, a great deal of attention is given to the sperm count, when motility and penetrability may be more important parameters of sperm function. The current development of the human sperm-hamster ova penetration test may eventually help the clinician determine whether sperm can function effectively regardless of the numbers or the percentage of motile forms.<sup>11</sup>

In conducting an infertility evaluation, it is no longer enough just to order a certain study; the benefits and limitations of that study must be understood (ie, a single plasma progesterone is not a sufficient assessment if searching for a luteal phase defect). One or preferably two timed endometrial biopsies (dated by the criteria outlined by Noyes et al<sup>12</sup>) showing at least a two-day lag in endometrial development and correlated with the temperature graph for that cycle are needed for diagnosing luteal insufficiency.

## Diagnostic Evaluation

Evaluation of the ovulatory, tubal, peritoneal, cervical mucus, and uterine factors and of the cervical mucus-sperm interaction will be necessary in the diagnostic workup of infertility in the woman.

### Ovulation Factor

There is no clinically useful way, other than achieving a normal pregnancy, to determine if an ovum is healthy. The methods of assessing ovulation are, by necessity, indirect. A reliable history of regular, cyclic menses with an interval of 26 to 34 days associated with moulimina and cramps the first or second day correlates with ovulation occurring 95 percent of the time. The thermogenic properties of progesterone make the use of basal body temperature recordings simple and usually reliable in the motivated and informed patient. The luteal phase should be 11 to 15 days. A single progesterone level drawn on the fifth to seventh day after presumed ovulation (based on the basal body temperature chart) can be helpful. A reading of

greater than 3 ng/mL is compatible with ovulation for most laboratories. A timed endometrial biopsy, approximately 8 to 10 days after suspected ovulation or temperature rise, histologically dated and correlated with basal body temperature recordings, should provide documentation that ovulation and appropriate maturation has occurred.

In performing an endometrial biopsy, the following suggestions are made:

1. Apply the tenaculum to the anterior cervical lip slowly, giving the patient time to adjust to the discomfort.
2. If this step is unduly uncomfortable, perform a paracervical block before proceeding.
3. Obtain the sample high in the fundus (the anterior surface is usually more accessible).
4. A single strip of tissue obtained with a Novak biopsy curet is sufficient for study.
5. Always note the patient's cycle day on the requisition; ask the pathologist to date the endometrium.
6. A gentle endometrial biopsy can be obtained during a conceptive cycle without fear of interrupting a pregnancy. The physician and the patient may be more comfortable, however, if barrier contraception is used during the cycle the biopsy is obtained.

### Tubal Factor

Assessment of fallopian tube patency can be accomplished easily with transuterine carbon dioxide insufflation (Rubin's test), hysterosalpingography, or laparoscopy with transuterine instillation of diluted indigo carmine dye. The author's current preference for the initial tubal assessment is the hysterosalpingogram.

### Peritoneal Factor

Diagnostic laparoscopy with tubal lavage is recommended as part of the total infertility evaluation. Because of the cost and potential risks to the patient, it is usually performed toward the end of the fertility investigation, unless the clinical picture warrants an earlier assessment (ie, a strong suspicion of endometriosis or chronic pelvic in-

Table 1. Cervical Mucus Scoring				
Descriptive Factors	Scoring*			
	0	1	2	3
Amount	None	0.1 cc	0.2 cc	0.3 cc or greater
Spinnbarkeit	None	1-4 cm	5-8 cm	8 cm
Ferning	None	Atypical	2+	3+ to 4+
Viscosity	4+	3+	2+	1+
Cellularity (white blood cells per high power field)	>10	6-10	1-5	Occasional

\*Cervical mucus score greater than 10 is favorable, cervical mucus score less than five is hostile  
From Moghissi KS: The cervix in infertility. Clin Obstet Gynecol 22:32, 1979

flammatory disease). The findings at laparoscopy will provide an etiology for the infertility approximately 20 percent of the time. The incidence of significant pelvic findings increases if the patient is over 30 years old, has had prior pelvic infections, previous pelvic surgery, or has clinically significant pelvic pain.

### Cervical Factor

If favorable preovulatory cervical mucus is present consistently, conception is more likely to occur. The term *favorable* is somewhat difficult to quantitate, but generally speaking, the periovulatory mucus should be grossly clear, thin, and elastic, stretching at least 8 cm (spinnbarkeit) and can usually be obtained from the endocervix in quantities of 0.1 to 0.3 cc. Microscopically, it is relatively acellular, with one to five white blood cells per high power field. When it is allowed to dry, a delicate arborization is seen. Moghissi<sup>1</sup> has suggested a scale to evaluate the periovulatory mucus more precisely (Table 1). The mucus may be favorable for several days for some women and only for 48 hours for other women. The human endocervix with its mucus production acts as a reservoir in

which sperm remain motile for as long as 18 to 24 hours. If favorable mucus is not present, the chances for conception are reduced. Cervical mucus is more commonly investigated as part of an in vivo sperm-cervical mucus assessment, the postcoital (Sims-Huhner) test. A sample of preovulatory cervical mucus is obtained high in the endocervical canal six to eight hours following coitus with two days' abstinence prior to the test. The mucus is examined grossly and under the microscope. At least 10 motile sperm per high power field should be seen, and at least six fields examined at 400 $\times$ . If the test is abnormal, it should be repeated, paying close attention to precise timing in the cycle. Poor timing and poor technique are the most common cause of the abnormal postcoital test.

