Post-Graduate Medical Journal

LONDON, AUGUST 1944

THE ENDOCRINE TREATMENT OF STERILITY

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According to Meaker—in approximately 30 per cent of sterile marriages is some condition found which alone makes conception impossible, such as occlusion of the vas deferens or atrophy of the testes in the male; or occlusion of the Fallopian tubes in the female. In the majority of sterile couples more than one factor usually operates to militate the chances of conception. Meaker found in a series of 200 cases an average of 4.8 factors. It is not only to the genito-urinary tract we must look for correction, but such factors as chronic intoxication, deficient diet and exercise, and endocrine disorders must be taken into consideration. It is perhaps not widely realised that the delicacy of spermatogenesis is such that the existence of toxins in the body from some chronic source of infection may have a markedly deleterious effect on this function. If this applies to the spermatozoa we can but surmise that it may also apply to the ovum, whose duration of viability we are, unfortunately, not able to ascertain in individual cases. Twenty-four hours is the duration of life ascribed to the unfertilised ovum. Any factor lessening even by so much as one hour this short span of life is of importance, hence the value of eradicating minor as well as major causes of subfertility.

Subfertility in the Male

When the urologic causes of subfertility in the male are excluded, we are left with constitutional and endocrinal causes. Now, whether constitutional defects act by inducing hormonal insufficiency or by diminishing the reactivity of the germinal epithelium in the testes, it is difficult to know, but it is thought their action is rather that of an endocrinal depressant.

The two main endocrinal factors operative in male subfertility are thyroidal and pituitary. Moneck has shown that in some 15 per cent of subfertile men the basal metabolic rate is in the range of -10 to -18 per cent, and that administration of thyroid brings about marked improvement in the quality of the semen. It is noteworthy that very few of the sub-thyroidal males demonstrate clinically any of the usual signs or symptoms of thyroidal deficiency, which can only be detected if the B.M.R. is estimated as a routine procedure. Since the activities of the endocrine glands are so dependent on each other, restoration to normal function of one improves the activity of the others. Grosser pituitary deficiencies resulting in one or other of the known clinical types are readily detected, but minor deficiencies may not produce detectable clinical lesions, and yet exert a depressant effect on normal secretion. Unfortunately, there are no easily obtainable and satisfactory tests that can enable us to detect with certainty minor degrees of pituitary dysfunction. Moreover, rendering detection more difficult is the fact that some of the functions of the pituitary gland and the hormonal output controlling that function may be normal, whereas another function may be subnormal. For example, the growth hormone of the pituitary gland may be excreted in normal amounts, yet the gonadotropic hormone excretion be deficient or excessive.

The gonadotropic hormone stimulates testicular function which, in turn, diminishes gonadotropic hormone production, so that probably a state of dynamic equilibrium is maintained between the two. Hence, excessive gonadotropic hormone production may be as important as too little. Hence also the importance of not giving excessive doses of either hormone so as not to risk disturbing the function of the other. To ensure normal fertility in the male, it is essential that the pituitary produce gonadotropic hormone, and that both the seminiferous epithelium and the interstitial cells of the testes be capable of reacting to it. Pituitary deficiency may disturb the function of the testis as a whole, manifested in impairment of both spermatogenesis and testicular secretion, or disturb only the function of the seminiferous epithelium and cause deficient spermatogenesis.

Testicular reactivity may be impaired in those subjects who take insufficient exercise or

too excessive diet, and where there is a deficiency of vitamin E intake. It is stated that deprivation of this latter substance may lead to such atrophy of the seminiferous epithelial cells that regeneration cannot take place.

In normal males some gonadotropic hormone is excreted during the twenty-four hours, so that hypogonadotropism should not be diagnosed unless very small traces or none are obtained on more than one occasion. Diagnosis should not be based on one negative finding, for even in the normal male excretion may be periodic.

On Hormonal Treatment in General

All hormones given to stimulate genital function should be given intermittently. The dose should be the smallest that is found to be therapeutically efficient for that individual.

If hormones are given in large doses over a prolonged period, the serum of the treated individual may develop anti-hormone, which counteracts the effect of the injected hormone.

Different workers recommend greatly varying therapeutic doses. This discrepancy is probably due to the difference in reactivity of individuals.

