WORLD HEALTH ORGANIZATION
TECHNICAL REPORT SERIES

No. 471

ENDOCRINE REGULATION OF HUMAN GESTATION

Report of a WHO Scientific Group

WORLD HEALTH ORGANIZATION

GENEVA

1971

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the Director-General of the World Health Organization concerning the legal status of any country or territory or of its authorities, or concerning the delimitation of its frontiers.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature which are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

PRINTED IN SWITZERLAND

CONTENTS

WHO SCIENTIFIC GROUP ON ENDOCRINE REGULATION OF HUMAN GESTATION

Geneva, 14–18 September 1970

Members :

Professor E. Diczfalusy, Reproductive Endocrinology Research Unit, Swedish Medical Research Council, Karolinska Hospital, Stockholm, Sweden (*Chairman*)

Dr E. Hochuli, Head, Department of Obstetrics and Gynaecology, Cantonal Hospital, Münsterlingen, Switzerland

Dr A. Klopper, Department of Obstetrics and Gynaecology, University of Aberdeen, Scotland (*Rapporteur*)

Dr C. Lauritzen, Professor of Obstetrics and Gynaecology, University of Ulm, Federal Republic of Germany

Professor G. C. Liggins, Postgraduate School of Obstetrics and Gynaecology, The University of Auckland, New Zealand

Professor L. S. Persianinov, Director, Scientific Institute of Obstetrics and Gynaecology, Ministry of Health of the USSR, Moscow, USSR (*Vice-Chairman*)

Dr J. I. S. Robertson, Medical Research Council Blood Pressure Research Unit, Western Infirmary, Glasgow, Scotland

Dr B. N. Saxena, Department of Medicine, Christian Medical College and Hospital, Vellore, Tamil Nadu, India

Professor P. K. Siiteri, Departments of Biochemistry and Obstetrics and Gynecology, Southwestern Medical School, The University of Texas, Dallas, Tex., USA

Professor S. Solomon, Departments of Biochemistry and Experimental Medicine, McGill University, Montreal, P.Q., Canada (*Rapporteur*)

Representatives of other organizations :

International Federation of Gynaecology and Obstetrics :

Professor M. C. MacNaughton, University Department of Obstetrics and Gynaecology, Royal Maternity Hospital, Glasgow, Scotland

International Planned Parenthood Federation :

Professor Sir Alan Parkes, Galton Foundation, London, England

Secretariat :

Dr A. Kessler, Chief Medical Officer, Human Reproduction, WHO, Geneva, Switzerland (*Secretary*)

ENDOCRINE REGULATION OF HUMAN GESTATION

Report of a WHO Scientific Group *

A WHO Scientific Group on the Endocrine Regulation of Human Gestation met in Geneva from 14 to 18 September 1970. The meeting was opened by Dr H. Mahler, Assistant Director-General, who welcomed the members on behalf of the Director-General.

1. INTRODUCTION

During the past decade a considerable amount of new information has been accumulated on various aspects of the endocrinology of gestation. The endocrine control of the reproductive process in general, and that of gestation in particular, is difficult to study in the human species. Therefore, many of our present concepts have been inferred from the results of animal experiments. Unfortunately, the endocrine regulation of gestation shows great variation from one species to another. Animal models must be chosen with great care. Species such as the dog and rat differ from man in their reproductive processes to such an extent that they are not useful as models for man. Even some primates, such as the rhesus monkey, are not suitable models for man, and the baboon or chimpanzee may be much better test animals. In view of this variation, great caution must be exercised when extrapolating results from animal models to clinical conditions.

The present Group was convened to assess the available information on the hormonal factors that may be involved in implantation and in the maintenance and termination of gestation in man, and also to review recent developments in the diagnosis and management of pathologic forms of pregnancy. Its main objective was to identify research areas that may be of direct relevance to an improved understanding of these problems. The Group was aided in its work by the reports of several previous WHO Scientific Groups.[1]

---

* A selected bibliography to this report is available, on request, from Chief, Human Reproduction, World Health Organization, 1211 Geneva 27, Switzerland.

[1] *Wld Hlth Org. techn. Rep. Ser.*, 1964, No. 280; 1965, No. 303; 1965, No. 304; 1965, No. 313; 1969, No. 424.

The Group realized that gestation in the human species is influenced not only by hormones but also by other homoeostatic mechanisms as well as by environmental, nutritional,[1] social, economic, and other factors. How these interact with the hormonal regulation of gestation was not considered by the Group.

2. THE ENDOCRINOLOGY OF OVOIMPLANTATION

2.1 Endocrinological prerequisites for implantation

Although endocrinological factors are known to operate on the maternal organism to enable implantation to occur, it is possible that the blastocyst itself requires some hormonal conditioning.

In women, implantation can occur in extra-uterine sites, such as the ovary or the mesentery. In mice, under experimental conditions, implantation has been achieved in a variety of unlikely sites, such as the testis; on the other hand, the endometrium, unless brought to a suitable state by hormonal action, resists implantation. Evidence is available from animal experiments on the nature of the changes that have to take place in the endometrium before it loses its resistance to implantation. Although the secretory transformation of the endometrium by progesterone[2] is essential to the survival of the early conceptus, it appears that oestrogen, acting on such a progesterone-conditioned tissue, may be the essential element in removing endometrial resistance to implantation. Animal experiments also suggest that a further effect of oestrogen on the endometrium is to stimulate the production of enzymes that act on the blastocyst and cause lysis of the zona pellucida, thus making it possible for the fertilized egg to adhere to the uterine mucosa.

A second target for hormonal pre-conditioning essential for implantation is the tubal mucosa. There is evidence predominantly from animal studies that the rate of transport of the egg through the tube and the secretion of tubal mucin are controlled both by progesterone and by oestrogen. If the fertilized egg is conveyed too rapidly, it reaches the uterus before resistance to implantation has been overcome, while too slow a passage may result in the delivery of the egg too late for successful implantation.

2.2 Hormonal regulation of implantation

According to present concepts, an oestrogen " surge " in the rat occurs at the time of implantation. In man, a secondary rise in blood oestrogen levels is frequently seen around day 20 of the menstrual cycle at the time

---

[1] *Wld Hlth Org. techn. Rep. Ser.*, 1965, No. 302.

[2] For the systematic names of steroids used in this report, see Annex p. 32.

when implantation occurs. This rise may be associated with the other chemical events that take place in the endometrium at this time, such as changes in protein synthesis.

If a secondary rise in oestrogen secretion is an essential feature of implantation, it would appear possible to prevent pregnancy by interfering with this occurrence. So far attempts to suppress the oestrogen effect, e.g., by the use of anti-oestrogens, have had little success.

2.3 The role of the corpus luteum

It is generally agreed that the function of the corpus luteum is essential to the continued existence of the newly implanted ovum and it is therefore of interest to examine the means whereby progesterone secretion is maintained in the corpus luteum of early pregnancy. The problem is compounded by the fact that a uterine luteolytic effect, such as exists in the sheep and the pig where it is counteracted by the blastocyst, has not been demonstrated in man. In animal experiments, luteolytic activity has been demonstrated in the case of some of the prostaglandins and it may be that one or other of these compounds will prove to be essential for controlling the life of the corpus luteum. It is of interest that prostaglandin $F_{2\alpha}$ causes a fall in progesterone production by the sheep ovary and that infusions of this compound will cause abortion in women. Although such abortions are more liable to occur in very early pregnancies when corpus luteum function plays a dominant role, prostaglandins also cause uterine contraction and it is likely that this activity rather than luteolysis is the reason for their abortifacient effect in women.

