IS REPEATING THYROID SCREENING OF THE HEALTHY NEWBORN IS BENEFICIAL?

By

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ABSTRACT

Background: *Some cases of congenital hypothyroidism may be missed by first neonatal screening. This study aimed to evaluate thyroid stimulating hormone TSH and free T4 of healthy full term at 7^{th} and 28^{th} day for detection of the missed cases of hypothyroidism at 1^{st} neonatal screening.*

Methods: *This prospective study was performed on 100 healthy term neonates born at Zagazig University Hospitals and Al-Azhrar Hospital. The study was done on healthy full term new born at Neonatal Intensive Care Unit of Zagazig University hospital and Al-Azhrar Hospital and was under go follow up for TSH and free T4 at 7^{th} and 28^{th} day of life .Newborns were classified into two groups based on their age at 7^{th} and 28^{th} day of life. The following was done 1. Demographic data of the studied cases. Clinical assessment, Laboratory tests: included TSH and Free T4 concentration.*

Results: *Congenital hypothyroidism among the studied Cases at 7^{th} day was (3%). Congenital hypothyrodism among the studied Cases at 28^{th} day was (9%). Higher prevalence of CH among patients with positive maternal history of thyroid disorders. Higher prevalence of CH among patients delivered by cesarean section (C/S). Our results showed that history of thyroid disorders had a high risk for CH. There were statistically significant increases of maternal age among Cases with Congenital Hypothyroidism than Cases with euthyrodism. There were statistically significant decrease in weight and length among Cases with Congenital hypothyrodism than Cases with euthyrodism.*

Conclusion: *2^{nd} Neonatal screening of all healthy newborns at 28^{th} day of life is very important, since some cases of congenitl hypothyroidism can be missed in the 1^{st} neonatal screening at the 4^{th} day of life.*

Key words: *Thyoid Screening Repeated, Healthy New Born.*

INTRODUCTION

Congenital hypothyroidism (CH) is the most common etiology of preventable mental retardation and impaired cognitive-physical development among children and is more common in Asian and African population **(Rastogi and LaFranchi, 2010)**.

Since its symptoms are usually concealed at birth, the importance of screening is obvious **(Mutlu et al., 2012)**. Regarding variations in Thyroid Function Tests (TFTs) among different ages and geographical regions, determining reference interval specified by age and region is required for precise diagnosis **(Jain et al., 2008)**.

Newborn screening (NS) for CH is one of the major achievements of preventive medicine. The problem of CH has been resolved in developed countries by routine newborn screening **(Demers LM and Spencer, 2003)**.

Some cases of congenital hypothyroidism may be missed by first neonatal screening at 4th day of life , So the utility of routine second screening of TSH and T4 that will be important for healthy full term to detect significant cases of congenital hypothyroidism **(Elmlinger et al., 2001)**.

Most infants with CH are normal at birth and show no signs, emphasizing the importance of screening program in early detection of CH and screening for detection of missed cases of CH **(Shamshiri et al., 2012)**.

Aims of the Work

This study aimed to evaluate thyroid stimulating hormone TSH and free T4 of healthy full term at 7^{th} day and 28^{th} day for detection of the missed cases of hypothyroidism at 1^{st} neonatal screening at 1^{st} 4 days of life.

PATIENTS AND METHODS

I. Patients:

This follow up prospective study was performed on 100 healthy term neonates born at Zagazig University Hospitals and Al-Azhrar Hospital during the period of the study and selected by simple random method during the period from May 2019 to January 2020.

Our newborns study was classified into two groups based on their screening time at 7th and 28th day of life.

Ethical consideration:

1. The aim of the study was explained to the parents of each participate before collection of data.

2. Verbal consent was taken from parents of each participate in the study.
3. Privacy of all data was assured.
4. An approval of the local ethical committee was obtained before the study.
5. The patient has the right to with draw from the study at any time,

The Inclusion Criteria:

1. Healthy full term ≥ 37 weeks.
2. All newborns were from normal pregnancies without any prenatal complications.
3. Apgar score of more than 7 in 1st minute of birth.
4. Neonate with no sepsis and other anomaly.

