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OFFSPRING OF MOTHERS WITH GRAVES' DISEASE FOLLOWED-UP FOR THE FIRST SIX MONTHS OF LIFE: A RETROSPECTIVE STUDY FROM A NIGERIAN TEACHING HOSPITAL.

ALPHONSUS N. ONYIRIUKA AND CATHERINE A. OSIDE

**Endocrinology and Metabolism Unit, Department of Child Health,
University of Benin Teaching Hospital, Benin City, Nigeria**

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Corresponding author: Prof A.N. Onyiriuka: alpndiony@yahoo.com

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ABSTRACT:
The offspring of a mother with Graves' disease is at increased risk of morbidity (both immediate as well as long-term) and mortality. The aim of the study was to retrospectively assess the concentrations of the serum Thyroid Stimulating Hormone (TSH), Thyroxine (T4) and Triiodothyronine (T3) as well as the anthropometric measurements in the first 6 months of life among offspring of mothers with Graves' disease. In this study, the case files of all infants born to mothers with Graves' disease who were referred to the Paediatric Endocrinology Clinic, University of Benin Teaching Hospital (UBTH), Benin City were retrieved and audited. The thyroid function tests (TFT) results as well the anthropometric data obtained in the first 6 months of life for offspring of mothers with Graves' disease were recorded. Of the 10 neonates born to mothers with Graves' disease, the thyroid function was normal in eight (80.0%) and abnormal in two (20.0%). Of the two infants with abnormal thyroid function, one had Transient Hyperthyrotropinaemia (elevated TSH with normal fT4) and the other had Euthyroid Hyperthyroxinaemia (elevated fT4 with normal TSH and no clinical symptoms). No case of neonatal Graves' disease was observed. In the first 6 months of life, there was no statistically significant difference in anthropometric measurements between offspring of mothers with Graves' disease and their counterparts whose mothers did not have Graves' disease. **Conclusion:** Majority of infants born to mothers with Graves' disease had normal thyroid function but the two leading abnormality of thyroid function observed in the newborn were Transient Hyperthyrotropinaemia and Euthyroid Hyperthyroxinaemia. No statistically significant difference was observed in the anthropometric measurements of offspring of mothers with Graves' disease and those of mothers without Graves' disease.

Keywords: Maternal Graves' disease, offspring, neonate, hyperthyrotropinaemia, hyperthyroxinaemia.

INTRODUCTION:

Graves' disease may be present before or emerge during pregnancy. It is often associated with elevated level of thyroid-stimulating hormone receptor antibodies (TSHR-Ab) in the mother. TSHR-Ab has a structure similar to that of immunoglobulin G, a property which enables it to cross the placenta into the fetus [1]. It is

estimated that 10% of the mother's serum level of TSHR-Ab is transferred to the fetus in the 17th to 22nd weeks of gestation and 50% is transferred to the fetus in the 28th to 32nd gestational weeks. Subsequently, the level in the fetus gradually increases and exceeds the mother's level in the term newborn [1]. The TSHR-Ab is heterogeneous in terms of molecular and functional properties and is subdivided into stimulating or blocking or neutral subtypes, depending on their effect on fetal thyroid-stimulating hormone receptor [2-4]. In addition, it may be transformed into a stimulating or blocking activity during gestation [2,3]. The fetal thyroid-stimulating hormone receptor begins to respond to transplacentally-acquired maternal TSHR-Ab from 20th weeks of gestation [4]. Thus, maternal Graves' disease may influence fetal thyroid function when TSHR-Ab cross the placenta, bind to fetal thyroid-stimulating hormone (TSH) receptors, leading to fetal or neonatal hyperthyroidism. However, the placenta acts as a barrier, so usually only neonates whose mothers have high titres are likely to be affected [5]. Although neonatal hyperthyroidism is rare, it is potentially life-threatening. The presence of persistent TSHR-Ab in the mother or ≥ 3-folds increase during pregnancy is a risk factor for neonatal hyperthyroidism [2,6]. In addition, a significant amount of antithyroid drugs used in the treatment of hyperthyroidism in the mother may cross the placenta, leading to fetal hypothyroidism [5]. This is in contrast to thyroxine which only crosses the placenta in small amounts [6]. The onset of overt neonatal hyperthyroidism can be delayed due to maternal antithyroid drugs or coexistence of thyroid stimulating hormone receptor blocking antibodies [3]. Occasionally, the neonate may have central hypothyroidism due to an elevated free thyroxine (fT4) in the fetus arising from maternal or fetal thyrotoxicosis with suppression of the fetal hypothalamic-pituitary-thyroid axis [6]. Goitre in the offspring may be related to the hyperthyroidism or the dose of the antithyroid drug given to the mother [3].

