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Editor's Note*—All living organisms have the inherent drive to procreate, making reproduction one of the strongest human motivations. The inability to conceive, diagnostically referred to as "infertility," is defined as 12 months of unprotected intercourse without establishing a pregnancy. The innate desire to have a family often leads these couples to seek medical treatment.*

The real diagnosis in the vast majority of "infertility" cases is more aptly termed "conception inefficiency"—that is, most couples retain the ability, albeit dysfunctional, or the conception potential and it is only in rare circumstances that establishing a pregnancy is not possible. This semantic distinction is not an esoteric argument—it reflects the current state of medical treatment, it places a more accurate "spin" on the medical difficulties the physician and patient encounter, and, taken to heart, it should significantly change the psychological approach toward treatment from the patient's perspective.

Almost 2.7 million Americans (7.1% of married couples) have difficulty conceiving.[1,2] This leads to a host of problems, always including feelings of frustration, guilt, and anger, and often directly affecting friends, family, and most important, the marriage. Evaluation and treatment are not without their stresses as well. Taking daily temperatures, timing intercourse, collecting specimens, disrupting work schedules, injecting multiple medications, and undergoing uncomfortable and invasive procedures becomes a way of life.[3] The loss of intimacy is real. The humorous portrayal of the spouse who suddenly has to hurry home mid-day because his wife is "ovulating" would be a welcome relief for many couples undergoing fertility treatment. Current practice guidelines suggest evaluation and treatment should be as concise and direct as possible.[4]

When a couple presents for evaluation of conception difficulties, the basic workup can be divided into four broad categories: male factor, ovulation disorders, structural problems, and systemic/immunologic abnormalities. (See Table 1.) While the classic definition of conception inefficiency is a year of unprotected intercourse, this situation clearly doesn't apply to known obstructive problems—tubal occlusion either iatrogenic or infectious, vas occlusion either voluntary or congenital, or absence of a partner. The definition and decision to evaluate the couple should also be modified in situations such as advancing age,[5,6] progressive diseases, and coital difficulties.[7]

Another important issue is fecundity, the speed at which con-

Conception Inefficiency

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ception will occur. Compared to lower mammals, humans have a lower fecundity rate[8] (see Table 2). This background inefficiency generates considerable frustration for patients, prolonged treatment courses, and difficulties in designing good scientific studies on effective treatment. Many of the former "standard" therapies have fallen by the wayside as scientific studies have dispelled their usefulness. The current direction toward evidence-based therapy[9] is changing the approach that many physicians take in dealing with these reproductive problems.

Reproductive Process

In review of the basic reproductive process, under hypothalamic-pituitary stimulation, oocytes are recruited in the ovary from a potential oocyte pool that has been in the ovary since early fetal development. This cohort of activated primordial oocytes is stimulated in its development by follicle-stimulating hormone (FSH) released from the pituitary under control of pulsatile gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus. Eventually, a dominant follicle results, presumably containing the best oocyte of the recruited group from that cycle. Meanwhile, estrogen produced by the developing follicle stimulates proliferation of the endometrium and negatively influences further FSH production. The oocyte within this follicle undergoes final maturation and is released following pituitary secretion of luteinizing hormone (LH). Ovulation occurs about 35-36 hours following initiation of the LH surge. Assuming timely intercourse occurs, the sperm traverse the vaginal canal, and travel up through the cervix, uterine cavity, and fallopian tubes. Cervical mucus effectively acts as a sperm reservoir up to five days, constantly releasing spermatozoa for travel through the upper female reproductive tract.

Fertilization occurs in or near the distal end of the fallopian tube, which then nurtures the resulting embryo as it reverses the sperm's course, traveling back down the fallopian tube and into the uterus, a process that usually takes 5-6 days. During this time, progesterone is secreted from the corpus luteum (former ovulatory follicle that is now luteinized) and converts the endometrium to a secretory or supportive form, which allows the embryo, upon reaching the endometrial cavity, to undergo implantation. Once attachment has occurred, the trophoblast begins developing vascular supply and soon starts secreting human chorionic gonadotropin (hCG), which is used in blood tests to confirm an early conception.

Table 1. Etiologies of Conception Inefficiency

Male factor	35%
Ovulatory	28%
Tubal damage	13%
Endometriosis	6%
Coital problems	5%
Cervical factor	3%
Unexplained	10%

Major Fertility Factors

Male Factor. Male factors are the most common reason why conception does not occur. Criteria that make up a normal semenalysis are listed in Table 3. The sperm density should be at least 20 million spermatozoa per mL and the motility should be at least 40%. Forward progression further qualifies the motility, ranging from sluggish (1+) to highly directional (4+). Sperm density alone is not a great predictor of fertility in that only 15% of men with a count of less than 10 million/cc have difficulties fathering a child.[10] A more useful number is the calculated number of motile sperm delivered (i.e., sperm density × by semen volume × by percent motility). It is calculated that maximal conception rates occur when at least 20 million motile sperm are delivered during intercourse.[11] Another means of evaluating sperm potential is termed *critical morphology*.[12] The laboratory, using precise criteria, can provide an evaluation of the percent of normal sperm present based on the structural appearance of the spermatozoa. This appears to have a better correlation with conception rates than does the sperm density alone.

