Increased risk of congenital hypothyroidism due to prolonged use of synthetic progesterone during pregnancy

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Abstract

Until the 10th week of pregnancy, the corpus luteum produce the most of progesterone hormone. Zinc and potassium allow the thyroid hormone to enter the cell and then to be converted to the active form known as T3. Estrogen can cause copper retention if zinc or progesterone levels are too low. The aim of this study is to estimate the effect of synthetic progesterone taken during pregnancy on the increasing risk of congenital hypothyroidism in newborn. A case control study comparing neonates born to mothers whom received synthetic progesterone during pregnancy to neonates of mothers with no history of receiving synthetic progesterone. Neonates with abnormal thyroid function test were recorded. The serum values of T4, T3, TSH were done for all included mothers to exclude any thyroid disease. Mothers with suspected thyroid disorders, use of antiseptics, drugs, or any agents containing iodine were not included. Preterm neonates and those with suspected thyroid agenesis (by thyroid ultrasonography) were also not included. Women received synthetic progesterone had neonates with abnormal thyroid function test. This is significantly associated with the timing and duration of synthetic progesterone use in gestational period. In conclusion; the use of synthetic Progesterone during gestational period is associated with increased risk of congenital hypothyroidism.

Keywords: Progesterone; Thyroid function test; Congenital hypothyroidism

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Introduction

In pregnancy, the role of progesterone is unclear; however, it is known that the effects of progesterone on the myometrium are to suppress the action of estrogen by inhibiting the replacement of cytosolic estrogen receptors and it exerts a direct effect on the biosynthetic processes of the uterus through its own cellular receptor [1]. In women,

the role of progesterone withdrawal as a mechanism of parturition has been questioned because maternal, fetal and amniotic fluid concentrations of progesterone are sustained before the onset of labor and delivery [2]. Nevertheless, the progesterone withdrawal theory remains a leading hypothesis because no other mechanism for the onset of human parturition has been definitively established and because synthetic anti progestins stimulate myometrial contractions [3]. Whereas inhibitors of 3B-hydroxysteroid dehydrogenase, which lower systemic progesterone levels, induce labor and delivery in women [4]. Progestins are available in *natural* or *synthetic* formulations for oral, intramuscular or vaginal administration (in the form of a suppository or gel). *Natural* (micronized) progesterone is an exact duplicate of the progesterone produced in the corpus luteum and the placenta. It is therefore more readily metabolized by the body and is associated with minimal side effects. The two natural progesterone includes progesterone and 17-hydroxyprogesterone. The plasma concentration will depend on the dose and route of administration [5]. *Synthetic* progestins are progesterone derivatives and nor testosterone derivatives; its chemical structure is very similar to that of the natural progesterone. 17 alpha hydroxyprogesterone caproate (17OHP-C) is a 17-hydroxyprogesterone derivative; it is the most commonly used synthetic progestin given intramuscularly. It has been isolated from both adrenal glands and corpora lutea. The synthetic corporate ester is inactive when given by mouth but works as a long-acting progestin when administered intramuscularly. Pharmacokinetic studies have shown that once-weekly IM administration of 17OHPC would provide continuous systemic serum levels of 17OHP-C. The half-life of 17OHP-C was estimated to be approximately 7.8 days [6]. The route of administration plays an important role in the drug's safety and efficacy profiles. Oral progesterone has not been used for prevention of PTB because of its first-pass hepatic metabolism, lack of efficacy data, high side-effect profile and extreme variability in plasma concentrations. Transvaginal administration of progesterone avoids first-pass hepatic metabolism and is associated with rapid absorption, high bioavailability, and local endometrial effects [7]. It has been shown to provide higher and more sustained progesterone concentrations and is the preferred route of administration in many cases. Although this route offers no local pain and fewer side effects, it is associated with variable blood concentrations [8]. Progesterone aids in the retention of zinc and potassium in our cells. Zinc and potassium

allow the thyroid hormone to enter the cell and then to be converted to the active form known as T3. Further, progesterone facilitates the action of thyroid hormone. Estrogen is known to interfere with thyroid hormone and increase fat storage. Progesterone has been known to do the opposite. It aids thyroid action and encourages the use of fat for energy. Estrogen is also associated with copper. Copper is required for the synthesis and release of estrogen. Estrogen can cause copper retention if zinc or progesterone levels are too low. Copper has been found to be an antagonist of thyroid hormone. Abnormally elevated calcium levels in the tissue correlate with elevated copper. It appears that calcium and copper can elevate together and then block the effects of thyroid hormone. So that, a progesterone-estrogen imbalance can interfere with thyroid function. When progesterone is low, and estrogen is dominant (even when TSH blood levels are normal), if symptoms of hypothyroidism are present, high estrogen levels could be the cause. [9, 1].

