A CONSIDERATION OF STERILITY FACTORS IN THE LIGHT OF SUBSEQUENT PREGNANCIES

I. Factors in the Female

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We are indebted to the *Reports of the Biological and Medical Committee* published earlier this year for the latest estimate of involuntary childlessness in this country. We note that the work of this committee formed part of a general investigation by the Royal Commission on Population, but we submit that when it comes to dealing with the childless couple our thoughts are far removed from the evil consequences of depopulation. We prefer to think that the problem is of a more personal nature closely linked with the happiness of the would-be parents. The figures arrived at can be regarded only as approximate but the estimates of 8 per cent. likely to be involuntarily childless, 4·5 per cent. restricted involuntarily to one child and a further 5·5 per cent. so restricted to two children give some idea of the magnitude of the task confronting those who elect to seek the cause of this state of affairs. In recent years this matter has attracted the attention of many gynæcologists and urologists and others, and has provided the material for countless publications and many conferences. In fact, so numerous and extensive are the implications and ramifications of this subject in all its aspects embracing etiology, investigation and treatment that it is beyond the scope of this paper to do more than present to you certain conclusions which we have reached as a result of four years' experience in this field. The evidence for these conclusions is chiefly provided by a number of patients whose patience and fortitude whilst undergoing investigation were rewarded by pregnancy and, to a lesser extent, by a larger number of patients, who, so far, have been less fortunate.

Analysis of 107 Pregnancies

For the purpose of this study a consecutive series of 107 pregnancies occurring in patients investigated and treated in our sterility clinic has been reviewed. The cases have been divided into three groups: primary sterility, secondary sterility and habitual abortion.

Primary Sterility

In this group there were 70 pregnancies. The average age of the patients was 29 years, the youngest being 21 and the oldest 41 years.

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Average length of time of marriage was four years eight months, the shortest period being fifteen months and the longest twelve years. Because of the intrusion of the war years, affecting most marriages, it has been difficult to estimate accurately the exact duration of effective married life. Taking into account war service and the practice of contraception, we found that the average period of effective marriage was three years and eight months. Contraception had been practised by only 20 per cent. of these patients. Apart from the isolated case of fifteen months' marriage, investigated on account of age, this would appear to be a typical series of cases of primary sterility.

Investigation revealed definite etiological factors in 68 cases. Thus in only 2 cases no obvious cause to account for the period of infertility could be discovered and in 75 per cent. of patients more than one factor was discovered. The average frequency of coitus was found to be five times per month. Those conditions considered to contribute towards the state of infertility are summarised and grouped under six headings according to whether the factors are general, local, cervical, endometrial, tubal or male.

Etiological Factors

General Factors

	Number of Cases
Malnutrition and obesity	8
Infrequency of intercourse	4
History of previous appendicitis (six appendicectomies)	7

Local Factors

	Number of Cases
Polycystic ovaries	10
Intact hymen	4
Hypoplasia	4
Retroverted uterus	3
Trichomonas vaginitis	2

Cervical Factors

	Number of Cases
Chronic infection	20
Deficient secretion	7
Hypoplasia	4
Displacement by retroversion	3
Tight internal os	3

Endometrial Factors

	Number of Cases
Recurrent amenorrhœa	1
Recurrent amenorrhœa with occasional anovular cycles	1
Irregular menstruation with occasional anovular cycles	1
Regular menstruation with occasional anovular cycles	1

Tubal Factors

	Number of Cases
Inactive patency	11
Obstruction	9
Spasm	8

Interference with tubal function was found to be associated with previous appendicitis (six appendicectomies) in 7 cases, polycystic ovaries in 5 cases, retroversion of the uterus in 2 cases, and hypoplasia in 1 case.