If a semenalysis is abnormal, the first step is to repeat the analysis, usually at least 2-3 weeks later. Spermatogenesis is a 72-day process and may have been disrupted by high fevers, medications, etc.; thus, a second count should be delayed to minimize the effect of a transitory suppression. When potential count abnormalities are confirmed, an initial evaluation of the partner should include a thorough medical

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Table 2. Percentage of Married Women who are Infertile by Age

Age	Infertile
20-24	7.0
25-29	8.9
30-34	14.6
35-39	21.9
40-44	28.7

Table 3. Normal Semenalysis

Sperm density	> 20 million/cc
Sperm motility	> 60%
Semen volume	1.5-5 cc
Forward progession	> 2
Morphology	> 60% (standard) > 14% (strict)

and genital exam, blood levels of FSH, LH, prolactin, and testosterone. The exam may identify a varicocele or other structural anomalies; a urologic consultation is often warranted in these circumstances.

Other tests that are sometimes helpful include seminal fructose (absence indicates ductal blockage),[11,13] a hamster egg penetration assay[14] or hemizona assay (assessment of sperm functional capacity),[15] hypo-osmotic swelling (assessment of membrane integrity),[16] and selective staining techniques (assessment of structural components).[15,17] Karyotyping may also yield explanations in a small number of cases. Unfortunately, except for structural disorders, which have some potential for surgical correction, men with other abnormalities leading to low counts or poor motility have few options for establishing a conception except for intrauterine inseminations[18] or high-tech procedures such as in vitro fertilization (IVF), with or without intracytoplasmic sperm injection (ICSI).[8,19] There are no currently proven diet changes, vitamin supplements, or activity changes that will enhance sperm numbers or motility.

In situations when the sperm density is extremely low or even zero, testicular biopsy has been used as a diagnostic tool. If spermatogenesis is disrupted or abnormal, then while there is no correction available, decisions can be made regarding further treatment options—IVF with ICSI[20] vs. donor insemination.[21] Both of these options have pros and cons, more depending on the couple's personal choices regarding these procedures than technical issues.

Male factor problems have been the most significantly affected by the recent technological advances in reproductive medicine. With the advent of successful retrieval of functional spermatozoa by testicular biopsy and using the ICSI process, the number of men who are truly infertile can be reduced to 1% or less. This may be the single biggest advance in fertility treatment in the last 10-15 years. However, the advancing edge of science has also presented concerns; there does seem to be an increase in abnormalities in children born through the ICSI process when sperm from men with chromosomal abnormalities have been identified.[22]

Ovulatory Factors. Ovulation disorders also play a significant role in conception inefficiency. These problems can range from amenorrhea, the lack of cycles at all, to the subtle luteal phase defects that may only be detected by endometrial biopsy. An initial evaluation of the woman should include some measure of ovulatory activity. This may start by obtaining several months of basal body temperature charting, which attempts to document the thermogenic shift that occurs in a woman following progesterone secretion. While generally indicative of ovulatory activity, at least a third of women ovulate more than 48 hours off from where the temperature rise occurs.[23] Basal body temperature (BBT) charts have no predictive value in the present cycle (i.e., cannot tell you when you are going to ovulate) and the data collection are a significant source of stress—a woman must confront her "failure" to conceive every morning as her first waking thought. Nevertheless, it is the least expensive and most widely used initial means of assessing ovulatory cycles.

Except for actually flushing an oocyte from the fallopian tube/uterus or achieving a conception, all measures of ovulation are indirect inferences. Over-the-counter LH kits, which measure the urinary excretion of the serum gonadotropin LH representing the ovulatory surge, are predictive within 36 hours in at least 90% of women when ovulation will occur. The testing should be done with the first voided urine in the morning and testing should begin several days prior to the suspected day of ovulation. This timing can be calculated by taking the length of the last several cycles and subtracting 16-17 days. Since the luteal phase is usually 14 days from ovulation to menses, this timing allows 1-2 days of baseline negative tests prior to the LH surge.