Graves' disease occurs before pregnancy in 0.4-1.0% of women and in 0.2-0.4% during pregnancy, representing the most common cause (85%) of either overt or subclinical hyperthyroidism in women of reproductive age [5,6]. Such pregnancies have been associated with adverse effects on the fetus and the newborn. In this regard, transient neonatal hyperthyroidism occurs in 1.0% of infants born to mothers with Graves' disease, with an estimated incidence of 1 in 50,000 neonates [7]. In addition, other abnormalities of thyroid function in neonates born to mothers with Graves' disease include transient central hypothyroidism, transient primary hypothyroidism and transient hyperthyrotropinaemia (elevated TSH with normal free T4 levels and no clinical symptoms) [8,9]. The reported incidence of the transient neonatal hyperthyrotropinaemia varies from 1 in 17,000 in Japan [9] to 1 in

8,260 in Europe [11]. It is estimated that the incidence of transient hypothyroidism due to the transplacental passage of TSH receptor binding antibodies is 1 in 180,000 neonates [12]. Apart from the above neonatal thyroid disorders, maternal Graves' disease has been linked to intrauterine growth restriction and low birthweight [5,7,13]. Although several reports on transient neonatal hyperthyroidism exist in literature [14,15], recent case studies indicate that this transient clinical condition is still overlooked by clinicians, leading to occurrence of preventable complications [16-18]. In addition, consensus guidelines on management and follow up of offspring of mothers with Graves' disease does not exist [19]. Therefore, there is the need to raise the alertness of physicians on the subject. Fetal hyperthyroidism can be identified by fetal tachycardia (> 160/min), advanced bone age, presence of goiter and increased blood supply, using Doppler ultrasound [4].

Fetal goitre is considered to be present if neck circumference value is above 95th percentile [20]. The clinical manifestations of neonatal hyperthyroidism include low birthweight, tachycardia, exophthalmos, extreme jitteriness, vomiting, diarrhoea, poor postnatal weight gain, sweating and goitre [5,7].

Reports of studies on follow up of infants born to mothers with Graves' disease have produced mixed results. Some investigators found no abnormality [21,22] while others reported impaired intellectual functions and abnormal morphology of the thyroid gland [23,24]. In addition, there is lack of data on many neonatal outcomes. In literature, reports of available studies suggest that breast-fed infants of mothers treated with methimazole (carbimazole) had no thyroid dysfunction or adverse effect on physical and mental development [25,26].

The purpose of this study was to retrospectively assess the concentrations of the serum TSH, T4 and T3 as well as the anthropometric measurements in the first 6 months of life among offspring of mothers with Graves' disease.

SUBJECTS AND METHODS:

During the 5-year period (2012-2016) covered by this review the case files of all (10 in total) infants born to mothers with Graves' disease who were referred to the Paediatric Endocrinology Clinic, University of Benin Teaching Hospital (UBTH), Benin City were retrieved and audited. Information obtained from the case files included maternal age, parity, relevant medication history, results of thyroid function tests (TFT) and antithyroid stimulating antibodies tests. With regard to the infant, information obtained included weight and gestation at birth.

The birth weights and the gestational ages were confirmed from the hospitals where each of the infants was delivered. The infants were

examined by a consultant paediatric endocrinologist and the documented physical findings were reviewed. In particular, clinical evidence of neonatal hyperthyroidism was sought. Consent was obtained from each of the mothers before including mother-infant pair data for analysis. Permission to conduct this study was obtained from the appropriate authority. All the infants (subjects and controls) were followed up till the age of 6 months. The anthropometric measurements of the infants born to mothers with Graves' disease were analysed at the age 3 and 6 months and the results were compared with those of age- and sex-matched infants born to mothers without Graves' disease or any other medical illness during pregnancy.

