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Article

Treatment with dexamethasone's effects on pregnant women and their fetuses Guinea pigs' Thyroid and Adrenal Hormones

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Abstract
Among the common small laboratory animals, the guinea pig has a thyroid and adrenal hormone pattern most similar to that in humans. Daily administration of 10mg Dexamethasone s/c from 55 days of pregnancy for 6 days resulted in a depression of fetal body and organ weight and depression of maternal and fetal plasma T4, T3, and cortisol concentration. However, an increase in fetal plasma T4 and T3 concentration rates suggests enhanced de-iodination of T4. In human fetuses, late in gestation, a rise in plasma cortisol may not be necessary for organ maturation. Considerable species differences have been observed concerning the type of hormone secreted by the adrenal cortex.

Keywords: Dexamethasone, fetal cortisol, Thyroxin, Triiodothyronine, Guinea pigs.

Introduction

Among the common small laboratory animals, the guinea pig has thyroid and adrenal hormone patterns most closely approximated in humans. The development of adrenocortical secretion in the fetus, a pregnant female guinea pig, has been studied. In pregnant guinea pigs and their fetuses ,plasma T4 and T3 levels were decreased during the few days of gestation when fetal and maternal plasma cortisol concentrations were high. The synthetic glucocorticoid dexamethasone was administered to investigate the cause of this decrease further.

Materials and Methods

Dexamethasone (Decadron MSD LTD) was administered daily to pregnant guinea pigs on day 55 to 60 days of gestation to increase plasma glucocorticoid activity, which resembled that generally seen in late gestation. The treatment effects were observed on maternal plasma concentrations of cortisol, thyroxin (T4), triiodothyronine (T3) and fetal plasma of cortisol, T4 and T3. The fetal body weight, thyroid, adrenal and pituitary, and placental weights were recorded. After controlled mating, female guinea pigs from the breeding colony were maintained in a routine environment of the colony. Dexamethasone in a dose of 10mg (s/c) daily from day 55 to day 60 of gestation. On gestation day 60, the last injection was given six hours before sampling began. A blow to the neck killed the guinea pigs, and blood was quickly collected into an EDTA tube. The fetuses were quickly bled by cardiac puncture. Fetal carcasses and placenta, adrenal and pituitary were

removed, cleaned of surrounding connective tissue and weighed on an Oertling balance.

The adrenal and thyroid glands were frozen at -20oC until assay. Five ml of blood were collected from the mother by cardiac puncture. Blood samples were transferred to EDTA tubes and centrifuge immediately. The plasma was aliquot and stored at -20C until assay. Case 411 Analyzer device by Roche company works with technology Electrochemical lumuno assay. ECL technology for immunoassay analysis. For plasma thyroid hormone. Treated groups have been compared with normal as control. All results have been presented as the mean ± the standard error of the mean where n= the number of samples in each group. Significant limits have been determined using Students' t-testing. P≤ 0.05 were considered significant.

Results

The absolute weight of the left adrenal and thyroid glands in the dexamethasone-treated fetuses was significantly (P ≤ 0.001) less than those of untreated fetuses. The relative weights (mg/100 g body weight) were also significantly less (P≤ 0.05) in treated fetuses. Fetal body weights of dexamethasone-treated fetuses were significant (P≤ 0.01)—less than those of untreated fetuses. There are no significant differences in the pituitary and placental absolute or relative weights, as shown in Table 1. There were no signs of abnormal development.

	Body weight	Placental WT		Thyroid WT		Adrenal WT		Pituitary WT	
		Mg	gm/100gm body weight	mg	mg/100gm body weight	mg	mg/100mg body weight	Mg	mg/100gm body weight
Normal	57.0 ± 0.9 (26)**	4.2 ± 0.2 (12)	7.9 ± 0.4	21.2 ± 0.6 (26)***	37.8 ± 1.2 *	9.9 ± 0.5 ***	17.2 ± 0.9 *	2.4 ± 0.2	4.3 ± 0.3
Dexa	52.0 ± 1.8 (17)	3.8 ± 0.3 (17)	7.2 ± 0.3	17.5 ± 0.8 (17)	33.8 ± 0.9	7.4 ± 0.3	14.3 ± 0.6	2.0 ± 0.2	3.9 ± 0.5
SE=Standard Error ; *= enormous quantifiable differentiation (P<0.05)									

Table 1. Comparison between the relative and absolute weight of thyroid. Adrenal and pituitary glands dexamethasone-treated and normal fetuses (mg/100 gm body weight).

