A STUDY ON PLASMA AND SALIVARY OESTRADIOL AND PROGESTERONE IN FIRST TRIMESTER OF NORMAL PREGNANCY

THESIS
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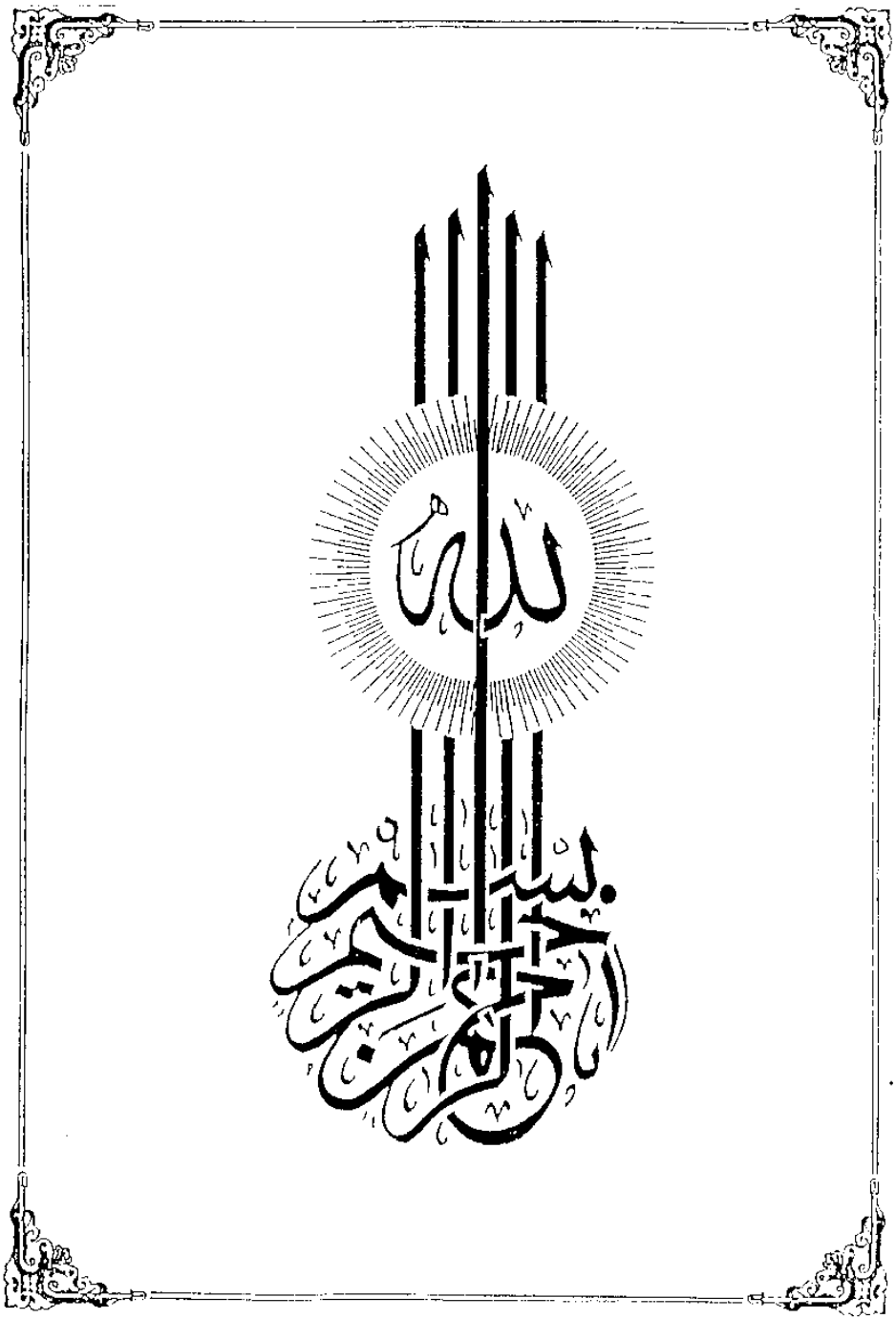

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INTRODUCTION

In recent years, it has been demonstrated that human foetal membranes and maternal decidua contain enzyme activities capable of producing and metabolizing steroid hormones (Mitchell et al, 1982). Because of the intimate anatomic relationship between these structures and the myometrium, and the modulating role that steriod hormones may have on the generation of prostaglandins within the pregnrant uterus (Thorburn et al, 1979), such metabolic activity by the foetal membranes and decidua may be an important determinant of myometrial contractility. Although the specific functions for the various steroids produced throughout pregnancy are not definitely known yet progesterone and oestradiol have been frequently used as predictors of early pregnancy outcome (Kunz & Keller, 1976, Jouppila et al, 1980 & Jens et al, 1984).