The Exclusion Criteria:

1. Newborns who had the history of congenital anomaly.
2. Newborns with intra uterine growth retardation.
3. Newborns with thyroid disease in themselves or their mothers. Taking medications that affect thyroid function such as corticosteroids, dopamine or propranolol in them or their mothers, and pituitary disease were excluded.
4. Preterm infants (< 37 weeks).
5. N.B with any evidence of Neonatal Sepsis.

II. Methods:

1. Demographic data of the studied cases included:

Postnatal age, mothers age, sex, Mode of delivery, Residence, history of thyroid disorders, history of iodine intake.

2. Clinical assessment of the studied cases included:

- Anthropometric measurements.
- Vital signs.
- Abdomen, chest and heart examination.

3. Laboratory tests:

In order to separate the serum from the cells, clotted blood samples obtained by venipuncture from all subjects were centrifuged. Samples were stored at temperature of -70°C until assayed.

Serum samples were evaluated for quantitative measurement of TSH and Free T4 concentration by an immunoenzymometric assay and competitive enzyme immunoassay.

III. Statistical analysis:

The data were coded, entered and processed on computer using Statistical package for social science (SPSS) (version 24).The results were represented in tabular

and diagrammatic forms then interpreted.

Mean, standard deviation, range, frequency, and percentage were use as descriptive statistics.

The following test was done:

- **Chi-Square test X^2** was used to test the association variables for categorical data.
- **Student's t-test** was used to assess the statistical significance of the difference between two population means in a study involving independent samples.
- **Student's paired t-test** was used to assess the statistical significance of the difference between two population means in a study involving paired samples.

P value >0.05 is non-significant (N-S).

P<0.05 is significant (S).

RESULTS

Table (1): Demographic data of the studied cases

		Rang	Mean ± SD
mother age(years)		19 - 38	25.40± 3.96
		No.	**%**
Sex	**male**	57	57.0
	female	43	43.0
Mode of delivery	**CS**	57	57.0
	NVD	43	43.0
Residence	**RURAL**	35	35.0
	URBAN	65	65.0
Maternal \\\\history of thyroid disorders	**Yes**	9	9.0
	No	91	91.0
Maternal history of iodine intake	**Yes**	5	5.0
	No	95	95.0

This **Table (1)** shows that most of our studied cases were male (57%), delivered by C.S (57%), from urban area (65%), with maternal history of thyroid disorders (9%) and iodine intake in (5 %) of mothers.

Table (2): Clinical assessment of the studied cases (n.100)

	Rang	Mean ± SD
Weight(kg)	2.11 - 4.10	3.14 ± 0.34
Length(cm.)	49 – 53	50.98 ± 1.19
HC(cm.)	33.00 - 38.50	35.647 ± 1.19
HR(b/m)	118 – 158	135.57 ± 9.63
RR (c/m)	35 – 68	49.35 ± 6.757
Temperature (c)	35.90 – 38	37.25 ± .41

Table (3): Laboratory finding of thyroid TSH and T4 at 7th day

		Rang	Mean ± SD
TSH at 7th days :		0.50 - 12	2.2 ± 1.90
Normal TSH(,6-10 iu/ml)	**No.**	97	
	%	97	
Abnormal TSH (>10iu/ml)	**No.**	3	
	%	3	
Free.T4 at 7th days:		0.60 - 1.80	1.09 ± 0.27
Normal f.T4 (,8-2ng/dl)	**No.**	97	
	%	97	
Abnormal f.T4 (<,8ng/dl)	**No.**	3	
	%	3	

This Table shows that the Mean of the TSH (2.2 ± 1.90) and Free.T4 (1.09 ± 0.27) with abnormal TSH>10 iu/ml &Free T4<0.8 ng/dl in 3 cases (3%).

Table (4): Thyroid screening among the studied Cases at 7th day

		No.	%
Cases	**Congenital hypothyroidism**	3	3.0
	Normal thyroid function	97	97.0

Table (4) shows that the studied cases were 3 cases with congenital hypothyrodism (3%) and 97 with normal thyroid function (97%).

