

Hormonal Changes in Pregnancy*

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Because of the time factor involved, it would be an impossible task to present the vast body of biochemical information accumulated during the last decade on the endocrine aspects of pregnancy. However, certain key points can be made concerning the feto-placental unit and the hormone levels and effects in normal gestation. These concepts will be discussed not merely for their academic value, but also as a base to evaluate our present diagnostic and therapeutic endeavors in obstetrical practice. With the audience's indulgence, an occasional personal conjecture will be interjected concerning hormonal mechanisms and clinical practices.

Feto-Placental Unit. The fetus and the placenta are incomplete steroidogenic systems. They lack the capability of synthesizing all necessary steroidal hormones from more simple precursors in contrast to the ovaries, testes, and adult adrenal cortex. To complete the task a well-coordinated interdigitation of the synthetic capabilities of fetus, placenta, and *mother* is required. Since the mother is involved, one wonders whether the term "feto-maternal-placental unit" would not be more appropriate.

First the fetal adrenal cortex and then the placenta will be discussed; hopefully, emphasizing the information which may have practical clinical significance.

A. Adrenal Cortex. The fetal zone of the adrenal cortex persists only during gestation, constitutes about 80% of the gland, and is active in steroid metabolism. In the first trimester, it is believed this zone is primarily stimulated by human chorionic gonadotrophin (HCG); ACTH gaining prominence in control thereafter.

The biochemical capabilities and limitations of the fetal adrenal cortex are shown in Fig. 1. Utilizing

acetate as a precursor, the fetal zone more readily synthesizes the $\Delta 5-3\beta$ hydroxysteroids pregnenolone and dehydroepiandrosterone (DHEA) than the $\Delta 4-3$ ketosteroids such as cortisol and aldosterone. This is because of a relative block in 3β -hydroxy dehydrogenase and $\Delta 5$ isomerase activity. Thus, the synthesis of large amounts of DHEA and its sulfate is favored, and they are transported to the placenta as such or after 16α -hydroxylation by the fetal adrenal or liver. The placenta can metabolize these androgens to estrogens as will be shown shortly.

However, such a biosynthetic lack would leave the fetus in jeopardy because of a cortisol and aldosterone deficiency. This is rectified by the fact that the fetal zone can utilize the readily available placental progesterone to produce these needed hormones. In fact, after the tenth week of gestation, the increasing placental progesterone secretion may enhance the 17α , 21 , and 11β hydroxylase capability of the fetal adrenal cortex to produce the corticoids. Also, the ready passage of maternal cortisol across the placenta is a secondary protective mechanism.

B. Placenta. This endocrine organ is incapable of synthesizing large quantities of progesterone and estrogens from the simple precursor acetate. However, it can efficiently convert maternal plasma cholesterol to progesterone as shown in Fig. 2. This is clinically important for it means that an intact maternal-placental circulation will produce essentially normal progesterone levels even though a fetal demise has occurred. The progesterone produced by the placenta can be metabolized by the mother and fetus to less active progestational metabolites or can be utilized by the fetal adrenal as already described. Since a 17α -hydroxylase deficiency in the placenta precludes the conversion of progesterone to androgens and subsequently estrogens, another mechanism must exist for placental estrogen synthesis.

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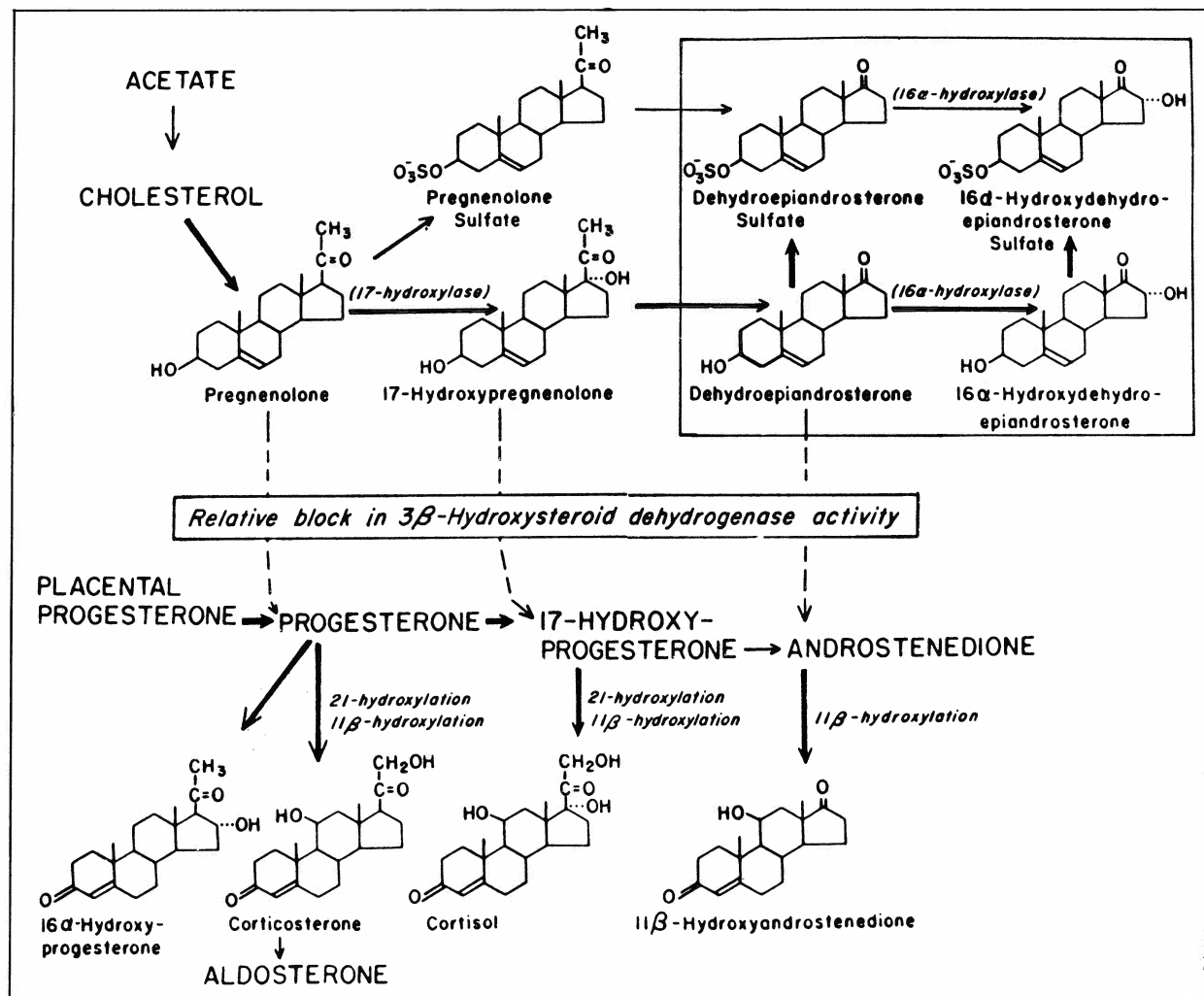


