AN EVALUATION OF THE VARIOUS FACTORS IN INFERTILITY

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In the final drama of conception there are but two players, the ovum and the sperm. This might suggest that an assessment of the quality of these players would be simple and that it should be easy to determine why, in spite of tremendous physiological preparations, the drama is so relatively seldom enacted. If this were so the study of fertility and infertility would be simple. Unfortunately it is not. In the first place nature is as reluctant in its liberation of matured human ova as it is profligate in its production of sperms. For this reason alone it is impossible to study both players directly, and our knowledge of the ovum must be derived from evidence which at best is little more than circumstantial. This much we do know, however, that for the act of conception to be successfully achieved the performance must be so delicate, and the timing so accurate, that minor lapses can jeopardize the result. During the last 20 years much has been learned of the physiology of conception, but much more has still to be discovered before this miracle of the beginning of life can be fully understood.

In endeavouring to assess those factors which may cause infertility it is necessary to keep clearly in mind three guiding principles. The first is that *physiological and constitutional factors are of greater importance than anatomical ones.*

No longer is the practitioner justified in telling a woman there is no reason why she should not have a baby simply because he has found her pelvis, and its contents, to be anatomically perfect. Conversely, if in the course of his examination he discovers such pathological entities as fibroids or ovarian cysts, he is not entitled, in the light of modern knowledge, to state, without further investigation, that these are responsible for infertility. In fact it is most unlikely that they are. In the same way the most optimistic, or pessimistic, report from the laboratory on a jar specimen from the male does not justify the opinion that he is either beyond reproach or beyond redemption. Conception does not occur in the test tube and, as will be recorded later, tests *in vitro* can be misleading.

The second principle is that *absolute, or incurable, infertility is much less common than was until recently believed.*

More childless marriages are due to a combination of varying causes of subfertility in one or both partners than to absolute sterility in either.

The third guiding principle is intimately connected with the second. It is that *while conception is an essential beginning, the ability to conceive is not of necessity associated with the ability to reproduce.* Many women desirous of having children conceive without difficulty only to abort on repeated occasions. There is now evidence to suggest that at least one important reason for this is subfertility in the male.

If anatomical causes were mainly responsible for infertility an evaluation of these causes would be relatively simple, but as already stated they are not. If the three principles propounded above are accepted it follows that the problem of evaluating the factors responsible for infertility is now most complex. No longer can a prognosis be given on a superficial assessment of the problem as it concerns a given couple, but as compensation for the extra investigation now required there is the assurance that with increasing knowledge of the intricacies of the subject the field of effective therapy becomes ever wider.

Because the problem is now complex it is the more necessary to keep clearly in mind a general comprehensive picture of those conditions which must be fulfilled before conception can occur. In discussing these conditions with patients (and it is well to emphasize at the outset that both partners require investigation and both should understand the problem involved) it is of great help both to the doctor endeavouring to explain, and to the layman endeavouring to understand, if a simple little sketch is used to illustrate the explanation. This sketch should portray the uterus, the tubes and ovaries, and the cervix in the vaginal vault (Fig. 1). It can be so simple that no artistic talent is required to make it intelligible. With this sketch as a guide it is easy for the patient to see that before a baby can develop, four requirements must be fulfilled. There must be an ovum and a sperm meeting in a healthy tube, with a healthy and carefully prepared endometrium waiting to welcome the outcome of the union. In this way it is also easy to explain to the dominant male that however potent he may be there are on occasions

FIG. 1.—Simple sketch to illustrate conditions essential for conception (see text).

1. Healthy sperms in cervix.
2. Ovulation.
3. Normal tube.
4. Healthy endometrium.

difficulties encountered by the sperm in the journey it must make from the testicle to the tube. Possibly for the first time he then begins to realize that potency and fertility are not synonyms. It is true that a diagram oversimplifies a process of wonderful complexity, but it is equally true that if an enquiring couple can be given an intelligent idea of what must take place before pregnancy can begin they will be the more likely to co-operate in the necessary investigations based on the explanation they have received.

With the guiding principles and the simple sketch as a background an attempt can now be made to evaluate in greater detail the factors responsible for infertility. They will be considered under the headings of the ovum, the sperm, the passages, and the endometrium, although on occasions consideration of one factor must involve some consideration of another.