Table (5): Laboratory finding of thyroid TSH and T4 at at 28th days

		Rang	Mean ± SD
TSH at 28th days :		0.66 - 15	3.06 ± 3.49
Normal TSHat 28th days (,6-10 iu/ml)	**No.**	91	
	%	91	
Abnormal TSHat 28th days (>10iu/ml)	**No.**	9	
	%	9	
Free.T4 at 28th days :		0.3 – 1.9	1.02 ±.27
Normal F.T4 at 28th days (,8-2ng/dl)	**No.**	91	
	%	91	
Abnormal T4 at 28th days (<,8ng/dl)	**No.**	9	
	%	9	

Table (5) shows that the Mean of the TSH (3.06 ± 3.49) iu/ml and Free.T4 (1.02 ±.27) ng/dlز

Table (6): Thyroid screening among the studied Cases at 28th day

		No.	%
Cases	**Congenital hypothyroidism**	9	9.0
	Normal thyroid function	91	91.0

Table (6) shows that the studied cases were 9 cases with congenital hypothyrodism (9%) and 91 cases with normal thyroid function (91%).

Table (7): Correlation between thyroid function and Demographic data

			Cases with Congenital hypothyroidism	Cases with euthyrodism	X^2	P. value
Sex	**Male**	**No.**	7	50	1.742	.18
		%	77.8%	54.9%		
	Female	**No.**	2	41		
		%	22.2%	45.1%		
Mode of delivery	**CS**	**No.**	8	489	4.348	.011
		%	88.9%	53.8%		
	NVD	**No.**	1	42		
		%	11.1%	46.2%		
Residence	**RURAL**	**No.**	8	27	12.625	.001
		%	88.9%	29.7%		
	URBAN	**No.**	1	64		
		%	11.1%	70.3%		
Maternal history of thyroid disorders	**Yes**	**No.**	9	0	100.000	.001
		%	100.0%	.0%		
	No	**No.**	0	91		
		%	.0%	100.0%		
Maternal history of iodine intake	**Yes**	**No.**	5	0	53.216	.002
		%	55.6%	.0%		
	No	**No.**	4	91		
		%	44.4%	100.0%		
post natal age until 7th days	**Rang**		3 -7	5 – 7	**t.test** -7.315-	.001
	Mean ± SD		4.33 ± 1.12	6.34 ± 0.75		
post natal age from 28thdays	**Rang**		28 – 30	28 – 30	**t.test** .073	.942
	Mean ± SD		28.66 ± 0.71	28.65 ± 0.72		
Maternal age	**Rang**		21 – 38	19 – 34	**t.test** 9.111	.001
	Mean ± SD		33.89 ± 5.06	24.56 ± 2.66		

Table (7) This table show that there was statistically significant difference between both groups regarding mode of delievery, Residence, Maternal history of thyroid disorders, Maternal history of iodine intake and mothers age.

There were statistically significant decreases in post natal age until 7th days.

Table (8): Correlation between thyroid faction and Clinical assessment

		Cases with Congenital hypothyroidism	Cases with euthyrodism	t.test	P. value
Weight(kg)	**Rang**	2.11 - 4.10	2.60 - 4.10	-3.690-	.001
	Mean ± SD	2.76 ± 0.76	3.18 ± 0.25		
Length(cm)	**Rang**	49 – 50	49 – 53	-4.487-	.002
	Mean ± SD	49.42 ± 0.349	51.14 ± 1.138		
HC(cm)	**Rang**	34.80 - 38.50	33 – 38	5.702	.001
	Mean ± SD	37.52 ± 1.12	35.46 ± 1.03		
HR(b/m)	**Rang**	118 – 154	120 – 158	-3.974-	.0001
	Mean ± SD	124.22 ± 11.35	136.69 ± 8.74		
RR(c/m)	**Rang**	45 – 68	35 – 59	5.531	.001
	Mean ± SD	59.78 ± 9.52	48.32 ± 5.49		
Temperature	**Rang**	35.90 - 37.20	36.80 - 38.00	-8.486-	.0001
	Mean ± SD	36.41 ± 0.37	37.34 ± 0.31		

Table (8) this table show that, there were statistically significant increase in HC and RR and significant decrease in weight, length, HR and Temperature among Cases with Congenital hypothyroidism than Cases with euthyrodism.

