EVALUATION OF THE INFERTILE COUPLE

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FERTILIZATION is an exceedingly complex process involving many fundamental questions of cellular biology. Each year our knowledge increases and with this our understanding of the biochemical aspect of reproduction. The entire mechanism is related to emotional as well as physical health. Hormonal production is dependent upon stimuli from the cerebral cortex, the hypothalamus, the pituitary, the adrenals, the thyroid, and the ovaries. Only recently has the amazing interrelationship of these hormones been appreciated.

Study of the infertile couple must show whether or not male and female gametes are produced and whether or not the passageways needed for their union are patent. It must also show whether or not physiologic and biochemical functions of the female reproductive tract are favorable to migration of spermatozoa, to transfer of the ovum to the fallopian tube, to fertilization of the ovum, and to growth of the resulting embryo.

For fertility, there must be an orderly sequence of biochemical changes and coordinated muscular activity in the female reproductive tract. Such an environment is dependent on general health, normal functioning of many endocrine glands, and the ability of the reproductive system to respond to changing biochemical stimuli. Stress, caused by illness, fear, or frustration, has a significant effect on the ability of the reproductive tract to function normally.

The purpose of this paper is to discuss the procedure we use at the Cleveland Clinic to study the infertile couple, to show how the results are used to evaluate the causes of infertility, and to point out the factors that are most important in evaluating the probability of pregnancy. The procedure is planned so that absolute cause for sterility if present may be found early, in the interest of saving the couple time and unnecessary expense.

Initial Interview

Both husband and wife are urged to be present at the initial interview. This gives the physician an opportunity to determine whether or not severe emotional problems exist in this marriage which would make pregnancy undesirable. Presence of both husband and wife also provides opportunity to expose fears the couple may have, to alleviate them if possible, and to lay the groundwork for the couple's cooperation. The understanding that can be developed in the interview helps to assure completion of the necessary tests, and often is effective therapy. The couple is given a sheet of typed instructions describing tests that require special preparation or that must be performed at specific times in relation to the day of ovulation.

During the initial interview, medical histories of the husband and the wife are recorded, and a physical examination of the wife is performed. When pelvic surgery has been done, a record of pelvic findings, and a pathologist's report is obtained from the hospital where such surgery was performed. The wife is questioned in detail about menstrual, sexual, and marital histories. Menstrual history includes age at onset of menstruation, amount of flow, occurrence of dysmenorrhea, and thorough discussion of any change in regularity. Sexual history includes data on frequency of coitus, whether or not lubricants are used, frequency of orgasm in the wife, and whether or not dyspareunia is a problem. Information as to whether or not pregnancy was ever achieved in the wife, or by the husband, in this marriage or in previous marriages is valuable.

During a complete physical examination, endocrine stigmata are noted. Distribution of fat and of hair, texture of skin, span-to-height relationship, and shape of the hands are significant. Hereditary and physical defects that would make pregnancy inadvisable or impossible are evaluated.

The first step in the pelvic examination is inspection of the cervix by means of the speculum. Papanicolaou spread of cervical secretions is taken for cytologic study. Cells of the vagina are obtained on a swab, and are then suspended in saline solution to determine the presence or absence of vaginitis or cervicitis. When *Trichomonas* or *Monilia* are found, treatment is initiated at once. Suspicious lesions of the cervix are biopsied. A small, elongated cervix is indicative of inadequate ovarian function. The position of the cervix is of little importance in the process of insemination unless the uterus is fixed in a retroverted position. The pelvis is systematically examined for ovarian pathologic change, endometriosis, and uterine abnormalities.

At the first interview we routinely order a Wassermann blood test, a complete blood count, urinalysis, and blood sugar determinations. When no absolute cause for sterility is found, blood typing, and determination of basal metabolic rate and of serum protein-bound iodine concentration are also included.