Fig. 1—Pathways of steroid metabolism in the human fetal adrenal cortex. The major secretory products are boxed in. (Reprinted with permission from Villeg, *New Eng. J. Med.* 281: 473, 1969.)

As depicted in Fig. 3, the placenta produces estrogens from androgens of maternal and fetal adrenal origin. Androstenedione, DHEA, and testosterone are converted by the placenta to estradiol and estrone. It is estimated that the mother and fetus each contribute about 50% of the androgens which are made into these 2 estrogens. Since the ability to 16 α -hydroxylate androgens is essentially limited to the fetal adrenal and liver, the fetus is the major contributor of 16 α -hydroxylated androstenedione, DHEA, and testosterone which are converted by the placenta to estradiol. The maternal contribution to estradiol at term is less than 10% and probably arises from her adrenal androgens which escape conversion to estradiol and estrone on passage through the placenta to fetus. In the fetus, however, her androgens can be hydroxylated at the 16 α

position before recirculation back to the placenta where synthesis to estradiol can occur.

The above information indicates that the clinical assay in pregnancy of plasma progesterone or its major metabolite, pregnanediol, in the urine would mirror placental integrity. On the other hand, estrogen assays, particularly urinary estradiol, would reflect fetal integrity.

Hormone Secretion Patterns and Effects in Normal Gestation.

A. Progesterone. The corpus luteum appears to be the initial source of progesterone in pregnancy. Subsequently, it is produced by the placenta in increasing amounts from maternal cholesterol. This transition of secretion from one gland to the other is shown in Fig. 4. Both plasma 17 α -hydroxy progesterone and progesterone of corpus luteum

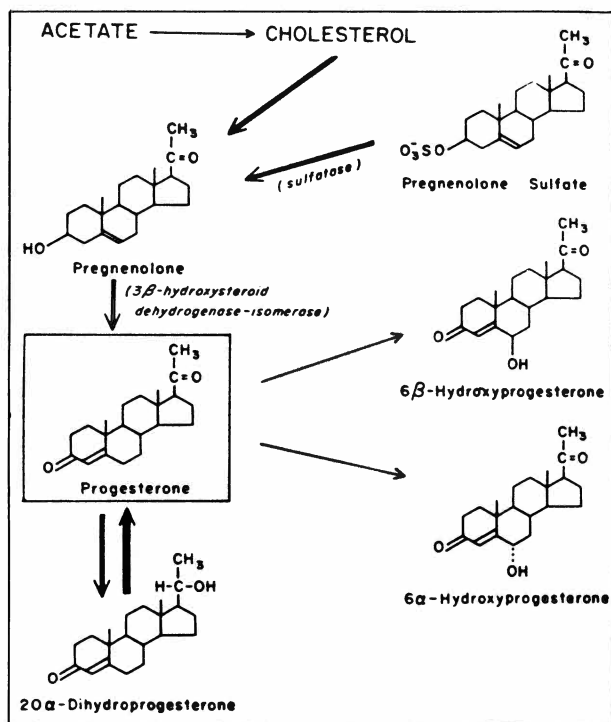


Fig. 2—Principal precursors and metabolites of progesterone in the human placenta. The major steroid secreted by the placenta (progesterone) is boxed in. (Reprinted with permission from Villee. *New Eng. J. Med.* 281:473, 1969.)

origin are seen to peak at 3–4 weeks after ovulation. At 6–8 weeks post-ovulation, the progesterone reaches a nadir while the 17α -hydroxy progesterone continues to decline. Since the placenta lacks significant 17α -hydroxylase capability, it is assumed that the secondary rise in progesterone reflects placental function. It is of interest to note that HCG—believed to maintain the corpus luteum of pregnancy—continues to rise while both hormones of corpus luteum origin are declining.