The aim of this work is to trace the level of these steroids in early normal gestation in both plasma and saliva in order to develop a reference curve for cases of early pregnancy disturbance.

REVIEW

PROGESTERONE

Willard Allen et al in (1929) published the first of their series of papers on extracts of corpus luteum that produced a special uterine reaction (Progestational proliferation). In (1930) and (1932), he prepared a purified progestin. In (1930), Butenandt described the structure of pregnanediol (C_{21} $H_{36}O_2$). By (1934), Butenandt et al crystallized the corpus luteum hormone. In 1935, the health organization of the league of Nations set up international standards for some of the sex hormones, including the new hormone of the corpus luteum.

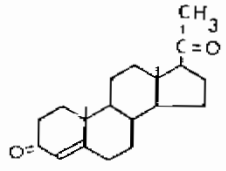
Butenandt and Slotta in (1935) would probably propose the name luteosterone. Alen and Corner had wanted the name progesterone and after discussion they all settled on the name progesterone (progest of progestin and sterone of luteosterone).

Allen et al 1930 discovered two important observations the first is that progesterone does not work in immature rabbits without oestrogen priming, and the second being if too much oestrogen is used, progesterone has no effect. The effects of progesterone leading to pseudopregnancy in the rat and such changes are

" insufficient to warrant their use as a test for corpus luteum extracts ".

Chemistry of the progestins :

Winterstein et al (1934) described chemistry of the progestins. Chemically, the progestins are sterols containing carbon, hydrogen, and oxygen atoms and are hydrophobic compounds, although the oxygen atoms and the double bond add a component of hydrophilic nature to the molecule. The parent chemical structure of the sterols is the three six-membered carbon cyclic ring strucutre, phenanthrene, to which a cyclopentano ring is attached. Since in the sterols the phenanthrene ring is saturated, rather than unsaturated, it is termed perhydrophenanthrene. Thus, the basic structure of the progestins is cyclopentanoperhydrophenanthrene to which angular methyl groupsare attached at carbon 10 and 13 and an ethyl group at carbon 17. The structure of the most biologically active, natural progestin, is progesterone.



Progesterone

Progesterone has functional groups that modify the parent structure, including a double bond between carbons 4 and 5 and ketone groups at carbons 3 and 20.

Although the term progesterone is a trivial name and not systematic chemical nomenclature, it has gained universal acceptance through its longstanding use. The systematic nomenclature for progesterone is pregn-4-ene-3, 20 dione. A common metabolite of progesterone follows reduction of the ketone at carbon 20 to form a secondry alcohol group 20 ∝-hydroxy pregn-4-ene-3-one (20 ∝ -O H P). In more recent terms which assign an absolute configuration of the alcohol at the carbon 20 center of asymmetry, the side chain with the 20 hydroxyl group is 20 S. The other site of metabolism of

progesterone is ring A reduction with saturation of the double bond between carbons 4 and 5 to form " dihydro " compounds. Since the reduced carbon atom at position 5 is assymetrical, the hydrogen can be either on the α side (trans to the carbon 19 methyl group) or β side (Cis to the carbon 19 methyl group). 5 α -pregnan-3, 20-dione. (5 α D H P) or 5 β -pregnan- 3, 20 - dione. The reduced progestins, 20 α O H P and 5 α D H P, do not appear to be able to stimulate the rodent uterus, but 5 α -D H P may be able to mediate some of progesterone's action in the pituitary-central nervous system. A final site of reduction of progesterone is the 3 ketone group to form either a 3 α-hydroxyl group which is axial to the carbon skeleton or a 3 β -hydroxyl group which is in the plane (equatorial) of the A ring. Biologically, reduction of the 3-carbonyl group does not readily occur unless the double bond of the A ring has first been reduced.

