
DECISION MAKING IN INFERTILITY

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PREFACE

Decision trees provide an intriguing and innovative way to learn. In fact, much of the information currently found in formal textbooks on the management of the infertile couple is predicated on this type of thinking. Thus *Decision Making in Infertility* is an attempt to formalize the concept of decision making and to approach it in an encyclopedic fashion. Descriptive detail is by necessity absent. However, an attempt has been made to cover the physiologic, pathologic, and surgical aspects of infertility and its ramifications. Special emphasis has been placed on the reproductive endocrine components of male and female infertility and on the latest information on laparoscopic surgery, in vitro fertilization, and embryo transfer; the offshoots of GIFT and embryo freezing have also been included.

A major effort has been expended to coordinate the overlapping areas. Our major goal was to define and conceptualize patterns for patient referral.

The text represents the "Yale Way" to approach the problems of infertility.

Alan H. DeCherney, M.D.
Mary Lake Polan, M.D., Ph.D.
Ronald D. Lee, M.D.
Stephen P. Boyers, M.D.

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INTRODUCTION

Decision making is crucial to the diagnostic and therapeutic work-up of the infertile couple. Although there are specific therapies for specific disease entities, most infertile couples require extensive diagnostic and therapeutic measures to solve their problem.

Some topics are presented in a single tree; several are presented in a series of trees arranged sequentially. However, the focus of every chapter is the decision tree. The text amplifies the information presented in the tree, but is usually not essential for following the decision-making process. The references have been selected to support and to elucidate each chapter.