The secondary rise in placental progesterone continues to increase progressively to a maximum plateau at 36–40 weeks. This is seen from our data in Fig. 5, where the level at 8 weeks of 2 micrograms % increases linearly to about 14 micrograms % at term. The curve seems to parallel that of placental weight and is of similar configuration to that of urinary pregnanediol as depicted in Fig. 6.

It is important to note that no significant drop in progesterone occurs prior to labor. However, during parturition we and others have found a slight downward trend of mean values and this may be a reflection of placental ischemia secondary to the uterine contractions. There is a rapid drop in the plasma progesterone after delivery of the placenta verifying the hormone's short half-life.

It has been estimated that the term placenta

produces 200–300 mgms of progesterone daily. The role of this large amount of hormone is not well defined, but possible metabolic functions are:

1. The maintenance of growth and development of the fetus; for example, it is a precursor steroid for the synthesis of corticoids by the fetal adrenal cortex.
2. An immunosuppressive agent to protect the feto-placental homotransplant.
3. A defense mechanism acting on the myometrium to prevent premature expulsion of the fetus.
4. Prepare the breasts for lactation.
5. Mediate a variety of biochemical events; for example, antagonize at the renal tubule the effects of the increased aldosterone concentration found in pregnancy.

B. The Estrogens. Quantitatively, estriol is the major estrogen of human pregnancy. Its biologic potency, however, is significantly less than that of estradiol and estrone. The urinary excretion curve for estriol is presented in Fig. 7; the amount rising from low early levels to high levels at term. An acceleration in the increase is apparent during the last few weeks. There seems to be a good correlation between the estriol curve and that for the fetal weight. Klopfer, reviewing the literature, found the average levels to be 10.1, 14.2, 19.8, and 26 mgms at 28, 32, 36, and 40 weeks respectively. Similar curves for urinary estradiol and estrone have been found, but the amounts are in the microgram range. These two estrogens, like estriol, probably reflect the status of the feto-placental unit. Munson in our group has assayed unconjugated estradiol in the plasma of normal pregnancies. A mean value of 200 nanograms % in early pregnancy (9–16 weeks) rose to 1196 nanograms % during the last 8 weeks. A curve configuration similar to urinary estrogen excretion patterns was obtained.

I suspect that the estrogenic effects of pregnancy are primarily due to estradiol, the most potent of these 3 estrogens. It mediates the growth and function of the maternal reproductive organs and probably is important to fetal growth and development. The reason for the large mass of estriol production is not clear. There is little evidence at the moment that it is involved in the start of human labor.

A biochemical effect of estrogen in pregnancy or when given to a woman exogenously is the increased liver synthesis of certain steroid hormone binding globulins. The increased hormone binding