That chorionic gonadotrophin (HCG) exerts a luteotropic function has long been a tenet of the endocrinology of gestation, and there is adequate evidence that injection of HCG will prolong the life of the corpus luteum. The relative importance of LH and HCG in the maintenance of the corpus luteum is less evident.

Evidence is accumulating that 17α-hydroxyprogesterone is one of the principal biosynthetic products of the freshly formed corpus luteum and that the concentration of this steroid in blood may be one of the most reliable indicators of corpus luteum function. These findings are particularly relevant to the evaluation of corpus luteum function in early pregnancy following the induction of ovulation with urinary or pituitary gonadotrophin, and in this context assays of plasma 17α-hydroxyprogesterone and/or urinary pregnanetriol may be helpful.

2.4 The hormonal interruption of early pregnancy

There are two ways in which endocrine manipulation might be used to interrupt early pregnancy. Firstly, drugs might be used to interfere with the production of hormones essential to nidation or the maintenance of early pregnancy. Secondly, natural hormones might themselves be used to upset the balance of hormones essential to the process of implantation. The administration of oestrogens to laboratory animals after mating has long been known to prevent the establishment of pregnancy. The administration of massive doses of oestrogens following intercourse has been tried with limited success,[1] and there is no reason to suppose that oestrogens will cause the loss of an ovum once it has been implanted.

2.5 Future studies

Steroid hormones, such as oestradiol and progesterone, are present in very low concentration in biological fluids at implantation, and the changes in hormone concentration that determine the processes of implantation may be too slight to be demonstrated by the techniques available until recently. This picture has been transformed by the evolution of protein-binding techniques, particularly radioimmunoassay for the estimation of steroid hormones, and the use of this tool is likely to give a more reliable picture of the endocrine events that are a part of implantation. Some aspects of implantation that clearly invite further study are the role of the prostaglandins and the factors controlling tubal transport.

3. NON-STEROID HORMONES OF THE HUMAN PLACENTA

The human placenta produces at least two main non-steroid hormones, human chorionic gonadotrophin (HCG) and human chorionic somatomammotrophin (HCS). These two protein hormones are elaborated in very large amounts during human pregnancy. In addition, a number of biologically active substances have been extracted from human placental preparations but their synthesis within the tissue has not been demonstrated, except in the case of renin. These include human chorionic thyrotrophin (HCT), adrenocorticotrophic hormone (ACTH), melanocyte stimulating hormone (MSH), oxytocin, insulin, acetylcholine, placental uterotrophic hormone (PUH), relaxin, and juvenile hormone.

3.1 Human chorionic gonadotrophin (HCG)

3.1.1 *Production of HCG*

Although HCG is known to be synthesized by human chorionic tissues its site of synthesis in the cytotrophoblastic cells or in the syncytiotrophoblastic cells, or in both, remains to be established. The homogeneity and

[1] *Wld Hlth Org. techn. Rep. Ser.*, 1969, No. 424, p. 20.

heterogeneity of HCG are currently being investigated. Current observations indicate that HCG is a heterogeneous substance composed of at least three different types of molecule. Apparently, the heterogeneity of HCG is due to variations in the nature of the carbohydrate portion of the molecule. HCG cross-reacts immunologically with LH, FSH, and TSH, which indicates that there are structural relationships between these molecules. In addition, an HCG antiserum neutralizing factor is present in different gonadotrophin preparations.

The luteinizing or interstitial cell stimulating activity of HCG is by now well established, but it is not clear whether or not follicle-stimulating hormone (FSH) activity is present in all preparations. Indeed, there are preparations of HCG obtained by Sephadex gel filtration that exhibit FSH-like activity, while other preparations have no such activity. In addition, preparations containing varying amounts of immunologically active but not biologically active material have been separated.

3.1.2 *Physiological role of HCG*

Placental synthesis of HCG continues throughout gestation and production per gram of placenta is highest during the first trimester. HCG is detectable in serum and urine 8–10 days after ovulation ; peak values are found about the 60th day of gestation, and by the 80th day the values drop to a lower level and remain low until delivery. There are considerable differences in the values found, depending on whether bioassays or immunochemical assays are used to measure HCG. The disappearance curve of HCG using radioimmunoassay has two linear components, a rapid phase with a half-life (T½) of 8–11 hours and a slower phase with a half-life of 23–27 hours. At the moment, there is no evidence as to the nature of the factors that control the production or release of HCG. The role of HCG in regulating the corpus luteum during early pregnancy is under investigation. The most recent information suggests that HCG may play a role in the regulation of ovarian steroidogenesis in the first 4 weeks of gestation.

The role of HCG in pregnancy is poorly understood. There is an arteriovenous difference of HCG in the umbilical cord indicating uptake or metabolism of the hormone by fetal tissues. It has been postulated that the early high levels of HCG stimulate the synthesis of steroids by the fetal adrenals. HCG given to the new-born has been reported to cause an increased excretion of urinary dehydroepiandrosterone. On the other hand, dehydroepiandrosterone administered to the mother during the third trimester of pregnancy leads to a decreased titre of urinary HCG. Following the administration of oestriol, an increase in the titre of HCG was reported. On the basis of these findings, it has been postulated that there is a feedback control between HCG and fetal steroid production. The amount of HCG that is transported to the fetus is small; most of it is transported to the maternal compartment. It has also been reported that in the perfused placenta HCG stimulates the aromatization of neutral steroids. The significance of this finding remains to be established.

It has been suggested that HCG may play a role in initiating the development of the maturation of the fetal Leydig cells and the development of the fetal ovaries. It has recently been reported that the human fetal pituitary contains immunoreactive LH as early as the eighth to tenth week of gestation.

3.1.3 *Clinical application of HCG measurements*

HCG assays are most useful in the diagnosis of pregnancy and in the management of trophoblastic disease. These assays are of very limited value in the management of pregnancies complicated by toxaemia, diabetes, Rh isoimmunization, threatened abortion, ectopic pregnancy, retarded fetal growth, or prolonged pregnancy.

3.2 Human chorionic somatomammotrophin (HCS)

3.2.1 *Production of HCS*

It is well established that HCS is elaborated by the syncytiotrophoblastic cells. The molecular weight of HCS is approximately 20 000 and it exists as a single polypeptide chain. Its amino acid sequence is similar to that of human growth hormone (HGH) and the partial immunological cross-reactivity between the two hormones is due to common antigenic determinants in the two molecules. HCS is synthesized by the placenta throughout pregnancy and during this time its placental concentration remains constant. Using radioimmunoassays, maternal serum HCS can be detected as early as the 6th week of pregnancy and rises progressively to a plateau at 34 weeks. The rate of disappearance of HCS from maternal blood using radioimmunoassay is described by a double exponential curve, the first component corresponding to a half-life of 11 minutes and the second to a half-life of several hours. The production rate of HCS has been calculated to be approximately 1 g per day. It is not yet known what mechanism(s) control the synthesis and release of HCS.

3.2.2 *Physiological role of HCS*

The growth-promoting activity of HCS is considerably weaker than that of HGH. Somatotrophic, lactogenic, mammotrophic, luteotrophic, diabetogenic, and erythropoietic activities of HCS have been demonstrated in a variety of animal species. A synergism between HCS and HGH, as well as between HCG and erythropoietin, has also been noted in animal studies. The role of HCS in regulating the endocrine changes occurring during human pregnancy is not clear. It has been shown that HCS stimulates insulin release and that it antagonizes insulin activity *in vitro*. It has been postulated that HCS causes a suppression of the hypothalamic releasing factor (GRH)[1] during the third trimester and in the early post-partum period. Some growth-promoting activity has been demonstrated in hypopituitary dwarfs.