All the infants (subjects and controls) were breast-fed. The controls were healthy infants whose anthropometric measurements were obtained for another study during the same period. Maternal Graves' disease was diagnosed based on elevated free thyroxine (fT4) and very low or undetectable TSH concentrations in serum and positive TSHR-Ab, using second-generation thyroid-binding inhibitory immunoglobulin (TBII) assay. TSHR-Ab measurements were performed either in the second or third trimester of pregnancy, depending on the time of diagnosis of the maternal disease and availability of fund.

Statistical analysis:

Descriptive statistics such as frequencies, means, standard deviations were used in describing all the variables. The Student's t-test was used, where appropriate, in ascertaining the significance of differences between two means with the p-value set at < 0.05.

RESULTS:

During the period under review, there were 10 cases of infants born to mothers with Graves' disease who were referred to UBTH clinic. These mother-infant pairs constituted the study population. The mean age of the mothers with Graves' disease was 30.7±3.4 years; age range was 25 to 38 years. Three of the mothers were primiparous while the remaining 7 were multiparous. All the mothers had carbimazole and propanolol at some stage of pregnancy. Maternal TSHR-Ab was positive in the mothers but the serum titres were low-to-moderate in concentration. All the infants were delivered at term. Three of the infants were delivered by caesarean section and the remaining 7 were spontaneous vertex deliveries. Of the 10 mothers, 4 were diagnosed before and 6 during pregnancy. All the infants had good Apgar Scores. The mean age of the infants at the time of referral was 5.1±1.3 days, age range 3 to 10 days. The results of the anthropometric measurements in the first 6 months of life of the subjects and the controls are presented in Table 1. There were no statistically significant differences between the two groups.

Table 2 shows that the thyroid function remained normal in the first 6 months of life in the eight infants whose tests were initially normal. Of the 10 neonates born to mothers with Graves' disease, the thyroid function was normal in eight (80.0%) and abnormal in two (20.0%). Of the two neonates with abnormal thyroid function, one had hyperthyrotropinaemia (elevated TSH with normal T4) and the other hyperthyroxinaemia (elevated T4 with normal TSH). Neonatal Graves' disease was not observed in any of the cases. As shown in Table 3, the TSH value normalized by the age of 3 months and remained so till age of 6 months. Similarly, as depicted in Table 4, the fT4 value normalized by the age of 3 months and remained so till the age of 6 months. The developmental milestones of the two infants with an initial abnormal thyroid function test (hyperthyrotropinaemia and hyperthyroxinaemia, respectively) were appropriate for their age. During the first 3 months of life, L-thyroxine was administered to the only infant with neonatal hyperthyrotropinaemia. The other infant with neonatal hyperthyroxinaemia had no treatment but was closely monitored in the first 6 months of life for clinical manifestations of Graves' disease.

Table 1: Comparison of mean weight, length and head circumference at birth, 3 and 6 months of age of infants of mothers with and without Graves' disease

Anthropometric parameter	IGDM	INGDM	p-value
Mean weight at birth	2.99±0.48kg	3.10±0.35	< 0.05
Mean length at birth	46.4±1.6cm	46.5±1.40	< 0.05
Mean OFC at birth	34.0±0.92cm	34.5±0.76	< 0.05
Mean weight at age 3 months	5.1±0.30	5.0±0.40	< 0.05
Mean length at age 3 months	58.0±2.4	58.5±2.2	< 0.05
Mean OFC at age 3 months	36.0±0.90	36.2±0.93	< 0.05
Mean weight at age 6 months	6.2±0.50	6.1±0.45	< 0.05
Mean length at age 6 months	66.0±2.6	66.1±2.7	< 0.05
Mean OFC at age 6 months	41.1±0.87	41.0±0.90	< 0.05

IGDM = Infants of Graves' disease Mothers
INGDM = Infants born to non-Graves' Disease Mothers
OFC = Occipitofrontal circumference

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Table 2: Mean serum TSH, T3 and T4 concentrations of the eight infants with initial normal thyroid function tests

Thyroid Function Tests parameters	Reference interval	At presentation	At 3 months of age	At 6 months of age
TSH µIU/L	0.37-3.50	2.03±0.50	1.92±0.65	1.71±0.55
Free T3 pmol/L	4.4-7.3	5.5±0.34	4.90±0.48	5.30±0.39
Free T4 pmol/L	7.2-16.4	10.2±1.30	10.73±0.85	12.50±0.76