Patients and methods

It is a case control study includes cases diagnosed in Al- Hussein pediatric hospital in AL-Diwaniya city between April 2011 till February 2016. A 2218 neonates were screened, 43.5% (965) were newborn of mothers who had a history of threatened abortion in the first trimester and Synthetic progesterone treatment (as injection or tablet or both) are used, and we classified it as (group 1). 3.21% (31) patients of group 1 had intact glands in thyroid ultrasound. Of these 31 patients, 54.84% (17) have transient hypothyroidism as clinical and laboratory follow up show normal thyroid profile after 1 month of withdrawal of treatment. The remaining 45.16% (14) patients were diagnosed as permanent hypothyroidism as a trial of withdrawal of replacement therapy was associated with a reduction of T4 levels. The remainder of mothers, 56.5% (1253) (group 2) had no history of taking Synthetic progesterone treatment and shows only 0.01% (1 newborn) with abnormal thyroid function test. The serum values of T4, T3, TSH were done for all included mothers to exclude any thyroid disease. Mothers with suspected thyroid disorders, use of antiseptics, drugs, or any agents containing iodine were not included. Preterm neonates and those with suspected thyroid agenesis (by thyroid ultrasonography) were also not included. Specimens for measurement TSH concentrations are collected at least 72 hours after birth because there is a TSH surge in the first 24 to 36 hours of life. Screening before 48 hours produces a high rate of

false positive results due to this surge. All 3 to 7 days neonates were screened using a dry blood spot on filter paper taken from a prick heel capillary blood sample. TSH was measured using enzyme linked immune-Sorbent assay (ELISA). Samples were considered positive if the neonatal TSH (NTSH) concentration were ≥15μu/ml. If NTSH was ranging from 15 to 40μ u/ml another dry sample was taken within 2 days for re-measurement of NTSH. Samples were considered positive if the second NTSH was ≥15μu/ml and serum total T4 is less than 85 nmol/L (< 7 ng/dl). Treatment with levothyroxine 10–15μg/Kg/day was initiated for neonates, then we try to discontinue the replacement treatment at the age of 2 weeks, after normal TSH and T4 levels. Infants were re-checked again at age of 4-8 weeks to ensure normal thyroid function without oral hormone treatment.

Statistical analysis

By using version 20 (SPSS) comparison between groups was done, P values equal to or less than 0.05 were considered statistically significant.

Results

A 2218 neonates were screened, 965(43.5%) newborn of mothers had a history of taking of Synthetic progesterone treatment (as injection or tablet or both) and we classified it as (group 1). The remainder of mothers 1253(56.5%) (group2) had no history of taking synthetic progesterone treatment. By comparison to both groups regarding age of mothers, parity, sex of neonates and mode of delivery there is no significant statistical value, but there are significant values regarding birth weight P value 0.05 and numbers of neonates whom need admission to the hospital P value 0.05. Table 1. By comparison of neonates with mothers that had a history of taking progesterone during pregnancy 965(43.5%), they appeared to have 31(3.21%) neonates with abnormal thyroid function test in contrast to mothers not received progesterone 1253(56.5%) which show only one neonate with abnormal thyroid function tests. P values 0.001. Table 2. Mothers mainly start taking Synthetic progesterone treatment for the first trimester 782(81%) and those mothers shows high numbers of neonates with abnormal thyroid function test (30 neonates), while the numbers of mother decrease in second and third trimester using progesterone treatment associated with decrease in number of neonates suffering from abnormal thyroid function test. Table 3. Prolonged

usage of progesterone therapy throughout gestational periods was associated with increased numbers of neonates with CH, i.e. it is only one case of CH with using progesterone for less than 5-week durations while the number increase to reach 28 cases of CH by using progesterone for 5-10 weeks duration. It is interesting to see that there were two cases of CH had a history of mothers taking progesterone for more than 10 weeks duration. Table 4.

Table 1.

Demographic distribution of total cases

Characteristic		Group 1 965 (43.5%)	Group 2 1253 (56.5%)	P-value
Age of mother	18-25 year	442 (45.8%)	562 (44.8%)	0.4
	25-35 year	328 (43%)	430 (34.4%)	0.5
	> 35 year	195 (20.2%)	261(20.8%)	0.5
Parity	Nillipara	618 (64.1%)	855 (68.2%)	0.3
	Multipara	347 (35.9%)	398 (31.8%	0.4
Sex of neonates	Female	403 (41.8%)	572 (45.6%)	0.4
	Male	562 (58.2%)	681(54.4%)	0.4
Birth weight		3250±650 g	2900±300 g	0.05
Mode of delivery	Vaginal	642 (66.5%)	854 (68.1%)	0.3
	Caesarian section	323 (33.4%)	399 (31.9%)	0.4
Outcome after delivery	Need admission	292 (30.3%)	164 (13.1%)	0.05
	No need	673 (69.7%)	1089 (86.9%)	0.1

Table 2.