Ultrasound monitoring of follicular growth and the subsequent collapse of the follicle can also be used to document ovulation but, more frequently, is used to help control ovulatory activity by the administration of hCG when a mature follicle is visualized. The preovulatory follicle grows in a linear pattern once it reaches 12-13 mm in diameter. While a mature oocyte may reside in an unstimulated follicle of 18 mm, when the woman is treated with clomiphene citrate (an ovulatory agent), the follicle usually needs to reach 24 mm in diameter in order to contain a mature oocyte. With monitoring alone, observation of the collapse of the follicle can provide additional evidence of ovulatory activity.

Serum progesterone levels in the luteal phase are probably the most commonly used test to document adequacy of ovulation and are classically obtained seven days following ovulation. Several progesterone levels during the luteal phase can be used to construct a graph, with the "area under the curve" (AUC) being a more precise measure of the ovulatory quality.[24] Progesterone is critical in establishing an appropriate receptive uterine environment for the embryo to implant. It is produced by the corpus luteum under LH stimulation and, with its decline in the late luteal phase, is responsible for the eventual onset of menses. With implantation, the trophoblastic cells begin to manufacture hCG, which also activates the LH receptor and maintains progesterone production from the ovary. Eventually, the developing

placenta takes over progesterone production for the remainder of the pregnancy and the corpus luteum regresses.

An endometrial biopsy, long the gold standard by which all other methods of assessing ovulation were compared, is now facing challenges. Classically, histologic dating of an endometrial biopsy sample obtained late in the luteal phase should correlate within 48 hours of the actual cycle day based on the subsequent menses.[25] Recent work with endometrial integrins and other functional markers may change how we eventually look at an adequate endometrium.[26] In the final analysis, while progesterone levels are probably the best screening test for ovulatory activity, it is the landing site for the embryo that we are most concerned about and we need to have a better assessment of this function.

Associated with ovulatory activity are a number of hormones that may enhance or suppress ovulation. The most important of these hormonal problems are thyroid function and prolactin levels. While having a general metabolic effect, both hyper- and hypothyroidism may affect the ovulatory process. Elevated prolactin levels suppress both the hypothalamus and in the pituitary interfering with gonadotropin release. Prolactin is also luteolytic (i.e., it will disrupt corpus luteum function and, thus, decreasing progesterone secretion). Any abnormality in ovulatory activity should initially be evaluated by a serum TSH and prolactin level.

If increased hair growth is present, then additionally serum testosterone and dehydroepiandrosterone (DHAS) would be indicated. Ovarian theca cells use cholesterol and acetate precursors to synthesize androstenedione and, to a lesser extent, testosterone. Normally, the aromatase system in the granulosa cells quickly converts these androgens to estrogens in a normally developing follicle. However, if there is poor follicular growth and, therefore, poor granulosa cell layer development, these androgens may spill over into the bloodstream and clinically cause difficulties. Mild changes may lead to oily skin and some increased hair growth. Marked increases in adrogens can lead to virilization. At the same time, peripheral conversion of these androgens to estrogens may further alter the ovulatory efficiency by providing false feedback information to the hypothalamus and pituitary, leading to even less effective gonadotropin stimulation of the ovary. This, in turn, leads to poorly developed follicles. This vicious cycle may end up as polycystic ovary syndrome or a variant thereof.[27]

Evaluation of ovulatory activity should at least include a mid-luteal progesterone and, eventually, an endometrial biopsy. In a classic 28-day cycle, the progesterone can be timed on day 21; otherwise, review of the total length of the last several cycles and subtracting seven days will time it appropriately. The endometrial biopsy was classically timed 1-2 days prior to onset of menses, but recent data may support a mid-luteal evaluation as being more predictive of a good cycle.[28] In confusing situations, follicular collapse documented by ultrasound may be an additional tool.

Anatomic Factors. Structural disorders leading to conceptional inefficiency can be divided into cervico-vaginal, uterine, tubal, and peritoneal. Cervico-vaginal abnormalities are mostly congenital: vaginal agenesis, transverse septum, and duplicated vaginal or cervical canals. Cervical stenosis—either intrinsic or iatrogenic from surgical procedures such as cone biopsies, LEEP procedures, or multiple cervical dilatations—is seen on occasion. Corrective measures are generally surgical, although on occasion, poor function of the remaining cervix may lead to inseminations or even gamete intrafallopian transfer (GIFT) procedures. Laminarial tents in some women have been effective in resolving this problem.

Uterine abnormalities include congenital changes such as a uterine septum, a bicornate structure, or even a duplicated system (didelphic). Fusion of the Mullerian ducts in the mid-line may be incomplete or fail completely, leading to a variety of these abnormalities. In some circumstances, these structural changes need to be corrected, but at other times are found incidentally at the time of a delivery. A conservative approach to these problems is warranted since, except for hysteroscopic resection of a uterine septum, the other abnormalities require significant major surgical intervention.

