THE POSSIBLE ROLE OF HIGH ESTRIOL LEVELS IN PREGNANCY.

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SUMMARY

Estriol production and excretion rise much more than estradiol or estrone in pregnancy. The ratio estriol/estradiol progressively increases in the course of human gestation. Although the mechanism is well understood there is still no understanding of the role played by such changes. Taking into account that estriol has inherent antiestrogenic properties and that the hypothalamus of the fetus and newborn can be experimentally demaged by the administration of estradiol, it is postulated that estriol could protect those neural structures due to its higher affinity of binding to the specific estrogen receptor sites. Since pregnant diabetics frequently have low levels of free plasma estriol while free plasma estradiol and estrone remain normal, it is suggested that these patients offer a good model to test the hypothesis. If their daughters have a higher incidence of menstrual disorders then this might be due to a lower degree of protection of their hypothalamus by estriol during their gestation. If this is the case then it might be justifiable to administer estriol in pregnancy whenever its values are below normal.

Biosynthesis of estriol in pregnancy

For a number of years it has been known that the excretion of urinary estriol increases in the course of human pregnancy.

Estriol (E3) excretion is significantly greater than that of estrone or estradiol (1, 2). Extensive metabolic studies have led to the conclusion that this is due to the supply of a precursor by fetal adrenals (dehydroepiandrosterone sulfate DHEA SO4), which is aromatized by the placenta and later excreted as estriol by the pregnant woman (3,4). Indirect clinical proof of such a metabolic pathway is the low excretion of estriol in the presence of an anencephalic (due to a lack of fetal ACTH resulting in hypoplastic adrenals and thus in an almost complete lack of excretion of DHEA SO4). In a few cases the placenta has been shown to be deficient in aromatizing enzymes (5) resulting in poor estriol biosynthesis from the fetal substrate.

The diagnostic significance of estriol in pregnancy

When there is an intact feto-placental unit (6) (i.e. a normally functioning fetal adrenal and a placenta with good aromatizing potential) a decrease in estriol excretion below the level of normality is considered to be an early indication of fetal distress (7). It might be caused by changes at the placental level (e.g. vascular) which interfere with fetal nutrition, as in diabetics (8, 9), or by fetal disturbances (10). Although the origin of estriol is well understood, as well as the prognostic significance of its low excretion values, the physiologic role played by this weak estrogen is far from clear.

The biological effect of estriol

Estriol is a very peculiar estrogen that has been repeatedly called an “impeded estrogen” (11). It is simultaneously an estrogen and an antiestrogen, depending on the parameter selected for the study of its effect (12).

Thus, if the maturation index of the vaginal epithelium is considered as an end point there is no doubt that an atrophic smear can be changed into an estrogenic smear under the effect of estriol and that the secretion of cervical mucus can be equally stimulated by this estrogen. Nevertheless, the proliferative effect of estriol on the endometrium is rather low as compared with its stimulatory action on the vaginal epithelium (13). Molecule for molecule it is clear that estriol is weaker than estrone or estradiol in terms of biological activity.

Conversely, if estriol is added to a potent estrogen (e.g. estrone) and then injected into an animal there is a significant decrease of the biological activity that would otherwise be observed if estrone had been injected alone (11). Both groups of experiments indicate that estriol has indeed inherent estrogenic and antiestrogenic activities.

On clinical grounds the antiestrogenic properties of estriol have been studied by some investigators in an attempt to treat advanced human breast cancer with apparently good results (14).

We have as well started a preliminary study in ovulatory patients who complain of mastodynia. This symptom is generally considered to be due either to absolute or relative hyperestrogenism; treatment with gestational steroids is frequently followed by improvement of the patient. We are treating some of these patients only with estriol; thus far, the results obtained seem to indicate that this can be a good treatment for those women who ovulate.

The mechanism of action of estrogens

Recent studies of the mechanism of action of estrogens at the molecular level seem to offer a logical explanation for these biological properties of estriol. In summary, cells of target tissues contain a receptor (estrophil) in the cytosol fraction that specifically binds estradiol, as a first step in hormone action (15, 16). This activates other complex mechanisms which end in the stimulation of RNA and protein synthesis. Experimental evidence (15) indicates that estradiol-17β is the active hormone at the molecular level and that estrone might first have to be converted into estradiol before becoming biologically active. These conclusions are derived from the measurement of the affinity of the various natural estrogens to the estrophil as...
compared to their own biological activity.

Estriol cannot be converted either to estrone or to estradiol. Nevertheless it has a high affinity for the estrophil and is able either to block the receptor site (17) or to displace estradiol from its binding site (14, 17).

Since only the estradiol-estrophil complex activates nucleic acid synthesis these experiments may explain why estriol has antiestrogenic properties.

The sexual differentiation of the hypothalamus

One of the major differences between male and female hypothalamic function is that whereas in the former the secretion and/or release of FSH and LH follow a more or less steady pattern, in the latter there is a typical cyclic activity (18). In anovulation associated with above normal plasma testosterone levels gonadotrophin secretion is very similar to the male pattern.