EPIDEMIOLOGY OF INFERTILITY

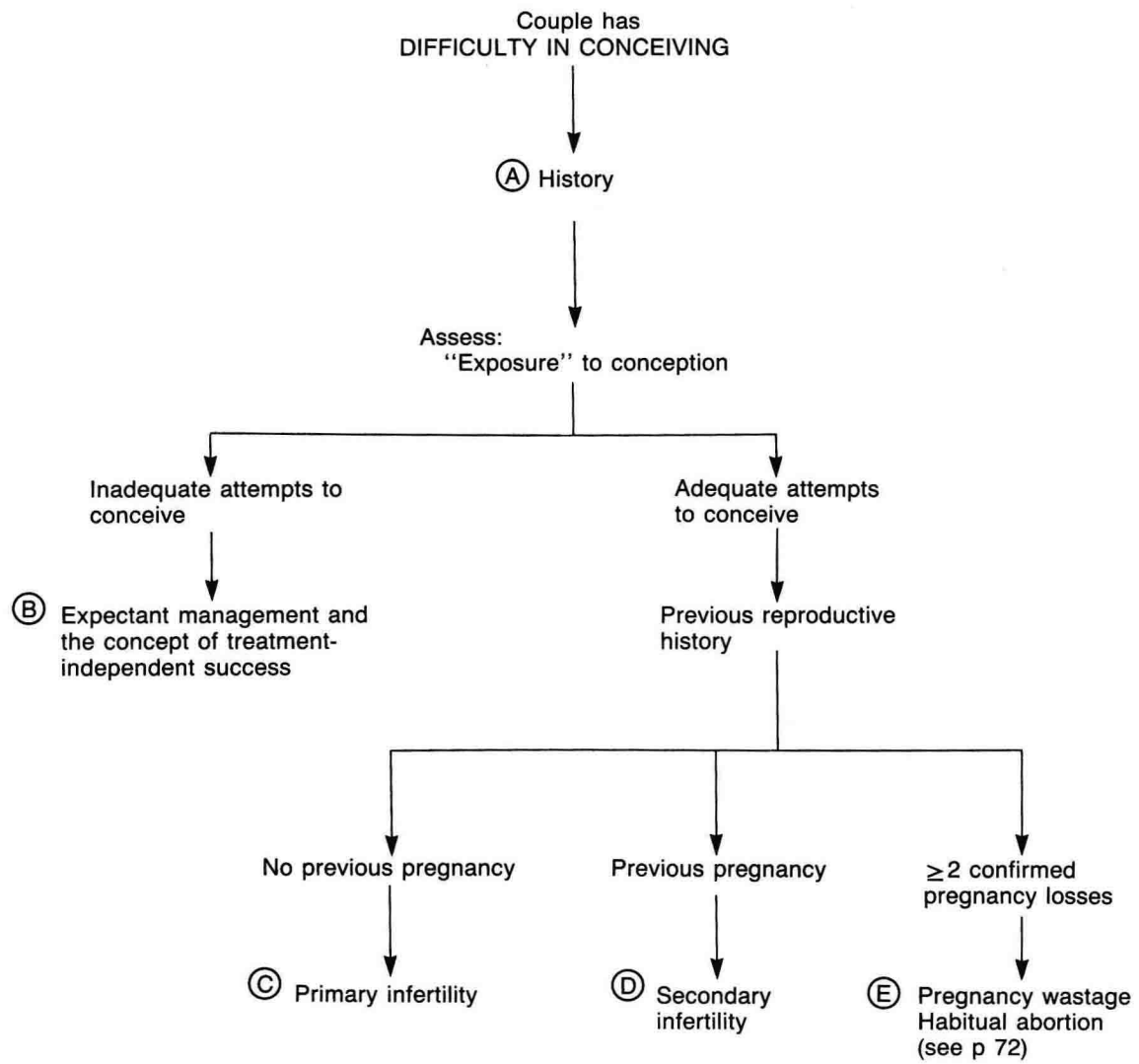
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- A. Most clinicians diagnose infertility when conception does not occur after a couple actively attempts pregnancy for 1 year; 80 to 90 percent of couples who achieve pregnancy do so within 1 year. In younger patients, or in those in whom regular sexual exposure is doubted, some clinicians delay the active investigation and treatment of infertility for up to 2 years. The couple's contraceptive history must be taken into account in the definition of infertility; after discontinuation of oral contraceptives, certain medications (e.g., Thorazine, danazol), or intra-uterine devices, the first 2 to 3 months may be less than optimal for achieving pregnancy owing to temporary ovulatory dysfunction or an unfavorable endometrium. Infertility is becoming more prevalent; current textbooks estimate the overall incidence of infertility as 10 to 15 percent of married couples. Many of these couples can be helped; current techniques offer an overall pregnancy incidence of 50 percent in infertile couples. Reports of success must be compared to age-specific cohorts; no longer will tubal anastomoses be 80 percent successful, because even "fertile" people in their late 30s and 40s will conceive only 50 to 60 percent of the time. This realization will prompt technological advancement and stimulate research into methods to "preserve" gametes (in vivo and in vitro) until pregnancy is desired. Technological advancement of in vitro fertilization has initiated discussion as to the limits of who can conceive at what cost. Ethical considerations are being raised daily in infertility practices.
- B. For over a century, observant clinicians have noted spontaneous "cures" for sterility, recognizing such "successes" as being a coincidence rather than a consequence of treatment. In a study published in 1969, 35 percent of 1,145 infertile patients conceived without treatment: 7 percent after interview and sperm count, 4 percent after vaginal examination and removal of tenacious cervical mucus, and another 17 percent after performance of a tubal patency test. A more recent article compared 597 couples treated for infertility with 548 untreated couples; pregnancy incidences did not significantly vary between the groups—41 percent vs. 35 percent respectively. Furthermore, many of the pregnancies in the "treated" group were sufficiently remote from therapy that the question of treatment-independent success was raised. The authors conclude the need for untreated control groups in fertility studies, because 23 percent of the 1,145 couples conceived without therapy.
- C. The most common clinical classification of infertility is that distinguishing between primary and secondary infertility. "Primary infertility" means that the couple has never achieved pregnancy.
- D. "Secondary infertility" implies a previous conception within the couple. Less clear in this distinction is the situation where one (or both) members of a couple seeking evaluation for infertility have had pregnancies with another partner. It is much preferred to detail the reproductive experience of each member of the couple. Similarly, use of the word "sterility" should be relegated to patients with permanent conditions irreversible by today's treatment options (e.g., congenital absence of the uterus or ovaries).
- E. Pregnancy wastage is defined as the inability to carry a conceptus to live birth and includes both spontaneous abortion and stillbirth in the strict sense. However, infertility specialists typically refer to pregnancy wastage as first- and second-trimester spontaneous abortions. Demographic usage of "infertility" includes both infecundity and pregnancy wastage. Spontaneous abortion is the form of pregnancy wastage of greatest concern to the clinician treating infertility. Approximately 15 percent of clinically recognized pregnancies end in spontaneous abortion; according to sensitive assays of human chorionic gonadotropin (hCG), as many as 40 to 60 percent of fertilized ova fail to survive. The traditional definition of habitual abortion mandates 3 or more confirmed pregnancy losses prior to evaluation. In current practice, most specialists will evaluate a couple with two or more first or second trimester losses (see p 72).