Regarding the use of female hormones—to explain the apparent contradiction in treatment recommended, it should be pointed out that there is a great deal of overlap in the effect of oestrogenic and corpus luteum hormones. This is not surprising when one reflects that the two hormones are produced by the same cells which, after producing only oestrogenic hormone, become converted to produce progesterone as well.

HORMONAL TREATMENT IN THE MALE

Thyroid Deficiency.

The most certain response to treatment is in those cases of thyroidal deficiency, the majority of treated cases showing marked improvement in testicular function.

The dose of thyroid given is graded according to the deficiency and the response to treatment. This latter is demonstrated by subsequent tests of the Basal Metabolic Rate, and improvement of testicular function as shown by semen analysis.

Androgenic Hormones.

The effect of androgenic hormones on spermatogenesis is uncertain, but they certainly stimulate the accessory glands of the male genital system, causing increased libido. In some cases there appears to be some improvement in spermatogenesis, but the results in any one case are uncertain and must be checked by repeated semen analyses.

The main uses, therefore, of androgenic hormones are in cases of oligospermia (scanty amount of seminal fluid), and in impotence or diminished libido. The less certain action is in cases of oligospermia (scanty spermatozoa), asthenospermia (low viability), and teratospermia (abnormal forms).

Testosterone acetate or propionate is usually used. Some workers recommend a dose of not more than 5 mgm. twice a week for twelve injections in the first instance. Others obtain good results with doses amounting to 25 mgm. twice a week for a similar period. Perandren (synthetic testosterone) may be given instead.

One month after cessation of the course, the seminal analysis should be repeated and treatment continued if some improvement has been shown, but the condition not yet fully restored to normal.

Failure of improvement, or a deleterious effect on spermatogenesis, is an indication not to pursue that treatment in future.

Large doses, or long continuance of treatment, may depress pituitary function.

In cases when it is not possible to attend for injections, methyl testosterone may be given orally in daily doses of 5 to 20 mgm. The small dose given daily for three to four weeks may have no effect in some individuals, whereas 20 mgm. given daily for a much shorter period may.

Gonadotropic Hormones.

Firstly, let it be said that there are many diverse opinions regarding the value of these preparations. It may be because some experiments are carried out with a gonadotropic hormone obtained from one source, and others from another, or it may depend on the, as yet not very satisfactory, method of assessing which preparation to give and how much.

In the male, different factors in the gonadotropic hormones exert their main influence (a) on testicular secretion, (b) on spermatogenesis. It is not possible to extract these specific hormones from the anterior pituitary gland, but a gonadotropic hormone can be obtained from each of the following sources (see below) which exert slightly different effects. For instance, the hormone obtained from the anterior pituitary is capable of restoring testicular activity in hypophysectomised males even after testicular degeneration has taken place, whereas pregnancy urine does not—but exerts a more specific action on spermatogenesis.

Gonadotropic hormones may be obtained from the following sources:—

1. The anterior lobe of the pituitary gland.
2. Pregnant mare's serum (mainly follicle-stimulating hormone).
3. Pregnancy urine (chorionic hormone or mainly luteal-stimulating hormone).
4. Menopausal urine.

Although they are all classified as gonadotropic hormones, their actions are not identical, some provoking certain responses more than others.

Small amounts of gonadotropic hormone are excreted in the urine of the normal male—but tests for detection of the presence of hormone have to be done on laboratory animals, hence quantitative estimations, with any degree of accuracy, are difficult. The amounts of gonadotropic hormone excreted daily are not constant, and may vary from day to day in the same individual. If a known amount of gonadotropic hormone is given, only a small amount of the given quantity is excreted in the urine. The significance of this fact is that it is difficult to prove that absence of hormone in the urine is necessarily a criterion of deficient production. It may be possible to have the gonadotropic hormone excretion in the urine estimated. If this is normal, there is no value in giving gonadotropic hormone, with the possible exception of the hormone obtained from pregnancy urine, from which benefit may occasionally be derived. As in many cases it is difficult to obtain analyses for gonadotropic hormone excretion, from a practical point of view, when spermatogenesis is deficient, the hormone obtained from pregnant mare's serum or from the anterior pituitary is given separately or combined in doses of 20 Evans units, 2 to 3 times a week for 4 to 6 weeks. If there is failure to obtain improvement the preparation obtained from pregnancy urine may be tried, 20 Evans units injected daily for 14 days, the course planned to terminate just at the time ovulation is due in the wife. The improvement appears to be in increased viability of the spermatozoa.

