Función tiroidea, anticuerpos tiroideos y desarrollo posnatal temprano en recién nacidos de madres con trastornos tiroideos.

Stoltefaut, M.; Fröschle, G.M.; Haddad, M.; Perez, A.; Blohm, M.E.; Deindl, P.; Singer, D.; Ebenebe, C.U.

Early Human Development, Vol. 167 Nr. Página: 105561Fecha de publicación: 01/04/2022

Resumen

ANTECEDENTES: La disfunción tiroidea durante el embarazo es relativamente común y puede causar complicaciones obstétricas e influir significativamente en el desarrollo fetal. OBJETIVOS: Nuestro objetivo fue evaluar las características clínicas y de laboratorio posnatales en los primeros días de vida en los bebés nacidos de madres con un trastorno de la tiroides.

DISEÑO DEL ESTUDIO Y SUJETOS: Realizamos un estudio retrospectivo de un solo centro con neonatos nacidos entre enero de 2010 y mayo de 2020. Se analizaron los parámetros de laboratorio tempranos y los hallazgos clínicos en neonatos de madres con diferentes trastornos de la tiroides materna.

RESULTADOS: Se incluyeron 314 recién nacidos de madres con tiroiditis de Hashimoto, 171 con hipotiroidismo no de Hashimoto, 42 con enfermedad de Graves, 12 con hipertiroidismo no de Graves y 190 recién nacidos de madres sin disfunción tiroidea. No se observaron diferencias demográficas, clínicas y de laboratorio entre los recién nacidos de madres con trastorno de la tiroides y madres sanas. FT3 y fT4 se correlacionaron positivamente con la edad gestacional ($p < 0,001$; $p < 0,001$) y negativamente con la máxima pérdida de peso posnatal ($p = 0,043$; $p < 0,001$). Los valores altos de fT3 se asociaron con niveles más bajos de bilirrubina máxima ($p = 0,020$).

CONCLUSIÓN: A pesar de un mayor riesgo de morbilidad debido a la exposición transplacentaria a anticuerpos maternos, la mayoría de los recién nacidos de madres con trastornos tiroideos muestran un desarrollo posnatal y pruebas de función tiroidea normales durante los primeros días de vida.

05561

ScienciaDirecta

Desarrollo Humano Temprano

revista Página de inicio: www.elsevier.com/locate/earlhumdev

Función tiroidea, anticuerpos tiroideos y desarrollo postnatal temprano en recién nacidos de madres con trastornos tiroideos

Meike Stoltefaut [a, 1], Glenn Malin Frogle.. [a, 1], Munif Haddad [b], Anna Perez [a], Martín Ernest Blohm [a], Philipp Deindl [a], Dominique Singer [a], ChineduUlrich Ebenebe [a, *]

[a] *División de Neonatología y Cuidados Intensivos Pediátricos, Hospital Infantil Universitario, Centro Médico Universitario Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburgo, Alemania*

[b] *Departamento de Química Clínica, Centro Médico Universitario Hamburg-Eppendorf, Martinistr. 52, Hamburgo 20246, Alemania*

INFORMACIÓN DEL ARTÍCULO

Palabras clave:
trastorno de la tiroides
hipotiroidismo
Graves' disease
tiroiditis de Hashimoto
neonato

RESUMEN

Fondo: Thyroid dysfunction during pregnancy is relatively common and can cause obstetric complications and significantly influence fetal development.

Aims: We aimed to evaluate postnatal clinical and laboratory characteristics in the first days of life in infants born to mothers with a thyroid disorder.

Study design and subjects: We conducted a retrospective single-center study with neonates born between January 2010 and May 2020. Early laboratory parameters and clinical findings in neonates of mothers with different maternal thyroid disorders were analysed.