Male Factor

	Number of Cases
Defective spermatogenesis	20

Therapeutic Measures

When dietetic faults were discovered, advice was given and when obesity was marked, thyroid was administered. In 17 cases of chronic infection the cervix was dilated and cauterised, whilst in 5 patients dilatation of the cervix only was performed, the indications being tight internal os in 3 and dysmenorrhœa in 2 cases. Stretching of the introitus under anæsthesia was carried out for the cases of intact hymen, and trichomonas vaginitis was treated by acetarsol and lactic acid douching. In 3 patients with cystic ovaries, laparotomy was performed on account of pelvic pain. In each case the ovaries were partially resected; in one tubal adhesions were separated, and in another the uterus was suspended by the Gilliam operation. Twelve patients were treated by œstrogens, the indications being hypoplasia, deficient cervical secretion or inactive tubes. The 2 cases of recurrent amenorrhœa received œstrogen and progesterone therapy. Particularly in the 17 patients showing evidence of tubal spasm or obstruction, insufflation, and sometimes repeated insufflation, was considered to be therapeutic. In the case of the retroversions, 2 were variable and the uterus was anteverted at the outset of pregnancy, whereas in the third, correction was required during pregnancy and abortion occurred. In 60 patients advice was given regarding the optimum time for intercourse immediately after investigation and active treatment had been completed.

The time interval between giving this advice and conception was as follows :—

	Number of Cases		
Before investigation and treatment had been completed	10	67·1%	90%
Within one month following advice on intercourse	21		
Within two months following advice on intercourse	11		
Within three months following advice on intercourse	5		
Within six months following advice on intercourse	16		
Within twelve months following advice on intercourse	6		
Over twelve months following advice on intercourse	1		
Total	70		

Secondary Sterility

In this group there were 29 pregnancies. For convenience of grouping we have included, in this category, cases with the history of full-time delivery or abortion or ectopic gestation, each followed by a genuine period of infertility. The average age of the patients was 31 years

8 months, the youngest being 21 years and the oldest 39 years. The average interval between last pregnancy and investigation was four years five months, the shortest period being one year following abortion, and the longest twelve years. The average number of times of intercourse per month in these patients was six.

Investigation demonstrated etiological factors in 27 cases. In 55 per cent. of these patients more than one factor was discovered.

Etiological Factors

General Factors

	Number of Cases
Infrequency of intercourse	4
History of appendicitis (six appendicectomies)	6
History of ectopic gestation	3
History of salpingo-oophorectomy	1
Diabetes	1

Local Factors

	Number of Cases
Retroverted uterus	5
Polycystic ovaries	5
Uterine fibroids	1

Cervical Factors

	Number of Cases
Chronic infection	13
Displacement by retroversion	5
Deficient secretion	4

Endometrial Factors

Nil

Tubal Factors

	Number of Cases
Obstruction	5
Inactive patency	2
Spasm	2

Disordered tubal function was found to be associated with previous appendicitis (four appendicectomies) in 4 cases, polycystic ovaries in 3 cases; salpingectomy for ectopic pregnancy in 2 cases and retroversion of the uterus in 2 cases. In one additional case one tube and ovary had been removed but the function of the remaining tube was normal. In the third case of previous ectopic gestation the remaining tube showed normal function.

Male Factor

	Number of Cases
Defective spermatogenesis	8

Therapeutic Measures

In 13 patients the cervix was cauterised after dilatation. Two cases of retroversion were treated surgically and, in both, pelvic adhe-

sions were divided. In the remaining 3 cases of retroversion, 1 was variable and the uterus was in an anteverted position at the onset of pregnancy, whilst 2 were retroverted during pregnancy and required correction, and 1 of those patients aborted. Œstrogen therapy was given in 2 cases, the indications being tubal inactivity. In all cases insufflation was regarded as a therapeutic measure and advice on optimum time for intercourse was routine. The time relationship between giving advice on intercourse and conception was as follows :—

	Number of Cases		
Before investigation and treatment had been completed	7	79%	86%
Within one month following advice on intercourse	8		
Within two months following advice on intercourse	6		
Within three months following advice on intercourse	2		
Within six months following advice on intercourse	2		
Within twelve months following advice on intercourse	2		
Over twelve months following advice on intercourse	2		
Total	29		

