ENDOCRINES IN THEORY AND PRACTICE

This article is one of a series on Endocrinology contributed by invitation

THE HORMONE TREATMENT OF SOME DISORDERS OF PREGNANCY

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PART I

Pregnancy is normally accompanied by profound modifications of the whole endocrine system. The ovary, thyroid, parathyroid, adrenal, pancreas, and pituitary undergo well-recognized functional, and even structural, alterations, and a new ductless gland—the placenta—is temporarily added to the system. The products of these glands play a major part in the normal progress of pregnancy, and anomalies in their relative quantities or qualities are important factors in the causation of many of the pathological states; hence hormone treatment for disorders of gestation is being rapidly developed. Rational organotherapy is dependent on endocrinology, but since the origin and functions of the various hormones have been discussed elsewhere in this series only a brief relevant summary of physiological principles is included here.

Physiological Principles

The preparation of the endometrium for the successful embedding of the ovum is dependent on the corpus luteum hormone (progesterin). The same hormone, by a direct action on the muscle, also inhibits uterine contractions and thus prevents expulsion of the ovum. Nevertheless in the human subject the corpus luteum is not essential to the progress of pregnancy after the sixth to eighth week. During the later stages of gestation uterine quiescence is determined by humoral factors whose identity is not yet proven: it is possible that the placenta secretes a progesterin-like principle.

The gonadotropic hormones (prolan, prolan A and B), as their name denotes, act primarily on the gonad, and since they are responsible for the persistence and activity of the corpus luteum they indirectly inhibit uterine activity. In the human subject, however, they may also have a direct effect on uterine muscle, and this possibility is of importance in therapy, since it has never been convincingly demonstrated that the present preparations of gonadotropic hormones (from pregnancy urine or placenta) have a luteinizing action in woman.

As pregnancy advances the uterine muscle hypertrophies, its spontaneous contractions increase in number and amplitude, and it develops a sensitiveness manifested by enhanced ability to respond to both mechanical and chemical stimuli. These changes are the result of the direct action of oestrogenic hormones (oestrin) on the myometrium. The continuance of pregnancy is dependent on a hormonal balance in which the inhibiting principles predominate, and any disturbance of the balance which leads to an ascendancy of the oestrogenic hormones brings about the termination of pregnancy in the form of abortion or labour. But it is of prime practical importance to realize that this balance is not a simple quantitative one: thus a uterus under the influence of progesterin cannot

be excited by oestrogenic substances, even if they are administered in relatively large amounts.

The role of the posterior lobe of the pituitary during pregnancy is still in dispute. It is quite possible that the powerful oxytocic secretion of this gland is concerned in initiating and sustaining the expulsive uterine contractions of parturition.

Principles of Treatment with Placental and Ovarian Hormones

HORMONE PREPARATIONS

Only preparations standardized in approved animal or international units are recommended. All others are relatively impotent and worthless. Whole-gland products or "cocktail" preparations are whole-heartedly condemned. Under present conditions of manufacture or extraction reliable preparations are inevitably costly.

The standardized preparations most commonly used and easily available in this country are:

Corpus luteum hormone (progesterin; progesterone).

Proluton (Schering Ltd.).
Progesterin (Organon Laboratories).
Progesterin (British Drug Houses).
Lutren (Bayer).

Oestrogenic substances (oestrin).

(a) *Ketohydroxyoestrin*:
Progynon (Schering Ltd.).
Menformon or folliculin menformon (Organon Laboratories).
Oestroform (British Drug Houses).
Theelin (Parke, Davis and Co.).
(b) *Oestradiol benzoate*:
Progynon B (Schering Ltd.).
Di-menformon (Organon Laboratories).
Oestroform B (British Drug Houses).

Gonadotropic hormones (prolan, prolan A, prolan B).
(From placenta and pregnancy urine.)

Pregnyl (Organon Laboratories).
Antuitrin "S" (Parke, Davis and Co.).
Gonan (British Drug Houses).