Other structural distortions including uterine fibroids, polyps, adhesions, or, on occasion, a forgotten IUD, need to be addressed surgically and all have good success rates. Uterine fibroids present an uncertain dilemma, often not interfering mechanically but always with the threat of significant growth making later surgical correction more difficult.[28] The surgical correction is not without problems either, as it may leave the uterus weakened and sometimes a myomectomy then requires a patient to deliver via cesarean section. Postoperative adhesions following a myomectomy may lead to tubal dysfunction. Finally, chronic endometritis, although not common, creates an adverse environment for embryo implantation and would be a relatively rare problem.

Imaging the uterine cavity and tissue sampling are the direct ways to make a diagnosis of these problems. A hysterosalpingogram (HSG), which uses a nonionic water-soluble dye injected transcervically and visualized via fluoroscopy, is probably the current standard technique.[30] More recently, sono-hysterograms obtained by injecting saline in the uterine cavity under ultrasound guidance have achieved similar rates of abnormality detection. Surgical evaluation of the uterine cavity via hysteroscopy, using CO_2, Hyskon, or isotonic solutions to distend the uterine cavity and allow visualization, is another standard procedure.

Correction of many of the abnormalities identified by endoscopic evaluation can be accomplished simultaneously at the time of the diagnostic procedure. If a submucous fibroid, endometrial polyps, uterine septum, or adhesions are present, hysteroscopic excision can be accomplished on an outpatient basis. Endometrial changes such as hyperplasia can be treated with hormonal suppression and endometritis can be corrected with antibiotics. Other uterine abnormalities, such as intramural or subserosal myomas, may require a laparotomy to excise, and since clear evidence that this will enhance pregnancy rates is not available, individual judgment on the appropriateness of surgical intervention needs to be discussed with the patient. Uterine position is no longer thought to play a significant role in conception efficiency—a "tipped" or retroverted uterus is not a cause of conception difficulties.

Tubal disorders leading to conception problems are mostly acquired. There are few instances of congenital tubal disorders, although DES may have induced some functional changes.[31] Too little is known about tubal function to devise any tests to

assess its functional capabilities. Evaluation of tubal histology and structure via falloposcopy has not currently reached standard of care levels. Therefore, the internal architecture in general is assessed by the HSG film[33] and the external mobility by laparoscopy. Damage or obstruction of the tube(s) can occur from infectious causes, currently *Chlamydia* being the most common,[32] surgical procedures in the abdomen, and ectopic pregnancies whether surgically or medically treated. Since the tube carries out an extensive list of activities, from allowing sperm to swim upstream while generating countercurrent movement of the embryo toward the uterus and providing appropriate nutrient and supportive environment for both to identify and pick up the oocyte in the peritoneal cavity, no suitable substitute is available.

Surgical procedures to correct tubal disease are available, including microsurgical reconstruction of the fimbriated end of the tube, clearing of pelvic adhesions, and, in the case of a previous tubal ligation, anastomosis of the remaining tubal segments. With the advent of IVF procedures and the constantly improving success rates,[33] less surgical intervention is being carried out. This is probably a beneficial change; repair of tubal damage rarely yields more than a 40% pregnancy rate (except reversals), it is clearly more expensive than IVF, and it carries significantly more risk for the patient.

Peritoneal abnormalities include endometriosis as the most significant disease process. Endometriosis is most simply normal endometrium—both stroma and glandular tissue—located outside of the endometrial cavity. The most common sites are the ovaries, followed by the pelvic cul de sac, then other peritoneal surfaces. It can rarely appear in such distant sites as the lungs and brain. The incidence is projected to be one in seven reproductive age women.[34] Endometriosis seems to be associated with immunologic changes in the peritoneal cavity and it may be inefficiencies in this function that allow the endometrial tissue to develop. The implants appear to cause difficulties in several ways. In the mildest forms, it must be some product(s) secreted by the implants that cause difficulty. Peritoneal fluid from women with early stage endometriosis diminishes both fertilization and embryo growth in mouse IVF cultures. Clinical studies now document the resultant diminished conception rate and improvement with ablation of these implants.[35] As the amount of disease increases, the inflammatory response generated eventually causes adhesive disease, incorporating any or all pelvic organs including uterus, tubes, ovaries, and bowel.

The diagnosis of endometriosis remains a surgical procedure. Monitoring of the disease activity can sometimes be accomplished post-treatment with CA-125 assays, but an elevated level is not diagnostic of the disease. Symptoms include menstrual cramps often starting prior to menses, pain with intercourse, irregular menstrual bleeding, etc. The severity of the disease poorly correlates with the symptoms—advanced disease with endometriomas and severe adhesions may well be asymptomatic, whereas incapacitating pelvic pain often seems to result from a few small endometriotic implants. Treatment is often surgical, although hormonal suppression with progestational agents such as OCPs and Depo-Provera; impeded androgens like Danazol; and GnRH agonists such as Lupron, Synarel, and Zoladex are probably equally effective.