The following suggestions are made for cervical mucus study:

1. Use an open-sided speculum if available.
2. Initially, a single sample of endocervical mucus obtained high in the canal is adequate for evaluation.
3. Wipe excessive secretions and debris away from the exocervix before obtaining specimen.
4. Use a tuberculin syringe without a needle with the plunger withdrawn slightly and applied to the os so that some suction is formed.
5. Use a long, slender scissor (Metzenbaum) to

cut off the trailing mucus thread after aspirating it from the canal.

### *Sperm-Cervical Mucus Interaction*

This category is an extension of the cervical factor evaluation. If the postcoital examination (the *in vivo* sperm-cervical mucus interaction study) is abnormal on two occasions, appropriate timing or faulty coital technique is not a consideration, and an endocervical infection or oligospermia has been excluded, an *in vitro* sperm-cervical mucus interaction study must be obtained. Although these studies are not difficult to perform, the family physician usually finds it simpler to refer the couple at this point. To perform the assessment correctly, one needs to have access to donor semen and donor mucus for comparison. Using the *in vitro* sperm-cervical mucus interaction studies, one can determine whether sperm penetrability is reduced or whether an immune process as the cause of infertility should be suspected. An excellent postcoital examination on two occasions accompanied by normal sperm penetration in an *in vitro* study mitigates against an immune cause of infertility.

### *Uterine Factors*

Even though the uterus plays an obvious and critical role in reproduction, the times when the uterus *per se* is the sole etiology of infertility are uncommon.

The etiologic role of chronic endometrial infection is not understood. Tuberculous endometritis is uncommon in the United States, but it needs to be considered. A great deal of emphasis has been placed recently on the causal role of mycoplasma. The dilemma is not resolved, and random or empiric treatment with tetracycline should be discouraged. An endometrial biopsy obtained late in the proliferative phase demonstrating plasma cell infiltrate in the stroma and granulomatous lesions supports the presence of T ureaplasma, and in those infertile women a course of tetracycline is warranted.

Uterine myomas are an infrequent cause of infertility. Myomectomy is warranted only if the

uterine cavity or tubal course is distorted. If absolutely no other cause of infertility can be identified, surgical removal of the myomas could be discussed with the patient.

The same principle applies to uterine anomalies. Patients with uterine anomalies may experience an increased incidence of pregnancy complications, but their fertility is usually not compromised. When there are mullerian defects, be certain to evaluate the patient for renal anomalies and ovulatory dysfunction, specifically a luteal phase defect.

The presence of uterine synechiae warrants further study with hysteroscopy; the scarring should be treated. The causal role of a few small intrauterine adhesions is difficult to evaluate, but with intrauterine adhesions it seems logical to question whether some tubal disease might be present. In patients with synechiae associated with a pregnancy episode complicated by curettage or endometritis or both (Asherman's syndrome), the prognosis for an uncomplicated full-term pregnancy is poor in spite of surgery and medical therapy.<sup>13</sup>

Finally, physicians should also be aware of the possible effects of intrauterine diethylstilbestrol (DES) exposure on fertility. In addition to the cervical defects, other uterine anomalies such as a T-shaped appearance of the uterus, constricting bands in the cavity, and uterine hypoplasia have been identified in DES daughters. The issue has currently not been resolved; however, it appears that the incidence of conception is not reduced, but the incidence of complications, particularly spontaneous abortions, is increased.<sup>14</sup>

The basic means available to investigate these uterine factors are pelvic examination, hysterosalpingogram, and hysteroscopy. Hysteroscopy does not need to be performed routinely on every woman with infertility. Commonly, an abnormal hysteroqram provides the primary indication for this specialized operative procedure.

## **Current Management**

### *Disorders of Ovulation*

The use of clomiphene should be limited to those patients who ovulate infrequently or not at

all, as evidenced by their history, basal body temperature determinations, serum progesterone levels, or endometrial biopsy. Initial dosage should be 50 mg daily for five days beginning on cycle day 5. If the patient clearly has polycystic ovary syndrome, it is prudent to begin with a three-day course of therapy, as these patients may be very sensitive to this medication. Particular attention should be paid to such problems with therapy as headaches, visual problems, and pelvic pain. The dosage can be increased up to 100 mg/d for five days to achieve ovulation. If the patient ovulates at that dosage, six months of therapy is warranted. If higher doses are required, it may be appropriate to refer the patient, depending on the level of experience of the physician. Since clomiphene does interfere with cervical mucus production in some patients, a mucus examination or a post-coital examination should be carried out the first or second cycle of ovulation. The frequency of follow-up visits depends on the patient's symptoms, her reliability, and the physician's experience with this medication. Patients requiring large doses of clomiphene (1,000 mg or greater per cycle), human chorionic gonadotropin therapy, or menotropins (Pergonal) should be monitored by an individual who has significant experience with these regimens and who has ready access to serum estradiol assays.