3.2.3 *Clinical application of HCS measurement*

There is some controversy as to whether HCS estimation in maternal serum is of value in the management of various types of pathological pregnancies. It appears that HCS measurement may be useful for the diagnosis of impending abortion. HCS titres correlate well with the weight of the placenta but not with that of the fetus. It may well be that HCS estimations are most useful in the diagnosis of pregnancies involving placental pathology, especially when there is an associated maternal hypertension.

3.3 Other biologically active factors extracted from the human placenta

In addition to HCG and HCS a number of biologically active substances have been extracted from the human placenta. Foremost of these is human chorionic thyrotrophin. Materials having the biological activity of adrenocorticotrophic hormone (ACTH), renin, melanocyte-stimulating hormone, oxytocin, insulin, acetylcholine, placental uterotrophic hormone, relaxin, and juvenile hormones, as well as a number of other factors, have been identified in placental tissue. Although all these hormonal activities have been extracted from placental tissue, it is not known whether they are synthesized in this organ. Neither is it known whether these biologically active materials have any role in the physiology of the placenta.

4. STEROIDOGENESIS IN THE FETO-PLACENTAL UNIT

Human pregnancy is characterized by large increases in the maternal excretion of urinary pregnanediol, oestrogens, and some classes of C_{21} steroids. The site of elaboration of the precursors of these urinary steroids and the interplay of the fetus and the placenta in the formation of the precursors and the end products have been the subject of numerous investigations during the last 10 years. As a result of these studies, the concept of the feto-placental unit has been evolved to describe the interdependence of the functions of the placenta and fetal tissues in the elaboration of oestrogens during human pregnancy. According to this concept, human fetal tissues contain the steroid hydroxylating enzymes and sulfokinases

[1] GRH = growth hormone releasing hormone.

that the placenta lacks, while the placenta contains the sulfatases, aromatizing enzymes, and 3β-hydroxysteroid dehydrogenases that the fetal tissues lack, and it is by an integration of these functions that the feto-placental unit elaborates its end products.

As in other endocrine tissues, steroidogenesis in the feto-placental unit involves the degradation of cholesterol to pregnenolone and transformation of this steroid to progesterone. Progesterone is then hydroxylated at C_{11}, C_{17} and C_{21} to form hydrocortisone, as has been demonstrated for the adult adrenal gland. A good deal of current knowledge concerning steroidogenesis in the feto-placental unit has been derived from studies in which labelled precursors were either perfused through mid-gestation fetuses or were injected into the umbilical vein at mid-gestation. As a result, the data obtained describe what happens at mid-gestation and should not be extrapolated to the events occurring at later stages of pregnancy. Furthermore, such data describe the biosynthetic pathways operating in the feto-placental unit and cannot readily be used to indicate whether one pathway is quantitatively more significant than another.

4.1 Precursor role of acetate and cholesterol

From present knowledge, it appears that the placenta does not form cholesterol from acetate to any great extent, and that maternal cholesterol is utilized by the placenta to form neutral steroids, such as pregnenolone and progesterone. The role of cholesterol as a precursor of neutral steroids in fetal tissues is now being investigated. Fetal tissues at mid-gestation can synthesize cholesterol from acetate, and acetate can serve as a precursor of neutral steroids in the fetus. However, the quantitative importance of these precursors in comparison to the pregnenolone and progesterone coming from the placenta remains to be established.

4.2 Precursor role of progesterone and pregnenolone

The placenta converts cholesterol to pregnenolone, which is transformed in turn to progesterone. Pregnenolone and progesterone reaching the fetus are metabolized by many fetal tissues. Progesterone is hydroxylated by the fetal adrenal at different carbon atoms, such as C_{11}, C_{16}, C_{17} and C_{21} to form biologically active steroids such as hydrocortisone; some of these steroids are conjugated with sulfuric acid. In addition, progesterone is extensively reduced at C_{20} and at C_3. The double bonds at C_4 and C_5 are also reduced in many fetal tissues, and some of these products are conjugated with sulfuric and/or glucuronic acid. Pregnenolone is converted by the fetal adrenals to 17α-hydroxypregnenolone and this steroid is oxidized to dehydroepiandrosterone. Dehydroepiandrosterone is 16α-hydroxylated by the fetal liver and the 16α-hydroxydehydroepiandrosterone formed can be transported to the placenta, where it is converted to oestriol. Pregnenolone and its metabolites exist in the fetus mainly as conjugates with sulfuric acid. This is due to the high activity of the sulfokinase enzymes present in fetal tissues and the low amounts of the sulfatases found. When these conjugates reach the placenta they are readily hydrolysed by the sulfatases present in this tissue.

4.3 Formation and metabolism of C_{21}-hydroxysteroids

In addition to the role of pregnenolone and progesterone, the formation and metabolism in the feto-placental unit of 17α-hydroxyprogesterone, 16α-hydroxyprogesterone, and 15α-hydroxyprogesterone have also been investigated. It is now known that 16α-hydroxyprogesterone is extensively reduced at C_{20}, that the functional groups in the A and B rings are also reduced, and that some of the metabolites are conjugated with sulfuric and glucuronic acids. Furthermore, 16α-hydroxyprogesterone is not hydroxylated in the feto-placental unit. It was found that 17α-hydroxyprogesterone can be converted to androstenedione and testosterone by the fetal testes and adrenals at mid-term, and that it is reduced at C_{20} as well as in the A and B rings by a large number of fetal tissues. Again, some of the reduced metabolites are conjugated with sulfuric acid as well as with glucuronic acid. Recently, it has been found that 15α-hydroxyprogesterone is excreted in maternal urine during the second and third trimesters of pregnancy, and that this steroid is uniquely formed in the feto-placental unit and not in the maternal compartment. This steroid does not seem to be metabolized by the fetal tissues or by the placenta.

The metabolism of deoxycorticosterone, corticosterone, and hydrocortisone has also been studied in the fetus at mid-term. These steroids are actively metabolized by fetal tissues to reduced products and are hydroxylated at C_6 and C_{11}. A similar course of metabolism can be demonstrated with the 21-sulfates of these corticosteroids. As corticosterone sulfate and hydrocortisone sulfate do not seem to be hydrolysed by the placenta, these conjugates may cross to the maternal circulation in an unaltered form. At present, the contribution of the fetal adrenal to the total corticosteroids in the mother is not known.

The origin of aldosterone in the fetus remains to be clarified. Evidence that the fetal adrenals are capable of converting corticosterone to aldosterone has been obtained in the perfused fetus and using *in vitro* incubation techniques.

4.4 Precursor role of dehydroepiandrosterone sulfate, dehydroepiandrosterone, androstenedione and testosterone

Dehydroepiandrosterone sulfate secreted from the maternal adrenals is converted to oestradiol in the placenta. This conversion increases in magnitude up to the 34th week of gestation, when approximately 40–50% of the circulating steroid is used for this synthesis. It has been calculated that, during late pregnancy 90% of the oestriol in the maternal compartment is derived from precursors elaborated in the feto-placental unit. These precursors are derived both from placental pregnenolone and from pregnenolone formed from acetate in the fetal compartment. It has been demonstrated that pregnenolone injected into the umbilical vein can be transformed to 16α-hydroxydehydroepiandrosterone sulfate in the fetus and that this steroid can serve as a precursor of oestriol in the placenta.