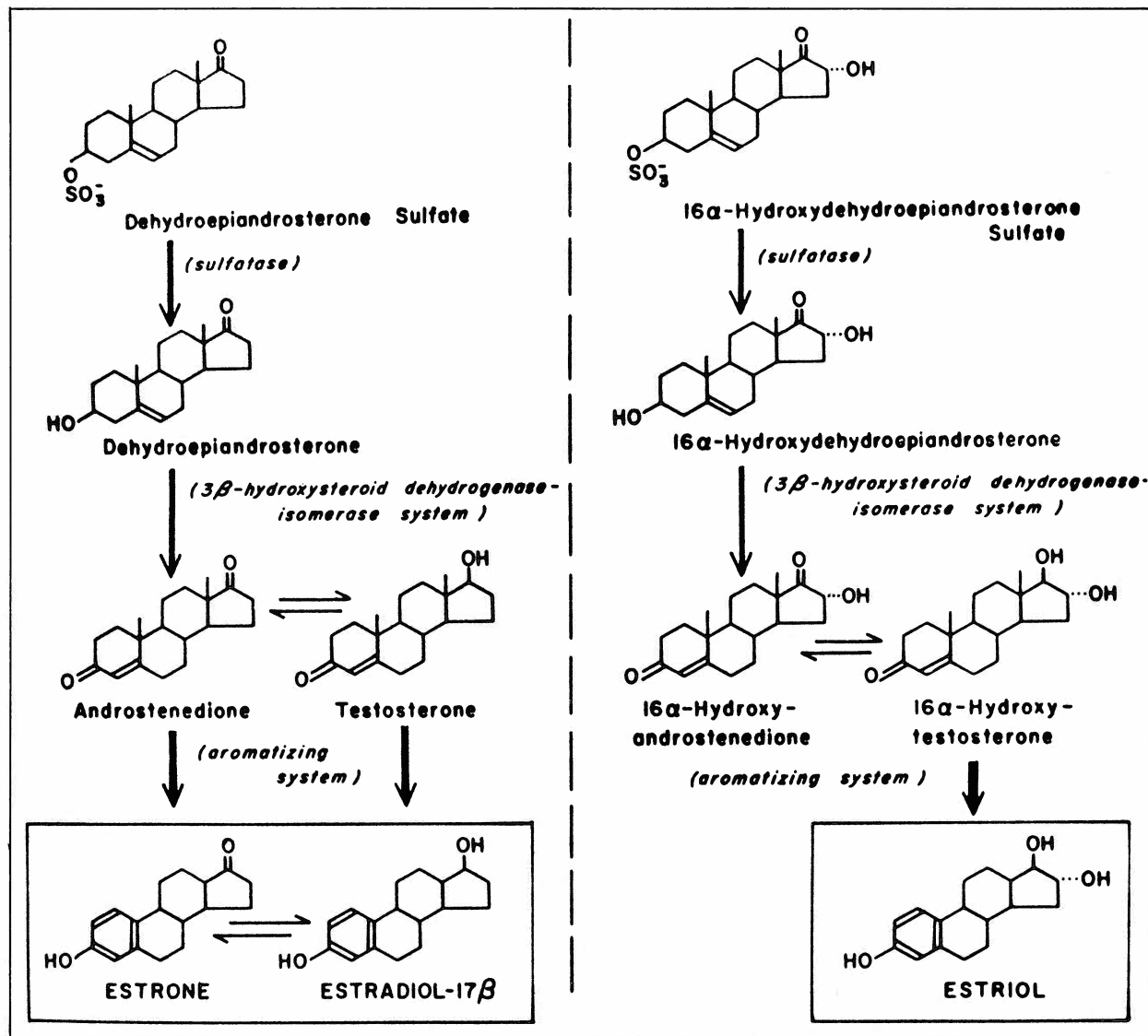


Fig. 3—Synthesis of estrogens by the human placenta. The pathways for the conversion of C19 steroids to estrogens are shown. The major estrogens secreted by the placenta are boxed in. (Reprinted with permission from Villee, *New Eng. J. Med.* 281: 473, 1969.)

results in elevated concentrations of serum thyroxine (also the PBI), plasma cortisol, and testosterone. However, the amount of free or unbound hormone, and presumably the biologically active fraction, is unchanged. Unless this estrogen effect is taken into account, the clinician can be misled by the elevated laboratory result. The only exception to this physiologic change is for plasma cortisol in pregnancy. The large amount of placental progesterone in pregnancy plasma competes with cortisol for binding sites on transcortin and increases the free cortisol fraction. Therefore the pregnant woman is actually in a state of mild adrenal hypercorticism.

C. Human Placental Lactogen (HPL). This polypeptide hormone secreted by the syncytial trophoblast is immunologically similar to but distinct from human growth hormone. Metabolically it appears to be a weaker growth hormone. Its pattern of secretion into the blood is shown in Fig. 8; the increasing concentration throughout pregnancy parallels the curve for placental weight. Like progesterone, its blood concentration reflects placental rather than fetal integrity. Fetal death may not significantly drop the level for a period of time as long as the materno-placental circulation is intact. The placental secretion is essentially unidirectional into the mother; much lower levels being found in