Results: We included 314 newborns of mothers with Hashimoto's thyroiditis, 171 with non-Hashimoto's hypothyroidism, 42 with Graves' disease, 12 with non-Graves' hyperthyroidism, and 190 neonates born to mothers without thyroid dysfunction. No demographic, clinical, and laboratory differences were observed between neonates from mothers with a thyroid disorder and healthy mothers. FT3 and fT4 correlated positively with gestational age ($p < 0.001$; $p < 0.001$) and negatively with maximum postnatal weight loss ($p = 0.043$; $p < 0.001$). High fT3 values were associated with lower maximum bilirubin levels ($p = 0.020$).

Conclusion: Despite an increased morbidity risk due to the transplacental exposure to maternal antibodies, most neonates born to mothers with thyroid disorders show normal postnatal development and thyroid function tests during the first days of life.

1. Introduction

(TSH) receptor antibodies (TRAb) may be found in patients with

of women and subclinical hypothyroidism affecting possibly another 10% [1].

The most common cause of hypothyroidism during pregnancy in iodine-sufficient areas of the world is Hashimoto's thyroiditis (chronic autoimmune thyroiditis), characterized by specific thyroid autoantibodies [2]. These antibodies to thyroglobulin (ATG) and thyroid peroxidase (ATPO) can cross the placenta barrier, but the effect on the neonate is unclear [3]. Also blocking thyroid-stimulating hormone higher risk for low birth weight and congenital malformations of the circulatory system [5].

Graves' disease is the most common cause of hyperthyroidism, with a lifetime risk of 3% for women and a prevalence of 0.1%–2.7% in pregnancy [2,6,7]. It is caused by is an autoimmune inflammation of the thyroid mediated by TRAb, which can be detected in 80% to 95% of affected patients. In Graves' disease, stimulatory TRAb is five times more frequent than blocking TRAb [6]. Transplacentally transferred

Abbreviations: ATPO, anti-thyroid peroxidase antibodies; ATG, anti-thyroglobulin antibodies; fT3, free triiodothyronine; fT4, free thyroxine; GA, gestational age; IgG, immunoglobulin G; TG, thyroglobulin; TPO, thyroid peroxidase; TRAb, TSH receptor antibody; TSH, thyroid-stimulating hormone.

* Corresponding author.
E-mail address: c.ebenebe@uke.de (C.U. Ebenebe).
[1] These authors have contributed equally to this work and share the first authorship.

https://doi.org/10.1016/j.earlhumdev.2022.105561
Received 29 November 2021; Received in revised form 16 February 2022; Accepted 22 February 2022
Available online 26 February 2022

stimulating TRAb can cause the severe clinical picture of neonatal hyperthyroidism, including low birth weight, goiter, periorbital oedema hyperthermia, irritability, diarrhea, feeding problems, lack of weight gain, tachycardia, heart failure, elevated blood pressure, hepatosplenomegaly, cholestasis, and thrombocytopenia [6].

Due to the potential impact of maternal thyroid disorders on the foetus, we routinely measured thyroid blood values and antithyroid antibodies in all affected neonates during the last decade. This study retrospectively analyses the early postnatal development in a large cohort of infants born to mothers with thyroid disorders. We investigated correlations between maternal thyroid function, neonatal laboratory parameters, and early postnatal clinical findings.

2. Methods

2.1. Study design and subjects

We conducted a retrospective study with neonates born between

expressed as mean and standard deviation (SD). The strength of associations among thyroid parameters and between maternal thyroid function and neonatal characteristics and thyroid parameters was determined using the non-parametric Mann-Whitney *U* test. Correlations of continuous variables were analysed using Spearman's rank correlations. A two-tailed p-value <0.05 was considered significant. The Holm-Bonferroni method was applied to adjust the statistical inference of multiple comparisons.

3. Results

During the observational period, we identified 553 neonates from mothers with a diagnosed thyroid disorder. We excluded 14 neonates due to either an incomplete dataset or the presence of exclusion criteria. We included 314 newborns from mothers with Hashimoto's thyroiditis, 171 with non-Hashimoto's hypothyroidism, 42 with Graves' disease, and 12 with non-Graves' hyperthyroidism. The control group consisted of 190 healthy neonates born to mothers without thyroid dysfunction.

neonates born to mothers with thyroid disorders received laboratory diagnostic. Neonates were divided into four groups according to the maternal thyroid disorder: Hashimoto's thyroiditis, hypothyroidism (non-Hashimoto's thyroiditis), graves' disease, and hyperthyroidism (non-Graves' disease). Randomly selected healthy newborns of mothers with normal thyroid function served as a control group. We excluded neonates treated on the neonatal intensive care unit, born with a chromosomal aberration, or with a gestational age (GA) $< 36 + 0$ weeks.