The Ovum

The extent to which the ovum *per se* can be responsible for infertility is at present not known. It has been generally assumed that one matured ovum is as good as another although it would be surprising if, in fact, this were so, even in these days of equality. It is surely not beyond the realm of probability that an ovum may appear to be a veritable queen among ova but still at heart be a bad egg. On occasions, however, there is no ovum, or at least no evidence of one. The extreme examples of this are found in those rare cases of primary hypogonadism associated with persisting primary amenorrhoea, or the even rarer cases in which, in spite of satisfactory breast and external genital development, 'ovaries' in the inguinal canals prove on section to be testes. These

are extreme examples of the absence of ova, and such cases, because they are rare, do not contribute appreciably to infertility in a community. On the other hand failure of ovulation in ovaries which appear to be otherwise normal is relatively common and is found in approximately 5 per cent. of women complaining of sterility. It is true that in many of these, failure to ovulate is a temporary phenomenon and without treatment the ovaries will later return to normal function. On occasions these anovulatory cycles are found in association with other evidence of glandular dysfunction and particularly with subthyroidism. The long recognized fact that the administration of thyroid to women complaining of sterility is so frequently followed by pregnancy is probably to be explained in this way. The thyroid so improves the general metabolism, and particularly the harmony of the glandular orchestra, that ovulation occurs again, and pregnancy results.

On other occasions ovulation is suspended by pelvic inflammatory disease involving the ovaries, but fortunately it is remarkable how even extensive pelvic abscesses will usually resolve and leave healthy functioning ovaries. An interesting suggestion has recently been made by Palmer of California that thickening of the ovarian tunica may prevent the liberation of matured ova. This suggestion merits further investigation as the remedy is not beyond the scope of modern surgery.

When assessing the importance of the ovum as a source of infertility it should not be forgotten that usually only one matured ovum is liberated each month, and its effective life in terms of its capacity for fertilization is short, probably about 24 hours. This being so, however potent the ovum, however virile the sperms, and however favourable the other factors, the couple will be infertile if intercourse does not occur during the transient active life of the female cell, or so near to it that the sperms will retain their powers to fertilize. Failure to fulfil these conditions is undoubtedly a cause of at least temporary infertility, but to what extent such failures exist in a community it is difficult, if not impossible, to assess. A couple having intercourse only once or twice a month can very easily miss for long periods extending into years the fertile days surrounding ovulation. This is particularly liable to be the case if, as often happens, the time of maximum desire in the female does not coincide with ovulation. Another common reason for failure is incorrect information on the fertile period, for all who handle infertility patients are aware of many, anxious to conceive, who have timed intercourse on the incorrect belief that the few days immediately preceding a period are the most fertile ones. The classical examples of infertility due to incorrect timing of intercourse are

recorded by Kurzrok (1928). Two orthodox Jewesses, by observing the Mosaic law concerning intercourse during the 'unclean' period immediately following menstruation, were infertile because in their cases short menstrual cycles resulted in the fertile periods and 'unclean' periods coinciding. Pregnancy occurred in each case when the religious custom was abandoned. It is clear from the above that lack of sexual urge and ignorance are very real factors in causing infertility. Fortunately, if the will to conceive is present, the remedy is easy and advice when acted upon will bring success. It is sometimes forgotten that there is nothing mystical about basal temperature charts. They merely act as one way of focusing attention fairly accurately on the fertile period. To summarize, it is probable that failure of the ovum due to the varying causes outlined is the factor responsible in approximately 10 per cent. of infertile unions.

The Sperm

The importance of the sperm was at first ignored in most fertility investigations. Perhaps, as a natural consequence, this importance was later, in the opinion of many, slightly exaggerated, but a valuable result has been that research has revealed a great deal concerning its physiology and pathology. Kenneth Walker (1948) believes it to be a fair assumption that in about one-sixth of all barren unions the husband is so infertile that it is unlikely any woman mated to him would conceive. Furthermore he believes that in two-thirds of cases male subfertility is a factor responsible for the infertile union. If this assumption is correct it follows that the male is at least as responsible as the female for infertile unions, and possibly more so. The question to be answered is how the various male factors may be evaluated. It must be appreciated at the outset that it is not possible to give absolute figures to illustrate the respective importance of these factors, but in a study of 1,000 males whose wives complained of infertility one would expect to find that approximately 300 would produce semen specimens which were well within normal limits. Approximately 100 (10 per cent.) would be found to have complete aspermia, but when it is realized that this symptom, for symptom it is, may indicate a variety of underlying causes, it will be appreciated that no single one, however tragic its presence may be to the individual concerned, is of itself a major factor in causing infertility. The conditions which may result in aspermia vary from bilateral testicular atrophy following orchitis to failure to ejaculate; from blockage of ducts to paresis following presacral neurectomy. Five hundred, or 50 per cent., would show some evidence of subfertility as