Subfertility in the Female

Ovarian activity and menstruation are under hormone control. The anterior pituitary is the controlling gland of sexual function. The action exerted on the ovary is through the gonadotropic hormone of the anterior pituitary. Two factors are operative,

- (a) follicle-stimulating responsible for maturation of the ovum within the developing follicle,
- (b) luteal-stimulating responsible for the production of the corpus luteum from the granulosa cells left after rupture of the mature follicle.

Without these alternating stimuli, the ovary cannot function, and unless the ovary functions normally, fertilisation of an ovum cannot take place, nor the uterine endometrium prepare for its reception. The average menstrual cycle in the normal woman is of twenty-eight days duration. During the first half of the cycle (which commences on the first day of menstruation) the follicle-stimulating hormone of the anterior pituitary stimulates development of a Graafian follicle which secretes an oestrogenic hormone. It must not be assumed that because the woman menstruates regularly and the endometrial biopsy reveals normal cyclical changes, the follicle of necessity contains a healthy ovum capable of fertilisation. The ovarian hormone *oestradiol* exerts the following effects on the different parts of the female genital tract:—

On the Fallopian tube

- (a) renders the musculature more contractile,
- (b) maintains the ciliated tubal epithelium,
- (c) produces hyperplasia.

On the uterus.

(a) Brings about glandular proliferation, mitosis of the cells in the process of repair after menstruation, and hypertrophy of the muscle fibres. Owing to its action on vasomotor activity it increases the blood supply to the uterus.

(b) Renders the uterine musculature more responsive to the oxytoxic stimuli of the pituitary.

On the vagina.

Causes proliferation of the vaginal epithelium, increases mucoid secretion and the glycogen content of the cells. (This can be studied by the vaginal smear method devised by Papanicolaou, and is used as an indication of the degree of oestrin activity present.)

At or about the fourteenth day of the menstrual cycle the follicle ruptures and the ovum passes into the Fallopian tube. This is brought about by the movements of the tube, which at the time of ovulation embraces the ovary so that the ovum is more or less sucked into the tube. The granulosa cells which are left in the ruptured follicle undergo a change in that they now contain a lipid and acquire a yellow pigment Carotin. They still continue to elaborate an oestrogenic hormone, although they now in addition produce the hormone of the corpus luteum—progesterone, and the stimuli from this hormone take precedence. That oestrin continues to be produced is demonstrated by the oestrin excreted in the blood and urine as shown graphically. The maximum output of oestrogenic hormone, moreover, occurs during the mid-menstrual phase, and varies from below 100 to 800 i.u., although the average daily output for the mid-menstrual phase should not fall below 250 i.u. per 24 hours. An excretion of 1000 i.u. per diem is excessive.

During pregnancy, when there is a fully functioning corpus luteum, the output of oestrogenic hormone is at its highest, and may reach a figure of 450,000 i.u. per diem.

Since oestrogenic compounds may be free or bound, the amount extracted from the urine need not necessarily be an indication of production, although repeated findings of small amounts in the urine may be considered pathological.

ENDOCRINE THERAPY IN THE FEMALE

When oestrogenic hormones were first produced, it was thought that they took the place of the ovarian hormones, but it was found that the cyclical changes produced in the uterus by the ovarian hormone could only be simulated if oestrogenic hormones were given during the first half of the cycle and progesterone in the second half.

The international unit of oestrogenic hormone represents one ten-millionth gram of crystalline preparation.

The different oestrogenic preparations vary in their rate of absorption according to their chemical composition. Those of slowest absorption have the more prolonged effect. The effects of these different preparations and their actions can be studied by means of vaginal smears taken from oophorectomised women.

It is also found that the threshold of response varies in different individuals. What will provoke a response in one will not be sufficient to exert the same effect in another.

The extract obtained from the ovaries has been given the name *oestradiol*.

The uses of oestrogenic hormone.**1. To stimulate a hypoplastic uterus and tubes.**

A hypoplastic uterus can be detected in various ways:—

(a) By bimanual examination, which reveals a thin hard cervix often longer than normal, frequently a sharply anteverted uterus harder, and one might use the term, less plastic than normal.