Clinical patient data were obtained from the digital medical chart (Soarian, Siemens Healthcare, Erlangen, Germany) and included the following neonatal data: birth weight, gestational age, and maximum postnatal weight loss. Analysed neonatal serum values included TSH (as a part of the newborn metabolic screening) and total bilirubin in all neonates as well as free triiodothyronine (fT3), free thyroxine (fT4), ATPO, and ATG in neonates of mothers with thyroid dysfunction. We measured TRAb antibodies only in neonates from mothers with Graves' disease. In addition, we collected data regarding maternal thyroid disorder and their thyroid medication. Maternal thyroid laboratory values were not measured as part of our clinical routine.

The study protocol was approved by the ethics committee of the local medical chamber of Hamburg (2020-10105-BO-ff).

2.2. Laboratory procedures

Neonatal blood collection for thyroidal parameters was routinely conducted together with the newborn metabolic screening at the age of >36 h. The analysis of thyroid hormones and antibodies was performed by sandwich Immunoassays. For fT4, and fT3 the luminescent oxygen channeling technology (LOCI®) on the Dimension Vista® analyser (Siemens Healthineers, Erlangen, Germany), for TPO- and TG-antibodies paramagnetic microparticles as solid phase and direct chemiluminescence of acridinium ester for detection on the ADVIA Centaur XP-Analyser (Siemens Healthineers, Erlangen, Germany) and for Trab time-resolved amplified cryptate emission (TRAC technology) on the Kryptor analyser (Thermo Fischer Scientific, Dreieich, Germany) were used. TSH was measured from *dried blood* spots from the newborn metabolic screening using a dissociation-enhanced lanthanide fluorescence immunoassay (GSP Neonatal hTSH assay, PerkinElmer Life Sciences, Rodgau, Germany). Serum bilirubin was measured with a pointof-care blood gas analyser (ABL90 FLEX, Radiometer, Krefeld, Germany).

2.3. Statistical analysis

Statistical analysis was performed using SPPS Version 27 SPSS (IBM, NY, USA). Data on patient demographics and laboratory values are shown in Table 1. When compared to the control group, the only demographic variables that differed significantly were gestational age ($p < 0.001$), birth weight ($p < 0.001$), and birth weight percentile ($p = 0.008$) in neonates from mothers with non-Graves' hyperthyroidism. No differences in laboratory thyroid parameters between the different groups were observed. Depending on the thyroid disorder, 50–79% of the mothers received thyroid medication (Table 1).

The association between neonatal thyroid parameters and clinical characteristics and among neonatal thyroid parameters is shown in Table 2. FT3 and fT4 correlated positively with gestational age ($p < 0.001$; $p < 0.001$) and negatively with maximum postnatal weight loss ($p = 0.043$; $p < 0.001$). High fT3 values were associated with lower maximum bilirubin levels ($p = 0.020$). TSH correlated negatively with the weight percentile ($p = 0.026$) and postnatal maximum weight loss ($p = 0.009$). In patients with maternal Graves' disease, we observed no correlation between TRAb and clinical parameters or laboratory values.

4. Discussion

Various physiological thyroid function changes occur during pregnancy. Maternal thyroid dysfunction can cause not only obstetric complications, such as hypertension, placental abruption, and preterm delivery but can also significantly influence fetal development. Therefore, we aimed to evaluate postnatal clinical and laboratory characteristics in the first days of life in infants born to mothers with a thyroid disorder by comparing them with neonates of mothers with normal thyroid function.