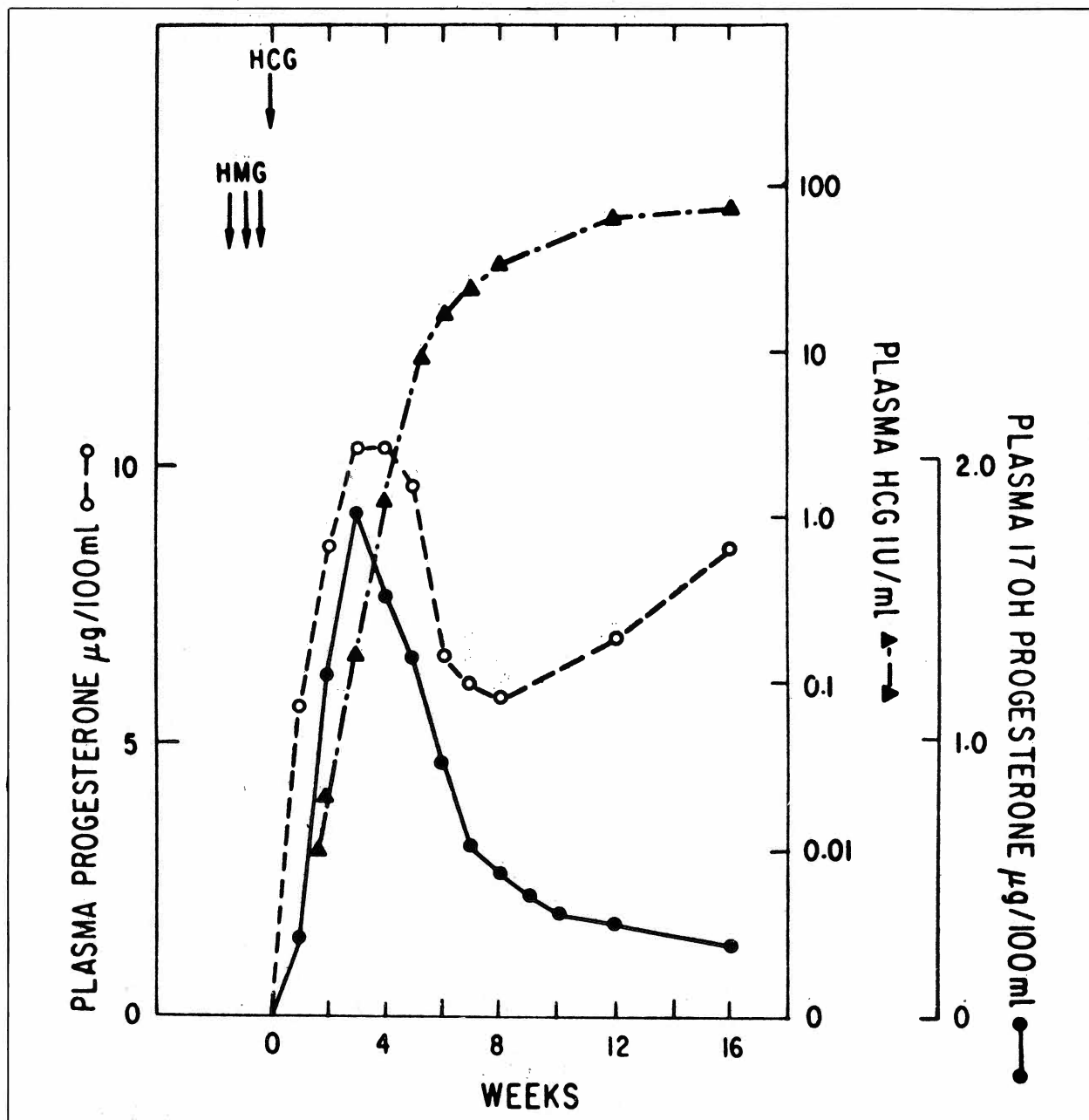


Fig. 4—Mean plasma levels of progesterone, 17-hydroxyprogesterone, and HCG following induction of ovulation with HMG-HCG and subsequent conception. (Reprinted with permission from Yoshimi, *et al. J. Clin. Endocr.* 29: 225, 1969.)

the fetus. The daily production can be as high as 400 mgms.

Possible roles of HPL are preparation of the breasts for successful lactation and indirect growth hormone effects. These include increased nitrogen retention, increased maternal fatty acid utilization sparing glucose for transmission to the fetus. The fetus, like the adult brain, utilizes essentially glucose only for its energy requirements. HPL is antagonistic to insulin and as a consequence may be an important

factor in the diabetogenic effect of pregnancy.

D. Human Chorionic Gonadotrophin (HCG).

The blood and urine levels of this glycoprotein secreted by the cytotrophoblast differ from the curves seen for the previously discussed hormones and is shown in Fig. 9. The concentration in the blood peaks at about 60 days, then decreases to $\frac{1}{4}$ to $\frac{1}{3}$ of the peak value throughout pregnancy with a lower secondary rise at term.