Gonadotropic hormones are easily destroyed by heat, and should be kept in a cool store and injected from a cold syringe. Even under ideal conditions solutions of these hormones rapidly deteriorate, and they should not be used later than four months after manufacture.

MODE OF ADMINISTRATION

Oral administration of hormones, other than thyroid and oestrogenic extracts, is futile. Moreover, capsules of the latter have a very limited application, since these hormones are only one-fifth as active when administered by mouth as when injected parenterally. The gonadotropic, pituitary, and corpus luteum hormones are completely inactivated by digestive juices. Intramuscular or subcutaneous injections are, with a few exceptions, preferable to intravenous medication.

DOSAGE

Most hormones are better given in divided doses than in a single massive one. In the body they are quickly destroyed, inactivated, or excreted, and to obtain a maximal and continued effect injections should be repeated at regular and frequent intervals. Continuity of treatment

is further improved if the hormones are given in an oily medium: absorption from the tissues then takes place more slowly. Most preparations of corpus luteum and oestrogenic hormones are now supplied as solutions in oil.

TIME RESPONSES

As a rule there is no *immediate* response to injections of these hormones. The inhibiting action of progestin and gonadotropic hormones is seen in a few hours, although it is stated that when large doses are used an effect may be produced within fifteen to thirty minutes. Oestrogenic substances, however, do not influence uterine contractions until six to twelve hours have elapsed, and the maximum effect is not apparent until at least twenty to twenty-four hours after an injection.

Threatened Abortion

The hormone treatment of threatened abortion does not replace, but is accessory to, the present well-established methods of treatment with sedatives and rest. Gross causes such as uterine retroflexion must be excluded or corrected. The object of organotherapy is essentially to allay expulsive uterine contractions by inhibition of the muscle. For this purpose corpus luteum hormone should be administered intramuscularly in doses of 2 international units daily from the onset of symptoms until one week after pain and bleeding have ceased. Subsequently, especially for patients with a known tendency to abort, injections of 1 international unit should be made twice weekly up to the thirty-second week of pregnancy. For patients showing no response to treatment the dose may be increased, and 10 international units, in single or divided doses, may be injected daily without harmful effect.

As an alternative to progestin, gonadotropic hormones may be administered—also with the object of bringing about uterine quiescence. The dosage should be 100 rat units, injected twice daily; this should be continued until the patient has been free from symptoms for one week. On occasion the amount prescribed may be increased to as much as 500 rat units daily, but the present commercial preparations are apt to give rise to mild local or general reactions when injected in large amounts.

Although good results are reported for the treatment of threatened abortion with progestin or prolan, failures are not infrequent. This is only to be expected when the foetus is dead or the membranes ruptured, and success is unlikely, and indeed undesirable, in the presence of foetal abnormalities—a common cause of abortion.

Whereas either of these methods of hormone treatment may be used with advantage, progestin therapy is the more efficacious.

Repeated Abortion and Habitual Death of the Foetus

In many cases of habitual abortion, defective placental implantation, or repeated intra-uterine death of the foetus, no cause can be found. In such circumstances it is conceivable that an upset in the pregnancy endocrine balance is the underlying fault.

The management of such cases is based on the same principle as is that for the treatment of threatened abortion, and has for its object the maintenance of uterine quiescence. Treatment should be begun as early as possible in pregnancy or perhaps before conception occurs. In the latter case the object is to prepare a healthy pregravid endometrium, and to this end 1 international unit of progestin should be injected twice weekly during the second half of each menstrual cycle—beginning about

the sixteenth day after the first day of the last menstrual period. This progestational treatment is less important than therapy during pregnancy, and is of theoretical rather than practical value. Moreover, its application is difficult, and it may have to be continued for several months, because the occurrence of conception is so fortuitous.