Systemic/Immunologic Causes. The last of the four major categories includes immunologic and medical causes. Cervical mucus evaluation, commonly termed a post-coital test or Sims-Huhner Test, has been a longstanding component of a fertility evaluation. However, meta-analysis of its predictive value has left serious questions as to its validity.[36] Classically, the couple timed intercourse 2-12 hours prior to the evaluation timed at mid-cycle. Quality of mucus was evaluated by various parameters and the numbers of directional motile sperm were determined. Dysfunctional movement or shaking suggested sperm antibodies that could then be further evaluated with blood and semen testing. Unfortunately, random testing for sperm antibodies in the general population yields a high false-positive rate and, therefore, is not a good screening option.

Treatment alternatives ranged from using condoms to minimize antigen exposure to steroid suppression, but have now centered on intrauterine inseminations with poor cervical mucus, whether secondary to sperm antibodies, inadequate production, or poor quality. Antisperm antibodies are not thought to reside in the upper reproductive tract, so bypassing the cervical canal entirely appears to be effective in many of these cases.

There is accumulating information regarding other immunologic factors that may affect fertility. Inadequate clinical trials and anecdotal reports have made interpretation of data difficult. Regardless, the uterine environment seems to be an immunologic priveleged site and failure to protect the implantation of the embryo and developing fetus could result in tissue rejection. Currently, there are no routinely available tests to evaluate this possibility. However, in situations where other immunologic diseases are present (i.e., lupus, Hashimoto's thyroiditis, etc.), it is reasonable to evaluate present activity of the disease as a possible etiologic factor.

A variety of metabolic diseases also affect conception efficiency, including diabetes, liver and kidney disease, any debilitating condition, and psychiatric conditions, including depression. Most of the former disrupt the hormonal communication between the central system and the ovary, and the latter generally alter hypothalamic function, leading to problems. In addition, some of the medications used to treat these medical illnesses may also interfere with reproductive potential.

Unexplained

Following a thorough evaluation with appropriate testing, there still remains between 8-10% of couples with no obvious cause for their conception difficulties. The emphasis with these couples is that there is a precise scientific reason why conception is not occurring, although science has not yet been able to evaluate all of the processes needed for a successful pregnancy. Most important, there are a number of treatment options available that are successful.[37]

Evaluation

Diagnostic protocols vary depending on the area of the country, the prevailing insurance coverage, and facilities available. A conservative but quick approach to defining the reproductive system begins with the couple. Both husband and wife should be counseled on the evaluation, the need for mutual support, and to dispel any misconceptions regarding the process. A semenalysis, mid-luteal progesterone, a hysterosalpingogram (HSG), and a post-coital test can be accomplished in one menstrual cycle and will provide a direction to head in further evalu-

ation more than half of the time. Based on these findings, an endometrial biopsy and, eventually, a laparoscopy may be recommended. A prolonged testing phase for conception difficulties should be relegated to the history books.

Treatment options will vary depending on the particular problem(s). There are some circumstances where simply improving coital timing by reviewing the conception process is sufficient. With a normal semenalysis, intercourse should be timed every 48 hours at a minimum during the mid-portion of the cycle, centered around the anticipated day of ovulation. This can be estimated by subtracting 14 days from the average cycle length. While no clear study exists to document the time needed following intercourse before the woman arises, 20-30 minutes should allow the spermatozoa sufficient time to reach the cervix. Common sense would dictate no douching or tub bath in the next several hours.

If difficulty in timed intercourse develops, male inseminations may be the most appropriate resolution. Insemination techniques range from the simple cervical introduction of fresh semen—limited to 0.5-0.6 cc, the maximum capacity of the endocervix—to intrauterine insemination with washed sperm. The latter has better success rates and allows the separation and evaluation of the quality of motile sperm being introduced. Risks include general cramping and discomfort, a dramatic prostaglandin-type reaction with severe cramps, breathing difficulties, nausea/vomiting, and diarrhea resulting from semen reaching the uterine cavity, and endometritis/pelvic inflammatory disease (PID) from bacterial introduction into the upper reproductive tract.