Testosterone and androstenedione are readily aromatized to oestrone and oestradiol in the placenta. Both steroids are converted to testosterone sulfate in the fetus and this steroid is transferred across the placenta without hydrolysis. Testosterone, androstenedione, and dehydroepiandrosterone are extensively metabolized by fetal tissues at mid-pregnancy. The reduced products are conjugated in the fetal tissues with sulfuric acid.

4.5 Control of steroidogenesis

It is known that the fetal pituitary is necessary for the growth of the fetal zone of the fetal adrenal but the nature of the trophic hormones that are elaborated by the fetal pituitary and exert this control is not known. Efforts have been made to determine the factors that control the formation of steroids by the placenta, but these studies have not yet been fruitful. Because data on steroidogenesis in the human feto-placental unit have mostly been obtained from the use of labelled precursors at mid-gestation, little is known about the changes that occur in the evolution of steroid-metabolizing enzyme systems in the second half of pregnancy. The newborn infant synthesizes corticoids as well as Δ^5-3β-hydroxysteroids without the aid of external precursors. The stage of development at which maturation of the enzyme systems that enable the fetus to make these transformations occurs is not known. From the data presented above it is evident that a large number of steroids are elaborated by the feto-placental unit at mid-gestation. The role of these steroids in the growth and maintenance of the human fetus is not known.

5. SIGNIFICANCE OF STEROIDS IN PLASMA AND URINE FOR FETAL VIABILITY

5.1 Interpretation of steroid assays

The biosynthetic origins of the steroid metabolites measured in blood and urine during pregnancy are complex. It is therefore hazardous to make inferences about altered precursor production in the feto-placental unit on the basis of such measurements. For example, at least four pathways for oestriol formation exist, but their relative quantitative importance may differ considerably in normal pregnancy and in obstetric disease.

Most of the steroid metabolites measured at present result from an interplay between fetal, placental, and maternal metabolism. Their levels in maternal biological fluids therefore reflect a variety of biosynthetic activities. As clinical interest centres upon fetal viability, it is natural that most attention should have been given to those steroids whose biogenesis depends in large part upon steps carried out in the fetal compartment. Thus, urinary oestriol, the formation of which involves the addition of a hydroxyl group at C_{16}—largely a fetal activity—is a more useful index of the fetal state than urinary pregnanediol, which is derived mainly from placental progesterone. The problem is compounded by the fact that it has not yet been possible to identify the rate-limiting steps that are affected in specific obstetric diseases; one cannot therefore identify the specific enzymatic defect responsible for a particular change in steroid levels.

5.2 Choice of steroid for assay

Urinary oestriol assays are widely used in obstetrical practice and it is generally concluded that determinations of this compound are more useful than are those of urinary pregnanediol. Oestrone and oestradiol assays have proved less successful, partly because these steroids are present in much lower concentrations and are therefore more difficult to measure, and partly because the fetal and the maternal compartments make nearly equal contributions to the urinary excretion of these steroids.

The measurement of steroids that are produced only by the fetus and that are not further metabolized in the placenta or the maternal organism would be expected to give a more accurate indication of the fetal state. It has been suggested that at least three steroids may fulfil these requirements. The first of these is oestetrol, a compound having an additional hydroxyl group at the 15α-position of oestriol. Although it is probable that this compound is formed predominantly in the fetus, it remains to be shown that its measurement in urine will give a more reliable indication of the fetal state than the assay of urinary oestriol. The limited evidence at present available suggests that when assays of oestetrol and oestriol are performed on the same urine samples, the values parallel each other, the oestetrol remaining a constant fraction of the oestriol value. Another steroid of interest in this context is 11-dehydro-17α-oestradiol, which appears to be exclusively a product of fetal metabolism. A third compound that has been firmly established as a purely fetal steroid is 15α-hydroxyprogesterone, but at present only limited information is available on its quantitative measurement during normal pregnancy and none at all in abnormal pregnancy.

5.3 The clinical context of steroid assays

There is general agreement that serial urinary assays give a much more reliable indication of the fetal state than do single estimations. This is due mainly to the extreme variations in the day-to-day excretion of oestriol as observed by many investigators. Even a prolonged fall in oestriol excretion should be interpreted only in the context of the whole clinical picture, i.e., previous obstetric history, stage of gestation, blood pressure, etc. It is clear that oestriol assays alone are not a reliable guide to the management of a particular patient. The most effective use of serial oestriol assays occurs when they are combined with other available indicators of the fetal state, and thorough clinical evaluation. Taken by themselves, oestriol assays may occasionally be of value as an indication that interruption of pregnancy is unnecessary, even though clinical findings suggest that the fetus is in jeopardy.

5.4 Clinical value of urinary oestriol assay

Despite great advances in methodology, the clinical value of oestriol measurements is not clear. More well-controlled, prospective studies are needed in order to determine the proper role of oestriol assays in modern obstetrical practice. Other techniques may be found to be more valuable, but at present urinary oestriol assays are the most widely used. On the other hand, the speed and simplicity of plasma assays may well prove to have many advantages for the analysis of clinical situations, despite the need for skilled technicians and the considerable initial outlay for instrumentation.

5.5 Steroid assay in plasma

Urinary steroid assays have inherent limitations, some of which may be overcome by the use of plasma assays. The possibilities of plasma assays have in the past been much limited by methodological inadequacies. This situation is likely to be transformed by the introduction of protein-binding techniques and, particularly, the related technique of radioimmunoassay of steroids. The future value of plasma assays will, however, depend entirely on the magnitude of the variability of normal levels. Precise definitions of the physiological factors, such as diurnal variation, activity, or posture, that may influence plasma steroid levels will be a prerequisite for the application of such assays in obstetric disease.

6. CATECHOLAMINES IN PREGNANCY

6.1 Assay techniques for catecholamines

Information about the role of substances such as epinephrine and norepinephrine in pregnancy has been circumscribed by the techniques available for the assay of these catecholamines in biological materials. Until recently, investigations were hampered by the fact that these amines are present in such low concentrations that assays had always to be done close to the limit of sensitivity. At the same time the methods available, such as fluorimetry, were relatively non-specific. The introduction of new techniques, such as double isotope derivative methods, will make possible a more thorough evaluation of the role of catecholamines in pregnancy.

6.2 Clinical applications

Catecholamine determination during pregnancy is mainly of interest for the diagnosis of phaeochromocytoma. When this condition presents as toxaemia of pregnancy, it may be very difficult to arrive at the correct diagnosis. The findings in normal and pathological pregnancy are fragmentary and contradictory, and there are particularly large species variations. In some instances, only small amounts of catecholamines—or none at all—could be detected in the uterus, an observation that suggests that the innervation of the uterus plays little if any role in determining its contractility. There is some evidence that in pathological pregnancy the secretion of catecholamines may alter and in toxaemia the urinary values for epinephrine and norepinephrine may increase. At most this change is a modest one, for the levels of vanillyl mandelic acid, a principal metabolite of epinephrine and norepinephrine, do not change. At the same time, the levels of catecholamines such as epinephrine may change rapidly in toxaemia and are affected by such simple measures as rest in bed. It is possible by means of epinephrine drip infusion to inhibit labour, whereas norepinephrine will stimulate inadequate labour, even when it is resistant to oxytocin. In addition, substances resembling epinephrine are in clinical use for inhibiting premature labour.

