STUDY OF MATERNAL RISK FACTORS CONTRIBUTING IN THE DEVELOPMENT OF CONGENITAL HYPOTHYROIDISM

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ABSTRACT

Background: The study was conducted to assess maternal factors contributing in the development of congenital hypothyroidism (CH) in their neonates whom were diagnosed by public health insurance newborn screening program during study period from January to December 2017 in Sharkia governorate.

Methods: The study had been conducted on selected sample of 50 mothers; they are selected according to their neonates' thyroid profile and divided into two groups: Group 1 (cases): selected 25 mothers having neonates diagnosed with CH. Group 2 (control): selected 25 healthy neonates and their mothers. All mothers in our study were subjected to full history assessment, physical exam and specific laboratory testing including (TSH, Free T4, Free T3, Anti TPO and Anti TG). On other hand, baseline characteristics and screening laboratory results of neonates diagnosed with CH were obtained from their registered profiles in public health insurance organization in Sharkia governorate.

Results: Clinical parameters of mothers included revealed that mothers having previous history of thyroid disorders as well as maternal abortion rates were higher in case group compared to control group and this difference was statistically significant. Clinical and demographic results of neonates diagnosed with CH, showed that neonatal birth weight was lower in case group compared to control group and this difference was statistically significant. The presence of maternal thyroid dysfunction (mainly hypothyroidism) was higher in case group compared to control group and this difference was statistically significant. Maternal auto-thyroid antibodies (Anti TPO and Anti TG) were higher in case group compared to control group and this difference was statistically significant.

Conclusions: Maternal risk factors in our study contributing in the development of CH were highly related to the presence of maternal thyroid disorders either controlled on treatment or not. As well as, thyroid laboratory dysfunction (mainly sub/hypothyroidism) in mothers induced mostly by autoimmune thyroid state confirmed by presence of higher levels of auto-thyroid antibodies (Anti TPO and Anti TG) which proved to be significant and these autoimmune antibodies in its turn increase the rates of maternal miscarriage, neonatal prematurity and low birth weight as reported in our study.

Abbreviations: CH= congenital hypothyroidism, **TSH**= Thyroid Stimulating Hormone, **Anti TPO**= anti thyroid peroxidase antibodies, **Anti TG**= anti thyroglobulin antibodies.

Key words: congenital hypothyroidism, maternal, autoimmune thyroid.

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INTRODUCTION

Congenital hypothyroidism (CH) is the most common cause of preventable mental retardation and occurs in 1 in 2000–4000 newborns. It can be either permanent or transient[1].

Newborns with permanent dysfunction mainly results from mal-development which is represented as thyroid dysgenesis (ectopia or agenesis) or dyshormonogenesis. These infants require lifelong thyroid hormone replacement therapy whereas the underlying causes of transient functional impairment are less clear and may include maternal factors such as iodine deficiency, excessive iodine intake, anti-thyroid medication or presence of antibodies against thyroid tissue which transferred during pregnancy [2].

Also neonatal very low birth weight (<1500gm) and prematurity (<37 weeks gestation), immaturity of thyroidal iodine organification and exposure to excess iodine (e.g. use of iodinated disinfectants or contrast agents) may contribute to transient CH [3].

Moreover Iodine deficiency is a global health problem. The UNICEF categorized Egypt as one of the countries with low iodinated salt consumption with large number of neonates exposed to iodine deficiency [4].

Despite the unquestioned public health success of newborn screening programs and management of CH, there are still gaps in knowledge. For example, one important challenge in understanding the epidemiology of CH is that some newborns will have transient CH, a temporary depression of thyroid hormone concentrations that can last from several days to several months [5].

Several studies have investigated the role of genetic, environmental and autoimmune factors in the etiology of CH. Though the roles of autoimmune factors in the pathogenesis of CH have been supported in many studies, the findings are controversial because some evidences have reported their role in both transient and permanent forms of CH, but others have reported their role only in the transient form. Bogner and colleagues showed that cellular cytotoxicity induced by maternal autoantibodies have an important role in the pathogenesis of CH [6].