Hypothyroidism occurs in about 2.5% of pregnancies, with autoimmune Hashimoto's thyroiditis being the most common cause, characterized by specific thyroid autoantibodies ATG and ATPO [1]. TRAb can also be found in Hashimoto's thyroiditis, although much less frequently and in much lower concentrations than in Graves' disease. Unlike TRAb, ATG and ATPO have no obvious pathophysiological potential but are surrogate inflammatory process parameters [3]. This study detected no demographic, clinical, and laboratory differences between neonates from mothers with hypothyroidism, including Hashimoto's thyroiditis, and neonates from healthy mothers (Table 1).

Hyperthyroidism occurs in 0.4–1.7% of pregnant women, with the most common cause being Graves' disease [7,8]. The probability of neonatal hyperthyroidism has been reported to correlate with the level of TRAb concentration [9]. However, we detected no correlation between TRAb levels and clinical parameters or thyroid laboratory values.

Observed neonatal hyperthyroidism symptoms may be increased excitability, insufficient weight gain, vomiting, diarrhea, fever, sweats, tachycardia, or goiter. Since thyrostatic drugs are also transplacentally transmitted, they may affect the child's thyroid function until they are

Table 1

Neoanatal demographic characteristics and thyroid serum values in the different maternal thyroid function groups.

Characteristics	Control n = 190	Hashimoto's thyroiditis n = 314	Hypothyroidism n = 171	Graves' disease n = 42	Hyperthyroidism n = 12
Demographics					
Gestational age, weeks	39.6 (1.3)	39.3 (1.3)	39.4 (1.4)	39.4 (1.4)	38.0 (0.7)**
Birth weight, g	3452 (430)	3378 (512)	3405 (483)	3386 (546)	2803 (413)**
Weight percentile, %	49.7 (26.9)	47 (29)	47 (29)	47 (32)	23 (24)**
Maximal weight loss, %	7.0 (2.2)	7.2 (2.2)	6.9 (2.3)	6.7 (2.5)	6.8 (2.4)
Laboratory values					
Highest total bilirubin, mg/dl	8.7 (4.4)	8.3 (4.0)	8.3 (4.4)	7.5 (4.6)	8.1 (2.6)
TSH, μU/l	3.1 (1.6)	3.1 (1.6)	3.1 (1.6)	2.8 (2.3)	3.8 (2.9)
FT3, pmol/l	N/A	6.1 (1.8)	5.8 (1.7)	6.7 (2.6)	5.5 (1.3)
FT4, pmol/l	N/A	40.0 (8.7)	37.7 (7.0)	40.3 (11.2)	44.8 (9.0)
ATPO, kU/l	N/A	480 (904)	366 (581)	226 (338)	360 (578)
ATG, kU/l	N/A	43.0 (46.3)	43.3 (62.8)	35.0 (57.9)	17.6 (4.5)
TRAb, U/l	N/A	N/A	N/A	5.0 (11.3)	N/A
Maternal thyroid medication, n (%)					
Levothyroxine	0	247 (78.7)	128 (75.3)	17 (40.5)	0
Carbimazole	0	0	0	5 (11.9)	4 (33.3)
Methimazole	0	0	0	3 (7.1)	1 (8.3)
Propylthiouracil	0	0	0	4 (9.5)	1 (8.3)
None	190 (100.0)	67 (21.3)	42 (24.7)	13 (31.0)	6 (50.0)

Values are shown as mean and (SD) unless stated otherwise.

Values were compared between the different groups using the Mann-Whitney *U* test.

P values were adjusted using Holm–Bonferroni method (*p < 0.05, **p < 0.01).

Abbreviations: N/A, not applicable; fT3, free triiodothyronine; fT4, free thyroxine; TSH, thyroid-stimulating hormone; ATPO anti-thyroid peroxidase antibodies; ATG, anti-thyroglobulin antibodies.

Table 2

Association between neonatal thyroid parameters and clinical characteristics and among neonatal thyroid parameters.