Table (9): Comparison of results of thyroid function (TSH, T4) at 7^{th} days and 28^{th} day

		7^{th} days	28^{th} days	Paired t.test	P. value
Free.T4	**Mean ± SD**	1.09 ± .278	1.02 ± .273	-31.3-	0.000
TSH	**Mean ± SD**	2.27 ± 1.90	3.06 ±3.4	-84.6-	0.000

Table (9) there were statistically significant decreases in Free.T4 at 28^{th} days than 7^{th} days.

There were statistically significant increases in TSH at 28^{th} days than 7^{th} days.

DISCUSSION

This study showed that, congenital hypothyrodism among the studied Cases at 7^{th} days was (3%). While Cases at 28^{th} days were (9%).

This was comparable to rates of second-screen identified cases in previous single state studies where they found that 10.4% in the Northwest Regional Screening Program **(LaFranchi et al., 1985)**, 5.1% in Texas **(Levine and Therrell, 1986)**, 7.7% in Washington State **(Doyle et al., 1995)**, and 18.5% in Colorado

(Maniatis et al., 2006). All of the cases detected on the routine second screen in the current study appear to have been clinically significant. Although these cases appear normal at 1st screening.

CH is a common preventable cause of mental retardation. The overall incidence of CH ranges from 1 in 3000 to 1 in 4000 live births in different parts of the world, **(Valizadeh et al., 2011)**.

The incidences in Arab countries are as follows: Lebanon, 1 in 1823 **(Daher et al., 2003)**; Bahrain, 1 in 2967; **(Golbahar et al., 2010)** United Arab Emirates, 1 in 1778 **(Golbahar et al., 2010)**; Palestine, 1 in 2133 **(Khatib and Ayyad, 2014)**. These statistics indicate that the incidence of CH in Arab countries is greater than the global incidence. A study performed by the Atomic Energy Commission of Syria with the aid of the International Atomic Energy Agency and the collaboration of the ministries of Higher Education, Health, and Defense between 1995 and 2002 confirmed this finding. **(Hamadeh et al., 2002)** The fore mentioned study screened >40,000 newborns and noted a CH prevalence of 1 in 2176 **(Hamadeh et al., 2002)**.

(Saoud et al., 2019) A retrospective study performed for 5 years at Children's University Hospital, Damascus, identified 70 patients with CH, and the incidence of CH was 1 in 2259. Three of these patients had not undergone confirmatory testing (two were discharged after their parents took responsibility and one died before confirmation); therefore, 67 patients were included. This number of cases obtained does not reflect the frequency of this disease as specialist doctors can diagnose the condition in outpatient clinics and follow-up tests can be performed at any private laboratory.

This delayed diagnosis of CH in Syria might be associated with the lack of a newborn screening program. We compared our results with the results of previous studies. In a Danish study, **(Jacobsen and Brandt, 1981)** 10% of patients were diagnosed within the first month, 40% within the first three months, and 70% within the first year of life. In a Turkish study, **(Tarim and Yordam, 1992)** the mean age at diagnosis was 49.22 months, with 55.4% of patients diagnosed after 2 years of age and only 3.1% diagnosed during the neonatal period. In an Iraq study, **(Nasheiti, 2005)** the mean age of diagnosis was 2.3 years, and the authors diagnosed only 10 (25%) patients in the neonatal period.

This study showed that, there was no statistically significant difference between Cases with Congenital hypothyrodism and Cases with euthyrodism regarding sex.

This disagrees with **(Sun et al., 2011)** who found that, higher prevalence of CH among females than males.

The incidence is greater in females than in males (2:1) **(Agrawal et al., 2015)**.

In **(Saoud et al., 2019)** study, most of the patients were male, with a female: male ratio of 1:1.33.

Furthermore, our finding is inconsistent with the results of a Syrian study, **(Ramadan, 2011)** an Iraq study (female: male ratio of 1.6:1), **(Nasheiti, 2005)** Aturkish study who found (female; male ratio of 1.15;1) **(Jacobsen and Brandt, 1981)** This could be explained by a coincidental high rate of male births during the study period or by the nature of our society that tends to prefer and recognize males and pays more attention to males than to females.