Diagnostic Infertility Studies of the Husband

The procedure for collecting semen is given to the husband at the first interview, with the request that the specimen by obtained after abstaining from coitus for four days. The specimen is obtained by friction unless this is contraindicated by religious considerations. In such cases the husband may have intercourse and may use a special perforated plastic sheath that does not affect the motility of spermatozoa. The specimen is brought to the laboratory within an hour after collection. Volume, viscosity, pH, the number of spermatozoa per milliliter, and the total number are determined. Motility is graded on a scale of 0 to 4+ then, and again after four hours. Any unusual characteristics of the specimen, such as agglutination of the spermatozoa, are noted. A stained slide is used to study the

morphologic characteristics of the spermatozoa. We use the MacLeod standard for normal semen; namely, a minimum of 20 million spermatozoa per milliliter with 40 per cent showing good linear progression and 60 per cent having normal form; the most important single factor is the quality of motility, that is, the percentage of the spermatozoa that show good linear progression.[1]

When the semen fails to meet this standard, the analysis is repeated, and the husband is referred for complete physical examination to the endocrinologic service. Standard laboratory studies, as listed for the wife, are performed; endocrine assays are made when necessary. These often include determination of the basal metabolic rate, the serum protein-bound iodine, and less often the urinary 17-ketosteroids and pituitary gonadotropin. When azospermia or severe oligospermia is present, the husband is referred to a urologist for testicular biopsy and other urologic tests.

Diagnostic Infertility Studies of the Wife

In the event that spermatozoa show good linear progression, we proceed with special fertility tests of the wife to evaluate the uterus, the fallopian tubes, and the cervix. Only if the husband has been known to produce pregnancy do we proceed with these tests without obtaining a semen analysis.

Tests of fallopian tubes. To eliminate the fallopian tubes as the cause of the infertility, it is necessary to establish that the tubes are open and that their functioning is normal. Three structures are important: (1) the musculature, (2) the cilia, and (3) the endothelium. The Rubin test and the salpingogram will show whether or not the tubes are patent. The kymographic record taken during the Rubin test shows the amount and the variation of pressure in the fallopian tubes. This gives some indication of muscular physiologic activity, since Hartman and Stavorski[2] demonstrated that the fluctuations in pressure are caused by the activity of the fallopian tubes alone.

All secretions of the female reproductive tract vary with the concentration of estrogen and progesterone. These will be discussed under the evaluation of ovarian function. It is known that the cilia of the fallopian tubes move 20 per cent more effectively at the height of estrogen production at ovulation[3] than they do postmenstrually. No tests have yet been devised which can be used routinely to demonstrate the efficiency of the cilia in transfer of the ovum in the fallopian tubes.

Precautions are essential when the Rubin and salpingogram diagnostic tests are made, because these procedures require invasion of the abdomen. There must be no infection present in the pelvis. Carbon dioxide gas is used in the Rubin test, and a suitable physiologic solution for salpingography. Both tests must be performed before ovulation. It is helpful to do the Rubin test only a few days in advance of ovulation, so that the kymograph will indicate the conditions present

when fertilization would be occurring. The pressure within the uterus must be known at all times and must not exceed 200 mm. of Hg.

The sources of error in doing these tests can be minimized by checking the apparatus for patency and leakage, by good technic in performing the test, and by allaying the patient's fears; fear may cause spasm of the fallopian tubes. Before the test is started, the position of the uterus is determined so that the cannula can follow the direction of the cervical canal without pressure, unless stenosis is present. To minimize pain, no tenaculum is used for the first test. The carbon dioxide is allowed to flow at the rate of from 20 to 30 ml. per minute, thus gradually increasing the intrauterine pressure. If leakage occurs the tenaculum can then be used. The fallopian tubes are considered to have normal patency if rhythmic oscillations occur which are characteristic of normal tubal function. These are in the range of 60 to 120 mm. of Hg, with oscillations that vary from 10 to 20 mm. of Hg. Such a finding must be followed by shoulder pain, when the patient sits up, for the diagnosis of a patency to be absolute.