TSH= Thyroid stimulating hormone; T3 = Triodothyronine; T4 = Thyroxine

Table 3: Serial serum TSH, T3 and T4 concentrations of the only infant with hyperthyrotropinaemia (elevated TSH)

Thyroid Function Tests parameters	Reference interval	At presentation	At 3 months of age	At 6 months of age
TSH* µIU/L	0.37-3.50	8.25*	2.60	2.35
Free T3 pmol/L	4.4-7.3	4.20	5.50	6.80
Free T4 pmol/L	7.2-16.4	12.35	10.70	13.45

TSH= Thyroid stimulating hormone; T3 = Triiodothyronine; T4 = Thyroxine;
*TSH = High

Table 4: Serial serum TSH, T3 and T4 concentrations of the only infant with hyperthyroxinaemia (elevated T4)

Thyroid Function Tests parameters	Reference interval	At presentation	At 3 months of age	At 6 months of age
TSH µIU/L	0.37- 3.50	2.25	1.95	2.55
Free T3 pmol/L	4.4-7.3	4.03	4.50	5.8
Free T4 pmol/L**	7.2-16.4	23.63**	14.0	12.60

TSH= Thyroid stimulating hormone; T3 = Triodothyronine; T4 = Thyroxine;
**Free T4 = High

DISCUSSION:

Our data indicate that 80.0% of infants born to mothers with Graves' disease have normal thyroid function. A similar finding (83.5%) has been reported by Mitsuda et al [15]. However, in contrast to the frequency (5.6%) of neonatal Graves' disease reported by Mitsuda et al [15], we did not find any case of neonatal Graves' disease. The absence of neonatal Graves' disease in our present study may be partly explained by the rarity of this clinical condition. Secondly, our small sample size may be another factor. Our study involved only 10 infants compared to 230 in the study by Mitsuda et al [15]. The rarity of neonatal Graves' disease is amply reflected in its estimated incidence of 1 in 50,000 neonates [5]. In addition, the relatively low titres of maternal serum TSHR-Ab may have contributed to our finding. This view is based on the report of previous studies which have shown that the higher the titre of maternal serum TSHR-Ab the greater the risk for neonatal Graves' disease [2,27-29].

In our present study, 10.0% of neonates born to mothers with Graves' disease had transient hyperthyrotropinaemia (elevated TSH with normal free T4 levels and no clinical symptoms). This finding agrees with the prevalence rate of 9.95% reported from Mexico [30]. In another study involving 230 neonates born to mothers with Graves' disease, 7.8% had hyperthyrotropinamia [15]. In the Mexican study, the high prevalence of transient neonatal hyperthyrotropinaemia was attributed to deficiency in maternal iodine intake [30]. A similar high prevalence rate of transient neonatal hyperthyrotropinaemia has been reported from other regions with iodine deficiency [31]. Could this be a factor in high prevalence observed in the present study? According to the criteria proposed by World Health Organisation (WHO), United Nations Children's Fund (UNICEF) and International Council for Control of Iodine Deficiency Disorders (ICCIDD), neonatal hyperthyrotropinaemia prevalence greater than 3% is an indirect index of iodine deficiency in the population under consideration [32]. In addition, other investigators have documented the usefulness of measurement of neonatal TSH level in identifying iodine deficiency in a given population [33]. Whatever the explanation for the hyperthyrotropinaemia observed in the present study, it calls for further research into the subject by simultaneous measurements of serum TSH and urinary iodine concentration (UIC). Measurement of UIC is the gold standard for identification of iodine deficiency in a target population. If such laboratory evaluation protocol confirms the existence of iodine deficiency, targeted iodine supplementation in mothers of reproductive age is warranted in our society. Although our sample size was small, this prevalence rate was by far higher than the reported incidence in Japan and Europe [10,11], countries with relatively adequate maternal iodine intake.