The possible effects that some drugs given to pregnant women may have upon the production of catecholamines by the fetus have given rise to disquiet. When reserpine is given to pregnant guinea-pigs, there is a considerable fetal mortality, apparently due to exhaustion of the adrenal medulla. It is unlikely that a similar effect occurs in human pregnancy, for many hypertensive women have been treated for a long time during pregnancy with reserpine without such untoward effects.

6.3 Physiological role of catecholamines in pregnancy

There is no clear evidence that either norepinephrine or epinephrine has functions peculiar to pregnancy. During human pregnancy there are no notable changes in plasma epinephrine or norepinephrine levels. Attention has centred on their possible role in labour. No consistent changes related to the onset of labour can be detected either in the peripheral circulation or in the uterine muscle. However, occasional rises in the concentration of epinephrine during painful or prolonged labour have been noted. There are such large differences between various species in their reactions to epinephrine and norepinephrine that little can be inferred from animal experiments about the role of these substances in the human uterus. Both epinephrine and norepinephrine cause contraction of strips of non-gravid human uterus. In the progesterone-dominated uterus, epinephrine causes relaxation of the musculature of the corpus *in vivo* and a narrowing of the isthmic canal, whereas in the oestrogen-dominated uterus it causes contraction of the corpus and dilatation of the isthmic canal. In the gravid uterus this effect is modified, the norepinephrine-induced contractions being smaller, while some areas of the gravid uterus cease altogether to respond to epinephrine. Possibly this change is hormone-mediated, for progesterone will reduce the contractile response to epinephrine.

In vitro experiments show that epinephrine causes an increase of lactic acid formation in the placenta. Whether or not similar effects occur under normal or pathological conditions *in vivo* remains to be determined.

7. RENIN, ANGIOTENSIN AND ALDOSTERONE IN HUMAN PREGNANCY

Levels of renin, angiotensin and aldosterone have all been found to be higher in women with normal pregnancies than in non-pregnant women. The aldosterone is elaborated by the maternal adrenal cortex. Its possible role in the homoeostasis of pregnancy and the mechanisms whereby the increased secretion is achieved have been the topic of numerous investigations in the past decade.

7.1 Aldosterone

Increased secretion rates of aldosterone have been observed by the fifteenth week of pregnancy, the time of the earliest reported studies, and in some series a progressive increase in secretion rate towards term has been noted. This already high rate of aldosterone secretion can be still further increased by sodium restriction, and it can be suppressed by sodium loading. The metabolic clearance rate of aldosterone is the same in pregnancy as in the non-pregnant state : consequently plasma aldosterone concentration is usually greatly increased. To date, no specific aldosterone-binding protein has been demonstrated in plasma. Evidence has been produced for an altered peripheral metabolism of aldosterone during pregnancy. There is no indication that an alteration in the plasma sodium or potassium concentration or increased ACTH secretion is responsible for the rise in aldosterone secretion ; the renin-angiotensin system seems more likely to be responsible, although the evidence is at present inconclusive.

7.2 Renin, renin substrate and angiotensin

Plasma renin concentration is often increased during pregnancy, sometimes to very high values. The highest mean values have been reported in the first trimester, with considerable elevation as early as the fifth week after the last menstrual period. The mean level of plasma renin is lower in the second trimester and rises towards term. In some women, plasma renin may remain within the range of non-pregnant values throughout pregnancy. The concentration in plasma of renin substrate is consistently elevated in normal human pregnancy. This seems likely to be due to stimulation by oestrogens, since in the rat oestrogens cause an increase in renin substrate, and in man the administration of oral contraceptives containing synthetic oestrogens leads to similar elevation.

Few measurements of angiotensin II have so far been reported, but such values as are available show consistent increases. Using a radioimmunoassay technique, raised plasma angiotensin II concentrations have been found in the first trimester. While it seems likely that these increases are the product of the raised levels of renin and renin substrate, other factors may be relevant ; concurrent measurements of all three substances should clarify the issue. In one series, a significant positive correlation was found between the plasma aldosterone concentration and the product of the concurrent renin and renin substrate concentrations, but there was no correlation with the level of either renin or substrate. The addition of angiotensin II measurements to such a study is clearly crucial in order to help establish the precise quantitative relationship between the renin-angiotensin system and aldosterone production in pregnancy.

7.3 Activation of the renin-angiotensin aldosterone system in pregnancy

It has been shown that there is an increase in the glomerular filtration rate as early as the twelfth week, and that this is maintained into the third trimester. Such an increase would deplete the mother of sodium unless compensatory increases in tubular sodium reabsorption, such as might be produced by aldosterone, occurred. In the later stages of pregnancy, increasing maternal retention of sodium is also needed to provide for the placenta and fetus, and a further factor possibly affecting aldosterone secretion in the later stages of pregnancy is the natriuretic effect of the large amounts of progesterone elaborated by the feto-placental unit. The role of progesterone is not altogether clear, however, because the aldosterone secretion rate falls to non-pregnancy levels if the fetus dies and the placenta remains *in situ* and is still producing progesterone. In the pregnant woman, a number of other steroids have also to be considered as possible natriuretic agents, including oestriol, oestradiol, 16α-hydroxyprogesterone, 15α-hydroxyprogesterone, 18-hydroxydeoxycorticosterone, 18-hydroxycorticosterone and deoxycorticosterone.

7.4 Aldosterone, renin, renin substrate and angiotensin in hypertension of pregnancy

Aldosterone secretion rates, urinary aldosterone excretion, and plasma aldosterone are generally lower in pre-eclampsia than in normal pregnancy. In keeping with the aldosterone secretion, plasma renin has been found to be lower on the average in pregnant women developing hypertension in the third trimester than in control groups of normal pregnant women. By contrast, in hypertension of pregnancy complicating Rh iso-immunization or hydatidiform mole, the mean plasma concentration of renin was considerably above the already raised levels of normal pregnancy. No significant change in renin substrate was observed in a small number of women with toxaemia of pregnancy. To date, too few measurements of circulating angiotensin II have been reported in pre-eclampsia to permit worthwhile conclusions, but for the reasons stated above, such estimations are likely to provide more valid information than measurements of renin or its substrate.

7.5 Angiotensinases

Variable results have been reported concerning the angiotensinase activity of maternal blood, serum, and plasma. This aspect might be clarified by more specific studies of individual peptidases.

7.6 Renin in the uterus, placenta, and amniotic fluid

Renin, or an enzyme closely resembling it, has been found in human amniotic fluid, in the chorion, amnion, decidua, placenta, and myometrium. Tissue culture studies have indicated that human chorion can synthesize this enzyme. This is the only evidence to date of non-renal renin production, as opposed to storage. However, on balance present evidence indicates that the high levels of renin in maternal blood are derived from the maternal kidney rather than from the uterus or its contents.

8. HORMONAL INTERRELATIONSHIPS IN PREGNANCY

8.1 The role of hormones in pregnancy

Some of the hormones of the fetus and placenta appear to be concerned entirely with the mother, others only with the fetus. Thus HCS is secreted mainly to the maternal compartment and no action has been demonstrated as yet in the fetus. Other hormones, such as insulin, do not leave the fetal compartment in significant amounts and may be presumed to exercise their function entirely within the feto-placental unit. Some hormones, such as HCG, exist both in the feto-placental unit and in the mother and might be supposed to exercise functions in both, although it must be acknowledged that little is known at present of the functions of HCG in the fetus.