Its role in pregnancy is not clear, but tradition-

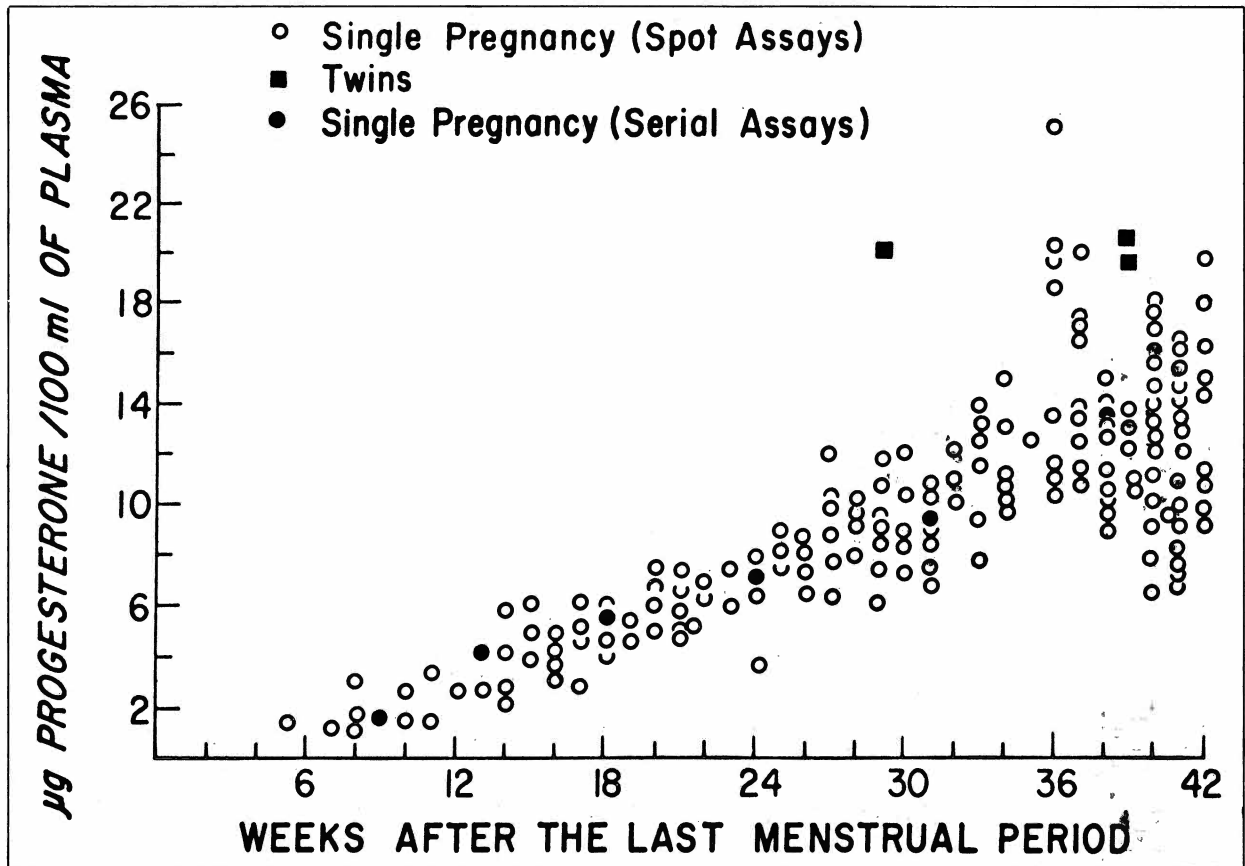


Fig. 5—The plasma progesterone concentration in normal pregnancy expressed as micrograms %. One hundred and twelve of these 179 determinations were reported previously. Note the progressive increase in concentration with advancing gestation. (Reprinted with permission from Yannone. *Steroids* 13: 773, 1969.)

ally is believed to maintain the corpus luteum of pregnancy. It may also regulate steroid secretion by other glands; its possible ACTH effect on the fetal adrenal cortex in early pregnancy has already been mentioned.

Clinical Implications.

A. Progesterone and Pregnancy Status. Plasma progesterone and urinary pregnanediol have been measured in a variety of obstetric disorders to prognosticate dysfunction or to establish its presence. Such diagnostic attempts have been less than satisfactory. Probably the primary reason for this is that the hormone concentration can remain in the normal range even with fetal death as long as the utero-placental circulation is intact. Other problems are the wide day to day variation in the same individual and the overlap of values in normal and abnormal gestation. Even when the hormone concentration is definitely subnormal, it is usually the effect of an uncorrectable dysfunction rather than the cause. Therefore exogenous progesterone substitution is

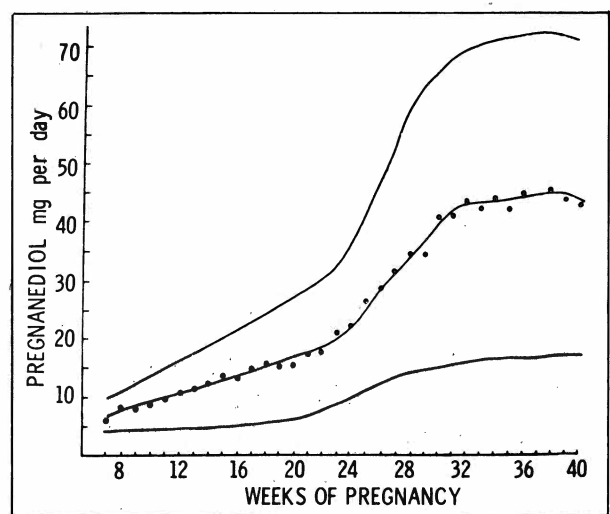


Fig. 6—Pregnanediol excretion in normal pregnancy. The dots represent observed means, the central line fitted means. The upper and lower lines show the 95% probability limits. (Reprinted with permission from Shearman. *J. Obstet. Gynaecol. Brit. Comm.* 66:1, 1959.)