Comparison of mothers on progesterone with mothers not received progesterone during pregnancy

Mothers on progesterone		Mothers not received progesterone		P-value
No.	Neonates with CH	No.	Neonates with CH	0.001
965 (43.5%)	31 (3.21%)	1253(56.5%)	1 (0.01%)	

Table 3.

Timing of starting progesterone therapy

Gestational age (weeks)	No. of cases	No. of neonates with CH
10-16	782 (81)	30
16-24	109 (11.3)	1
> 24	74 (7.7)	0

Table 4.

Duration of progesterone treatment

Weeks	No. of cases	No. of neonates with CH
0-8	256 (25.9)	1
8-12	679 (70.2)	28
>12	30 (3.9)	2

Discussion

Preterm (premature) birth: refers to any delivery occurring prior to 37 weeks of gestation. On February 3, 2011, the US Food and Drug Administration (FDA) approved the use of progesterone supplementation; specifically, hydroxyprogesterone caproate injections reduce the risk of recurrent preterm birth [11]. In this study, there is 965(43.5%) Mothers on progesterone treatment during pregnancy were had 31(3.21%) babies with abnormal thyroid function test, in comparison to 1253(56.5%) mothers not received progesterone were had 1(0.01%) neonate with abnormal thyroid function test. This result in agreement with a study done by Connolly F [12], has previously shown that exogenous maternal androgens have negative effects on both the fetal pituitary as well as the testes, they hypothesized that progesterone, being a steroid hormone, could also alter fetal development and its administration to pregnant women should therefore be researched in more details. There is a significant relation between the using of progesterone during pregnancy with birth weight as shown in this study (i.e the mothers on progesterone deliver babies with birth weight 3250 ± 650 g in contrast to mothers not using progesterone who deliver babies with birth weight 2900±300g with P value 0.05) this appear to be similar result of Hartwig IR[13] study which show that any increase in maternal progesterone by 1 ng/ml during the first trimester increased girls' birth weight by 10.17 g (95% CI: 2.03-18.31g). To the best of our knowledge, *Krassas*

GE, [14]. Estimates controlled ovarian hyper stimulation leads to increases in estradiol, which in turn may have an adverse effect on thyroid hormones and TSH. Ovarian hyper stimulation may become severe when autoimmune thyroid disease is present, depending on preexisting thyroid abnormalities. Autoimmune thyroid disease is present in 5-20% of unselected pregnant women. Isolated hypothyroxinemia has been described in approximately 2% of pregnancies, without serum TSH elevation and in the absence of thyroid auto antibodies. There is an association of increased rates of spontaneous abortion, premature delivery and/or low birth weight, fetal distress in labor, and perhaps gestation-induced hypertension and placental abruption in overt hypothyroidism. P. Sathi *et al* [15], the first randomized controlled trial data to show that treatment with luteal phase equivalent doses of oral micronized progesterone is associated with a significant increase in Free T4 values. This 12-week randomized controlled progesterone trial documented that Free T4 levels were significantly elevated in progesterone-treated compared with placebo-treated women. Those in agreement with our study that the duration of treatment is an important factor in developing abnormal thyroid function test which appears in neonates delivered to mother on progesterone treatments whom continue taking the drug for more than 8 weeks. There also was a trend, as previously documented [16, 17], towards lower TSH levels, although there was no TSH-Free T4 interaction. The absolute increase in Free T4 on progesterone therapy (+2.5 pmol/l; 95% CI: 1.9–3.0) is greater than the longitudinal 13-year, population-based normal within-person change of 0.04 pmol/l (95% CI: −0. 16, 0.24 [18]. Likewise, although small, the adjusted mean difference in the Free T4 increase between progesterone and placebo of 0.8 pmol/l is also greater than that within-person 0.04 pmol/l longitudinal change [19, 20] given that the coefficient of variation in the FreeT4 assay is three per cent and the mean Free T4 level is 13.7 pmol/l, the observed adjusted change is double the potential maximal analytical variability of 0.41 pmol/l. This result, therefore, shows that the increase in Free T4 during oral micronized progesterone therapy in comparison to placebo therapy is neither likely to be due to endogenous variance nor is it likely related to lack of analytical precision, T3 and T4 transport can be considerable. This is of special relevance in congenital hypothyroidism.

Conclusion

There is a strong relationship between the use of synthetic progesterone and the increasing risk of abnormal thyroid function tests. In newborn. But this depends on the gestational age and the duration of the treatment throughout the pregnancy.

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