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Original Article

Pathology Section

Abnormal Shape of Placenta as a Consequence of Maternal Thyroid Disorders-Does It Leave Any Microscopic Changes?

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ABSTRACT

Introduction: Thyroid disorders are common in the reproductive age group of women and these can cause significant perinatal outcomes.Though the effect of abnormal thyroid hormones on the foetus and its development is established, their effect on the placenta and its contribution towards the effect is not elaborately studied.

Aim: To compare the microscopic features of euthyroid placentae with those of mothers with thyroid dysfunction.

Materials and Methods: This is prospective observational study wherein placentae received from October 1 ,2017 to March 31, 2019 in the Department of pathology, Karnataka Institute of Medical Sciences, Hubballi, Karnataka, India, were collected, processed and analysed. A total of 539 cases were received for histopathological examination during this period, of these 64 cases had abnormal antenatal thyroid profile. These were compared grossly and microscopically with the control group of 64 euthyroid cases.

Results: The total sample of the study comprised of case group(n=64) and control group(n=64), mean age: mean age of the women 26.91±4.1 years. The case group samples included 3 hyperthyroid cases and 61 hypothyroid cases.In the control group, 3 (2.3%) foetuses were dead as compared to 6 (4.7%) foetuses in hypothyroid group and 3 (2.3% of total, 100% of hyperthyroid group) foetuses in hyperthyroid group (p< 0.001). Abnormal shape of the placenta was seen in 1 (0.8%) case in normal group as compared to 3 (2.3%) in hypothyroid group and 1 (0.8%) case in hyperthyroid group (p=0.018). However, there weren't any significant microscopic changes.

Conclusions: Maternal thyroid disorders result in abnormal shape of placenta and hence resulting in foeto-maternal insufficiency and subsequent foetal growth restriction and adverse foetal outcome.

Keywords: Hyperthyroid, Morphometry, Maternal Hypothyroidism, Perinatal outcomes

INTRODUCTION

Pregnancy has a profound impact on the thyroid gland and its function that not only the daily iodine requirement increases by 50% during pregnancy but also thyroid hormone [thyroxine (T4), and triiodothyronine (T3) synthesis increases. In a euthyroid woman, these physiological changes are seamless; however they result in pathological events in women with thyroid dysfunction. In early pregnancy, the placental human Chorionic Gonadotropin (hCG), being structurally similar to Thyroid Stimulating Hormone (TSH) stimulates thyroid hormone secretion resulting in decreased maternal thyrotropin concentrations [1]. It is proposed that early trimester thyroid levels influence placentation and first trimester Thyroid Peroxidase (TPO) Antibody (Ab) positivity was observed to produce placental features of Maternal Vascular Malperfusion [2]. Very few studies have been done regarding placental changes in maternal thyroid disorders. This study was carried out with an objective to study the placental changes in cases with maternal history of thyroid disorders by comparing them with those with normal maternal thyroid profile.

MATERIAL AND METHODS

This is a prospective observational study conducted in the Department of Pathology of Karnataka Institute of Medical Sciences, Hubballi, Karnataka, India, after getting ethical clearance vide KIMS/PGS/SYN/447/2017-18 from October 1, 2017 to March 31, 2019, on all placenta specimens, which were collected, processed and studied. A total of 539 cases were received for histopathological examination.

Inclusion criteria: Those cases that had abnormal maternal antenatal thyroid profile were taken as the study group. Those cases with normal thyroid profile were included as the control group, irrespective of the maternal, gestational age and clinical outcome. The cases and controls were compared grossly and Histopathologically.

Exclusion criteria: Cases with history of co-existing disorders like eclampsia, Gestational Diabetes Mellitus (GDM) or unbooked cases and those without thyroid function report and imaging findings were excluded from the study.

Following the inclusion and exclusion criterias, 64 cases(61 cases were hypothyroid and 3 cases were hyperthyroid) were taken as the study group while 64 euthyroid placentae were considered as control group.