This study showed that, there was statistically significant difference between Cases with Congenital hypothyrodism and Cases with euthyrodism regarding mother's history of thyroid disorders. Higher prevalence of CH among patients with positive mother's history of thyroid disorders.

A previous Iraq study reported parental consanguinity in 80% of patients and a family history of hypothyroidism in 60.7% of patients. **(Nasheiti, 2005)** Thus, it is important to educate the relatives of patients about the disease.

This study showed that, there was statistically significant difference between Cases with Congenital hypothyrodism and Cases with euthyrodism regarding mode of delivery. Higher prevalence of CH among patients with cesarean section (C/S) delivery.

This agrees with **(Hashemipour et al., 2010)** who reported that cesarean section (C/S)) and some unknown environmental factors such as micronutrients deficiency or other pollutants could be the probable cause of high prevalence of CH in different cities of the province.

Hemati et al., (2019) showed that 64.2% of neonates were delivered by C/S.

Supporting our data, a recent study by **(McElduff et al., 2005)** reported higher TSH levels at the

3rd day of life in babies delivered by C/S in a large cohort study of babies from thyroid screening.

In contrast, another study reported that the mean cord serum TSH level is higher in vaginal deliveries compared to elective C/S deliveries **(Turan et al., 2007)**.

The influence of the mode of delivery on the postnatal course of serum thyroxine (T4), free T4 (f-T4), and TSH has not been well characterized. It has also been claimed that anesthetic agents given to the mother and reaching the fetal circulation through the placenta may influence the postnatal course of thyroid adaptation **(Turan et al., 2007)**.

Our results showed that maternal history of thyroid disorders had a high risk for CH.

Weisz et al., (2005) found that, CH had history of maternal thyroid disorders.

This study showed that, there were statistically significant increases in maternal age among Cases with Congenital hypothyrodism than Cases with euthyrodism.

This agrees with results of a previous study in Turkey **(Kirmızibekmez et al., 2012)** who proposed that advanced maternal age may increase the risk of mutations in genes encoding some transcription factors associated with thyroid gland development.

This agrees also with another study **(Dayal et al., 2015)** who indicated that advanced maternal age was more common in children with thyroid dysgenesis.

This in agreement also with a study done by **(Turan et al., 2007)** who reported that children of older mothers (>39 years) had a higher incidence of CH (1:1,328) compared to younger mothers (<20 years, 1:1,703).

Our study showed that, there were statistically significant decrease in weight and length among Cases with Congenital hypothyrodism than Cases with euthyrodism

This agrees with **(Hemati et al., 2019)** who found that, there were statistically significant decrease in weight and length among Cases with Congenital hypothyroidism.

CH may be due to maternal factors such as iodine deficiency, excessive iodine intake, antithyroid medication or the presence of antibodies against thyroid tissue during pregnancy, low birth weight, prematurity, immaturity of thyroidal iodine organification, exposure to excess

iodine (use of iodinated disinfectants or contrast agents), and gene mutation.

CONCLUSION

From our study we concluded:

- Congenital Hypothyroidism may be missed in routine screening program at the 1st 4 days of life.
- Congenital hypothyroidism more common in babies delivered by cesarean section than NVD, Rural than urban and low birth weight.
- There are high risk factors of congenital hypothyroidism with maternal history of thyroid disorder, maternal history of iodine intake and maternal older age.

RECOMMENDATION

- Rescreening program of congenital hypothyroidism is very important to diagnose missed cases of congenital hypothyroidism in the 1st screening program, To avoid physical and mental disabilities in the future life of our kids.

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اعادة الفحص لوظائف الغدة الدرقية فى الاطفال حديثي الولادة

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قصور الغدة الدرقية الخلقي هو أكثر المسببات شيوعًا للتخلف العقلي الذي يمكن الوقاية منه وضعف النمو المعرفي، البدني بين الأطفال وهو أكثر شيوعًا بين السكان الآسيويين والإفريقيين.

