THYROTROPIN IN PLACENTA AND FETUS*

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Certain functional relationships are known to exist, between the maternal and fetal thyroid glands. Whether or not thyroid stimulating hormones (TSH) takes part in this relationship is a problem of interest. In the present studies, special attention was paid to the possibility that TSH may be produced in the placental tissue since reports on this subject have been limited and it is an unknown area. We have tried to investigate the problem by applying the chick assay method, and we have also devised a method of extraction of TSH.

EXPERIMENTS AND RESULTS

Placental TSH

Placental tissue, removed immediately after delivery of new borns, was macedrated by an electric mixer and lyophilized. After our previous report (Ueda and Mori, 1959; Ueda et al., 1962) that the extraction of TSH must be done in a neutral medium, we adopted the method of Bates-Condliffe (1960). By their method, we were able to recover 85% of TSH from the placental tissue. The chick method (Bates and Cornfield, 1957; Ueda et al., 1961) was chosen for the estimation of TSH. TSH was extracted from normal placenta and then assayed. As indicated in Table 1, the concentration was extremely low, from 14 to 17 μ units/g. Considering the suggestion of Sulman and Bergmann (1953) that extractions of gonadotropin and ACTH-like substance from placenta must be done within half an hour after delivery, we examined a placenta removed by caesarean section. The concentration of TSH found in this fresh placental tissue was extremely low: 16 μ units/g. This figure is the same as was found in placental tissue expelled spontaneously. As a precaution, aliquots of the same materials were assayed by the McKenzie method (1958). The result was the same as that obtained with chick method (Table 1).

Blood TSH of pregnant woman

For extraction, Bates' and Condliffe's method (1960) was employed. The chick method was used to determine TSH. Blood TSH estimation as listed in Table 2 showed 40 μ units/ml in new born baby, 30 to 160 μ units/ml in normal

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male adult and 60 to 140 µ units/ml normal female adult, while 60 to 190 µ units/ml in pregnant woman.

In estimating placental hormones, it should be borne in mind that the total amount of hormone contained in placental blood must be considered. According to Salhanick et al. (1956) roughly 10% of blood contained in placenta by weight ratio, however, following method of cyanomethohemoglobin by Crosby et al. (1954), our finding of an estimated blood amount left in placental tissue was found to be 15 to 35%. Hence, TSH could be estimated keeping in mind the blood TSH level and blood volume remaining in placenta. It was found that

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**Table 1. TSH content in human placenta**

<table>
<thead>
<tr>
<th>Case</th>
<th>Bates's method</th>
<th>McKenzie's method</th>
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<td></td>
<td>Normal delivery</td>
<td>Caesarean section</td>
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</table>

Mean values: 17 ± 3.4 (µ units/g ± S.D. *)

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**Table 2. TSH content in human sera**

<table>
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<th>Normal male adult</th>
<th>New born baby</th>
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Mean values: 110 ± 41 (µ units/ml ± S.D. *)

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* S.D. Standard Deviation
the placental TSH value barely reaches that in placental blood. From this fact it is not likely that TSH is produced in the placenta as suggested by Phillip (1955) and Akasu et al. (1955).

**TSH in the pituitary in pregnancy**

As already pointed out, it is of marked interest to study the reason for this elevation of blood TSH during pregnancy. An attempt was therefore made to isolate TSH and gonadotropin from the pituitaries of pregnant and non-pregnant rats by DEAE-cellulose column chromatography. Gonadotropic activity was determined by the mouse-uterine weight procedure. It was found that TSH content of the pituitary of pregnant rat was 12 μ units/mg which was far above 1 μ unit/mg in non-pregnant rat pituitary. On the other hand, the gonadotropin content was much higher in non-pregnant than in pregnant rats (Fig. 1). From this result, presumably the elevation of the TSH level of pregnant women’s blood is attributable to the pituitary gland rather than to the placenta. This fact also substantiates the fact that the secretory mechanism of TSH is diametrically opposed to that of pituitary gonadotropin during pregnancy, though their biochemical characters are very much alike.