Procedure

The trimester-wise reference range values in the first, second, and third trimesters were FT(3) (1.92-5.86, 3.2-5.73, and 3.3-5.18 pM/l), FT(4) (12-19.45, 9.48-19.58, and 11.32-17.7 pM/l), and TSH (0.6-5.0, 0.44-5.78, and 0.74-5.7 IU/ml), respectively [3]. The placentae were preserved in 10% formalin post-delivery and were sent to the Department of Pathology. The specimen was weighed and measurements taken. Umbilical cords were examined for signs of infection or thrombosis. Membranes were looked for signs of infection and amniotic fluid irritation, the organ was cut open by bread loafing and examined for parenchymal changes like infarct and fibrin deposition, villitis, calcification, acute thrombosis, abnormal maturation, endarteritis etc. Representative bits were taken, i.e. 2-3 sections from maternal and foetal side each, chorio-amniotic roll in one section, one section from umbilical cord in every case. Apart from this routine, whenever the authors encountered any lesion like infarct, thrombi, fibrin deposits, thickened and opaque areas in

chorio-amnion, plaques in umbilical cord, etc, the region of interest were sampled and studied extensively, after adequate fixation of 24-48 hours, processed, stained with haematoxylin and eosin and reported according to Amsterdam guidelines [4]. Special stains like Periodic Acid Schiff (PAS), Gomori Methanamine Silver (GMS), and Masson's Trichrome Stain (MTS) etc were used whenever required, however they did not yield any significant data in this study.

Syncytial Knots were counted in 100 tertiary villi and compared with the standards [5,6]. The microscopic findings were compared with the maternal thyroid levels and the foetal outcome.

STATISTICAL ANALYSIS

The results were statistically analysed using Statistical Package for Social Sciences (SPSS) version 24.0 by calculating mean, standard deviation, p-value (Paired t-test) etc.

RESULTS

Total 64 placentaes included in case group, 3 were hyperthyroid and 61 were hypothyroid. Two of the hypothyroid cases were newly diagnosed during third trimester while the rest were all known cases or cases diagnosed during early trimesters of pregnancy during routine screening and were all on regular treatment during conception. These 64 placentae of hypo and hyperthyroid mothers were compared grossly and microscopically to 64 placentae of control group with normal thyroid levels. Considering that all of them but 2 were already treated, this study can be considered as a reality check for the effects of thyroxin supplementations in the placentae.

The mean age of the women included in the study (study and control group)was 26.91±4.1 years, the youngest being 20 years and the oldest being 37 years of age. Women of all gestational age were included with a mean of 37.4±4.4 weeks. In the normal group, 3 (2.3%) cases were dead as compared to 6 (4.7%) cases in hypothyroid group and 3 (2.3% of total, 100% of hyperthyroid group) cases in hyperthyroid group (p< 0.001) and were found to be statistically significant. Growth retardation was seen in 20(15.6%) cases in normal, 27 (21.1%) cases in hypothyroid group and 0 case in hyperthyroid group (p= 0.246). Abnormal shape of the placenta was seen in 1 (0.8%) case in normal group as compared to 3 (2.3%) in hypothyroid group and 1 (0.8%) case in hyperthyroid group (p= 0.018). Hence abnormal shaped in the form of bilobed placenta, irregular shaped placenta etc were seen significantly increased in the thyroid disorder group.

None of the microscopic features showed statistically significant conclusive data, stating their limited use in explaining the increased mortality in the thyroid disorder group. Syncytial knots were increased in 10 (7.8%) cases in normal group as compared with 9 (7%) cases in hypothyroid group and 0 cases in hyperthyroid group (p= 0.4). Abnormal villous maturation in the form of immature villi was seen in 2 (1.6%) cases in normal group as compared to 1 (0.8%) case in hypothyroid group and 0 case in hyperthyroid group (p= 0.49). Ill-formed vasculo-syncytial membrane was seen in 6 (4.7%) cases in normal group; 8 (6.3%) cases in hypothyroid group and 1 case (0.8%) in hyperthyroid group (p= 0.2). Gross and microscopic infarct was seen in 2 (1.6%) cases in normal group as compared to 7 (5.5%) cases in hypothyroid group and 0 cases in hyperthyroid group (p= 0.13). [Table/Fig-1] shows the effects of thyroid disorders on the placentae and the foetus. [Table/Fig-2] shows gross and microscopic pictures of hypothyroid and normal placenta.