The role of many maternal autoantibodies such as anti TPO, anti Tg and TSH receptor blocking Ab (TRAb) has been investigated in the etiology of CH. Though studies in this field reported transient form of CH due to the above-mentioned autoantibodies, permanent cases of CH due to these antibodies have been reported too [7].

Thyroid autoimmune diseases are a common problem in women, and they may be asymptomatic. They may be undiagnosed during and after pregnancy and the autoantibodies may be transferred to fetus during pregnancy and result in hypothyroidism. Thus, the high prevalence of CH in our community as well as its transient form increases the importance of more etiologic studies in this field [8].

SUBJECTS AND METHODS

Study design: The current case-control study was conducted along period of 12 months extending from January to December 2017 in Public Health Insurance Organization in Sharkia governorate in cooperation with Endocrine and metabolism unit in faculty of medicine Zagazig University, Egypt.

Patients: The study had been conducted on selected sample of 50 mothers; they are selected according to their neonates' thyroid profile and divided into two groups: Group 1 (cases): selected 25 mothers having neonates diagnosed with congenital hypothyroidism. Group 2 (control): selected 25 healthy neonates and their mothers. The enrolled subjects were further subdivided according to their thyroid function tests into 3 categories: (normal, hypothyroidism and hyperthyroidism) and regarding the presence of auto-thyroid antibodies into 2 categories: (autoimmune positive and autoimmune negative).

All mothers in our study were subjected to full history assessment [with special attention to: age, occupation, residence, habits, obstetric history (offspring, abortion), history of thyroid illness, other common illness, history of drug intake (esp. antithyroid drugs, amiodarone), history of iodine exposure (contrast material, I 131), irradiation and family history], physical exam and specific laboratory testing including (TSH, Free T4, Free T3, Anti TPO and Anti TG).

Baseline characteristics and screening laboratory results of neonates diagnosed with congenital hypothyroidism were obtained from their registered profiles according to newborn screening program conducted by Public Health Insurance Organization in Sharkia governorate, in which all 3 to 7 day neonates were screened by TSH measurement using dry blood spot on filter paper taken from a prick heel capillary blood sample. Samples were considered positive if the neonatal TSH (NTSH) concentration was >15 µIU/mL. Another confirmatory venous sample was taken for measurement of serum TSH and Free T4 levels in in the central lab of ministry of health and population.

Exclusion criteria: Any patient with missed data.

Ethical clearance: Written Informed consent was taken from mothers to participate in the study. Approval for performing the study was obtained from internal medicine and medical biochemistry departments, Zagazig University Hospitals after taking

Institutional Review Board (IRB) approval (ZU-IRB #1387-1-4-2014).

Statistical analysis

The collected data were statistically analyzed using SPSS program (Statistical Package for Social Science) version 20 .Data were tested for normal distribution using the Shapiro Walk test.Chi square test ($\chi 2$) and Fisher exact was used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as mean ± SD (Standard deviation) for parametric and median and range for non-parametric data . Independent T test and Mann Whitney test were used to calculate difference between quantitative variables in two groups for parametric and non-parametric variables respectively.One-way ANOVA F-test and Kruskal-Wallis Test were used to calculate difference between quantitative variables in more than two groups in normally normal and non-parametric variables respectively. All statistical comparisons were two tailed with significance Level of P-value ≤ 0.05 indicates significant, p <0.001 indicates highly significant difference while, P> 0.05 indicates Non-significant difference.

RESULTS

Table (1): shows comparison between clinico-demographic parameters of mothers included in both groups (cases and control), in which maternal abortion rates and maternal history of thyroid disease was higher in in case group (mothers have neonates diagnosed with congenital hypothyroidism) compared to control group (mothers have healthy neonates) (9 versus 2 and 6 versus 0 respectively) and this difference was statistically significant (p= 0.037 and p=0.021 respectively).

Table (2): shows comparison between clinico-demographic parameters of neonates included in both groups (cases and control), in which neonate weight at birth was lower in in case group (neonates diagnosed with congenital hypothyroidism) compared to control group (healthy neonates) (Mean ±SD 3.1 ± 0.6 kg versus 3.4 ± 0.3 kg respectively) and this difference was statistically significant (p= 0.016).