Habitual Abortion

Eight patients giving a history of three or more consecutive abortions are included in this group. Etiological factors discovered on investigation were intermittent anovular menstruation (2 cases—one associated with hypoplasia), thyrotoxicosis (1 case), excessive length of tubes (1 case) and deficient spermatogenesis (1 case). In 3 patients no obvious cause could be demonstrated. In all cases treatment was instituted during pregnancy and included administration of œstrogens and progesterone. There were two abortions including one obvious fœtal abnormality (anencephaly). There is a tendency at the present time to consider cases of habitual abortion as endocrine disorders. Whilst this is admittedly true of some cases, we believe this practice to be dangerous. There are many other possible etiological factors to be considered in both the female and the male. These are indeed examples of subfertility and, as such, they merit and require the fullest investigation along the lines which we will now suggest should be adopted for all sterility patients.

Investigation of Sterility

From this analysis of a series of pregnancies we have indicated the responsible factors which have responded to treatment, at any rate to the extent of permitting conception. There are, of course, many other factors which may play a role in sterility but it is impossible and indeed unnecessary to discuss all of these in detail in this paper. However, it is evident that in order to discover all these possible factors a certain minimal routine of investigation will be essential. Our experience of sterility work has been confined to the past four years during which time we have seen some 700 patients. Of this number many have

defaulted, for various reasons, so that full investigation has not always been possible, but, in the majority we have attempted to account for all possible factors, capable of discovery, by following a planned campaign of investigation. Adopting the same grouping as before we will now outline the steps of our routine investigation.

(1) *General Factor.*—A comprehensive personal history is recorded which includes age, details of menstruation, illnesses, previous treatment and operations. In addition, information is obtained concerning marital relationships with special reference to contraception, frequency of intercourse and difficulties associated with coitus. General examination will be concerned with such matters as stature, distribution of hair and fat, and evidence of systemic disease.

The penalties of advancing years are unfortunately only too well-known and obvious. In the female the period of maximum fecundity lies between twenty to twenty-five years and thereafter there is a gradual decline in fecundity until the menopause is reached. For this reason it is imperative that, in the older patient, no time should be lost in seeking the cause of sterility and instituting appropriate treatment.

In the present state of our knowledge concerning the relationship between diet, general body metabolism and hormone production it is not easy to attribute infertility to any particular dietetic deficiency. In animals, avitaminosis will reduce fertility, but in the human only gross deficiencies, such as that of Vitamin B^1 in Beri-Beri, will lead to ovarian failure and amenorrhœa. The assumption is that the anterior pituitary is susceptible to Vitamin B stimulation and such action upon the pituitary is now also accredited to Vitamin A and proteins. If vitamins and amino acids are extremely deficient the first property of the pituitary to be lost is the production of F.S.H. with resulting amenorrhœa. Perhaps defective ovulation with diminished fecundity may result in less marked deficiencies. For this reason we have thought it wise to enquire into the diets of all sterility patients. In 200 consecutive and unselected patients the diet was found to be inadequate in 83 per cent. of cases. Deficiencies chiefly affected such items as fresh fruits, milk, cheese, vegetables and cereals, in other words, these substances chiefly responsible for an adequate intake of vitamins. In 58 per cent. of cases there was deficiency of first class protein. Certain types of obesity are also associated with defective ovarian function and thus with the complaint of sterility. In the series 28·5 per cent. patients were overweight and 45·5 per cent. underweight. Whilst making no extravagant claims we suggest that from the available evidence there is sufficient indication to consider dietetic errors as a possible factor in sterility, and corrective measures should be adopted where indicated.

The role of contraception in causing reduced fertility after discontinuation has evoked contradictory views from various authors. Rubin maintains that contraceptive methods undoubtedly affect fertility for longer or shorter periods after their use has been stopped,

and Green Armytage claimed that " she who will not when she may, when she wills she shall have nay." The opposing viewpoint is strongly supported by the inquiry conducted by the Royal College of Obstetricians and Gynæcologists which found no evidence to show that contraceptive methods were followed by impaired fertility when discontinued. We believe that the truth lies somewhere between these two extreme views. If hygienic methods are employed according to the advice of knowledgeable instructors then undesirable after-effects are unlikely, whereas if ill-advised methods are adopted then subsequent trouble may result. In the case of mechanical devices infection of vagina or cervix may result, whereas chemical preparations may lead to changes in the physical characteristics of the cervical and vaginal secretions which become temporarily inimical to spermatozoa. Some form of contraception is practised by 60 to 70 per cent. of married couples, for varying lengths of time, and this period must always be taken into account when calculating the effective duration of marriage.