Failure of carbon dioxide gas to pass through the fallopian tubes does not prove permanent obstruction, because spasm, thick mucus, or torsion of the tubes caused by adhesions may exist. When obstruction is encountered, we believe that the Rubin test should be repeated at least three times, preceded by the administration of antispasmodics, before a diagnosis of permanent obstruction is made. When a pressure of 200 mm. of Hg is maintained for several minutes it will often be followed by a flow of gas at normal pressure levels of from 80 to 100 mm. of Hg. All subsequent tests may continue to show a flow at this pressure. The Rubin test may therefore be therapeutic as well as diagnostic.

The salpingogram gives information concerning both the uterus and the fallopian tubes, and is a means for identifying congenital abnormalities, tumors of the uterus, and the location of tubal obstruction. This information is essential before a decision is reached concerning possible surgical therapy. The effectiveness of tubal surgery varies greatly with the location of the obstruction and the skill of the surgeon. Morton[4] states that salpingolysis results in about a 30 per cent pregnancy rate. Implantation of the uterine end of the tube into the uterine cavity yields about 10 per cent success.

Ovarian function. We use three procedures to evaluate ovarian function: (1) the basal body temperature, (2) endometrial biopsy studies, and (3) examination of the cervical mucus. Basal body temperatures are of great help, but they are frequently misused. They give information as to whether or not ovulation occurs, the approximate time it occurs, and some indication of the amount of progesterone produced after ovulation. When ovarian function is poor, even though ovulation occurs, the elevation of temperature may be so slight that ovulation can only be confirmed by endometrial biopsy studies. In most cases the temperature changes are sufficiently pronounced to be useful to time the Rubin, postcoital, and

endometrial biopsy tests.

The temperature chart may be used by the patient to time coitus with ovulation. This should be done only after she has received instruction from the physician concerning the advisability of such a procedure and its timing; tensions produced by the necessary procedural exactness may be detrimental to fertility. Because a basal body temperature rise takes place after ovulation, and because an unfertilized ovum will live only from 6 to 12 hours,[5] coitus after temperature rise will not result in pregnancy.

The endometrial biopsy study gives proof as to whether or not ovulation has occurred. The pathologist can see the changes in the endometrium produced by progesterone, and can evaluate whether or not they are comparable with the changes expected in the highly fertile woman.

Cervical mucus will change in physical and chemical properties with changing concentrations of ovarian hormones. In the absence of infection, repeated tests of mucus give accurate information concerning the day of ovulation. Postcoital tests demonstrate whether or not the mucus is favorable to the migration of spermatozoa. To make this evaluation we ask the couple to have intercourse at the time of ovulation, following abstinence for three or four days; the female partner is asked to remain in bed for one hour. Six to eight hours later the wife is examined. Mucus aspirated from the cervix with a pipet is put on a slide over which a cover glass is placed. The spinnbarkeit of the cervical mucus is measured. (The number of centimeters to which the mucus can be stretched before breaking is called spinnbarkeit.) Immediately premenstrually and postmenstrually the spinnbarkeit is from 1 to 2 cm. As the estrogen concentration increases before ovulation, the breaking point of mucus increases to between 10 and 15 cm. The day of maximum spinnbarkeit in the human female is the day of optimal receptivity to sperm. Maximum spinnbarkeit is found to occur just before the postovulation temperature change.

The mucus is allowed to dry on the slide after the spinnbarkeit test. It is then examined under the microscope to determine whether or not crystallization with arborization, called "ferning," has resulted. Roland[6] showed that ferning was related to high concentrations of estrogen, and that it occurred particularly at the time of ovulation. Campos da Paz[7] pointed out that progesterone inhibits fern formation.

Mucus from the mid cervix is placed on two slides, one to be stained with the Papanicolaou stain for later evaluation, the other for immediate study of sperm motility, the presence or absence of leukocytes, and an estimation of the percentage of cornified cells. Under a cover glass, this slide is examined under the microscope with a high-power, dry objective with a 10x ocular. The number of spermatozoa per high-power field is counted in at least four areas. The percentage of the spermatozoa that show good linear progression is determined,

as well as the percentage which are motile but show no progression, and those that are nonmotile.