Ovulatory management is one of the more frequently used treatment options. Following correction of any ancillary hormonal abnormalities—hypo- or hyperthyroidism, hyperprolactinemia, elevated adrenal or ovarian androgens, and normalization of metabolic disorders—appropriate glucose control, stable kidney and liver disease, and ovulatory stimulation can be undertaken. While a number of medications exist, generally initial attempts at correction are made with the anti-estrogen clomiphene citrate. By blocking estrogen feedback in the hypothalamus, clomiphene induces increased GnRH secretion, which leads to higher FSH production and improved follicular development. Generally, 3-4 good ovulatory cycles documented by serum progesterone and an endometrial biopsy are sufficient. On occasion, the addition of ultrasound documentation of appropriate follicular growth and administration of hCG (LH substitute) might continue for 2-3 more cycles. Failing to achieve a pregnancy with clomiphene, gonadotropins are indicated. The administration of FSH or hMG/FSH has a much higher success rate but also requires intense monitoring to avoid hyperstimulation and multiple births. This is often combined with IUIs to maximize success rates.[38]

Surgical correction of tubal disease and endometriosis can often be effective. Laparoscopy has become the main tool for dealing with anatomic difficulties associated with conception problems. The use of laser equipment, multiple puncture sites, and markedly improved equipment in the last several years has prompted much more aggressive outpatient procedures, including myomectomies, bowel resections, and tubal reconstructions.[39] Laparotomies have a shrinking list of indications but they probably include the worst situations with the above procedures.

Final options include assisted reproductive technologies (ART), including GIFT,[40] zygote intrafallopian transfer (ZIFT), and IVF.[41] Each of these processes usually involves the stimulation of multiple follicles using gonadotropins monitored with both ultrasound and serum estradiol levels. Once a reasonable number of mature follicles are identified, oocyte retrieval occurs. In a GIFT procedure, a laparoscopy is performed and the ovarian preovulatory follicles are aspirated to remove the oocytes. Surgical correction of any identified disease process is carried out, then 4-6 mature oocytes are returned to the fallopian tubes along with a highly motile, washed preparation of the male's sperm. As with all the ART procedures, additional oocytes can be fertilized and the resulting embryos cryopreserved.

ZIFT and IVF cycles both involve the same stimulation protocols as a GIFT, but instead of a laparoscopy, the ovarian preovulatory follicles are aspirated transvaginally and the fertilization (under controlled laboratory conditions) is undertaken. With ZIFT, several resulting embryos are placed in the fallopian tubes via laparoscopy, whereas with IVF, they are transcervically returned to the uterine cavity. All these procedures are performed on an outpatient basis and currently, IVF is essentially an office-based procedure (*see Table 4*). Data for GIFT and IVF are now pooled in this CDC report.[33]

The use of donor gametes, whether to replace absent spermatogenesis in an azoospermic husband as in therapeutic donor insemination (TDI) or to provide for the absence of functional oocytes (donor oocyte program),[42] is an area of increasing activity in ART programs. It eliminates the age restriction on the ability to conceive and opens multiple options for those couples unable to achieve a conception through their own gametes.

Table 4. ART Success Rates in the United States

	AGE		
	< 35	**35-39**	**> 39**
Live births/cycle (%)	28.7	21.3	8.7
Average # embryos Transferred	3.9	4.0	4.1
Multiple Birth Rate (%)	42.1	34.2	21.2

Initial Evaluation

A couple presenting to their primary care physician with questions about fertility can be assisted along this pathway in a concise and effective manner. Younger than 30 years and having met the general criteria of one year of unprotected intercourse and no previous surgery or uterine-tubal disease, the basic list of tests needed include a semenalysis, mid-luteal progesterone, and an HSG (*see Table 5*). Preconceptional health guidance issues were thoroughly addressed in a previous issue.[43] Clearly, if there has been extensive or obstructive pelvic disease or significant male factor problems are already known to exist, then referral is probably wise. Some direct treatment options would include:

- **Low mid-luteal progesterone (< 10 ng/mL).** Check TSH and prolactin levels. If normal, try clomiphene 50 mg days 3-7 of cycle. Assess adequacy of treatment by repeating progesterone on treated cycle. Plan 3-4 good ovulatory cycles. While long-term use of BBT charting is probably nonproductive, several months to evaluate the overall cycle activity is sometimes helpful.
- **Poor semenalysis.** Wait 2-3 weeks then repeat, having made sure the male is off all drugs and stops potentially harmful activities—no hot tub, heated water bed, smoking, excessive alcohol consumption, etc. Discuss coital timing—with a normal sperm density, minimum every other day during the middle of the cycle; otherwise make this a maximum.
- **Poor post-coital test.** If mid-cycle cervical mucus is thick and appears cellular, treatment with doxycycline is advised. The use of guianefesin has been helpful in some patients for thinning the cervical mucus if given daily during the follicular phase.