It is generally agreed that, in some women, emotional upset associated with worry or domestic difficulties may lead to various menstrual disorders. For this reason we have introduced, in recent years, a revue of social circumstances as a routine measure in history-taking in the belief that, by so doing, yet another possible etiological factor is investigated.

The frequency of intercourse and knowledge of the fertile phase are interrelated points which demand routine inquiry. We have already recorded the average frequency of coitus in the successfully investigated group, and this figure is equally applicable to the total number of patients who have attended the clinic. With an average of five times per month it means that many patients have intercourse much less frequently. If we accept the view that the available time for fertilisation to occur is limited to a 24-hour period each month, then in many instances this short fertile phase will be missed and thus infrequency of intercourse may in itself be one factor in causing infertility. We will refer to this point again.

(2) *Local Factor.*—The value of a careful pelvic examination to exclude infections, obvious maldevelopments, tumours, displacements or other abnormalities calls for no comment other than to stress the necessity of making such an examination under anæsthesia if there is any dubiety at all about the findings.

Hypoplasia is often difficult to assess although in some cases the stigmata are obvious. Tenting of the vagina, a button-like cervix with pin-hole os, a small acutely anteflexed or retroflexed uterus leave no doubt as to the diagnosis, but minor degrees are not easily recognised and may be of major importance in preventing successful embedding of the ovum and causing early abortion. Measurement of the utero-cervical canal is not always diagnostic as elongation of the supra-vaginal portion of the cervix associated with acute displacement will sometimes mask an actual reduction in the length of the uterine cavity.

Congenital retroversion of the uterus is frequently associated with hypoplasia, whereas the acquired type is found chiefly in cases of secondary sterility. We believe that this displacement of the uterus may reduce fertility by isolating the cervix from the seminal pool, distorting the fallopian tubes or preventing complete intercourse by reason of the dyspareunia due to associated prolapse of the ovaries.

Submucous fibroid tumours are frequently associated with congestion and hyperplasia of the overlying endometrium and this may well prevent successful embedding of a fertilised ovum. Large interstitial tumours may interfere with tubal function by causing mechanical obstruction, and abortion is not uncommon in the presence of these tumours.

It is difficult to explain why pelvic endometriosis should be commonly associated with the state of infertility. In fact, it is uncertain whether the state of infertility predisposes to the development of endometriosis or whether a single common factor is responsible for the development of both states or whether the endometriotic lesions, by anatomical disturbance, prevent successful conception. Whatever the explanation, endometriosis is by no means easy to diagnose as frequently the nature of the symptoms bears no relationship to the extent of the disease. This condition should always be kept in mind when examining sterility patients particularly those over 30 years of age.

Cervical Factor

The primary function of the cervix is to permit and facilitate passage of the sperm from vagina to uterine cavity. Any condition interfering with this property must be regarded as an etiological factor in sterility. Thus the sperm may fail to reach the cervix in the case of retroversion of the uterus, the sperm may fail to enter the cervical canal in cases of hypoplasia or stenosis, and the sperm may fail to pass through the cervical secretion in cases where this is altered by infection or hormonal deficiency. Assessment of cervical function must depend upon visual inspection and post-coital examination. It is known that the cervical secretion is in the optimum state for transmission of the sperm around the time of ovulation and thus, to be of any real value, the post-coital examination must be carried out at this time. Specimens are obtained from both upper and lower parts of the cervical canal. The test should be performed within 10 to 12 hours after intercourse and the specimens are examined immediately on the warm stage of the microscope. A negative or poor result indicates either a fault in the cervix or in the seminal fluid, and the latter possibility will be excluded by seminal examination. The post-coital examination does not obviate the necessity for full examination of the husband. We have noted, with some surprise, the frequency of cervical infection in the nulliparous patient. This finding is not easy to explain but we believe that, in some cases, contraception is the cause, and in others that a " virginal " erosion

provides a ready site for infection. We have noted a vast improvement in the post-coital test following cauterisation of the cervix in such patients.

