Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 17 (4), pp. 263–266 (1976)

The effect of allyloestrenol on human chorionic somatomammotropin synthesis of the placenta during normal pregnancy

By

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(Received 5 March, 1976)

The effect of allyloestrenol on human chorionic somatomammotropin (HCS) level in healthy pregnant women in the fifth to eighth months of gestation has been studied by radioimmune techniques. The HCS level showed a significant increase within 10 to 12 days. According to the results, allyloestrenol exerts a stimulating effect on the placental steroids as well as on HCS production.

The physiological role of the corpus luteum of pregnancy (true corpus luteum) and endogenous progesterone in disturbed gestation is well-known. For a long time progesterone offered the only possibility of protective hormonal therapy in the treatment of threatened abortion. The efficiency of this therapy was, however, considerably limited by its parenteral administration, rapid absorption and loss of activity as well as by the circumstance that even large amounts exerted a moderate effect [9].

To solve the problem, substances of progestative effect were sought for which would be more suited for therapy than crystalline progesterone. Two groups of new compounds were promising, the esters of progesterone, and the 19-norsteroids. The 19-norsteroid derivatives were originally synthetised for the inhibition of ovulation, but among them there was a compound, allyloestrenol, which had a marked progestative action instead of the ovulation-inhibitory effect. Its adequate oral absorption was an important advantage over the pregnancy-protecting substance 17-alpha-hydroprogesterone capronate synthetised by Junkmann [6].

Allyloestrenol has no hypophysis inhibiting effect and does not depress the action of the ovary or of the adrenal cortex. Its progestative potency in the carboanhydrase or the Clauberg test is of the same order of magnitude as that of progesterone and is much more efficient than the other 19-norsteroids.

Borglin [1, 2, 3] was the first to report on excellent therapeutic results with allyloestrenol (Gestanon®, Organon) in threatened and habitual abortion. Subsequently, numerous authors

[5, 7] published their favourable experiences with orally administered allyloestrenol.

The first important data concerning the mechanism of action of allyloestrenol were published by Szontágh et al. [10]. According to their histomorphological and histochemical examinations, the drug enhanced the secretory activity of the trophoblast, manifesting itself with an increased secretion of maternal pregnanediol and oestrogen. In the course of allyloestrenol therapy the syncitial layer displayed a considerable hyperactivity and this circumstance might be the basis of the increase in oestriol and pregnandiol excretion. Sas et al. [7] observed that after allyloestrenol treatment, 25% of the newborns weighed more than 3400 g at birth, and concluded from this fact that the drug ensured a favourable metabolic rate in these fetuses.

Thus it seemed interesting to investigate the connection between allyloestrenol treatment and the secretion of HCS, especially as earlier we have shown a correlation between fetal and placental weight and the HCS concentration in maternal serum [4].

Material and Methods

Examinations were carried out in 15 normal women in the second and third trimester of an undisturbed pregnancy, who had had no previous allyloestrenol therapy. The patients received 10 mg of allyloestrenol t.i.d. for 12 days. This amount was higher than the usual therapeutic dose, but the aim was to investigate the functional answer given by the 6 to 8 months old trophoblast to that dose. Estimation of HCS in maternal serum was done before and on the third, sixth, ninth and twelfth days after treatment.

The control group consisted of 15 normal pregnant women of identical gestational age who received no allyloestrenol nor any other pregnancy-preserving drug. In this group, serum HCS determination took place at the beginning and at the end of the 13-day period.

HCS determinations were carried out in 0.1 ml maternal serum, by radioimmune assay with the Phadebas kit (Pharmacia, Uppsala).

Results

Figure 1 shows the mean serum HCS level ± S.D. in both the treated and the control group, as evaluated by Student's t test. A significant difference was found between the two groups to the advantage of the treated one ($p < 0.01$). Thus, in the treated group during the period of observation the serum HCS values were

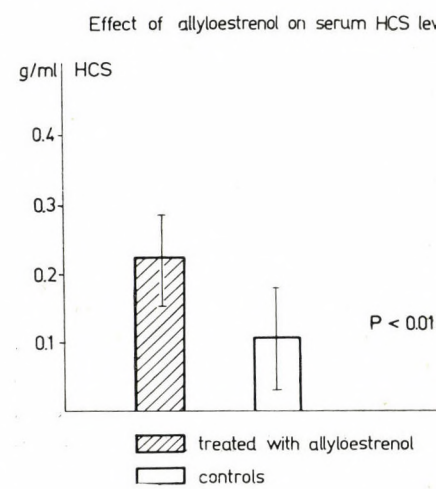

Fig. 1

more elevated than the physiological rate of increase with the progress of gestation in the control group. The criterion of variance was fulfilled insofar as the identity of the squares of scattering was established $\frac{s_1^2}{s_2^2} = 1.138$; $F = 3.57$). Fulfilment of the consequence of normal distribution requires the analysis of further cases.

It follows that allyloestrenol is capable of significantly increasing the HCS concentration in maternal serum, thus to enhance HCS synthesis by the syncytiotrophoblasts within the short period of 12 days.

Discussion

It is known that the pregnancy-preserving effect of allyloestrenol asserts itself by the normalization of endogenous progesterone production [10]. Semm and Bernhard [8] found that the oxytocinase level was considerably increased by allyloestrenol. The results of our recent work also seem to prove the "placentotropic" effect of the drug which, accordingly, has the ability to increase the serum level of the HCS excreted by the syncytiotrophoblast.

The observations that after allyloestrenol treatment mean birth weight of the newborn is higher [7] and that there is a correlation between the weight of the newborn and the HCS level of the maternal serum [4] are closely connected with the fact that allyloestrenol is able to stimulate the synthesis of HCS beside placental steroid production. The elevation of the endogeneous progesterone level as well as the increase of oxytocinase production result in the first place in the prolongation of gestation, whereas the increased HCS production seems favourably to influence the intrauterine development of the fetus.

In addition to the known clinical results, the data enumerated above may call attention to the possibility that allyloestrenol might be suited not only for the therapy of threatened and habitual abortions and premature delivery, but also for the successful therapy of chronic placental insufficiencies of various origin and of some of their consequences to the fetus.

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