8.2 Transplacental passage of hormones

The steroid hormones cross the placenta freely and, unless inactivated in the second compartment, will exert endocrine effects. This is illustrated by the effect of administering corticosteroids to pregnant women. They cross the placental barrier and interact with the fetal endocrine system to suppress the production of oestriol precursors by the fetal adrenal. The protein hormones do not cross the placenta.[1] However, their metabolism may be modified by the effects they exert individually on substances that cross the placenta. For example, the amount of glucose passing from mother to fetus is determined by the maternal glucose concentration, but fetal insulin secretion is controlled in turn by fetal glucose levels. This effect is seen most clearly in the hypertrophied pancreas of the fetus of a diabetic mother.

8.3 Chorionic gonadotrophin

The relationship of HCG to fetal steroid biosynthesis has not been clearly established. On the other hand, it has been firmly established that LH and HCG cross react immunologically and it is difficult to distinguish between the two in the maternal organism. However, recent studies in which these two proteins have been separately measured have given support to the thesis that HCG stimulates the *corpus luteum* in early gestation. Whether, in addition to HCG other factors are necessary for maintaining the *corpus luteum* is not known.

---

[1] HCG and HCS are released by the placenta directly into both the maternal and the fetal circulations and therefore constitute a special case.

8.4 Chorionic somatomammotrophin

As with HCG and LH, there is immunological cross reaction between HCS and human growth hormone (HGH). HCS has some growth-promoting activity, which lends support to the view that HCS and HGH may have correlated functions. Although growth hormone can be found in the fetal pituitary, indirect evidence, such as the normal growth of anencephalics, suggests that it is not of major importance for fetal growth. HCS antagonizes maternal insulin and may act as a fetal growth-promoting factor by making more glucose available to the fetus.

8.5 Thyroxin and triiodothyronin

Both these compounds cross the placental barrier, the flux between the two compartments being largely determined by the thyroid-binding proteins. The passage of thyroxin across the placenta is limited ; so much so, that a mother may fail to maintain a fetus with an absent thyroid in a euthyroid state. Since the maternal thyroxin-binding capacity is greater than that of the fetus, the gradient tends to be from fetus to mother, but the flow is insufficient to make good a maternal thyroid deficiency. Fetal colloid formation starts at about 8 weeks and iodine concentration around the 10th week. TSH cannot be demonstrated until the 12th week. The possibility therefore arises that chorionic TSH is the factor that initiates fetal thyroid secretion.

Long-acting thyroid stimulator (LATS) crosses the placenta from mother to fetus and may be the cause of occasional fetal hyperthyroidism. Such hyperthyroidism subsides within a few months of birth when the fetus is separated from the source of LATS.

8.6 Progesterone

The placenta secretes 2 or 3 times as much progesterone to the mother as to the fetus. Once in the maternal compartment, progesterone does not appear to make its way back to the fetus, although it can evidently pass from the fetal circulation to the mother. The maternal secretion of aldosterone is raised in pregnancy and this could be in part the consequence of the natriuretic effect of the progesterone secreted by the placenta.

8.7 Oestrogens

Large amounts of oestrogen, particularly oestriol, are secreted into the maternal compartment by the placenta. In the maternal compartment, the oestrogens are rapidly converted into the conjugated forms and as these are rapidly excreted by the kidney it is difficult to define any hormonal interrelationships in the maternal compartment.

8.8 Glucocorticoids

Adrenal steroids, such as cortisol and corticosterone, cross the placental barrier and, as in the case of thyroxin, the flux is determined by the binding proteins in either compartment. Alterations of maternal corticoid levels can effect fetal adrenal function. This is most clearly evident when corticosteroids are given to the mother and result in a lowered oestriol excretion because the supply of fetal adrenal precursors of oestriol is decreased.

9. THE ENDOCRINOLOGY OF LABOUR

9.1 Introduction

Several theories of the endocrine control of labour in humans have been proposed and their present status is reviewed below. Although the theories are discussed separately, it is not implied thereby that the onset of labour could not be the result of several interacting mechanical and hormonal influences, none of which is consistently dominant.

9.2 The progesterone block

According to the progesterone block theory labour in certain experimental animals is initiated by a change from progesterone dominance to oestrogen dominance, with the result that the myometrium becomes responsive to oxytocin. Spontaneous uterine activity consequently increases, leading in turn to activation of a reflex from the birth canal and an increase in oxytocin release from the posterior pituitary. In human pregnancy, there is no demonstrable fall in plasma progesterone before labour or during the early stages of labour. In addition, myometrial progesterone probably does not fall prior to parturition and pregnancy cannot be prolonged by the administration of progesterone. There is therefore no direct evidence that progesterone block is a mechanism of parturition in man.

9.3 The progesterone : oestrogen ratio

It has also been proposed that parturition is the result of a change in the progesterone : oestrogen ratio in favour of oestrogen. In human pregnancy, there is no rapid change in urinary oestrogens prior to parturition. Current evidence suggests that plasma concentrations of oestradiol and oestriol do not change before labour or in the early stages of labour. There is a prolonged gestation in anencephalic pregnancies and the urinary oestrogens are low, which might be taken as evidence in favour of the theory of a change in progesterone : oestrogen ratio. Following the administration of oestrogens to normal pregnant women, there is no convincing evidence of induction of labour except in one reported study. In this study,[1] the proportion of patients at term who started labour within 7 days of administration of 200 mg of 17β-oestradiol given intravenously showed a statistically significant difference from the proportion in a similar group who received an inert material. There is, therefore, inadequate experimental support for the progesterone : oestrogen ratio theory of the induction of labour.

9.4 Oxytocin

The use of intravenous infusions of oxytocin to induce labour in women has given rise to the view that labour is initiated by a physiological release of oxytocin, which occurs as a normal component of the process of parturition. There is no change in the plasma level of oxytocin, as determined by bioassay, before or during the early stages of labour. Radioimmunoassay procedures for the measurement of blood oxytocin have not as yet been applied to this problem, and very small changes in oxytocin levels may not be recognized by the bioassay procedures available. There is, therefore, no strong evidence that increased oxytocin secretion is an important factor in the initiation of parturition. Ethanol infusion inhibits uterine activity during human pregnancy. This action of ethanol is thought to be the result of an inhibition of oxytocin secretion from the pituitary. However, there is evidence that ethanol can also act directly on the myometrium although ethanol infusion has no apparent effect on myometrial response to oxytocin in the immediate postpartum period.

Oxytocinase, which is a non-specific enzyme, is increased during pregnancy, but there is no fall in the activity of this enzyme prior to labour. Consequently, high blood levels of circulating oxytocin due to a fall in oxytocinase activity cannot be considered responsible for the initiation of labour.

9.5 Serotonin

Serotonin (5-hydroxytryptamine) has a powerful oxytocic effect on the uterus. Serotonin is present in the placenta throughout human pregnancy. A biologically inactive metabolite of serotonin, 5-hydroxyindoleacetic acid, is present in amniotic fluid throughout human pregnancy, and increases with advancing gestation. The enzyme monoamine oxidase (MAO), which converts serotonin to 5-hydroxyindoleacetic acid, is present in the human placenta. The activity of this enzyme in the placenta and amniotic fluid falls progressively throughout pregnancy. An MAO inhibitor, pargyline hydrochloride, will cause abortion when injected into the amniotic

[1] Pinto, R. M. et al. (1967) *Amer. J. Obstet. Gynec.*, **98**, 540.

sac but whether other MAO inhibitors also have this action remains to be determined. Although increasing serotonin levels are present at various intrauterine sites as pregnancy progresses, there is no evidence that this hormone plays an important role in determining the onset of labour in man.