DISCUSSION

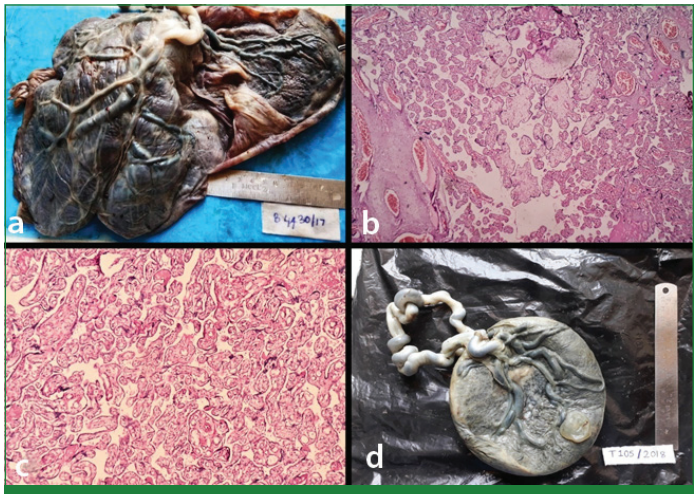
Of the 64 cases with maternal thyroid disorders, all 3 cases with maternal hyperthyroidism were associated with foetal death which was statistically significant in this study (p=0.001).

Placental disk dimensions are measured and expressed as Length (maximal linear dimension) * Breadth (greatest dimension of the axis perpendicular to this linear measurement) * Width (Both minimal and maximum thickness). Changes in the disk dimensions lead to abnormal shape of placenta. Shape of a placenta is determined by the site of implantation hence foetuses conceived by artificial reproductive technology tend to have abnormal shaped placentas [7]. Salafia CM et al., saw a significant correlation between large deviations of the placental shape from the mean and reduced placental efficiency and concluded that an abnormal placental shape is associated with an altered placental vascular architecture, which in turn is associated with a reduced functional efficiency [8].

In this study, grossly placentae of the hypothyroid group were associated significantly with abnormal shape of placentae (p= 0.018) implying that thyroxin hormone could probably play a role in the normal implantation of the placentae and hence the normal development. Thyroid hormone transporters and receptors are expressed in the trophoblast [9-12] and optimal concentrations are necessary to ensure appropriate placentation [13]. Thyroid hormone regulates secretion of several growth factors and cytokines that are critical for Extra Villous Trophoblast invasion and angiogenesis of maternal and foetal placental vessels, including angiogenin, angiopoietin 2 (Ang-2), Vascular Endothelial Growth Factor-A (VEGF-A), Interleukin 10 (IL-10) and Tumour Necrosis Factor- alpha (TNF-α) [14]. Furthermore, TH attenuates Epidermal Growth Factor (EGF)-initiated trophoblast proliferation

	Normal (Control Group)	Case group		p-value
		Hypothyroid (n=61 cases)	Hyperthyroid (n=3 cases)	
IUGR	20 (31.3%)	27 (44.3%)	0 (0%)	0.246
Dead	3 (4.7%)	6 (9.8%)	3 (100%)	<0.001
Increased syncytial knots	10 (15.6%)	9 (14.8%)	0 (0%)	0.758
Infarction	2 (3.1%)	7 (11.5%)	0 (0%)	0.168
Poor vaculo-syncytial membrane	6 (9.4%)	8 (13.1%)	1 (33.3%)	0.405
Abnormal maturation	2 (3.1%)	1 (1.6%)	0 (0%)	0.829
Obliterated vessels	2 (3.1%)	2 (3.3 %)	0 (0%)	0.951
Increased fibrin	6 (9.4%)	6 (9.8%)	0 (0%)	0.850
Calcification	5 (7.8%)	4 (6.6%)	0 (0%)	0.857
Villitis	0 (0%)	0 (0%)	0 (0%)	-
Villous oedema	1 (1.6%)	0 (0%)	0 (0%)	0.604
Abnormal shape	1 (1.6%)	3 (4.9%)	1 (33.3%)	0.018
Abnormal umbilical cord insertion	1 (1.6%)	1 (1.6%)	0 (0%)	0.975