Table (3): shows comparison between Presence of Autoimmune Antibodies (Anti TPO and/or Anti TG) in Mothers included in both groups (cases and control), in which the presence of Autoimmune Antibodies was higher in in case group (mothers have neonates diagnosed with congenital hypothyroidism) compared to control group (mothers have healthy neonates) (12 (48%) versus 4 (16%) respectively) and this difference was statistically significant (p= 0.033).

Table (4): shows comparison between Distribution of Mothers included in both groups (cases and control) according to their Thyroid function tests (TFT), in which the presence thyroid dysfunction was higher in in case group (mothers have neonates diagnosed with congenital hypothyroidism) where 6 mothers was hypothyroidism with TSH level >6 µIU/mL (including subclinical) and 2 mothers was subclinical hyperthyroidism with TSH <0.3 µIU/mL compared to control group (mothers have healthy neonates) and this difference was statistically significant (p= 0.009).

Table (5): shows comparison between Thyroid profiles in Mothers included in both groups (cases and control), in which the mean ±SD of maternal Anti TPO and Anti TG were higher in in case group (mothers have neonates diagnosed with congenital hypothyroidism) compared to control group (mothers have healthy neonates) (97.5 ± 137.1 versus 16.9 ± 6.7 and 364.7 ± 505.4 versus 106.7 ± 109 respectively) and this difference was statistically significant (P= 0.000 and P=0.013 respectively).

Table (1): Comparison between Clinico-demographic parameters of mothers included in both groups (cases and control).

		Group		X^2	p
		Case 25	Control 25		
Maternal Age (ys)	Median (range)	31 (22-41)	29 (25-38)	-0.196	0.846
	Mean±SD	30.4 ± 5.1	30.6 ± 5		
Maternal offspring	1.0	7 (28.0%)	3 (12.0%)	4.430	0.351
	2.0	4 (16.0%)	10 (40.0%)		
	3.0	9 (36.0%)	8 (32.0%)		
	4.0	3 (12.0%)	2 (8.0%)		
	5.0	2 (8.0%)	2 (8.0%)		
Maternal abortion	No	16 (64%)	23 (92.0%)	4.2	**0.037**
	Yes	9 (36%)	2 (8.0%)		
Maternal history of thyroid disease	No	19 (76%)	25 (100.0%)	4.3	**0.021**
	Yes	6 (24%)	0 (0.0%)		
Maternal exposure to iodine	No	25 (100.0%)	23 (92.0%)	2.083	0.149
	Yes	0 (0.0%)	2 (8.0%)		
Family history of thyroid disease	No	23 (92.0%)	23 (92.0%)	.000	1
	Yes	2 (8.0%)	2 (8.0%)		
Family history of common disease	No	23 (92.0%)	23 (92.0%)	.000	1
	Yes	2 (8.0%)	2 (8.0%)		
Family consanguinity	No	17 (68.0%)	21 (84.0%)	1.754	0.185
	Yes	8 (32.0%)	4 (16.0%)		

- Chi square test ($\chi 2$)
- *P* value **<0.05** was considered statistically significant(S)

Table (2): Comparison between Clinico-demographic of neonates included in both groups (cases and control)

		Group		X^2	p
		Case 25	Control 25		
Neonate sex	Male	15 (60.0%)	13 (52.0%)	.325	0.569
	Female	10 (40.0%)	12 (48.0%)		
Neonate birth	Term	24 (96.0%)	25 (100.0%)	1.020	0.312
	Preterm	1 (4.0%)	0 (0.0%)		
Neonate delivery	NVD	7 (28.0%)	8 (32.0%)	.095	0.758
	CS	18 (72.0%)	17 (68.0%)		
Neonate congenital anomaly	No	24 (96.0%)	25 (100.0%)	1.020	0.312
	Yes	1 (4.0%)	0 (0.0%)		
Neonate Weight at birth (kg.)	Median (range)	3 (2-4)	3.5 (3-4)	-2.5	**0.016**
	Mean±SD	3.1 ± 0.6	3.4 ± 0.3		

- Chi square test ($\chi 2$)
- *P* value **<0.05** was considered statistically significant(S)

Table (3): Comparison between Presence of Autoimmune Antibodies (Anti TPO and/or Anti TG) in Mothers included in both groups (cases and control).