نظرًا لأن الأعراض تظهر عادة عند الولادة، فإن أهمية الفحص واضحة. فيما يتعلق بالاختلافات في اختبارات وظائف الغدة الدرقية بين مختلف الأعمار والمناطق الجغرافية، فإن تحديد الفاصل الزمني المرجعي المحدد حسب العمر والمنطقة مطلوب للتشخيص الدقيق.

يعد فحص حديثي الولادة للكشف عن التهاب المفاصل الروماتويدي أحد أهم إنجازات الطب الوقائي. تم حل مشكلة قصور الغدة الدرقية الخلقي في البلدان المتقدمة عن طريق الفحص الروتيني لحديثي الولادة.

بسبب بعض حالات قصور الغدة الدرقية الخلقي قد يتم تفويتها عن طريق فحص حديثي الولادة الأول في اليوم الرابع من العمر، وبالتالي فإن فائدة الفحص الروتيني الثاني لل TSH

و T4 ستكون مهمة للكشف عن حالات قصور الغدة الدرقية الخلقية.

يكون معظم الأطفال المصابين بالتهاب المصل الطبيعي طبيعيين عند الولادة ولا تظهر عليهم أي علامات، مما يؤكد أهمية برنامج الفحص في الكشف المبكر عن قصور الغدة الدرقية الخلقي والكشف عن الحالات المفقودة منه.

الهدف من البحثِ: كان الهدف من هذه الدراسة هو تقييم هرمون TSH المنشط للغدة الدرقية و T4 خلال 7 أيام الاولى و بعد 28 يومًا للكشف عن حالات قصور الغدة الدرقية عند فحص حديثي الولادة.

المرضى وطرق البحث: أجريت هذه الدراسة على 100 طفل حديثي الولادة ولدوا في مستشفيات جامعة الزقازيق ومستشفى الأحرار.

تم إجراء الدراسة على فترة ولادة صحية كاملة ولدت في وحدة العناية المركزة لحديثي الولادة في مستشفى جامعة الزقازيق ومستشفى الأحرار وكانت قيد المتابعة لمتابعة TSH و Tt4 مجاني في 7 و28 يومًا من الحياة.

تم تصنيف المواليد الجدد إلى مجموعتين بناءً على أعمارهم في 7 و 28 يومًا من العمر.

تم كل ما يلي:

1. البيانات الديموغرافية للحالات المدروسة.

2. التقييم السريري للحالات المدروسة.

3. الاختبارات المعملية.

تم تقييم عينات المصل من أجل القياس الكمي لتركيز TSH وT4 مجانا بواسطة مقايسة الإنزيم المناعي واختبار مناعي إنزيم تنافسي.

النتائج المستنتجه من الدراسه:

- كان قصور الغدة الدرقية الخلقي بين الحالات المدروسة عند 7 أيام (3٪). كان قصور الغدة الدرقية الخلقي بين الحالات المدروسة عند 28 يومًا (9٪).

- أظهرت هذه الدراسة أنه لم يكن هناك فرق معتد به إحصائياً بين الحالات المصابة بقصور الغدة الدرقية الخلقي والحالات غير المصابه فيما يتعلق بالجنس.

- أظهرت هذه ارتفاع معدل انتشار قصور الغدة الدرقية الخلقي بين المرضى الذين لديهم تاريخ إيجابي من اضطرابات الغدة الدرقية.

- أظهرت هذه الدراسة أنه كان هناك فرق معتد به إحصائياً بين الحالات المصابة بقصور الغدة الدرقية الخلقي وارتفاع معدل انتشاره بين المرضى الذين تمت ولادتهم قيصريا.

- أظهرت هذه الدراسة أنه كانت هناك زيادة ذات دلالة إحصائية في سن الأم بين الحالات المصابة بقصور الغدة الدرقية الخلقي.

- أظهرت هذه الدراسة أنه كان هناك انخفاض معتد به إحصائيًا في الوزن والطول بين الحالات المصابة بقصور قصور الغدة الدرقية.

التوصيات:

بناءاً على ما سبق نوصي بأهمية اعادة الفحص لوظائف الغدة الدرقية فى الاطفال حديثي الولادة لتشخيص حالات قصور الغدة الدرقية التى فقدت فى الفحص الاولى.