estimated by density of population, abnormal forms, or impaired motility. In this connection it should be noted that Walker (1948), Harvey (1945) and Jackson (1945) in this country differ from Hotchkiss (1944) and Meaker (1934) in the United States of America in feeling that the importance of the density of sperm population has probably been over-emphasized, and that abnormalities of structure of sperms occur much more frequently in fertile men than the American workers have suggested. The significance of these abnormalities of density and structure as evaluated by him has been recorded by Walker (1948) in tabulated form. The remaining 100 (10 per cent.) would be classed as border-line cases. To summarize, it has been seen that whereas in infertile unions male factors are involved in probably over 60 per cent., in less than 10 per cent. is the male absolutely or incurably sterile.

The Passages

Reference has already been made to blockage of the ducts, efferent, epididymal or ejaculatory, in the male as being but one of the causes responsible for sterility in the small group of less than 10 per cent. Disordered activity in the male tract is responsible for a relatively small group in which are included premature ejaculation, failure to ejaculate, and impotence.

In the female, faults of the passages are both more numerous and more important. It was believed until quite recently that they were in fact the most common cause of sterility, but increasing knowledge has made possible a fairer assessment of their significance. Whereas originally the emphasis was on anatomical blockages there is now a greater appreciation of disordered physiology. In the first place due to ignorance, incompetence, or fear, either alone or combined, in many infertile unions the marriage has never been consummated. This is found in approximately 5 per cent. of couples complaining of a primary sterility, and this figure does not take into account those cases in which the chance of conception is reduced by such coital difficulties as vaginismus or severe dyspareunia.

The barrier of the cervix is one which has more recently been receiving attention, and it affords a good example of how disordered physiology can prevent the union of the ovum and the sperm. Increasing use of the Sims post-coital test and, when it is negative, of the mucus invasion test, has shown beyond question that hostility of cervical secretions to the invading sperms can prevent the latter from ascending to the tubes. Nor is this hostility found only in the presence of cervical infection. On the contrary a perfectly clean cervix will sometimes show it, while an infected one will

on occasions fail to arrest the sperms from a virile specimen. It is not possible at the present time to say to what extent this cervical barrier is a factor in preventing conception; but it would probably be a fair estimate to state that 20 per cent. of patients in whom there is a negative Sims test manifest some degree of cervical hostility and to that extent the cervical barrier is an important one.

The uterus itself seldom offers any obstruction to the meeting of sperm and ovum. While it is true that on occasions the removal of a fibroid, or the enucleation of an ovarian cyst, or the replacement of a retroverted uterus is followed by pregnancy, it is important that a sense of proportion should not be lost on the relationship of pelvic tumours and uterine misplacements to infertility. They do not constitute a major cause of difficulty although in individual and selected cases they may hinder conception, as for example when a fibroid is submucous or there is a severe degree of acquired retroversion as opposed to a congenital one. Ovarian tumours should, of course, be removed quite apart from any effect they may have on fertility or pregnancy. The frequent association of pregnancy and fibroids or pregnancy and retroversion should convince the most sceptical that these conditions are not major factors in producing infertility. The total incidence of retroversion, fibroids and cysts in a large series of women complaining of sterility is not over 15 per cent., retroversion being the most common finding of the three and occurring in approximately 10 per cent. The incidence in a group of comparable size of pregnant women would not be very different. Reference must be made at this stage to endometriosis, the incidence of which appears to be increasing. Although this condition is definitely associated with subfertility, pregnancy does on occasions occur in spite of the presence of widespread pelvic deposits.

Barriers in the tubes are much more common and more serious as a source of infertility. Originally thought to be the principle, if not the only major cause of sterility, these barriers have now been studied more widely and with greater precision because of new methods which have been utilized, particularly insufflation with the electrokymograph and the study of the uterus under the fluoroscope. Originally it was claimed that 40 to 50 per cent. of women who complained of sterility had organically blocked tubes, but the most recent figures published in this country (Sharman, 1947; Jackson, 1947; Stallworthy, 1948) record an incidence ranging from 10 to 20 per cent. Possibly even more important is the evidence that tubal blockage is more often due to disordered function in the uterus or tube than was originally imagined, and evidence was produced

from Oxford to suggest that functional barriers of this nature are more common than true organic occlusions. The possible applications of this to the field of therapy have still to be explored, but whatever the results of further work may be the fact remains that barriers in the tubes, be they organic mechanical blockages or zones of irritability and spasm, are the greatest single factor responsible for infertility in the female. They are found in at least 20 to 25 per cent. of all women investigated for infertility.