Absence of migrating spermatozoa in the postcoital test requires the study of cervical, seminal, and ovarian factors. Endocervical infections may be present without evidence of a lesion on the external surface of the cervix. All cervical infections should be treated, even though there is considerable controversy about the relation of infection to fertility and, specifically, to sperm migration. Many pregnancies occur when cervicitis is present; yet Grant,[8] who reported on 5000 postcoital tests performed in his infertility clinic, stated that when spermatozoa did not migrate into the mucus, 70 per cent showed the presence of polymorphonuclear leukocytes in the cervical mucus. His over-all incidence of subfertile seminal assays was 42 per cent; this would seem to be significant.

From the second slide, stained with Papanicolaou stain, the percentage of cornified cells is determined. Other characteristics are rated on a scale from 0 to 4+; these include mucus, trichomonads, spermatozoa, white blood cells, histiocytes, and bacteria. When less than from 75 to 90 per cent of cornified cells is found on the slide, we first determine whether or not the test was done from 14 to 16 days before the onset of menstruation. If it was not, the test is repeated in the next cycle at or just before ovulation. Also, during the next cycle, serial vaginal cytologic studies may be done to determine the day of maximum cornification. When the postcoital test shows few migrating spermatozoa and there is less than 50 per cent of cornified cells at ovulation, the patient is referred for endocrine evaluation. Basal metabolic rate, serum protein-bound iodine and serum cholesterol concentrations are determined. Urinary tests of gonadotropin, 17-ketosteroid, and other factors are performed as indicated.

When there is good sperm migration, even though the percentage of cornified cells is less than 50 per cent, the patient is not referred to the endocrinologist until other factors that might be causing the infertility have been carefully reviewed and have been evaluated. It should be remembered that the finding of many motile spermatozoa and a high percentage of cornified cells does not necessarily mean fertility, because anovulatory cycles will frequently show from 80 to 90 per cent cornified cells for many days, with sperm survival for two to three days.

Treatment with hormonal therapy for improvement of cervical mucus must be given with a thorough understanding of the many metabolic interrelationships of the hormones produced by the pituitary, adrenal, ovary, and thyroid glands. It must be remembered that estrogen will stop ovulation if given in large doses; and even small doses, given three to four days before expected ovulation, may be followed by an anovulatory cycle or amenorrhea.

Discussion

Our knowledge concerning the biologic changes occurring at the cellular level

in the process of reproduction is rapidly increasing; as tests are developed to demonstrate more of these changes, there will be fewer patients in whom no cause for infertility is found.

New tests must be developed for more accurate evaluation of the quality of motility and fertilizability of spermatozoa. New tests are needed to show how effectively the fallopian tubes serve their function in transferring the ovum and, finally, more tests are needed to show how well the uterus and the ovary function for the growth of the embryo.

Infertile couples should be completely evaluated within one year of failure to conceive. This interval should be less if the wife is more than 25 years of age. MacLeod, Gold, and McLane[1] have shown that 40 per cent of wives of infertile couples conceived within one year when the fertility of both husband and wife were rated as good; this decreased to 18 per cent when the wife was more than 25 years old. It is urgent that the couple be evaluated while the chances of success of pregnancy are the highest.

Summary

The evaluation of the infertile couple requires a detailed study of the reproductive anatomy and physiologic processes of both husband and wife, and how well these function as a biologic unit.

Our procedure for this evaluation has been outlined. It has been shown that it is insufficient to demonstrate that there is patency of the female reproductive tract, whether or not motile spermatozoa are being produced, and whether or not ovulation is occurring. The physiologic and biochemical factors in reproduction must be evaluated for accurate diagnosis of the cause or causes of infertility.

Studies of cervical mucus are considered to be a gross method of evaluating the biochemical factors in the female reproductive tract as a favorable medium for migration of spermatozoa. New tests are needed for adequate evaluation.

The number of successful pregnancies resulting from evaluation and treatment of the infertile couple will be proportional to the age of the wife, the completeness of the evaluation of the couple when they first consult the specialist, and the cooperation of the couple in completing a scientifically planned course of treatment.

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