(b) By hystero-graphy. Lipiodol shows the uterine cavity to be of a smaller volume than normal.

(c) By the passage of a uterine sound. Firstly the length of the cervix is measured, secondly the total length of the uterus, and from this Meaker's uterine index is assessed. This normally should not be less than 0.75. The formula for obtaining the index is:—

$$\frac{1}{2} \frac{\text{total length of uterus-length of cervical canal}}{\text{length of cervical canal}}$$

0.60 or less denotes hypoplasia. The ratio of adult corpus to cervix is 2:1, that of infantile 1:2.

Many cases of uterine hypoplasia are associated with absent or scanty menses. In the rare cases in which menorrhagia occurs, cystic glandular hyperplasia may exist, and on account of the hyperplasia, oestrin therapy is contra-indicated. Chauberg has demonstrated that the Fallopian tubes may be impermeable in cases of uterine hypoplasia, and that they, like the uterus, may respond to oestrin therapy and subsequently become patent.

Dosage.—50,000 i.u. of oestradiol benzoate may be given twice a week for the first two weeks of an imaginary 28-day cycle (if the menses are absent), and 30 mgm. of progesterone in the second two weeks, this course repeated over two to three cycles. A crystalline preparation, which can be injected intramuscularly, is active over two to three months and is slowly absorbed, is in course of preparation, and may be found to be preferable to oestradiol given in the above way.

Hypoplasia may be overcome, normal menses be resumed, tubal patency be obtained, and yet pregnancy may not follow. This may be due to absence of ovulation, which can be shown by a uterine biopsy.

2. *In the absence of tubal peristalsis.*

Tubal peristalsis can be demonstrated by the kymograph, using Rubin's insufflator or an apparatus of similar pattern. Absence of peristalsis denotes faults in the tube itself, or its fixation by adhesions. Faults in the tube itself are the result of inflammatory processes rendering it non-contractile, or causing such thickening that it acts merely as a rigid conductor. If a hystero-salpingogram is taken, a comparable picture shows poor and irregular filling of the tubes with doubtful or scanty spilling of opaque medium into the peritoneal cavity.

Short-wave diathermy is given to induce pelvic hyperaemia, and oestrogenic hormones are administered to produce tubal hyperplasia, and by means of the impulse to growth to stretch the lumen of the tube, thereby breaking down adhesions.

In many cases by these methods of treatment there is recovery of tubal peristalsis in one or other tube, but a number are beyond improvement.

3. *To increase endocrinal reactivity.*

In cases in which no obvious endocrinal disorders can be found, small doses of oestrogenic hormone, 0.1 mgm., can be given twice daily, and combined in suitable cases with gr. $\frac{1}{2}$ thyroideum siccum. It is in such cases that whole gland ovarian extracts are useful.

4. *In certain cases of recurrent abortion.*

There are instances of recurrent early abortion in which no non-endocrinal cause can be found that do not respond to progesterone therapy, even when this and vitamin E have been given in adequate amounts. These cases should be given oestrogenic hormone in addition to progesterone. Headache may precede the miscarriage. This is suggestive of overaction of pituitary hormone, which may, as at the menopause, be accompanied by a diminished oestrogen production.

1 mgm. of stilboestrol is given daily.

5. *Oestrin shock.*

Clauberg initiated this treatment for women who experienced anovulatory cycles. He assumed that a large dose of oestrin induced temporary inhibition of gonadotropic secretion, which was followed by a sudden release of stimulating ovulation. A dose of 50-100,000 international units is given about the twelfth day of the menstrual cycle.

The writer has had some cases of success by this method when biopsy has not revealed the occurrence of anovular cycles. It may be that the ciliated tubal epithelium is improved at the same time that tubal muscular activity is increased, rendering the tube more liable to catch an ovum. She has also used it to precipitate ovulation when the husband's leave does not coincide with the expected date of ovulation.

Time of Ovulation

It is of value to have some indication of the time of ovulation in order to be able to control the administration of hormones, and to time the optimum day of the cycle for conception. Rubinstein and Gluck in 1938 found that the rectal temperature in women varied according to the time at which it was taken in the cycle. It was necessary for the early morning temperature to be taken per rectum before even an early morning cup of tea had been taken. This should be charted with the accuracy to a 1/10th degree. The temperature curve showed a fall at ovulation rising immediately after, and maintaining an almost constant level with a slight rise during menstruation till the time of the next ovulation.