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EPIDEMIOLOGIC FACTORS: HISTORICAL CLUES

James M. Wheeler, M.D.

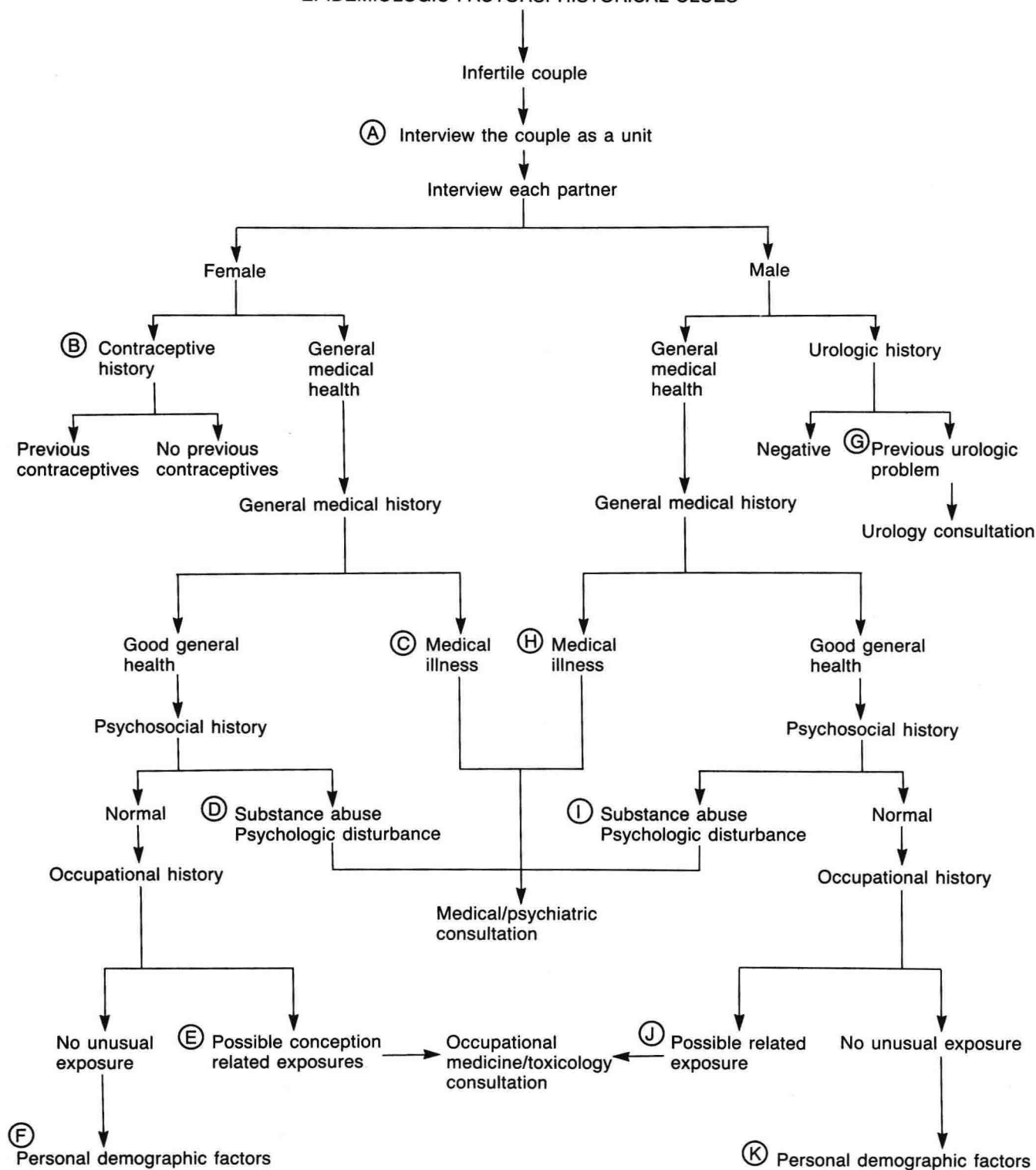
Mary Lake Polan, M.D., Ph.D.