If these options do not result in a pregnancy in 3-4 cycles or anatomic problems appear likely, then referral should be considered. Male factor problems can be further evaluated by a urologist, preferably one who has some interest in male fertility. Most gynecologists will often pursue a number of fertility issues in their office but may elect to subsequently or directly involve a reproductive endocrinologist in their care. These physicians have completed an extra 2-3 years of specialty training and should be able to provide any care necessary to arrive at a successful pregnancy.

When looking for an appropriate referral, personal experience with the physicians in the community is the most helpful. Usually your hospital's obstetrics and gynecology department or local medical school can provide good options. The American Society of Reproductive Medicine (ASRM) can also provide a list of members in the area who have an interest in evaluating and treating fertility problems. While board certification in obstetrics and gynecology, reproductive endocrinology, or urology is not an absolute stamp of approval, it is probably an excellent screening tool.

When considering where to go for the high-tech ART procedures, looking for board-certified reproductive endocrinologists is probably the safest approach for your patients. Success rates with IVF programs are published by the CDC under federal mandate and are listed by state. These statistics should not be the only criteria used though, since clinics differ significantly in their patient population; some move couples quickly to ART procedures whereas other clinics may only deal with those couples who have hardcore, longstanding problems. Any reputable clinic should be able to provide their live birth rate based on age, general fertility problem, and separated by whether male factor was involved. Equally important are local reputation, physician and laboratory credentials, and feedback from previous patient interaction.

While there are clearly no guarantees in medicine and certainly no assurances should be given concerning successfully treating conception difficulties, it would be fair to say that given unlimited ability to treat a couple with conception inefficiency, more than 95% can achieve a successful pregnancy through some option. More direct management of fertility problems, improving success of treatment options, and continued advancement in the ART arena have been a great benefit to the patient. The adage "persistence pays off" has never been more true than in this field.

The inability to conceive should be a vanishing problem.

Table 5. Conception Inefficiency

Initial evaluation

- BBT
- Semenalysis
- Mid-luteal progesterone
- Post-coital test
- Hysterosalpingogram

References

1. Templeton A, et al. Infertility—epidemiology and referral practice. *Hum Reprod* 1991;10:1391-1394.
2. Mosher WD, Pratt WF. *Fecundity and Infertility in the United States, 1965-1988*. Hyattsville, MD: National Center for Health Statistics; 1990.
3. Grell AL. Infertility and psychological distress: A critical review of the literature. *Socki Med* 1997;45:1679-1704.
4. Guidelines for the Provision of Infertility Services. ASRM. *Am Soc Reprod Med* Birmingham, Ala. 1996
5. Schwartz D, Mayaux MJ. Female fecundity as a function of age. *N Engl J Med* 1982;306:404-406.
6. Toner JP, Scott RT. Chronologic versus ovarian age—impact on pregnancy among infertile couples. *Semin Reprod Endocrinol* 1995;13:1.
7. Comhaire FH, et al. Towards more objectivity in diagnosis and management of male infertility. *Int J Androl* 1987;7(Suppl):1-53.
8. Jones H, et al. The 4th Bourn Hall Conference. *Hum Reprod* 1998;13(Suppl).
9. Grimes DA. Introducing evidence-based medicine into a department of obstetrics and gynecology. *Obstet Gynecol* 1995;86:451-457.
10. Sherins RJ, et al. Longitudinal analysis of semen of fertile and infertile men. In: Troen P, Nankin HR, eds. *The Testis in Normal and Infertile Men*. New York: Raven; 1977:473-488.
11. MacLeod J. Semen quality in 1000 men of known fertility and 800 cases of infertile marriages. *Fertil Steril* 1995;2:115-123.
12. Kruger TF, et al. Sperm morphologic features as a prognostic factor in in vitro fertilization. *Fertil Steril* 1986;46:1118-1123.
13. WHO. Collection and examination of human semen. In: *WHO Labo-*