Other rare causes of transient neonatal hyperthyrotropinaemia include defects in TSH molecule or the TSH receptor, a mild intrathyroidal synthetic defect, a hemithyroid, or a resetting of TSH-feedback control system [34]. In our present study, the TSH value normalized, suggesting that abnormal TSH molecule or TSH receptor defect was not the cause. Similarly, in a study in Europe, the elevated TSH values spontaneously normalized in 11 of the 16 infants within 6 months [35]. Hyperthyrotropinaemia in the newborn is usually treated [34], a practice in keeping with our management approach in the index case.

In the present study, one neonate was found to have hyperthyroxinaemia (elevated free thyroxine, fT4). This finding is not surprising because previous studies on neonatal screening for thyroid disorders have reported similar finding [36-38]. The differential diagnoses of neonatal hyperthyroxinaemia include neonatal Graves' disease (most common), familial dysalbuminaemic hyperthyroxinaemia (FDH) and resistance of thyroid hormone (RTH) [36]. In addition, other reported causes of neonatal hyperthyroidism are activating-mutation of TSH receptor and gain-in-function mutation of Gsα protein in McCune Albright syndrome [39,40]. Elevated fetal fT4 may be due to maternal thyrotoxicosis and may lead to a feedback suppression of the fetal hypothalamo-pituitary-thyroid axis, resulting in central neonatal hypothyroidism (low fT4 and low TSH) [7,34]. However, we were unable to determine the cause of the neonatal hyperthyroxinaemia in our patient because of inadequate laboratory facilities. Whatever the cause, our finding reinforced the importance of simultaneous TSH and fT4 measurements in neonatal screening for thyroid disorders. Generally speaking, rare thyroid diseases are known to present challenging problems for clinicians because of their rarity and variability in clinical manifestations [41]. However, they should be kept in mind as differential diagnosis of other diseases more commonly seen in clinical practice.

Although the mean birthweight was slightly lower in infants born to mothers with Graves' disease compared to their counterparts born to mothers without Graves' disease, the difference was not statistically significant. Maternal Graves' disease in pregnancy is known to be associated with delivery of low birthweight infants [10]. Post-natally, mean weight, length and occipitofrontal circumference values were not statistically different in offspring of mothers with Graves' disease compared with their counterparts born to mothers without Graves' disease. Other investigators have reported similar findings [22,42].

The management challenges encountered in our patients included late referral, inappropriate timing of measurement of maternal TSHR-Ab,

lack of measurement of cord TSHR-Ab and inadequate laboratory facilities. Factors that contributed to inappropriate timing of measurement of maternal TSHR-Ab were late booking and financial constraints. Some mothers could not pay for the tests until after a few months from the time of request. Together, inappropriate timing and lack of measurement of cord TSHR-Ab hindered classifying the infants into high or low risk groups. Such classification will promote provision of targeted care and follow up. However, in some cases the request for maternal TSHR-Ab measurement was in the third trimester and in others only a single test was performed, making it impossible to assess for persistence TSHR-Ab during the course of pregnancy. Information regarding all these factors are required for assessment of risks of occurrence of neonatal hyperthyroidism [4,28]. Timing of measurement of maternal TSHR-Ab levels is important because its level is known to fall in the third trimester of gestation [2], a situation that may lead to misinterpretation of laboratory results. Therefore, further education of physicians on the management of offspring of mothers with Graves' disease is warranted in our setting. Inadequate laboratory facilities resulted in our inability to investigate the cause of the neonatal hyperthyroxinaemia found in our present study.

In conclusion, in our present study 80.0% of infants born to mothers with Graves' disease have normal thyroid function but the two leading abnormality of thyroid function observed in the 20.0% with disorder were Transient Hyperthyrotropinaemia and Euthyroid Hyperthyroxinaemia.

During the first six months of life, the anthropometric measurements of offspring of mothers with Graves' disease did not differ from those of offspring of mothers without Graves' disease. We recommend that whenever TSHR-Ab positive women are identified during pregnancy, both the neonatal and the paediatric endocrinology units should be informed prior to delivery. In addition, stratification of infants born to mothers with Graves' disease into low and high risk groups for targeted approach to immediate management and follow up is advocated. The benefit of this approach is that it will lead to avoidance of performing unnecessary series of thyroid function tests on infants in the low risk group while promoting careful evaluation including thyroid function tests in those in the high risk group. Follow up of these infants is important because thyroid dysfunction may begin after a few to several weeks of life [34].

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