- A. The initial evaluation should include investigation of the couple as a unit. In particular, a careful sexual history should be elicited. Frequency of intercourse appears related to the age of both partners as well as the duration of the relationship. In fertile couples, a weekly frequency of four times produced the highest conception incidences; in infertile couples, instructions are usually given for intercourse to occur every other day during the week surrounding ovulation.
A general history and physical examination of both the male and female are included in the initial consultation regarding infertility; family history of genitourinary anomalies, endometriosis, leiomyoma uteri, and varicocele should be sought. Following couple interview, investigation of the woman and man proceeds.
- B. Women stopping oral contraceptives have a longer interval to delivery than women using other methods; this difference disappears 30 to 42 months after discontinuing the pill. Although some intrauterine devices (IUDs) are associated with pelvic inflammatory disease, there is no direct effect on delaying fecundity. There is no evidence that spermicides or barrier methods adversely affect fertility.
- C. Severe disturbances in nutrition (e.g., famine, anorexia nervosa), weight loss (e.g., medical or psychiatric disease), and strenuous activity (e.g., marathon runners, ballet dancers) are associated with ovulatory disturbances. Obesity may also be associated with anovulatory cycles because of tonic increase in estrogen levels.
- D. Severe stress causes anovulation and amenorrhea. Emotional tension may be associated with sexual dysfunction, including vaginismus and dyspareunia. Substance abuse should be investigated, although the association of recreational drugs and infertility is speculative. There is no clear association between excessive coffee drinking or cigarette smoking and infertility.
- E. Exposure to lead in the pottery or smelting industries, carbon disulfide in textiles, and benzene as a solvent in many industrial processes are examples known to increase the risk of infertility and pregnancy wastage.
- F. Infertility may affect all ethnic groups and socioeconomic classes. Patterns of etiology may vary because of class differences in nutritional status, exercise, genetic factors, and exposure to sexually transmitted diseases. In population studies, the probability of conception decreases with age. The expected percentages of nonsterile women who will conceive in 12 months of unprotected intercourse drops from 86 percent in the 20- to 24-year-old group to 52 percent in the 35- to 39-year-old group. Women over 35 years of age have a two-fold increase in spontaneous abortion compared to those 20 years of age or younger.
- G. In the male, gonorrhea can cause a blocked vas deferens; *Chlamydia* can cause urethritis and *Mycoplasma* may impair spermatogenesis. Mumps complicated by orchitis is the most common viral etiology, although fertility impairment from mumps orchitis is unusual. Hernia operations may compromise testicular blood supply. Scrotopexy of cryptorchid testes is associated with variable semen quality. Congenital anomalies and repair of the urinary tract or sacrum may affect ejaculation. Previously diagnosed varicocele is not an uncommon history.
- H. Any severe febrile illness may depress semen quality. Diabetics may have retrograde ejaculation. Cancer chemotherapy often permanently destroys the male's germinal epithelium.
- I. Impotence is often related to stress. There are case reports of azoospermia caused by severe anxiety, which is reversible upon alleviation of the stress. Marked abuse of alcohol and marijuana may induce a state of hypogonadism with abnormal spermatogenesis. Moderate quantities of alcohol and cigarettes seem to have no significant effect on semen quality. Certain medications such as cancer chemotherapeutic drugs, sulfasalazine, and tranquilizers may contribute to poor sperm quality. Males exposed to diethylstilbestrol in utero have an increased incidence of genital tract abnormalities, including epididymal cysts, maldescended and hypoplastic testes, and varicocele.
- J. Exposure to excessive heat or chemicals, especially benzene and petroleum products, may depress semen quality. Military personnel may have toxic exposures during active duty.
- K. Conception is more likely when the husband is less than 25 years of age compared with the husband 25 years or older, with a marked reduction in success when over 35 years of age. However, conceptions are known to occur at advanced age when men have minimal erectile function and semen quality.

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EPIDEMIOLOGIC FACTORS: HISTORICAL CLUES



ETIOLOGY OF INFERTILITY: FEMALE FACTORS

James M. Wheeler, M.D.