[Table/Fig-1]: Shows the comparison of various gross and microscopic features of placentae with maternal thyroid derangement with those having normal thyroid function. IUGR: Intrauterine growth retardation; Bold p-values are significant



[Table/Fig-2]: a) Abnormal Shape of Placenta in a case of maternal overt Hypothyroidism in a 36 week Primi, diagnosed in the third trimester; b) Microscopy of the same showing Distal Villous hypoplasia; C) Microscopy of Placenta from Control group showing normal tertiary villi D) Placenta of the same with a normal shape.

[10] motility [15] and invasion [16]. Low thyroid function has been associated with premature delivery [17,18] and high thyroid function has been associated with pre-eclampsia [19,20] and foetal growth restriction [21,22], which are adverse pregnancy outcomes that could be arising from impaired placentation in early gestation [23]. Lavie A et al., [24] studied the placenta of hypothyroid mothers conceived by in-vitro fertilisation and found that they were significantly associated with bilobed placenta, retroplacental haematoma, decidual arteriopathy and subchorionic thrombi. Additionally, there was a statistically significant relationship with non-reassuring foetal heart rate tracing in these foetuses. Barjaktarovic M et al., [25] concluded that a higher FT4 concentration in early pregnancy is associated with higher vascular resistance in the second and third trimesters in both the maternal and foetal placental compartment which might explain the association of FT4 with adverse pregnancy outcomes, including pre-eclampsia and foetal growth restriction.

Placental infarcts and poor vasculo-syncytial membrane were seen increased in hypothyroid group as compared with normal thyroid group, but the difference is not statistically significant in the present study. Mahdik K et al., concluded that Low Birth Weight (LBW) 31.6% (p=0.001), Neonatal Intensive Care Unit admission 42.1%, (p<0.001) and low APGAR (Appearance- Pulse- Grimace- Activity- Respiration) Score (21.1%, p=0.042) were statistically associated with maternal hypothyroidism [26].

Abalovich M et al., [27] demonstrated that women with overt hypothyroidism carry an estimated 60% risk of foetal loss when not adequately treated. A 24 years G4A3 (Recurrent pregnancy Loss) woman with hypothyroidism delivered a live foetus with adequate treatment in this study. But several cases with hypothyroidism had more than one foetal loss. For instance, a 26 year G6P4L1A2 women with severe hypothyroidism and no other comorbidities (Autoimmune disorders ruled out), delivered a dead foetus at 26 weeks of gestation. The placental examination revealed an irregular shaped placenta, with normal microscopic features. Leung AS et al., [28] demonstrated a 22% risk of gestational hypertension in pregnant women with overt maternal hypothyroidism. Allan WC et al., [29] similarly described an increased risk of foetal death among pregnant women with overt disease. Hence there is an association between overt maternal hypothyroidism and risk to the maternal-foetal unit as seen in this study.

Limitation(s)

Smaller sample size is a limitation.

CONCLUSION(S)

Maternal thyroid disorders had several adverse effects on the foetus resulting in foetal growth restriction and foetal death. However, there weren't any significant placental histopathological changes compared to those cases with normal thyroid profile, probably owing to the treatment. But abnormal placental shape was seen significantly more in cases with maternal thyroid disorders comparatively. Similar studies in different ethnic groups, diverse demographic factors are recommended to be studied in large numbers to generalise the results.

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