A series of classical experiments (19, 20, 21) have contributed to understanding of hypothalamic sexual development. If testosterone is injected into female 1 day old rats they will develop normally until they reach sexual maturation at the same time as their siblings. However, after a few regular ovulatory cycles they become anestrous and develop polycystic ovaries due to the loss of the normal cyclic activity of the female hypothalamus. This testosterone-induced change in hypothalamic function can, however, be duplicated when estradiol is instead injected under the same set of experimental conditions (22). Molecule for molecule less estradiol than testosterone is needed to obtain the same effects (23, 24).

This observation led to the suspicion that estradiol might be the effective hormone in inducing these experimental effects at the hypothalamus, not only because of its greater potency as compared with testosterone, but also in view of the fact that the hypothalamus has great aromatizing capacities (25, 26). Estradiol could thus be biosynthesized from testosterone at the hypothalamic level: this would explain the lower potency of the androgen as compared to estradiol. Other evidence for this concept derives from the experiments of McDonald and Doughty (27) who reported that when clomiphene citrate is given either with testosterone or estradiol no changes can be induced in hypothalamic function. These results indicate that clomiphene, as an antiestrogen, blocks the effect of estrogen, be it injected or biosynthesized from testosterone at the hypothalamic level: clomiphene has not been shown to be antiandrogenic.

Fetal protective mechanisms

It is important to mention how the fetus exists in an environment containing very large amounts of hormones. Thus DHEA-SO₄, the estriol precursor secreted by fetal adrenals, is not converted to more potent androgens because the fetus lacks the necessary enzymes, as demonstrated by Mancuso et al. (28). An alternative mechanism is for protection against androgens is the efficient conversion of androgens to estrone and estradiol by the placenta (29).

However, since there is no placental barrier to prevent the transfer of estrone and estradiol from the placenta to the fetal compartment (29) there is a need for other mechanisms to protect the fetus from estrogens since at the end of pregnancy it is exposed to large amounts of estradiol (30, 31). The 16-hydroxylating enzymes in the fetal liver may be involved in protecting the fetus against estradiol exposure by converting DHEA into estriol which is less available for conversion to estrone or estradiol (29). The importance of these fetal mechanisms is stressed by experimental evidence indicating that the placental production of estradiol and the amount of estradiol to which the fetus is exposed during pregnancy are important factors for its normal growth and development (32).

The role of estriol in pregnancy. The hypothesis

From the data presented above it is now possible to discuss a role for estriol on pregnancy. It is during the last trimester and the very early neonatal period that the hypothalamus seems to be most sensitive with regard to its sexual differentiation. It is precisely in the later period of gestation that estriol excretion rises dramatically while estrone and estradiol keep to approximately the same rate of increase that they had previously followed. Could it be that estriol, as an antiestrogen, has a protective role in the hypothalamus being bound to the estrophil and preventing the high levels of estrone and estradiol exerting effects at that level?

Testing the hypothesis

From the data reported in the literature if one calculates the ratio of estriol to estradiol and estrone or estriol to estradiol alone from the first to the third trimester of pregnancy it is clear that the values increase as term approaches (33,33a). This could mean that more estriol is needed at the target organ level to counteract the effects of the rising production of estradiol and estrone. It is necessary to point out that other studies (34) suggest that plasma estriol in pregnancy is mostly conjugated and thus incapable of counter acting the effects of unconjugated estradiol.

Some case histories may support this concept. Rakoff (35) described one patient who developed polycystic ovaries and whose mother had been inadvertently treated with androgens while already pregnant. We have studied one patient with high plasma testosterone levels, hirsutism and oligomenorrhea, whose mother had taken stilbestrol during the first trimester of gestation. The same type of treatment was reported by Herbst et al. (36) to be responsible for a high incidence of adenocarcinoma of the vagina in the offspring. This group of patients offers a further opportunity for study of the effect of estrogens administered during pregnancy on postpubertal hypothalamic-gonadal function.

These cases may be models of those instances where an absolute or relative decrease of estriol in relation to the circulating levels of potent estrogens or androgens in pregnancy might result in a dysfunctional hypothalamus.

Townsend et al. (37) found in a diabetic patient low levels of plasma estradiol associated with normal levels of estrone and estradiol. It is known that diabetic patients frequently have low levels of urinary (38) and plasma (9) estriol. Therefore it would be extremely interesting to do a prospective study in order to see if female born from diabetics who had "low estriol/normal estradiol and
estrone" values in pregnancy are more prone to anovulation and polycystic ovarian disease than their matched controls.

Those cases where there is a drop in plasma or urinary estrone, while estrone and estradiol stay within the normal range, would theoretically be more important than those where the three estrogens fall. I therefore suggest that whenever a low urinary estrone is found one should determine weekly, both in urine and plasma, the ratio of estradiol to estradiol and estrone. If this is done a generation later my hypothesis may be proved or disproved!

If this concept proves to be acceptable then it might be wise to administer estradiol during pregnancy when its level is low to help protect the fetal hypothalamus. This would of course be in addition to the other usual measures for overcoming or stopping fetal distress.

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