Endometrial Factor

Examination of the endometrium, at an appropriate time during the menstrual cycle, is carried out for two reasons: firstly to exclude local disease and secondly to determine the pattern of ovarian function.

From figures quoted in the literature there would appear to be a considerable geographical variation in incidence of unsuspected pelvic tuberculosis. In over 400 consecutive biopsies of the endometrium we have found evidence of endometrial tuberculosis in only 1 per cent. of cases.

Biopsy, as a rule, requires no anæsthetic and is carried out about the twenty-third day of a regular menstrual cycle and on the first day of menstruation in irregular cycles. The large majority of specimens will show normal premenstrual changes but deviations from normal will include evidence of an anovular cycle, an unripe endometrium or glycogen deficiency. From a study of the literature the impression is gained that anovular menstruation is a common feature in sterility patients. We believe, however, that most figures quoted are inaccurate for two reasons; firstly, that, in some instances, conclusions have been drawn from temperature records only, and secondly, that in other instances an insufficient number of consecutive menstrual cycles have been checked. We have analysed a consecutive series of 431 patients examined by endometrial biopsy. Of these, in 409 cases, secretory changes were found at the first biopsy. Of the remaining 22 patients, 7 gave the history of recurrent periods of amenorrhœa, in 9 patients evidence was found of occasional anovular cycles in association with irregular menstruation, and in only 6 patients did we find evidence of occasional anovular cycles associated with regular menstruation. Thus, in menstruating patients, 3·5 per cent. had occasional anovular cycles but the incidence of occasional anovular cycles associated with regular menstruation was only 1·4 per cent. In no patient of this series was there found to be consistent regular monthly anovular menstruation.

Little precise knowledge of the function of glycogen in the endometrium is available at the present time, but a deficiency of glycogen is occasionally noted and has been described by Zondek as Glycopenia Uteri. It is possible that this deficiency prevents successful embedding of the ovum and leads to early abortion and thus constitutes one of the theoretical indications for the administration of œstrogens in cases of threatened and habitual abortion.

Tubal Factor

From a study of 400 cases in which investigation of tubal function had been carried out we found evidence of disordered function in 33 per cent. of patients; in 12 per cent. there was total occlusion and in the

remaining 21 per cent. there was evidence of lesser degrees of disordered function. Thus with one-third of all sterile women showing some degree of interference with tubal function it is evident that some test for this factor must be included in the routine investigation. Reference has been made to the possible effect upon the tubes of such external influences as fibroids and retroversion. Variations in the response of tubal muscle to nervous and hormonal stimulation must also be mentioned. Hyperactivity induced by nervous stimuli is the likely explanation of tubal spasm and a typical example of hormonal inactivity is seen in hypoplasia. We believe, however, that infection, whether gonococcal, pyogenic or tuberculous, accounts for the majority of cases showing disturbance of function. Our concern is only with the results of infection as active disease constitutes an absolute contra-indication to investigation. Sequelæ to infection arise from the destruction of ciliæ and the formation of filmy adhesions in endosalpingitis, from fibrosis and rigidity of the muscular layer in interstitial salpingitis, and from dilatation of the tube and hydrosalpinx when the abdominal ostium has become sealed. External infection involving the appendix and peritoneum may be followed by adhesion formation embracing and kinking the fallopian tube.

In performing a test for tubal function and efficiency, evidence of patency alone is not sufficient; evidence of muscular activity must also be demonstrated. For this reason we advocate routine testing by means of insufflation, using carbon dioxide, and with a kymographic recording of the results. The test is carried out between the fourth and seventh days following cessation of menstruation, and, in the majority of cases, no anæsthetic is necessary. Before a final opinion can be given regarding the state of the tubes repeated insufflation is often required, and we have found anæsthesia to be helpful in assessing cases showing obstruction of doubtful origin.