		Group		X^2	P
		Case	Control		
		25	25		
Autoimmune Abs	-ve	13 (52%)	21 (84%)	4.5	**0.033**
	+ve	12 (48%)	4 (16%)		

- Chi square test ($\chi 2$)
- *P* value **<0.05** was considered statistically significant(S)

Table (4): Comparison between Distribution of Mothers included in both groups (cases and control) according to their Thyroid function tests (TFT).

		Group		X^2	P
		Case	Control		
		25	25		
TFT	Hyperthyroidism	2 (8%)	0	9.5	**0.009**
	Hypothyroidism	6 (24%)	0		
	Normal	17 (68%)	25 (100%)		

- Chi square test ($\chi 2$)
- *P* value **<0.05** was considered statistically significant(S)

Table (5): Comparison between Thyroid profiles in mothers included in both groups (cases and control).

	Case		Control		Test	P
	Mean ±SD	Median (range)	Mean ±SD	Median (range)		
M TSH (µIU/mL)	4 ± 6.5	2 (0.1-33)	2.4 ± 0.9	2.4 (0.5-3.8)	1.240	0.221
M FT4 (ng/dl**)**	1.3 ± 0.3	1.4 (0.5-1.7)	1.3 ± 0.1	1.3 (1.1-1.6)	-0.321	0.750
M FT3 (pg/dl)	3.1 ± 0.9	3.5 (1-4.5)	3.3 ± 0.7	3.6 (2.1-4.2)	-0.669	0.506
M Anti TPO (IU/mL)	97.5 ± 137.1	31 (9.1-509)	16.9 ± 6.7	16 (6.5-32)	-3.710	**0.000**
M Anti TG (IU/mL**)**	364.7 ± 505.4	106 (35.8-1876)	106.7 ± 109	68 (28-430)	-2.495	**0.013**

P value **<0.05** was considered statistically significant(S)

DISCUSSION

Congenital hypothyroidism (CH) is the most common cause of preventable mental retardation and occurs in 1 in 2000–4000 newborns. It can be either permanent or transient[1].

Newborns with permanent dysfunction mainly results from mal-development which is represented as thyroid dysgenesis (ectopia or agenesis) or dyshormonogenesis. These infants require lifelong thyroid hormone replacement therapy whereas the underlying causes of transient functional impairment are less clear and may include maternal factors such as iodine deficiency, excessive iodine intake, anti-thyroid medication or presence of antibodies against thyroid tissue which transferred during pregnancy [2].

Several studies have investigated the role of genetic, environmental and autoimmune factors in the etiology of CH. Though the roles of autoimmune factors in the pathogenesis of CH have been supported in many studies, the findings are controversial because some evidences have reported their role in both transient and permanent forms of CH, but others have reported their role only in the transient form [6].

The role of many maternal autoantibodies such as anti TPO, anti Tg and TSH receptor blocking Ab (TRAb) has been investigated in the etiology of CH. Though studies in this field reported transient form of CH due to the above-mentioned autoantibodies, permanent cases of CH due to these antibodies have been reported too [7].

Thyroid autoimmune diseases are a common problem in women, and they may be asymptomatic. They may be undiagnosed during and after pregnancy and the autoantibodies may be transferred to fetus during pregnancy and result in hypothyroidism [8].

Therefore, this study was conducted to assess the maternal risk factors contributing in the development of congenital hypothyroidism in their neonates whom were diagnosed by public health insurance newborn screening program during study period in Sharkia governorate. This case-control study had been carried out in Public Health Insurance Organization in Sharkia governorate in cooperation with Endocrine and metabolism unit in faculty of medicine Zagazig University, along period of 12 months extending from January to December 2017.

In current study, a selected sample of 50 mothers was included. The included mothers were selected according to their neonatal thyroid profile and divided into two groups: Group 1 (cases): selected 25 mothers having neonates diagnosed with congenital hypothyroidism. Group 2 (control): selected 25 healthy neonates and their mothers.