Changes in cortisol concentration:- The cortisol concentration of the adrenal gland (ng/100 mg adrenal tissue) was significantly (P≤0.01) less in the fetuses exposed to dexamethasone than those untreated of the same age. There was no apparent effect of dexamethasone administration on maternal or fetal plasma cortisol concentration, Table 2. Cortisol levels begin to climb during the second trimester, but they do not reach their peak until late pregnancy. In the last weeks before birth, cortisol levels are 2 to 3 times higher than normal1 in human pregnancy. Maternal plasma cortisol concentrations are elevated and reduced—change in thyroid hormone concentration. Thyroid hormone levels in the maternal and fetal plasma were less in dexamethasone-treated animals. Administration of dexamethasone resulted in a significant decrease (P≤ 0.0001) in the fetal plasma thyroxin concentration, as shown in Table 2. A significant (P ≤ 0.001) increase in the thyroxin concentration

(ng /mg tissue)was observed in the thyroid glands of dexamethasone-treated fetuses compared with untreated animals.

	Fetal Plasma ng/ml	Fetal gland ng/100mg tissue	Maternal plasma ng/ml
Normal	248.0 ± 23.6 (8)	1470 ± 119.0 (11) **	**3187 ± 13.0 (4)**
Dexa	232.6 ± 16.0 (15)	821 ± 142.0 (17)	**2705 ± 394.0 (4)**
SE=Standard Error ; *= enormous quantifiable differentiation (P<0.05)			

Table 2. Changes in the maternal plasma, fetal plasma and adrenal gland cortisol concentration.

The dexamethasone treatment also caused a significant ($P \leq 0.05$) decrease in the maternal plasma T4 and T3 concentrations of the 60-day pregnant guinea pigs compared with untreated pregnant animals, as listed in Table 3. No significant difference was found in the plasma T3/T4 ratio between the two groups Table 4. The T3 concentrations in the fetal plasma were significantly($P \leq 0.05$) lower in the dexamethasone-treated fetuses compared with untreated animals. The plasma T3/T4 ratio in the dexamethasone-treated fetuses was significantly ($P \leq 0.001$)higher than that of regular 60-day-old fetuses Table 4.

Fetal T4	T4/Gland ng/mg Tisse	Fetal T4 %
34.90 ± 2.00 (16) ***	0.99 ± 0.10 (6) ****	**0.41 ± 0.07 (5) ******
17.5 ± 30.00 (13)	1.69 ± 0.10 (13)	**0.16 ± 0.04 (6)**
SE=Standard Error ; *= enormous quantifiable differentiation (P<0.05)		

Table 3. Maternal and fetal plasma T4 concentration (ng/ml) and fetal % FT4.

	Fetal	Maternal	Maternal T3/T4 Ratio	Fetal T3/T4 Ratio
Normal	1.7 ± 0.1 (16) *	2.5 ± 0.1 (4) *	0.12 ± 0.01 (5)	**0.05 ± 0.01 (19) *****
Dexa	1.38 ± 0.06 (14)	1.92 ± 0.20 (4)	0.16 ± 0.03 (4)	**0.12 ± 0.02 (14)**
SE=Standard Error ; *= enormous quantifiable differentiation (P<0.05)				

Table 4. Fetal and maternal plasma T3 concentration (ng/ml).