Synthesis and secretion of progesterone :

Le Maire et al in (1972) described secretion of progesterone. Progesterone is secreted from the adrenal, the croups luteum and the placental trophoblast. Progesterone has long been known as an intermediate in

biosynthesis of corticosteroids by the adrenal. Approximately 0.75 mg/day is produced by the adrenal, which can be increased by the administration of A.C.T.H, this can be measured in the ovariectomized woman as pregnandiol and accounts for much of the progesterone production in the proliferative phase of the menstrual cycle (2 mg/day). In the luteal phase, progesterone production increases tenfold and can reach 50 mg/day prior to implantation.

Progesterone has been identified as a secretory product of the corpus luteum of the ovary throughout the luteal phase and by the corpus luteum through pregnancy, it is generally agreed that the developing trophoblast of the normally implanted fetus takes over progesterone production at 8 to 9 weeks gestation. Csapo et al (1973) found that removal of the cropus luteum has been followed by abortion at 49 $\pm$ 2 days (7 weeks) following the last menstrual period, by 61 $\pm$ 4 days (8 - 9 weeks) the ablation of the corpus luteum which results in abortion at 7 weeks leads only to a transient decrease in progesterone and a reversion to normal without abortion. Secretion of progesterone from the ovary containing the corpus luteum continues to term, but this secretion is only a small

component of total progesterone production at term. However, when one considers the local nature of the action of progesterone, as in its effect on myometrium adjacent to its placental production, and the multiplicity of progesterone metabolites that have been identified but whose functions remain unknown, the progesterone secretion by the corpus luteum of pregnancy at term may not be merely an insignificant reminder of man's ontogeny.

Metabolism of progesterone :

Little et al (1975) discussed aspects of progesterone metabolism. Progesterone itself is the principal progestagen with hormonal action. There is a small progestational effect of 20α-O H P on the endometrium in the Hooker - Forbes mouse bio-assay, but probably only as the result of enzymatic conversion to progesterone. In addition the 5α-reduced progesterone(5α-D H P) has some effect on behavior. In most instances the metabolite measured may only indicate specific sites of metabolism for example, 17α-O H P appears in the circulation in significant amounts just prior to ovulation and the appearance of the corpus luteum. At the time that the corpus luteum is replaced by the placenta as the

source of progesterone, 17 ∝-O H P peripheral concentration has been reduced to low levels. Thereafter, 17∝-O H P can be measured in increasing amounts from the ovarian vein (higher on the side with the corpus luteum), from the uterine vein and from the retroplacental space.

Billiar et al in (1975) found that 20 ∝-O H P appears to be the most constant metabolic product preliminary to excretion and results in the inactivation of progesterone's hormonal activity. For example, in perfusion of the Rhesus monkey head through the carotid artery with labelled progesterone a major metabolite of the skull and cranial tissues (sampled by the external jugular vein) or brain tissue (sampled through the sagittal sinus) is 20∝-O H P. In contrast, brain tissue could also reduce progesterone to 5 ∝-D H P and 5∝-reduction sites are present in areas of the brain known to be associated with progesterone and its behavioral effects (e.g., the midbrain), rather than excretion. The corpus luteum is also known to contain a significant concentration of both 20 ∝ - and 20 β-O H P, however, 20 β-O H P is not observed peripherally and is not known to have any hormonal action.

Plasma and tissue concentration of progestins :

It is well accepted by Csapo et al in (1971) that the ovarian corpus luteum is the prime source of secretion of progesterone in early pregnancy (i.e. for 6-8 weeks of pregnancy), thereafter, the placenta is the primary source of progesterone secretion untill term. During normal pregnancy, the plasma progesterone values increase to about 25 ng/ml 2 weeks after ovulation, which is about twice that of the non-pregnant cycle, and remain relatively constant untill about 10 weeks gestation (menstrual age), when palcental secretion takes over.

In normal pregnancy, as in pregnancy following chorionic gonadotropin (h C G) induction of ovulation, 17α-hydroxyprogesterone(17α-O H P) secreted by the ovary is elevated untill about 4 to 5 weeks after ovulation, and then it decreases to basal levels by the 12^{th} week of pregnancy (menstrual age), since the placenta of early and midgestation secretes little 17α-O H P. At about the 12^{th} week of pregnancy, the plasma levels of progesterone gradually increase from a mean of 25 ng/ml to approximately 80 ng/ml at the