As soon as pregnancy is established inhibitive hormones (progestin, 1 international unit twice weekly, or gonadotropic hormone, 100 rat units twice weekly) should be given and their administration continued until the thirty-second week of pregnancy. It is generally considered advisable to discontinue the treatment after this time for fear of prolonging the pregnancy past term: this is only a remote contingency. Some clinicians insist that doses as small as 1/25 rabbit unit of progestin are equally efficacious in preventing habitual abortion, and many state that it is unnecessary to continue treatment after the fourth month. In my opinion it is unwise to give less than the dosage recommended above.

For some years past habitual abortion has been treated extensively with corpus luteum tablets, and many clinicians have claimed results which are quite as imposing as those published for the newer progestin preparations. Such corpus luteum tablets, for oral use, contain very little, if any, progesterone, and are incapable of producing hormonal effects in the body. Treatment with these preparations is therefore purely empirical, and the claims made for their usefulness serve to emphasize the difficulty in assessing the value of any form of treatment for such a condition as habitual abortion.

Another form of organotherapy is now becoming increasingly popular—namely, the administration of thyroid. The rationale is more obscure than that which defines the use of other hormones, but it is based on the fact that the body during pregnancy makes great demands on the thyroid and that enlargement of this gland is frequently present in cases of habitual abortion. Moreover, there is experimental evidence to show that the presence of an optimum amount of thyroxine is important for the progress of normal pregnancy. Whatever the exact rationale may be, thyroid therapy is undoubtedly as good as, if not better than, the other forms of hormone treatment outlined above. It is less costly and can be given orally. The dose recommended is thyroid extract 1 grain each day throughout the duration of pregnancy. It may be combined with the other methods of hormone therapy. In spite of the difficulty in assessing results the evidence now accumulated leaves no doubt that treatment with gonadotropic, corpus luteum, or thyroid hormones is successful in a large number of cases. Of the types of organotherapy mentioned I prefer to use thyroid extract combined, when financial and other circumstances permit, with progestin.

Although it is permissible to assume the presence of an endocrinous causal factor in many cases of unexplained habitual abortion and death of the foetus, this assumption is not always justified, and other factors such as vitamin deficiency not infrequently play a part. Since the present state of knowledge precludes more accurate subdivision of these cases from the aetiological standpoint, treatment should never be limited to organotherapy. Attention to general health, and avoidance by the patient of constipation, coitus, and strenuous physical exercise, remain essential to the management of these cases. The administration of vitamin E is especially important accessory treatment. Furthermore, it is well to remember that for cases of habitual death of the foetus induction of premature labour is carried out as a routine by some authorities.

Finally, it must be emphasized that the successful culmination of one pregnancy as the result of treatment does not mean that the underlying cause of the abortions has been permanently corrected. Similar therapeutic measures must be adopted in each subsequent pregnancy.

Therapeutic Induction of Abortion

In view of the ability of oestrogenic substances to increase uterine sensitivity it seems at first sight that their administration in large amounts at any stage in pregnancy should lead to the onset of expulsive uterine contractions. However, reference has already been made to the fact that the so-called "hormone balance" does not imply a condition of simple quantitative equilibrium, but rather a qualitative state in which either oestrin or progesterin is dominant. This is certainly true for the human subject, and it is now proved conclusively that normal pregnancy cannot be terminated in its early stages even if millions of units of oestrogenic hormone, together with large doses of posterior pituitary extract, are administered. If, however, the foetus is dead and retained *in utero*—a condition which implies a disturbed hormone balance—expulsive uterine contractions can be developed by hormone agents (see later).

Induction of Labour, Prematurely or at Term

Use of Posterior Pituitary Hormone.—Extracts of the posterior lobe of the pituitary have long been used for purposes of medicinal induction of labour. Their injection is usually preceded by the administration of castor oil and one of the salts of quinine. I recommend quinine sulphate, 10 grains repeated three times at one-hourly intervals, followed by four injections, at one-hourly intervals, of 5 units of pituitary principle. Any medicinal method of induction of this type usually fails to bring on labour unless the pregnancy has reached term or unless the uterus is unduly sensitive.