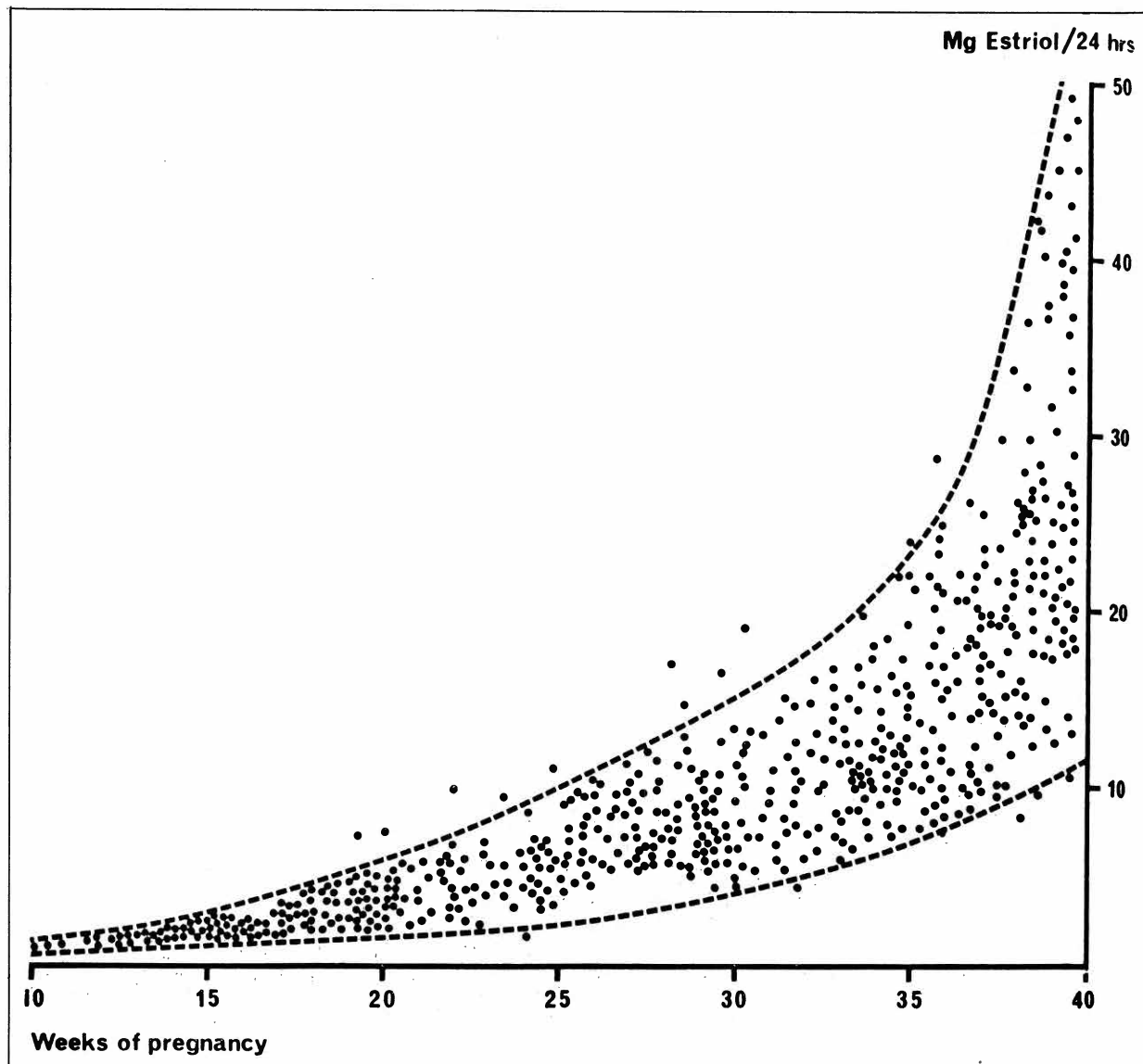


Fig. 7—Urinary excretion of estriol-16-glucuronide during pregnancy in 31 normal women. The upper and lower dashed lines are 95% confidence limits. (Reprinted with permission from Fuchs and Klopper (eds.). *Endocrinology of Pregnancy*, First Edition. New York: Harper and Row, 1971.)

generally of little value. Similar problems are encountered when serial assays for HPL are used as a diagnostic tool.

B. Progesterone and Adequacy of the Corpus Luteum; Abortion. Of probable clinical value are the use of serial plasma progesterone or urinary pregnanediol assays to evaluate corpus luteum adequacy in certain types of infertility and possibly a few cases of first trimester abortion. Although the majority of such abortions are due to uncorrectable causes such as chromosomal defects, a few could be due to corpus luteum dysfunction with disharmonious transition of steroid hormone production to

the placenta. When such corpus luteum inadequacy is incriminated, correction of the infertility or prevention of another abortion may be achieved by insuring an adequate corpus luteum. However, not by the use of exogenous progesterone replacement, but rather by the judicious use of ovulatory inductors such as Clomid® or the gonadotrophins to insure normal follicular maturation which will result in a normal corpus luteum.

C. Progesterone—Term and Premature Labor. Elucidation of the mechanism which institutes labor would enhance our capability to induce labor for medical or convenience reasons and to stop pre-

mature labor. The theory most often advanced to explain the mechanism which institutes parturition is the progesterone-block concept. This maintains that progesterone suppresses myometrial contractility during gestation and labor begins upon withdrawal of the hormone. However, our studies and those of others have not shown a significant and consistent drop in circulating progesterone prior to labor's onset. These findings do not exclude a protective role for progesterone as an effective decrease may occur that is not apparent in the circulating levels. One possibility that we investigated was that the concentration of free and active progesterone decreased with advancing pregnancy because of increased protein binding of the hormone. However, we found the percentage of binding to remain constant throughout pregnancy, which meant that as the total progesterone concentration rose so did the concentration in the bound and unbound fractions. With this negative finding we have turned to studies which may show decreased progesterone levels within the myometrial cells. Our results are too preliminary to draw conclusions.

In spite of our ignorance as to how labor starts, we are not totally devoid of therapeutic agents. Within reason labor can be induced at term with oxytocin. It is much less effective earlier in pregnancy. Prostaglandins such as F2 α appear to be effective at term as well as earlier in gestation. However, on parenteral use in the first 2 trimesters, the therapeutic-toxic difference becomes too narrow. This problem may be overcome by using the prostaglandin locally in the vagina to induce an indicated abortion or premature labor. Lastly, with judicious use of intravenous alcohol in premature labor, the expulsion of the fetus can be delayed a few days to a few months in about 65% of the patients.