Effects of Oestrin Therapy.

1. Oestrogenic hormone may fail to produce any effect. In such cases the uterus has never attained the stage of reactivity that will respond to oestrogenic stimuli. The underlying effect is of pituitary origin, or in the cases that are a sequel to pregnancy may be the result of hyperinvolution and atrophic changes in the ovary.

2. If given in large doses over a prolonged period there may be "oestrin withdrawal" bleeding from the endometrium a few days after cessation of treatment.

3. In the doses given for therapeutic purposes there are no carcinogenetic effects.

4. Leucorrhoea may be induced.

5. Large doses given during the luteal phase of the cycle may delay ovulation.

6. A low pelvic ache may be experienced. This is no doubt the result of congestion due to the induced hyperaemia.

7. The synthetic preparation stilboestrol may induce nausea, in which case the preparation hexoestrol may be tried. Should this latter also induce nausea, the natural preparation should be resorted to.

Corpus luteum hormone

The corpus luteum produces a hormone *progesterone*. The excretion product of progesterone is in the form of a derivative *pregnandiol*. The output in normal women shows fluctuations dependent on the phases of the menstrual cycle. Pregnandiol is absent from the urine during the first half of the menstrual cycle, but appears within forty-eight hours of ovulation, and disappears twenty-four hours before the onset of menstruation. The maximum excretion occurs between the sixth and second days premenstrually. The mean daily output should not be less than 3 mgm.

Action of Progesterone.

1. On the Fallopian tube.

(a) Production of secretion by the epithelium of the inner half of the tube during the latter half of the menstrual cycle. This secretion is probably necessary for the nourishment of the ovum, if fertilised, in its transit to the uterus, for of the four days spent in its passage along the tube, one day is in the outer half, where it becomes fertilised, and three days are in the inner half where the process of cleavage commences.

(b) Lessening of the tubal movements.

2. On the uterus.

(a) Production of the secretory phase in the glandular epithelial cells, of convulsion of the glands, of thickening of the endometrium and separation of the stroma into compact and spongy layers.

(b) Diminution of muscular activity and in the response to oxytoxic stimuli.

3. On the vagina.

Cessation of the proliferative phase.

Absence of progesterone is demonstrated by microscopical examination of an endometrial biopsy section taken a day or two premenstrually. Since progesterone stimulates secretory

changes in the uterine endometrium, absence of, or lessened degrees of, these changes denotes absence or diminution of progesterone production. It is important to ascertain at what date menstruation has occurred following biopsy before giving a report. If an anovular cycle occurs one month, biopsy should be repeated. Other cycles may be normal.

Clinical uses of Progesterone.

1. *In the treatment of recurrent abortion.*

Recurrent abortion may be the cause of childless marriages, although the individual is not sterile in the true meaning of the word. If all the non-endocrinal causes of recurrent abortion can be excluded, progesterone lack or deficiency must be thought of. One or more uterine biopsies taken premenstrually should show incomplete secretory changes. If possible, the pregnandiol excretion output should be estimated. An output of less than 3 mgm. per diem would be further confirmatory evidence. In cases of deficiency, progesterone should be given from the commencement of pregnancy in doses of 2-5 mgm. weekly and continued until the fifth month of pregnancy, or until one month after the latest date at which miscarriage has occurred.

Synthetic progesterone—ethisterone—is effective by mouth in doses of 5 to 20 mgm. daily. Vitamin E should be given daily for the first three or four months.

2. *In the treatment of threatened abortion.*

As soon as bleeding commences 5 mgm. of progesterone should be injected daily for three successive days. If bleeding ceases, smaller doses can be continued weekly. There may be "spotting" through the early months of pregnancy, and in such cases it is wise to give injections twice a week.

3. *In the treatment of sterility.*

Sometimes a woman gives a history that her periods are usually regular, but on two or three occasions menstruation has been delayed for a few days, and has then been heavier than usual. It is possible that these are early miscarriages, and are due to hormonal deficiency on her part. Deficiency of progesterone may be accompanied by insufficient production of chorionic hormone. In many of these cases who miscarry early the Zondek-Aschheim test has yielded a doubtful positive response.