Discussion

The effects of dexamethasone treatment on plasma hormone levels in pregnant and fetal guinea pigs were investigated in this study. The decrease in fetal body and organ weight observed in this study is supported by observations [3 and 4]. They

studied the effects of dexamethasone in species having short gestation (mice, rats, and rabbits) and documented both general body and specific organ growth inhibition. Dexamethasone was demonstrated in pregnant monkeys [5,6] for several weeks and reported retarded fetal growth and decreased adrenal weights. Glucocorticoid treatment at such dose levels reduces placental weight as listed in Table) Furthermore, it may interfere with placental function. This was also reported by [3] and poses a significant risk for the fetuses. In adult male guinea pigs. Prolonged dexamethasone treatment has no effects on body weight[7]. Early in pregnancy, administration of a high dose of dexamethasone lead to alteration in placental growth8 and fetal retardation growth late in gestation[9]. The adult male guinea pig treated with dexamethasone7 reported a decrease in adrenal weight, cortisol concentration, and serum cortisol. Other species have also reported a decrease in maternal and fetal plasma and adrenal cortisol. In monkeys, administration of dexamethasone for several weeks decreased basal levels of maternal cortisol5. Dexamethasone treatment of pregnant women during the third trimester causes a decreased cortisol concentration[10]. There is abundant evidence that glucocorticoids can affect the secretion of several pituitary hormones in addition to ACTH, including TSH [11], and they can inhibit the hypothalamus-pituitary-adrenal system[12]. This interference with the gonotrophic influence is manifested in the present study by decreased fetal adrenal weight and a decrease in adrenal gland cortisol concentration. Fetal adrenal cortisol release is probably depressed by the high circulating levels of exogenous dexamethasone. Thus, this study's lower fetal cortisol values are likely primarily of maternal origin. The cortisol transfer rate across the placenta increases with gestational age [12]. The high level of CBG and the low MCR in the fetal guinea pig[13] and the stress of dexamethasone injection could play a role in maintaining the high cortisol levels in the maternal and fetal guinea pigs. There was a decrease in the plasma T4 and T3 of the maternal and fetal guinea pig, as described in Table 2. after dexamethasone treatment. A reduction in serum T4 and T3 T3 was also reported in control human subjects and patients after dexamethasone treatment [14,15,16]. Furthermore, [17] suggested that the effect of dexamethasone treatment was partly mediated by depression of pituitary TSH and, hence, thyroid hormone secretion. Also, an increase in the rT3 after dexamethasone treatment was reported by [18, 19, 20]. They found the increase in the serum rT3 on the first day of dexamethasone treatment to be similar to the fall in T3. They suggested that the peripheral metabolism of T4 is directed to produce rT3 rather than T3. A later fall in T4 and T3 may be attributed to decreased plasma TBG concentrations. Fetal plasma T3 may be derived from two sources (i) secretion by the fetal thyroid and (ii) T3 release from peripheral tissue after monodeiodination of T4.In the fetus, cortisol can increase plasma T3 concentrations by increasing the production rate from T4 in the tissues [21]. The data of the present study suggest that the endogenous glucocorticoid shares the effects of dexamethasone on plasma thyroxin. The high glucocorticoid levels could affect the secretion and metabolism of the maternal and fetal thyroid, reducing fetal body weight and circulating T4 and T3 levels in the near term[22]. No severe side effects have been reported after administering corticosteroids during pregnancy except for a reduction in the fetal body's fetal breathing movement. Also, pregnancy is a stress of thyroid dysfunction in pregnant women .high. Subclinical hypothyroidism occurs in 10% of all pregnancies, effect 1- anemia 2-low birth weight, and mental retardation of neonatal 22. These effects may be the result of (I) changes in the liver activity mono-deiodinase, (ii) influence on the hypothalamus-pituitary-thyroid system to inhibit TSH production, and so reduce thyroxin synthesis and secretion from the thyroid gland, (iii) direct effect on the thyroid gland. In the fetuses, the T3/T4 ratio increased significantly compared with normal fetals of the same gestational age, Table 3. This means that there is greater T3 production from the reduced T4 level. The failure of high doses of

dexamethasone to induce parturition when administered to the mother agrees with observation 23, which showed that parturition occurs regularly after dexamethasone treatment. In preterm delivery, it prevents respiratory distress and neonatal mortality. Fetal cortisol is not a maturation.

Conclusions

In human fetuses, late in gestation, a rise in plasma cortisol may not be necessary for organ maturation. Considerable species differences have been observed concerning the type of hormone secreted by the adrenal cortex.

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