D. Estriol and Complicated Pregnancies. The most important clinical consideration at the moment is the value of serial estriol determinations in the management of high-risk pregnancies. While it can be helpful in certain complications of pregnancy such as diabetes mellitus, toxemia, and dysmaturity to evaluate the fetal status, it is not without pitfalls. First the clinician is at the mercy of the quality control of the laboratory doing his assays. Inaccurate results can lead to false security or ill-timed termination of pregnancy. Even with a good laboratory, the results may not always reflect the true status of the pregnancy. Unfortunately, our knowledge of estrogen metabolism in pregnancy is inadequate to explain such discrepancies any better than it can explain why Rh iso-immunized jeopardized preg-

nancies do not show subnormal estriol levels. Even more disconcerting is the fact that excellent clinicians using good laboratories are reporting perinatal losses in diabetic pregnancies no better or even

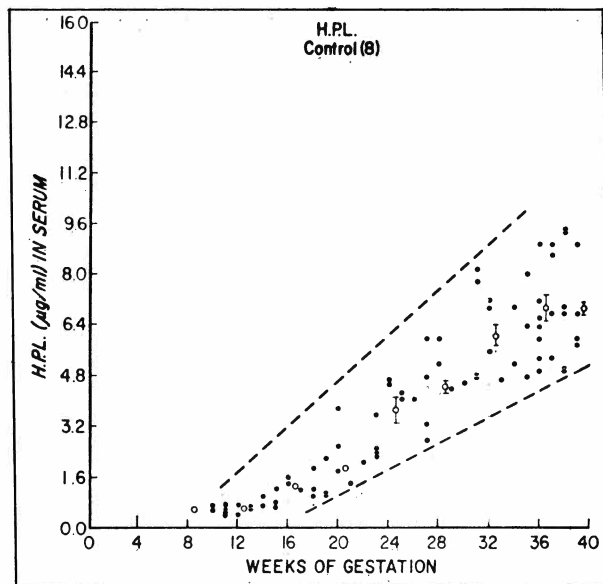


Fig. 8—Human placental lactogen (HPL) in serum. The 80 black dots represent individual values, the open circles represent the means for 4 week intervals and the vertical lines the standard error of the mean. The dash lines show the upper and lower limits of all determinations in the controls. (Reprinted with permission from Samaan, *et al. Am. J. Obstet. Gynec.* 104:781, 1969.)

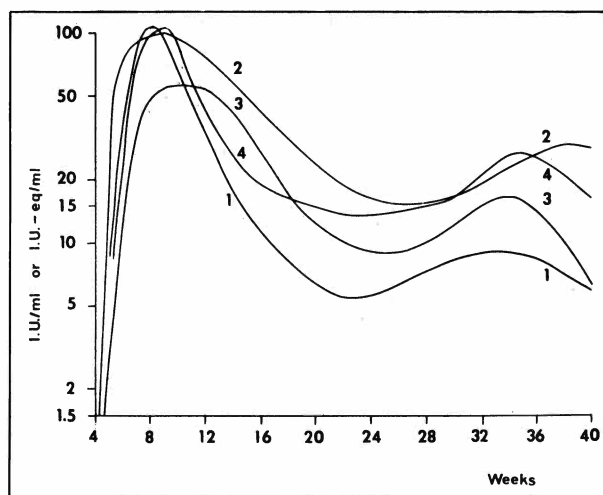


Fig. 9—Mean serum levels of chorionic gonadotrophin in normal pregnancy. The curves are based on results reported by various authors using different bioassay and immunoassay methods. Curve 1: uterine weight increase in rats; Curve 2: ovarian hyperemia in rats; Curve 3: complement fixation; Curve 4: hemagglutination. (Reprinted with permission from Fuchs and Klopfer (eds.). *Endocrinology of Pregnancy, First Edition*. New York: Harper and Row, 1971.)

worse than reputable clinics have reported prior to the availability of this assay. So far there has not been any conclusive evidence that a marked reduction in fetal mortality has been obtained because of estriol determination. In this light, the overzealous utilization of estriol assays as a substitute for rather than an adjunct to clinical management is foolhardy.

As an adjunct to clinical judgment, the literature seems to agree on certain helpful points. These are as follows:

1. Significant day to day variation requires serial assays to determine a mean for each patient.
2. In a suspect pregnancy, weekly or biweekly assays should be done from about the 30th week up to the time of reasonable maturity (about 34th week) at which time daily or every other day determinations should be carried out.
3. In any complicated pregnancy which is 34 weeks or beyond, any precipitous fall from normal levels of urinary estriol and which is verified over 2 or more consecutive days dictates immediate delivery.
4. Chronic low estriol levels in preeclamptic toxemia or dysmaturity do not necessitate interruption unless there is a precipitous drop from the low mean. Such babies left *in utero* may not grow very much, but they do achieve greater maturity.
5. Urinary estriol levels can be expected to be low in mothers with anencephalic mon-

sters or on glucocorticoid therapy for medical reasons.

The development of new specific and sensitive hormone assay methods and the increase in sophistication of metabolic studies has given us an impressive array of biochemical information concerning the physiology and endocrinology of pregnancy. However, the application of this knowledge to the improvement of obstetrical care has been difficult. This should not discourage us as medical science must like the infant learn to crawl before it can walk. Eventually we shall have all the facts needed to obtain the obstetrical results that we all desire. We have had a promising start.

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