It has been noted that when pregnancy follows conception from fertilisation by unhealthy spermatozoa, miscarriages are more likely to take place. The excretion of chorionic hormone in the urine in these cases is less than normal.

In cases such as the above progesterone (or chorionic hormone—see later) should be given during the second half of the menstrual cycle, when it is known there has been an opportunity for conception. 2 mgm. progesterone on the 20th, 23rd and 26th days of a 28-day cycle, and continued 2 mgm. weekly if menstruation does not occur. Alternatively one tablet of 5 mgm. ethisterone is given daily. Vitamin E should not be omitted.

4. *In the treatment of ovular menstruation.*

Although a sufficient number of cases have not been followed up to make a dogmatic statement, the existence of ovular menstruation appears to be associated with the inability to conceive. It has been observed that when this condition ceases pregnancy may take place. It is possible that an excessive fall of blood oestrin about the time of ovulation brings about "withdrawal bleeding" from the endometrium. It has been found that oestrin given in doses of 0.5 mgm. daily throughout the first half of the menstrual cycle, or 5 mgm. progesterone given one to two days before the expected onset of spotting will prevent this.

Genodotropic hormones

As with the other hormones the amount of gonadotropic hormone excreted in the urine of normal women varies. A fertile woman with regular cycles may excrete very little, whereas a less fertile woman may excrete more. Twenty-five rat units of gonadotropic hormone per diem has been given as the amount the normal woman excretes.

This is not constant, but it is normal to find it in the urine about the mid-menstrual or premenstrual phases.

Excessive amounts of gonadotropic hormone found in the urine of non-pregnant women is of diagnostic importance, and should suggest disturbed ovarian activity since the large amounts excreted in the urine at the menopause are associated with diminished oestrogenic output.

Excessive amounts may lead to the persistence of an active corpus luteum preventing further ovulation or to formation of small follicular cysts of the ovary due to failure of ovulation.

The actions of gonadotropic hormones are as follows:—

1. To stimulate ovarian reactivity and through the ovary—the uterus.
2. Those containing a follicle-stimulating factor may in certain cases take the place of oestrogenic hormones.
3. Those containing mainly a luteinising factor (of chorionic origin) may take the place of progesterone.

Too large or prolonged doses may inhibit ovarian activity.

Uses of gonadotropic hormones.

1. To take the place of oestrogenic hormone when it is desired to stimulate an infantile uterus. Since the ovary has to attain a certain stage of development before it is capable of responding to oestrogenic stimuli, it is in the writer's opinion preferable to commence with injections of pregnant mare's serum. 200 to 400 international units should be injected twice a week for a few weeks before resorting to oestrogenic hormones.

2. To induce ovulation, used as an alternative to oestrogenic hormones. If given intravenously ovulation may be induced within thirty hours. It has been stated by certain observers that a large dose of pregnant mare's serum can have this effect if injected at any time in the cycle, and that this has been proved in women who were injected previous to laparotomy for some reason. Although this may be true in some cases, hormones vary so in their action in different individuals that it is not likely to happen in every case. However, its practical significance is that a dose such as 400 international units of mare's serum may be given thirty hours before artificial insemination, to ensure ovulation, or to the male before intercourse in those cases where the sperm is known to be of low viability, or when on active service, before he returns on his 48-hours leave, in order to prolong the viability of the spermatozoa.

Chorionic hormone can be given in place of luteal hormone in many instances, and is cheaper. It may be used in the treatment of threatened or recurrent abortion. It is thought that the function of chorionic hormone is to assist in maintaining the secretion of progesterone from first the corpus luteum, and later the placenta, and in favour of this view (as has been stated before) the output of chorionic hormone in the urine is often low in those cases that subsequently miscarry.

Thyroid.

Minor degrees of hypothyroidism are often not detectable, but may be one of the factors operative in sub-fertility. There may be such suggestive symptoms as menstrual irregularities or prolonged periods. It is as a rule possible to type an individual—those definitely not hypothyroid, those possibly.

Administration of the dried gland in amounts compensatory with the deficiency, or in small doses of $\frac{1}{2}$ gr. twice daily in minor cases, may render the individual more fertile. Any benefit derived is probably due to stimulation of the other endocrines owing to the intercorrelated action of the different glands.

A lowered basal metabolic rate is not infrequently associated with recurrent abortions.