Characteristics	FT3	FT4	TSH	ATPO	ATG	TRAb
Gestational age	0.249**	0.116*	0.016	0.052	0.047	0.188
Birth weight	0.060	0.015	0.065	0.079	0.091	0.655
Weight percentile	0.045	0.068	0.104*	0.070	0.101	0.532
Maximum weight loss	0.268**	0.103*	0.098*	0.077	0.033	0.328
Highest bilirubin value	0.103*	0.043	0.019	0.013	0.002	0.228
FT3		0.571**	0.269**	0.030	0.065	0.173
FT4	0.571**		0.169**	0.044	0.015	0.203
TSH	0.269**	0.169**		0.037	0.033	0.320
ATPO	0.030	0.044	0.037		0.348**	0.111
ATG	0.065	0.015	0.033	0.348**		0.038

Values are shown as correlation coefficients. P values were adjusted using Holm–Bonferroni method (*p < 0.05, **p < 0.01).

TRAb was only measured in patients with maternal Graves' disease.

Abbreviations: fT3, free triiodothyronine; fT4, free thyroxine; TSH, thyroid-stimulating hormone; ATPO anti-thyroid peroxidase antibodies; ATG, anti-thyroglobulin antibodies.

a latency, which is one possible reason we did not detect specific clinical or laboratory characteristics in neonates born to mothers with Graves' disease. Nevertheless, neonatal hyperthyroidism due to maternal Graves' disease requires early recognition and treatment to prevent potential morbidity or mortality. Therefore, in neonates with maternal Graves' disease, van der Kaay et al. recommends determining TRAb as soon as possible to discharge those newborns with negative antibodies from follow-up and perform thyroid function tests initially at 3 to 5 and 10 to 14 days of life to identify delayed onset of overt neonatal hyperthyroidism [6].

Remarkably, in this study, neonates from mothers with non-Graves' hyperthyroidism had a significantly lower gestational age at birth ($p < 0.001$) and lower birth weight percentiles ($p = 0.008$) compared to the control group. However, this was probably because six out of twelve neonates in this group were twins with consecutive lower GA and birth weight. There were no differences between neonates from mothers with hyperthyroidism and healthy mothers when corrected for multiple pregnancies. The high percentage of twins in this group seems to be a coincidence. Conception occurred via in vitro fertilization in only one pregnancy.

antithyroid drugs have been associated with fetal hyperthyroidism and an increased risk of congenital malformations [11]. This study detected no apparent influence of maternal medical thyroid therapy on early neonatal development, consistent with data from Millar et al. [12].

Neonatal fT3 and fT4 correlated positively with gestational age ($p < 0.001$), which can be explained by the fact that fT3 and fT4 are lower in premature infants due to their immature thyroid hormone axis, generally without elevation of serum TSH levels [13]. Interestingly, fT3 and fT4 correlated negatively with the maximum postnatal weight loss ($p = 0.043$; $p < 0.001$). Although hypothyroidism is associated with failure to thrive [14], it is difficult to distinguish whether, in our cohort, increased weight loss was a result of low thyroid hormones or due to an underlying subclinical condition leading to both mild hypothyroidism and lethargy with insufficient drinking. High fT3 values were associated with lower maximum bilirubin levels ($p = 0.020$), consistent with findings that neonatal jaundice has been associated with congenital hypothyroidism [15]. However, we detected no association between maternal thyroid dysfunction and neonatal bilirubin values. A significant positive correlation between ATPO and ATG in our study was most likely due to the coexistence of these antibodies in Hashimoto thyroiditis. None of the

antibodies correlated with measured clinical parameters. Also, no differences in laboratory thyroid parameters between the different groups were observed.

This study has some limitations. Due to the study's retrospective design, we had to rely on the accuracy of the anamnestic data regarding the maternal thyroid disorder. We did not routinely analyse maternal thyroid parameters at admission for delivery, so we could not correlate them with the neonatal parameters. Also, we did not trace the development of the infants beyond the first days of life, notably the evolution of antibody-associated neonatal thyroid dysfunction in the first postnatal weeks.

5. Conclusion

Despite an increased morbidity risk due to a maternal thyroid hormone imbalance and the transplacental exposure to maternal antibodies, most neonates born to mothers with thyroid disorders show normal postnatal development and thyroid function tests during the first

Acknowledgements

None.