9.6 Prostaglandins

Infusion of the prostaglandins $PGF_{2\alpha}$ and PGE_2 into pregnant women has shown these compounds to be potent myometrial stimulators, capable of causing abortion during the first and second trimesters and labour near term. $PGF_{2\alpha}$ and PGE_2 have been identified in the plasma, amniotic fluid, and decidua of women in labour, but it is not known whether they can act directly in inducing labour. It remains to be demonstrated that the appearance of $PGF_{2\alpha}$ or PGE_2 during labour is the cause rather than the result of uterine activity.

9.7 Fetal regulation of parturition

The prolongation of pregnancy that may occur in pregnancies complicated by anencephaly or other fetal anomalies involving the brain stem and pituitary suggests that the human fetus may play a part in the regulation of parturition. Direct evidence is lacking, however, and it is necessary to turn to an experimental animal for a clearer demonstration of the fetal role.

In normal ewes at term, plasma progesterone decreases before the onset of labour. There is an increased excretion of urinary oestrogen during pregnancy. During the last week of pregnancy the fetal adrenal doubles in size. Hydrocortisone concentration increases in the fetus but not in the mother. Hypophysectomy of the fetus, section of the fetal pituitary stalk, and total adrenalectomy of the fetus all prolong gestation. Labour does not occur and the prolonged pregnancy ends in fetal death. When ACTH is administered to the fetal lamb, the fetal adrenal grows in size and when it attains the size of the adrenal at term parturition occurs. The same results can be obtained throughout the second half of pregnancy by the administration of glucocorticoids to the fetus. When ACTH is administered to the fetus, the events that occur in the ewe at term are reproduced; there is a decrease in plasma progesterone and an increase in fetal hydrocortisone concentration. When ACTH or glucocorticoids are infused into the fetus and progesterone levels maintained at a high concentration in the mother by administration of progesterone, the high plasma progesterone does not block the action of ACTH or the steroids. It is therefore clear that in the pregnant sheep the fetus provides the trigger for setting in motion the events that lead to labour and that it is capable of doing so without a preceding fall in maternal plasma progesterone levels. As yet, these data cannot be extrapolated to human pregnancy. It is hoped that elucidation of the detailed mechanism of the induction of labour in one species, such as the sheep, will provide basic knowledge that may be useful for the study of the initiation of labour in human pregnancy.

10. HORMONOLOGY OF PATHOLOGICAL PREGNANCY

Hormone levels alter during pregnancy and so does the incidence of various forms of endocrine pathology. It therefore seems appropriate to consider pathological pregnancies in terms of the stage of gestation. In this respect, there is a natural division between the pathology of early pregnancy —mainly spontaneous abortion—and the obstetric diseases of later pregnancy.

10.1 Endocrine causes of spontaneous abortion

The increasing weight of evidence that a substantial proportion of abortions are due to maldevelopment of the feto-placental unit has decreased the emphasis on the endocrine causes of abortion.

The endocrine causes of early abortion are usually considered in terms of either ovarian or trophoblastic deficiency. The role of the corpus luteum at implantation or in the first few weeks of pregnancy has already been mentioned, but ovarian deficiency is unlikely to be a major factor after 6–8 weeks gestation, for by this time the ovaries can usually be removed without causing abortion. Few data are available on hormones in very early abortion, so that it is difficult to assess the importance of luteal failure as a cause of abortion. There is some indication that the production of 17α-hydroxyprogesterone by the corpus luteum may be a good index of its function. If so, measuring this steroid in blood or its metabolite, pregnanetriol, in urine may well prove to be a sound way to assess luteal function in early pregnancy. Assays of serum HCS levels could also be of interest in relation to abortion.

The etiological role of defective trophoblastic steroidogenesis, particularly of progesterone, is open to question. Abortion is associated with a fall in levels of blood progesterone and urinary pregnanediol, but the weight of the evidence is in favour of this being the consequence rather than the cause of the abortion. Properly conducted therapeutic trials with synthetic progestational compounds do not support the view that substitution therapy is effective.

Investigations in the USSR have indicated that defective adrenal function may account for a proportion of abortions. Further studies of adrenal steroid levels in pregnant women with a history of recurrent abortion would be valuable and in view of the Russian findings it is suggested that double-blind trials with corticosteroid therapy should be undertaken.

10.2 Endocrine therapy of spontaneous abortion

Therapy should properly be related to the cause of the abortion. If it is accepted that endocrine deficiency causes a very small proportion of the total number of abortions much of the rationale for hormone substitution therapy disappears. It has been argued that all women at risk should nevertheless be treated with hormones in the hope of preventing the few abortions of endocrine origin, but such a view is not scientifically acceptable.

Substitution therapy with progesterone or orally active synthetic progestogens is the most popular form of endocrine therapy. The optimistic views at first held regarding its efficacy have not been supported by subsequent double-blind trials.

Treatment with chorionic gonadotrophin has been much less frequently tried. There is some evidence that it might be of benefit in stimulating luteal function following artificial induction of ovulation, and this finding might be extended to the use of chorionic gonadotrophin in very early threatened or recurrent abortion. The rationale of this approach requires that the treatment should be instituted within a few days of the first missed period ; hence, suitable patients will be encountered very seldom.

Oestrogen therapy has been tried from time to time in various forms of abortion, but there is no objective evidence of its value. Corticosteroid therapy in selected cases with objective evidence of relative adrenal insufficiency is an interesting departure ; but some doubts have been raised as to the wisdom of administering such steroids to pregnant women. There is by now considerable experience of the treatment of pregnant women with various adrenal steroids and no convincing evidence that this harms mother or child.

10.3 Obstetric diseases of later pregnancy

There are certain obstetric conditions in which hormone assays are very helpful and others in which they are less so. It is therefore necessary to categorize obstetric diseases very clearly before attempting to assess the value of any particular hormone assay. It is not sufficient to designate broad groups, such as pre-eclamptic toxaemia or diabetic pregnancy. Pre-eclampsia has many manifestations and hormone levels may vary accordingly. Diabetic pregnancy also presents a variety of states, in each of which the hormone levels may be different. The impact of treatment on hormone levels should be looked at more carefully.

Retarded fetal growth, although it probably embraces several causal categories, is a condition in which hormone assays may be very helpful.

It is generally accepted that serial assays of urinary oestriol excretion are the most useful in the diagnosis and management of this condition. In pre-eclamptic toxaemia the hormone levels are more variable. Urinary oestriol assays are probably the most useful endocrine monitor, but because there is such a strong placental element in the disease pregnanediol assays may also be of value. Chorionic gonadotrophin levels are usually raised in severe pre-eclamptic toxaemia, but there is a large overlap between the normal and pathological values. Aldosterone is lowered, but there does not appear to be much value in its estimation as a means of assessing feto-placental function. Estimations of HCS may be useful in those pathological conditions that are complicated by severe maternal hypertension.

The use of hormone assays in pregnancy complicated by diabetes is controversial. Many clinicians have found urinary oestriol assays helpful in this condition. However, it is unlikely that the effect on oestriol excretion in a woman with poorly controlled diabetes and superimposed toxaemia and a small baby and placenta will be the same as in another with diabetes of pregnancy and an overgrown fetus.

In pregnant women with Rh incompatibility, oestriol and pregnanediol excretion very often does not correspond to the fetal state; high levels may therefore give a false sense of security, although persistently low levels occasionally help to identify a severely affected infant. Because steroid assays have not proved helpful, the use of HCS and HCG assays has been explored, but without much success. The estimation of these two hormones remains most useful in molar pregnancy and chorionepithelioma.