Use of Oestrogenic Hormone.—In late pregnancy, when the influence of inhibiting factors is waning, the administration of oestrogenic hormones undoubtedly increases uterine sensitivity. Nevertheless they must be given repeatedly for several days, and even then their sensitizing action is so unreliable that the subsequent application of powerful oxytocic factors, such as quinine and posterior pituitary extract, fails to bring on uterine contractions in at least 50 per cent. of cases. A method of induction of labour which is uncertain and so slow as frequently to take seven or eight days to bring about its effect is of little practical value. But oestrogenic substance may be helpful as an accessory to mechanical induction of labour, more particularly when artificial rupture of the membranes or the intra-uterine insertion of bougies or stomach tube has failed to bring on expulsive uterine contractions. In such cases 20,000 to 40,000 international benzoate units (100,000 to 200,000 international units) of oestradiol benzoate injected intramuscularly, four-hourly, appear to improve uterine tone and lead to the onset of labour within twenty-four to forty-eight hours.

(To be continued)

At the March meeting of the Central Midwives Board for England and Wales the revised list of approved teachers, as submitted, was approved for the purpose of the conduct of training under the present rules of the Board, subject to satisfactory replies to questions in certain cases. The application of Eric Arthur Gerrard, M.D., for approval as examiner was granted.

MEDICAL RESEARCH COUNCIL

ANNUAL REPORT FOR 1935-6*

Clinical Research

The Medical Research Council staffs and supports (save for the post of director, which is endowed by the Rockefeller Foundation) the department of clinical research at University College Hospital, London, and supports the directors of the clinical research unit at Guy's and the neurological research unit at Queen Square. Some interesting work from each of these departments is embodied in the report of the Council.

The report from University College Hospital is largely occupied with Sir Thomas Lewis's studies of the effects of embolism and other work on vascular disorders. G. W. Pickering has been engaged here in a series of investigations concerning the mechanism of high blood pressure. It has been shown that the carotid sinus mechanism remains active in persistent hypertension, but the observation that changes in arterial and venous pressures produced by the intravenous injection of small quantities of adrenaline are greater in subjects with nephritic and malignant hypertension than in normal subjects and those with essential hypertension was not confirmed. A quick transfusion of as much as 600 c.cm. of blood from patients with essential hypertension into anaemic patients has been shown to produce only very small rises in blood pressure, no greater than those produced by similar quantities of normal blood.

At Manchester Royal Infirmary one of the many external research schemes supported by the Council has been directed to an investigation into the aetiology and treatment of pernicious anaemia and other diseases of the blood-forming organs. Some 800 patients with pernicious anaemia are now under regular observation, and in those who co-operate adequately it has been found relatively easy to maintain good health and normal blood counts by modern methods of treatment. Further work on the properties of haemopoietin supports the view that this intrinsic anti-anaemic principle of stomach is an enzyme, but the nature of the extrinsic factor has yet to be determined. At Aberdeen further investigations have been made on the treatment of pernicious anaemia by the Dakin and West liver fraction, anahaemin, and it appears that for most cases one injection of 5 c.cm. of anahaemin every eight weeks suffices to maintain the blood count at a satisfactory level.

In Sir David Wilkie's department at Edinburgh part-time grants have been made to two workers engaged on the study of causes of death after extensive burns. The tissue fluid from the burned area has been found to contain poisonous substances produced by chemical breakdown of the damaged cells and independently of bacterial action. Clinical observations suggest that the acute and severe toxæmia which develops soon after extensive burns can be successfully treated by extracts of suprarenal cortex. At Glasgow University other grantees have shown that fracture of bone with adjacent muscle damage leads to a rapid increase in the normal breakdown of protein, and hence to increased excretion of nitrogen in urine, and of creatine also; when the muscle only is damaged and the bone not fractured the nitrogen loss is much less.

Neurology

At Queen Square Hospital, London, a study of the dynamics of the cerebro-spinal fluid which the unit began

*Report of Medical Research Council for 1935-6. Cmd. 5378. London: H.M. Stationery Office. (3s. net.) Notice concluded from March 20 (p. 616).