All mothers in our study were subjected to full history assessment, physical exam and specific laboratory testing including (TSH, Free T4, Free T3, Anti TPO and Anti TG). On other hand, baseline characteristics and screening laboratory results of neonates diagnosed with congenital hypothyroidism were obtained from their registered profiles in public health insurance organization in Sharkia governorate.

According to demographic results of our study, the mean ± SD of age for mothers included in case group was (30.4 ± 5.1) with no statically significant difference compared to control group (30.6 ± 5). In contrast to our result **LaFranchi (2010)** reported an increase rate of congenital hypothyroidism (CH) neonates associated with advanced maternal age, in same line with **Harris and Pass (2007)** who found that CH is higher in preterm infants and infants born to older mothers [9, 10].

Regarding our clinical parameters results of mothers included, we found increase in maternal abortion rates in case group compared to control group (36% versus 8% respectively) and this difference was statistically significant (p= 0.037). These results were consistent with **LaFranchi (2010)** who states rise in incidence of CH in mothers having history of preterm birth and frequent miscarriage. This can be explained by fact that autoimmune thyroid disease is common in pregnancy possesses important risk factors both for the mother, the fetus, and newborn infant and the presence of anti-thyroid autoantibodies which cross the placenta is associated with a significant increment in miscarriages [9, 11].

In present study, we observed high prevalence of CH in mothers having previous history of thyroid disorders and receiving treatment compared to control group (24% versus 0% respectively) and this difference was statistically significant (P=0.021). Similar results were obtained by **Brent (1999)**, **Blazer et al. (2003)** and **Leung et al. (2009)** all of them reported that maternal thyroid deficiency, even subclinical, has been associated with adverse pregnancy outcomes. Fluctuations that occur in T4 metabolism during pregnancy make it difficult to maintain meticulous normal thyroid hormone values during gestation in hypothyroid mothers and may further impair maternal-fetal transfer of thyroxin despite apparently optimal maternal thyroid status. Also, prenatal vitamin supplements commonly taken during pregnancy are rich in iron and calcium, both of which inhibit thyroxin absorption [12, 13, 14].

Moreover, Hashimoto's thyroiditis is the most common cause of such hypothyroidism in pregnancy. Hence, there are a large number of children who have been exposed to thyroid autoantibodies in utero and who may have been hypothyroid during development [15].

In our study, although positive family consanguinity was higher in case group compared to control (32% versus 16% respectively). However, there was no statistically significant among studied groups, and this may needs further studies to asses if there is correlation between consanguinity and development of CH in newborn. Also family history of common diseases such as diabetes and hypertension had no statistically significant.

In current study, demographic results of neonates diagnosed with CH, the female to male ratio was 0.66 (40% and 60% respectively) with no statistically significant compared to control (48% and 52% respectively). These results were coincided with **Bekhit and Yousef (2013)** who reported the female to male ratio in Egypt was 0.7 in CH. Similar result was obtained by **Hashemipour et al. (2012**), on the other hand another study of congenital hypothyroidism newborn suggest a female to male ratio of a 2:1[3, 16, 17].

It was observed the increased incidence of caesarian section than normal vaginal delivery of newborn in both studied groups (72% and 68%) with no statistically significant in between; this may be due to use of modern modalities in delivery nowadays.

According to our results, the mean ± SD of neonatal birth weight was lower in case group compared to control group (3.1 ± 0.6 kg versus 3.4 ± 0.3 kg respectively) and this difference was statistically significant (P= 0.016). Our results were compatible with **Blazer et al. (2003)** who states that reduced foetal thyroxine may cause disruption to the development of the pituitary-thyroid axis of the newborn, foetal pituitary GH secretion and maturation in utero. These factors may be responsible for reduced neonatal birth weight of offspring born to mothers with inadequately controlled thyroid status. Also pregnant women whose TSH remained suboptimal may be more likely to give birth to a low birth weight infant [13, 18].