10.4 Treatment of obstetric disease with hormones

Although treatment of pre-eclamptic toxaemia with preparations such as stilboestrol has been advocated, it has not been widely adopted. It is generally agreed that the changes of hormone level in obstetric disease are the consequence, not the cause, of obstetric disease. Nothing has so far been gained by using hormonal replacement.

10.5 Future investigations on the hormonology of pathological pregnancies

Methods for the accurate estimation of hormones in biological fluids other than urine are becoming available. It remains to be seen how useful hormone assays done on blood or amniotic fluid will prove to be. If it can be shown that hormone levels in these fluids reflect the fetal state, such assays may largely replace the present urinary methods. Dynamic tests, such as the conversion of precursor steroids to oestriol by the feto-placental unit, have hardly been explored and may in the future play a useful role. This applies also to the assay of steroid hormones of purely fetal origin.

11. RECOMMENDATIONS

The Scientific Group recommended that studies of the following outstanding problems should be intensified :

The endocrinology of ovoimplantation

(1) The physiological, endocrinological and biochemical events taking place before and during implantation, and especially the nature of the signal that results in the maintenance of luteal function in the presence of a fertilized egg.

(2) The consequences of early or late implantation and the causes of very early abortion.

(3) The inhibition of implantation as a means of birth control, and especially the mode of action of substances that directly or indirectly have this effect.

(4) The relative importance of the corpus luteum and the feto-placental unit as sources of steroids in the early stages of gestation.

(5) The measurement of the prostaglandins and their possible significance for implantation and early pregnancy.

Non-steroid hormones of the human placenta

(1) The determination of HCS in plasma as an index of placental function in normal and pathological pregnancies.

(2) The factors involved in the control of the biosynthesis of HCS and HCG.

(3) The role of HCS and other substances in regulating fetal growth and in the regulation of maternal metabolic alterations.

Steroidogenesis in the feto-placental unit

(1) The control of steroid synthesis by trophic hormones and by steroids elaborated within the feto-placental unit.

(2) The effect of steroids elaborated in the feto-placental unit on the growth of the fetus.

(3) The maturation in the fetus of enzyme systems involved in steroidogenesis.

(4) The quantitative importance of various fetal organs, especially the fetal gonads and adrenals, in the elaboration of steroids.

(5) The effects of steroids elaborated in the fetus on the development of the fetal brain and on the development of immunological tolerance.

(6) The role of fetal hormones in modifying placental steroidogenesis.

(7) The factors regulating the passage of steroids and steroid conjugates across the placenta and the relative amounts of hormones secreted by the placenta to the mother and to the fetus.

(8) Steroid excretion in the newborn with a view to obtaining further information concerning fetal steroidogenesis at the later stages of gestation.

(9) The biological and metabolic activity of certain predominantly fetal steroids, with respect to both their hormonal and other biological activities.

Significance of steroids in plasma and urine for fetal viability

(1) The use of steroids of uniquely fetal origin and metabolites other than steroids as indicators of fetal viability.

(2) The biochemistry of the placenta and, in particular, the biosynthesis of materials other than steroids and the effect of disease on placental biochemistry.

(3) The hormonal changes of very early pregnancy.

(4) The transport functions of the placenta.

Catecholamines in pregnancy

(1) The development of more specific and more sensitive methods of assay of catecholamines to permit their role in normal and pathological pregnancy to be more clearly determined.

(2) The role of catecholamine precursors, such as DOPA, and of catecholamine metabolites.

(3) The clinical use of new compounds for the inhibition of premature labour.

Renin, angiotensin and aldosterone in human pregnancy

(1) The role of HCS in stimulating aldosterone secretion. In addition, further data are needed to determine whether angiotensin II alone can account for the changes in aldosterone secretion during pregnancy.

(2) The causes of changing aldosterone levels in pregnancy.

(3) The function of the renin found in the uterus and in the placenta.

(4) Renin, angiotensin and aldosterone levels, measured under controlled conditions in carefully classified toxaemias of pregnancy.

Hormonal interrelationships in pregnancy

(1) Identification of rate-limiting steps in fetal and placental steroid biosynthesis.

(2) Application of the recently developed protein-binding methods for steroid assay to the study of normal pregnancy and to the changes in pathological pregnancy.

(3) Steroid levels in normal and pathological pregnancy, with special attention to improved study design and critical reporting.

The endocrinology of labour

(1) Use of higher primates in studies on parturition.

(2) Fetal corticosteroid biosynthesis in late pregnancy and the possible roles of other feto-placental signals.

(3) The development of new methods for the measurement of prostaglandins and oxytocin and their role in relation to labour.

(4) The metabolism of hormones in the myometrium and endometrium in relation to labour.

(5) Application of the new protein-binding methods of steroid assay to the experiments in animals when labour is being examined.

(6) The factors concerned in the maturation of fetal organs.

Endocrinology of pathological pregnancy

The Group considered that a further meeting of experts should be convened to review present knowledge of hormonal changes in pathological pregnancy and the research needs in this field.

Annex

TRIVIAL AND SYSTEMATIC NAMES OF STEROIDS USED IN THIS REPORT

oestetrol	oestra-1,3,5(10)-triene-3,15α,16α,17β-tetrol
11-dehydro-17α-hydroxy-oestradiol	oestra-1,3,5(10),11-tetraene-3,17α-diol
oestrone	3-hydroxyoestra-1,3,5(10)-trien-17-one
oestradiol	oestra-1,3,5(10)-triene-3,17β-diol
oestriol	oestra-1,3,5(10)-triene-3,16α,17β-triol
dehydroepiandrosterone	3β-hydroxyandrost-5-en-17-one
16α-hydroxydehydroepiandrosterone	3β,16α-dihydroxyandrost-5-en-17-one
androstenedione	androst-4-ene-3,17-dione
testosterone	17β-hydroxyandrost-4-en-3-one
testosterone sulfate	3-ketoandrost-4-ene-17β-yl sulfate
dehydroepiandrosterone sulfate	17-ketoandrost-5-ene-3β-yl sulfate
16α-hydroxydehydroepiandrosterone sulfate	16α-hydroxy-17-ketoandrost-5-ene-3β-yl sulfate
progesterone	pregn-4-ene-3,20-dione
pregnenolone	3β-hydroxypregn-5-en-20-one
pregnanediol	5β-pregnane-3α,20α-diol
15α-hydroxyprogesterone	15α-hydroxypregn-4-ene-3,20-dione
16α-hydroxyprogesterone	16α-hydroxypregn-4-ene-3,20-dione
17α-hydroxyprogesterone	17α-hydroxypregn-4-ene-3,20-dione
17α-hydroxypregnenolone	3β,17α-dihydroxypregn-5-en-20-one
deoxycorticosterone	21-hydroxypregn-4-ene-3, 20-dione
corticosterone	11β,21-dihydroxypregn-4-ene-3,20-dione
aldosterone	11β,21-dihydroxy-3,20-diketopregn-4-en-18-al
hydrocortisone	11β,17α,21-trihydroxypregn-4-ene-3,20-dione
18-hydroxydeoxycorticosterone	18,21-dihydroxypregn-4-ene-3,20-dione
18-hydroxycorticosterone	11β,18,21-trihydroxypregn-4-ene-3,20-dione
corticosterone sulfate	11β-hydroxy-3,20-diketopregn-4-ene-21-yl sulfate
hydrocortisone sulfate	11β,17α-dihydroxy-3,20-diketopregn-4-ene-21-yl sulfate
pregnanetriol	5 β-pregnane-3α,17α,20α-triol