The efficacy of bromocriptine therapy in treating patients with amenorrhea-galactorrhea because of hyperprolactinemia is well documented. By inhibiting prolactin release, the amenorrhea rescinds and ovulation is induced in most patients. This drug has been approved for therapy of ovulatory disorders associated with hypoprolactinemia and no demonstrable pituitary tumor. In addition, there is evidence that it can correct ovulatory dysfunction in those who are euprolactinemic.<sup>15</sup> It is anticipated that the use of this drug will receive more study and eventually be released as an agent to induce ovulation in selected patients.

Ovarian wedge resection is being performed less frequently, as ovulation induction can usually be achieved with medical therapy. It is still indicated in patients who are unresponsive to clomiphene therapy, who are clinically androgenized, and who are unsuitable for menotropin whatever the reason. When wedge resection is performed, meticulous attention should be paid to hemostasis, using a fine polyglactin suture material and gentle

handling of tissue to avoid producing periovarian and tubal adhesions.

### *Improving Cervical Mucus*

When one is confronted with numerous leukocytes in the preovulatory cervical mucus, an attempt should be made to diagnose and treat the cervicitis. Systemic antibiotics may be more helpful than topical ones, depending on the organisms involved, and occasionally the judicious use of cryotherapy may be necessary to treat chronic symptomatic ectopy. If the mucus is scant or absent, oral estrogen therapy has been recommended. There appear to be at least two commonly reported regimens: (1) small doses of conjugated estrogen, 0.3 to 0.625 mg daily from cycle day 5 to 12, or (2) ethinyl estradiol 0.05 mg, one to two tablets on cycle days 10, 11, and 12. Neither regimen has proved superior. Clinically it is quite simple to improve the character of the cervical mucus; whether the pregnancy rate is improved has not received so much study as has the type of estrogen treatment. The use of donor mucus or bovine mucus in the treatment of mucus production disorders needs further study.

### *Tubal Microsurgery*

Almost every major city has someone who is qualified by training and experience to offer this procedure to selected patients. Microsurgery is less effective in restoring fertility in women with tubal damage due to infection than in individuals who have undergone tubal reversal. A recently published series reports a 64 percent pregnancy rate in selected patients.<sup>16</sup>

### *Progesterone Therapy*

Luteal phase defects have been found in 3 to 8 percent of couples experiencing infertility. Progesterone suppositories, 25 mg, inserted vaginally twice a day after the temperature rises with ovulation until menses occur is the treatment of choice.

As the suppositories must be compounded, some difficulty may be encountered getting the local pharmacist to stock them. A follow-up endometrial biopsy should be performed to ensure that the therapy is effective. There is no evidence to support the concept that the use of this natural progesterone in this dosage produces birth defects when used during a conceptive cycle.

### *Artificial Insemination*

Greater attention should be given to the use of artificial insemination, using the partners' ejaculate in patients with consistently poor cervical mucus and poor sperm-cervical mucus interaction presumably because of an autoimmune process. As the first third of the ejaculate contains 75 percent of the sperm in 90 percent of men, the use of split ejaculate can be tried.

### **Psychological Support and Patient Education**

Every provider dealing with infertile patients can anticipate encountering varying degrees of anxiety, anger, and depression. By expecting these responses, the physician need not be surprised about the anger or the hostility that may initially be directed at him or her. Also, every attempt should be made to see the couple as a biologic unit; both partners usually express a continuous need to be informed. It is helpful to emphasize to the couple that 90 percent of the time a cause of the infertility problem will be discovered; this assurance often buffers a significant amount of the frustration experienced. It is very important to explain each diagnostic study ordered, discuss the costs involved in the evaluation, and supply accurate and reliable information. Form a verbal contract, that is, perform a specific number of tests in a specific time frame and prescribe therapy for a specific time, and then offer the couple an opportunity to have the results of the tests or therapy summarized. Ask about their feelings before proceeding. Finally, after completing the initial eval-

uation or therapy, if unsuccessful, be willing to initiate an appropriate referral, as this constitutes one of the hallmarks of competence.

As might be predicted, the pregnancy outcome of infertile couples who conceive is not optimum. There is a higher incidence of spontaneous abortion, ectopic pregnancy, and perhaps perinatal loss. In a sensitive but candid way the couple should be appraised of this potential, and additional emotional and medical support may be warranted when the patient conceives.

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