![Fig. 1. TSH-activity and G-activity in the pituitary gland of non-pregnant and pregnant rat](image-url)

**Fetal thyroid gland**

The fetal thyroid glands in various stages of gestation were examined. The fetuses were obtained legal abortion and they were studied histologically. The epithelial cells of the thyroid gland in the first trimester were characterized by large deeply staining nuclei and contained no follicles. At the 4th month majority of cells were parenchyma arranged radially in the cellular cords of the thyroid gland (Fig. 2). There were many mitotic figures in the cells and colloid
could be detected only in the periphery at this time. At 5th month, these appear throughout the gland (Fig. 2). During this stage there was little differentiation but by the 8th month, lobulation seemed to be completed (Fig. 3). The epithelial cells are by then cuboidal or flat. In a short time more flat cells multiply and folliculas appear and then develop into the final glandular structure.

**Placental transmission of TSH**

Development of the fetal thyroid gland continues up to birth when it is morphologically complete. Whether or not glandular growth is under the influence of maternal TSH is still an open question. A study concerning placental transmission of TSH was carried out with rats. Pretiron (Schering Co’s thyrotropin) was administered to 4 groups of 200 g pregnant rats. The control group received saline injection while the 3 experimental groups received 100 μ units/day for 7 days.
1000 μ units/day for 2 days and 50000 μ units/day for 1 day respectively. Histological examination of the fetal thyroids showed no direct influence of TSH. This result suggests that this particular protein hormone does not pass through the placenta. This is in agreement with the finding of Crepax (1949), Peterson and Young (1952), Nikitovitch and Knobil (1955) and Knobil and Josimovich (1959). So we can say that growth of rat's fetal thyroid gland is in no way related to influence of maternal TSH.

**TSH in the pituitary of human fetus**

Since maternal TSH has nothing to do with growth of the fetal thyroid gland, we investigated the TSH concentration in the fetal pituitary. The materials used were fetal pituitaries obtained by legal abortion. These fetuses were measured by their crown-rump length. Their age was determined by the time of the last menstrual period. The hormone extracted from one part of the fresh fetal pituitary were assayed by the chick method. Another part of the gland was examined histologically. Quantitative estimation of TSH in the anterior pituitary of 28 fetuses was possible only after 12th week of gestation (Fig. 4).
The average figure obtained from the 15th to the 18th week of gestation was 2 μ units/mg, from the 18th to the 22nd week of gestation was 3 μ units/mg and by the 23rd week of gestation, it rapidly increased to 8 μ units/mg; by the 8th or 9th month of gestation, the values ranged from 9 to 12 μ units/mg which is close to the value in newborn fetus.

There is a marked increase of TSH in the fetal pituitary at the 23rd week of gestation, while at the same time there is an increase of PAS positive granular cells in the gland (Fig. 5). Moreover at that time the lobulation of the fetal thyroid gland is about completed. From these facts it is assumed that development of the fetal gland undoubtedly depends on TSH from fetal pituitary.

**SUMMARY AND CONCLUSION**

1. Extremely minute quantities of placental TSH could invariably be detected in placental tissue whether it was spontaneously delivered or removed at the time of caesarean section.

2. Blood TSH level of pregnant women was far higher than those of normal male or female adults.

3. The quantity of TSH in the pituitary of the pregnant rat was higher than in the non-pregnant, while gonadotropin was lesser in amount during the period of gestation than in the non-pregnant period. Hence, an assumption is made that the higher blood TSH level of pregnant women implies hypersecretion of TSH from the anterior pituitary.

4. The human fetal thyroid gland is filled with a colloidal substance early in the 4th month of gestation, and by the 8th month it develop lobes. The glandular organ structure is morphologically complete by the time of birth.

5. The fact that we have failed to observe histological differences between fetal thyroid glands of pregnant rats administered a TSH product and a group...
of animal without such a drug seems to substantiate the interpretation that no TSH is transmitted across the placenta.

6. Human fetal TSH in the pituitary could be estimated as soon as 12th week of gestation is past, and that the thyroid lobules are formed by the 23rd week of gestation at which time the TSH content increases rapidly with simultaneous appearance of PAS positive granules. Development of the fetal thyroid, therefore takes place solely under control of fetal TSH.

The site of origin of maternal TSH during pregnancy is the pituitary, not the placenta. It is assumed that the fetal pituitary-thyroid system is unrelated to the maternal one and possesses an independent functional capacity.

The pituitary-gonad system is in a resting state during embryonic life, but the pituitary-thyroid system assumes its function prior to term. It is thought that the difference in functional character of two systems during an embryonal period may be related to the dissimilarity of maternal secretory mechanism between gonadotropin and TSH in pregnancy.

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REFERENCES