So much for the evaluation of the factors responsible for preventing the simultaneous appearance of the ovum and the sperm on the tubal stage for the act of final union, but the survey is not yet complete. The act cannot be witnessed, and as stated at the beginning much of the evidence that it has, or has not, occurred is circumstantial. If pregnancy is established there is no doubt that union must have taken place, but if a period is merely delayed and then appears normal, or prolonged, there can be grave doubt on the important issue of whether conception occurred only to be followed by an early abortion. The answer can be found in the endometrium. Its histological study may provide positive evidence, in the form of chorionic elements, that pregnancy had occurred; or evidence strongly suggestive, though less positive, in the form of decidual or decidual-like changes.

On other occasions endometrial studies, which form an important part of the investigation of infertility, provide valuable information on the degree of preparation of the premenstrual endometrium and in this way serve as an index of hormonal activity. The extent to which an imperfectly prepared endometrium can be responsible for infertility in that it fails to provide an adequate nidus for the fertilized ovum cannot at the present time be determined accurately. To continue the analogy of the theatre the performance would fail to satisfy, however perfect the actors, if the stage and stage effects were incomplete. The belief that an imperfectly prepared endometrium may be an important factor in a relatively small group of selected cases, as for example in recurrent abortion, is the basis for the administration in such cases of oestrogen and progesterone therapy during the second half of the cycle once pregnancy is being attempted, and for its continuation during the first 16 to 20 weeks of gestation once it has occurred. It is also the basis for the treatment of threatened and recurrent abortion by large doses of oestrogenic hormone which, it is claimed by Smith, Smith and Schiller (1941), results in an increased production of progesterone. If the figure of 8 per cent., suggested by Lewis-Faning (1948), is the correct one for the incidence of

spontaneous abortion due to all causes, it would follow that inadequate preparation of the endometrium as a source of infertility must be responsible for considerably less than 8 per cent. of interrupted pregnancies.

The endometrial factor is important for yet another reason in that a study of biopsy specimens reveals the presence of a tuberculous endometritis in from 2 to 5 per cent. of women complaining of infertility. The available evidence suggests that the endometritis is always associated with tubal infection but in most patients in whom the unsuspected infection is detected in this way, there is no clinical, as opposed to pathological, evidence of tubal involvement. Furthermore, in many of them the tubes are patent and normal kymographic tracings may be obtained. None the less, in spite of these findings, conception does not occur, even though ovulation is occurring and the male specimen is adequate. The reason for this failure is not clear but may possibly be found in the action of tuberculous toxins on the ovum and the sperm. It follows, therefore, that tuberculous infection of the uterus and tubes is a serious factor in the causation of infertility.

The sketch with its portrayal of the uterus, the tubes and ovaries, and the vaginal cervix, has now served its purpose and acted as a text for the evaluation of factors related to the ovum, the sperm, the passages, and the endometrium. It has been mentioned already that the simple sketch, while serving a most useful purpose, does not do justice to the complexity of the problem. Nevertheless from the data available the following conclusions can be drawn. Male factors and female factors are responsible in approximately equal proportions in those cases in which one partner is primarily responsible. These account for probably 30 per cent. of all infertile unions, 15 per cent. being due to male and 15 per cent. to female factors. In both sexes inflammatory diseases and

their sequelae are the main sources of trouble. In the male they are responsible for testicular atrophy, duct blockage, and diminished vitality even when irreparable damage has not been produced, while in the female they cause tubal blockage, ovarian sclerosis, or depressed vital function as with tuberculous infections of the uterus and tubes. Some degree of subfertility is present in the male due to impaired semen production in approximately 60 per cent. of infertile unions, and there is probably a similar incidence of subfertility in the female due to cervical causes, uterine irritability, diminished ovarian function, and constitutional disorders such as subthyroidism. In both sexes there is a small incidence of absolute sterility due to congenital deformities and hypogonadism, a combined incidence which is almost certainly less than 5 per cent. Finally in a further 5 per cent. of cases infertility is due to ignorance and fear which, by preventing intercourse, preclude all possibility of union between the ovum and the sperm.

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