ratory Manual for the Examination of Human Semen and Sperm-Cervical Mucus Interaction. 3rd ed. Cambridge, UK: Cambridge University Press; 1992:3-20.
14. Johnson A, et al. A quality control system for the optimized sperm penetration assay. *Fertil Steril* 1995;64:832-837.
15. Oehninger S. Diagnostic significance of sperm-zona pellucida interaction. *Reprod Med Rev* 1992;1:57-81.
16. Chan SY, et al. Differential evaluation of human sperm hypo-osmotic swelling test and its relationship with the outcome of in vitro fertilization of human oocytes. *Hum Reprod* 1990;5:84-88.
17. Liu DY, Baker HWG. Tests of human sperm function and fertilization in vitro. *Fertil Steril* 1992;58:465-483.
18. Rammer E, Friedrich F. The effectiveness of intrauterine insemination in couples with sterility due to male infertility with and without a woman's hormone factor. *Fertil Steril* 1998;69:31-36.
19. Zayed F, et al. Comparison between stimulated in vitro fertilization (SIVF) and stimulated intrauterine insemination (SIUI) for the treatment of unexplained and mild male factor infertility. *Hum Reprod* 1997;12:2408-2413.
20. Van Steirteghem AC, et al. High fertilization and implantation rates after intracytoplasmic sperm injection. *Hum Reprod* 1993;8:1061-1066.
21. Kovacs G, et al. AID with cryopreserved semen: A decade of experience. *Br J Obstet Gynaecol* 1988;95:354-360.
22. Johnson MD. Genetic risks of intracytoplasmic sperm injection in the treatment of male infertility: Recommendations for genetic counseling and screening. *Fertil Steril* 1998;70:397-411.
23. Quagliarello J, Arny M. Inaccuracy of basal body temperature charts in predicting urinary luteinizing hormone surges. *Fertil Steril* 1986;45:334-337.
24. Abraham GE, et al. Evaluation of ovulation and corpus luteum function using measurements of plasma progesterone. *Obstet Gynecol* 1974; 44: 522-527.
25. Noyes RW, et al. Dating the endometrial biopsy. *Fertil Steril* 1950;1:3-12.
26. Grosskinsky CM, et al. Modulation of integrin expression in endometrial stromal cells in vitro. *J Clin Endocrinol Metab* 1996;81:2047-2054.
27. Nestler JE. Polycystic ovary syndrome: A disorder for the generalist. *Fertil Steril* 1998;70:811-812.
28. Lessey BA, et al. Integrins as markers of uterine receptivity in women with primary unexplained infertility. *Fertil Steril* 1995;63:535-542.
29. Rock, JA, Thompson JD. Leiomyomata uteri and myomectomy. In: *TeLinde's Operative Gynecology*, 8th ed. Philadelphia, PA: Lippincott-Raven; 1997:731.
30. Swart P, et al. The accuracy of hysterosalpingography in the diagnosis of tubal pathology: A meta-analysis. *Fertil Steril* 1995;64:486-491.
31. Schmidt G, et al. Reproductive history of women exposed to diethylstilbestrol in utero. *Fertil Steril* 1980;33:21-24.
32. Shepard MK, Jones RB. Recovery of *Chlamydia trachomatis* from endometrial and fallopian tube biopsies in women with infertility of tubal origin. *Fertil Steril* 1989;52:232-238.
33. CDC publications 1999.
34. Houston DE. Evidence for the risk of pelvic endometriosis by age, race and socioeconomic status. *Epidemiol Rev* 1984;6:167-191.
35. Marcoux S, et al. Laparoscopic surgery in infertile women with minimal or mild endometriosis. *N Engl J Med* 1997;337:217-222.
36. Griffith CS, Grimes DA. The validity of the postcoital test. *Am J Obstet Gynecol* 1990;162:616-620.
37. Collins J. An overview of medical care issues in unexplained infertility. In: *Treatment of Infertility: The New Frontiers*, Filicori M. Flamigni, (ed). Princeton, NJ: Communications Media for Education; 1998.
38. DiMarzo SJ, et al. Effect of controlled ovarian hyperstimulation on pregnancy rates after intrauterine insemination. *Am J Obstet Gynecol* 1992; 166:1607-1613.
39. Sanfilippo JS, Singh M. Contemporary operative laparoscopy. In: *Reproductive Endocrinology, Surgery and Technology*, Adashi EY, Rock RA, Rosenwaks Z, (eds). Philadelphia, PA: Lippincott-Raven; 1996:2063-2090.
40. Rombauts L, et al. Cumulative pregnancy and live birth rates after gamete intra-fallopian transfer. *Hum Reprod* 1997;12: 1338-1342.
41. Shushan A, et al. Subfertility in the era of assisted reproduction: Changes and consequences. *Fertil Steril* 1995;64:459-469.
42. Antinori S, et al. Oocyte donation in menopausal women. *Hum Reprod* 1993;8:1487-1490.
43. Sakula EP. A primary care approach to preconceptional care. *Prim Care Rep* 1997;3:99-106.

Physician CME Questions

36. What is the most common etiology of conception difficulties?
    a. Ovulation problems
    b. Tubal disease
    c. Endometriosis
    d. Male factor
    e. Antibodies

37. Which is the least accurate way of assessing ovulation?
    a. LH predictor kits
    b. BBT charting
    c. Endomctrial biopsy
    d. Serum progesterone
    e. Ultrasonography

38. ART procedures can be used to treat:
    a. male factor problems.
    b. tubal disease.
    c. endometriosis.
    d. ovulation defects.
    e. All of the above

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