After further evaluation of thyroid function tests for both mothers and neonates, our study revealed that the mean ± SD of TSH and Free T4 for neonates diagnosed with CH was (35.9 ± 23.7) and (0.9 ± 0.3) respectively. Furthermore, the mean ± SD of maternal TSH was higher in case group compared to control group (4±6.5 versus 2.4±0.5 respectively) and Free T3 was lower in case group compared to control group (3.1±0.9 versus 3.3±0.7 respectively) but both had no statistically significant.

According to our laboratory results, we further redistribute mothers depending on their thyroid function tests into 3 categories: normal, hypothyroidism (including subclinical) and hyperthyroidism (including subclinical) in which the presence thyroid dysfunction was higher in in case group (32%), where 6 mothers (24%) were hypothyroidism with TSH level >6 IU/ml (including subclinical) and 2 mothers (8%) were subclinical hyperthyroidism with TSH <0.3 IU/ml compared to control group and this difference was statistically significant (P= 0.009).

These results were convenient with **Dussault and Fisher (1999)** who documented that elevated TSH concentrations

were more frequent (7.0% versus 0.9%) in the mothers of hypothyroid newborns. Also maternal thyroid deficiency, even subclinical, had been reported by **Brent (1999)** to be associated with adverse pregnancy outcomes that may be improved by T4 replacement [19, 20].

In the same line, **Lazarus et al. (2012)** revealed that hypothyroidism induced by Hashimoto's thyroiditis is the most common cause of such hypothyroidism in pregnancy. Hence, there are a large number of children who have been exposed to thyroid autoantibodies in utero and who may have been hypothyroid during development. These data was reinforced by **Hulya Ozdemir et al. (2013)** who state that infants of mothers with thyroid problems are more likely to have elevated TSH and higher recall rate on neonatal thyroid screening [15, 21].

Furthermore, our present study showed that the mean ±SD of maternal Anti TPO and Anti TG were higher in case group (97.5 ±137.1 and 364.7 ± 505.4 respectively) compared to control group (16.9 ±6.7 and 106.7 ± 109 respectively) and this difference was statistically significant (P= 0.000 and P= 0.013 respectively).

Moreover, we further subdivided the enrolled mothers regarding the presence of auto-thyroid antibodies into 2 categories: (autoimmune positive and autoimmune negative), in which the presence of Autoimmune Antibodies was higher in in case group compared to control group (48% versus 16% respectively) and this difference was statistically significant (p= 0.033).

Similar results were obtained by **Stagnaro-Green (2009)** and **Lazarus et al. (2012)** who reported that autoimmune thyroid disease in pregnancy possesses important risk factors both for the mother, the fetus, and newborn infant depending on the type and amount of the anti-thyroid autoantibodies in utero which cross the placenta predispose to hypothyroid state during development [11, 15].

In another study supporting our results the mean maternal anti-TPO titers were significantly higher in infants with positive titers compared to infants with negative titers, suggesting that maternal TPO levels especially the high titers are transferred to the infant and are clinically more relevant [21].

Recently, our results were consistent with **Temboury Molina et al. (2015)** who state that higher TSH value in the newborn was related to higher levels of thyroid peroxidase (TPO) antibody during pregnancy. In same line with **Eun et al. (2013)** who found that Anti-TG antibody was significantly higher in children with congenital hypothyroidism compared to healthy controls, 119.4±34.7 IU/mL versus 80.6±19.6 IU/mL, respectively (P<0.001) [22, 23].

CONCLUSION

Maternal risk factors in our study contributing in the development of congenital hypothyroidism were highly related to the presence of maternal thyroid disorders either controlled on treatment or not. As well as, thyroid laboratory dysfunction (mainly sub/hypothyroidism) in mothers induced mostly by autoimmune thyroid state confirmed by presence of higher levels of auto-thyroid antibodies (Anti TPO and Anti TG) which proved to be significant and these autoimmune antibodies in its turn increase the rates of maternal miscarriage, neonatal prematurity and low birth weight as reported in our study. So, evaluation of thyroid function test as well as auto-thyroid anti bodies (Anti TPO and Anti TG) in all pregnant women is recommended. Also women with thyroid disorders or having auto-thyroid anti bodies should be followed closely throughout pregnancy and their newborn infants should be followed closely in the first months of postnatal life for thyroid dysfunction.

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