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- A. Infertility is diagnosed and treated within the context of a couple unit; the proportion of couples with female factors equals the proportion of couples with male factors, and many couples have multiple reasons for their infertility. Female factors are implicated in about 50 percent of couples conceiving; often, male factors are involved in addition to a suspected female factor.
- B. Ovulation can be proven only by direct observation of oocyte release from the ovaries. Clinically, biphasic basal body temperature charts, midluteal progesterone greater than 12 ng per milliliter, and secretory endometrium on biopsy suggest normal ovulatory cycles. Late luteal biopsy may also detect qualitative ovulatory dysfunction in the form of luteal phase defects.
- C. As usually cycling women may have an occasional anovulatory cycle, any diagnostic test suggesting anovulation should be repeated or confirmed with another type of test. About 15 percent of all infertile couples are diagnosed with anovulation. The hypothalamus may mediate anovulation in anorexia nervosa, states of extreme physical exertion (e.g., ballerinas, marathon runners), or stress. Disruption of the normal hypothalamic-pituitary tracts by tumors or vascular events can perturb gonadotropin release; hyperprolactinemia also produces anovulation via the hypothalamic-pituitary axis. Excess androgen production can arise from adrenal (tumor or hyperplasia) or ovarian (polycystic ovarian syndrome) sources; high tonic levels of circulating estrogen may be associated with obesity, estrogen secreting tumors, or exogenous estrogens. Diseases such as diabetes, Cushing's disease and syndrome, Addison's disease, and hyper- and hypothyroidism may be associated with anovulation. Lately, much controversy centers upon women who develop follicles but fail to release ova despite luteinization (luteinized unruptured follicle syndrome [LUF]). An inadequate luteal phase may be associated with LUF.
- D. In 5 percent of couples, the lower female genital tract hinders conception. Developmental abnormalities may inhibit conception in obvious ways as seen in transverse vaginal septa, or more subtle ways as in diethylstilbestrol-associated anatomic changes. Abnormalities of the cervix produced by surgery (conization, cautery) or infection (*Chlamydia*) decrease sperm penetration. Cervical mucus may possess antibodies that limit sperm motility and ascent into the uterus and tubes.
- E. Hysterosalpingography (HSG) may produce the first suggestion of uterotubal disease.
- F. Intrauterine adhesions are being diagnosed more frequently owing to the increased use of diagnostic hysteroscopy. However, the contribution to infertility of the various degrees and locations of intrauterine adhesions remains to be well defined. Hysteroscopy or HSG may also detect uterine developmental malformations and submucosal leiomyomas that distort the uterine cavity. Endometrial biopsy, in addition to its use in evaluating the luteal phase, may suggest chronic endometritis caused by infection (e.g., tuberculosis).
- G. Intrinsic tubal mucosal damage and external tubal distortion may be suggested by an abnormal HSG that requires confirming ovulation and treatment. See chapters on evaluation of tubal disease (pp 86, 88) and chapters on treatment of tubal obstruction (pp 94, 96, 98).
- H. Laparoscopy reveals tuboperitoneal disease in 20 percent of women with normal HSG; conversely, 5 percent of women with abnormal HSG have no disease identified at laparoscopy. Some form of tuboperitoneal factor is implicated in one-fourth of infertile couples. Previous salpingitis is perhaps the most common of these factors; the endosalpingitis typical of pelvic inflammatory disease is usually more devastating to tubal function than the exosalpingitis typical of postabortal salpingitis or periappendicitis. Endometriosis is diagnosed more frequently today because laparoscopy is usually included in the evaluation of the infertile couple; furthermore, as various forms of early endometriosis are identified, sometimes with the aid of light or electron microscopy, the prevalence of this diagnosis will probably increase.
- I. After thorough investigation, 10 percent of couples will lack a distinct diagnosis of their cause(s) of infertility. A complete review of the couple's evaluation is warranted to assure no oversights; a repeat history may reveal sexual dysfunction, nonproductive timing of intercourse, or the use of spermicidal agents as lubricants. Borderline test results may need to be repeated. Assuming satisfaction with the couple's evaluation, a period of expectant management will result in pregnancy in some couples. Artificial insemination techniques may then be elected (see pp 148, 152). In vitro fertilization and gamete intrafallopian transfer are the final options for the couple with unexplained infertility (see p 194).

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ETIOLOGY OF INFERTILITY: FEMALE FACTORS