From what has been said, it will be gathered that, in our opinion, the minimal investigation required, in all genuine cases of sterility, will consist of comprehensive history-taking, general and local examinations, endometrial biopsy, post-coital test, insufflation of the tubes and examination of the husband. Only in exceptional cases will additional procedures be indicated and these will include examination under anæsthesia, diagnostic curettage, examination of endocervical secretion, hystero-salpingography and laparotomy.

Summary and Conclusions

We have now concluded the evidence, mainly factual but sometimes circumstantial, in support of the case for full routine investigation of all sterility patients. However, before attempting to draw conclusions, we should like to make one small amendment to the rule. It has been noted that intercourse takes place so infrequently in some cases that it may well be that the opportune moment for conception is missed. If

the time factor is not vital because of age, we suggest that the general practitioner may play a part by giving the necessary advice to make coitus productive. The only really practical method of determining the presence, and approximate time, of ovulation is by recording the basal body temperature. If a chart is kept for three-monthly cycles, and a biphasic record is obtained, sufficient information is available to permit sound advice concerning the optimum times for intercourse. To obtain worthwhile records, detailed instructions must be given and, if these are followed accurately, the route by which the temperature is recorded is of little consequence. We have always used the oral route, with satisfactory results, but we understand that there are others who prefer to utilise the more inconvenient and distasteful rectal route. These patients should be referred for full investigation if conception has not occurred within six months.

We believe that the best way in which we can present our conclusions is by asking ourselves two questions. Firstly, " What is the object of sterility investigation ? " and the reply is, " In order that we can provide the patient with a reliable opinion as to the prospects of conception." Thus this opinion may assume one of three forms. Either we can say " there is nothing obviously wrong and, with timed coitus, conception should occur " or " there is a precluding factor but, with treatment, prospects of conception will improve " or " there is an absolute barrier to conception and, in the present state of our knowledge, we can do nothing to overcome it." It is very evident that only with complete knowledge of the functional capacity of the organs of reproduction can this opinion be given with assurance and honesty. Without this knowledge any opinion on the prospects of conception must be based on a foundation less secure than sand or straw. And surely the only way in which this information can be obtained is by carrying out the comprehensive routine investigation which has been described and which will discover etiological factors in some 90 per cent. of cases and more than one factor in 60 per cent. of cases.

The second question we ask is, " Is it really worthwhile ? " To answer this question completely we must take into account both the successful and the hopeless cases. Because of a high defaulter rate, for various reasons, it is notoriously difficult to assess results accurately, but we believe that the Biological and Medical Committee of the Royal Commission comes near to the truth when it states that " It would at present be unsafe to assume that more than 15 to 20 per cent. of involuntarily childless matings are preventable or curable by the methods now at our disposal." For our own clinic we estimate the conception rate to be around 30 per cent. but from this figure must be deducted wastage from abortion, ectopic gestation and fœtal abnormality amounting to about 15 per cent. of all pregnancies which gives an ultimate success rate of about 25 per cent. But our answer to the question, in the first instance, is " Yes," for we believe that only a small proportion of these patients would have achieved a successful pregnancy without help.

And, in the second instance, our answer is " Yes," for, in some 25 per cent. cases, we find evidence of absolute sterility and we are thus able to inform these patients that the chance of conception is negligible and thus clear the way for adoption. And, in the third instance, we again answer " Yes," for we believe that, as our knowledge of human sterility increases, the percentage of involuntarily childless matings will decrease. But this additional knowledge can be acquired only by painstaking investigation and scientific research and these are dependent on time and money and of all things in the world at the present day those in shortest supply and at the highest premium are " time and money."

We should like to take this opportunity of thanking all those who have rendered assistance in the Clinic and we mention, in particular, Sister Isdale for her untiring service, Sister Simpson for diet surveys, Miss Stirling for social histories, and Mr Leslie Mackenzie for help with the post-coital examinations.