References

[1] N. Nathan, S.D. Sullivan, Thyroid disorders during pregnancy, Endocrinol. Metab. Clin. N. Am. 43 (2) (2014) 573–597.
[2] G. Krassas, S.N. Karras, N. Pontikides, Thyroid diseases during pregnancy: a number of important issues, Hormones (Athens) 14 (1) (2015) 59–69.
[3] F.S. Balucan, S.A. Morshed, T.F. Davies, Thyroid autoantibodies in pregnancy: their role, regulation and clinical relevance, J. Thyroid. Res. 2013 (2013), 182472.
[4] Y.K. Chen, C.L. Lin, Y.J. Chang, F.T.F. Cheng, C.L. Peng, F.C. Sung, et al., Cancer risk in patients with Graves' disease: a nationwide cohort study, Thyroid 23 (7) (2013) 880–885.
[5] J.E. Haddow, G.E. Palomaki, W.C. Allan, J.R. Williams, G.J. Knight, J. Gagnon, et al., Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child, N. Engl. J. Med. 341 (8) (1999) 549–555.
[6] D.C. van der Kaay, J.D. Wasserman, M.R. Palmert, Management of neonates born to mothers with Graves' disease, Pediatrics 137 (4) (2016).

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Meike Stoltefaut: Methodology, Formal analysis, Investigation, Writing - original draft.

Glenn Malin Froschle: Methodology, Formal analysis, Investigation, Writing - original draft.

Munif Haddad: Resources, Writing - review & editing.

Anna Perez: Visualization, Writing - review & editing.

Martin Ernst Blohm: Visualization, Writing - review & editing.

Philipp Deindl: Visualization, Writing - review & editing.

Dominique Singer: Resources, Writing - review & editing.

Chinedu Ulrich Ebenebe: Conceptualization, Methodology, Formal analysis, Writing - original draft, Supervision, Project administration.

Declaration of competing interest

None.

1552–1565.

[9] J. Abeillon-du Payrat, K. Chikh, N. Bossard, P. Bretones, P. Gaucherand, O. Claris, et al., Predictive value of maternal second-generation thyroid-binding inhibitory immunoglobulin assay for neonatal autoimmune hyperthyroidism, Eur. J. Endocrinol. 171 (4) (2014) 451–460.

[10] A. Besancon, J. Beltrand, I. Le Gac, D. Luton, M. Polak, Management of neonates born to women with Graves' disease: a cohort study, Eur. J. Endocrinol. 170 (6) (2014) 855–862.

[11] D.S. Cooper, P. Laurberg, Hyperthyroidism in pregnancy, Lancet Diabetes Endocrinol. 1 (3) (2013) 238–249.

[12] L.K. Millar, D.A. Wing, A.S. Leung, P.P. Koonings, M.N. Montoro, J.H. Mestman, Low birth weight and preeclampsia in pregnancies complicated by hyperthyroidism, Obstet. Gynecol. 84 (6) (1994) 946–949.

[13] F.L.R. Williams, J. Simpson, C. Delahunty, S.A. Ogston, J.J. Bongers-Schokking, N. Murphy, et al., Developmental trends in cord and postpartum serum thyroid hormones in preterm infants, J. Clin. Endocr. Metab. 89 (11) (2004) 5314–5320.

[14] J. Alm, L. Hagenfeldt, A. Larsson, K. Lundberg, Incidence of congenital hypothyroidism: retrospective study of neonatal laboratory screening versus clinical symptoms as indicators leading to diagnosis, Br. Med. J. (Clin. Res. Ed.) 289 (6453) (1984) 1171–1175.

[15] C.F. Hinton, K.B. Harris, L. Borgfeld, M. Drummond-Borg, R. Eaton, F. Lorey, et al., Trends in incidence rates of congenital hypothyroidism related to select demographic factors: data from the United States, California, Massachusetts, New York, and Texas, Pediatrics 125 (Suppl 2) (2010) S37–S47.