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Review

Long term outcomes of infants born by mothers with thyroid dysfunction during pregnancy

Laura Lucaccioni[1], Monica Ficara[2], Valentina Cenciarelli[2], Alberto Berardi[1], Barbara Predieri[3], Lorenzo Iughetti[2,3]

[1]Neonatal Intensive Care Unit, Department of Medical and Surgical Sciences of the Mother, Children and Adults, University of Modena and Reggio Emilia, Modena, Italy; [2]Post-graduate school of Pediatric, Department of Medical and Surgical Sciences of the Mother, Children and Adults. University of Modena and Reggio Emilia, Modena, Italy; [3]Pediatric Unit, Department of Medical and Surgical Sciences for Mothers, Children and Adults, University of Modena and Reggio Emilia, , Italy.

Abstract. According to Barker's hypothesis, sub-optimal conditions during gestation might affect the predisposition for diseases in adulthood. Alteration in endocrine functions during pregnancy, such us thyroid function or glucose metabolism, are not exempt. It is well known that subclinical hypothyroidism and thyroperoxidase antibodies-positive euthyroidism during early pregnancy are associated with increased risk of gestational diabetes mellitus and both conditions influence pregnancy outcome and newborn development and metabolism at short and long terms. Fetal production of thyroid hormones starts from the 12th week of gestational age. The transplacental passage of maternal thyroxine (T4) is therefore essential for the fetal neurological development, especially during the first half of pregnancy. If this passage is interrupted, such as in premature birth, neonates are more susceptible to develop impaired thyroid function, because of physiological immaturity of their hypothalamic-pituitary-thyroid axis, acute illnesses and stressful events (sepsis, invasive procedures, drugs). The aim of this review is to investigate the short and long term effects of maternal dysthyroidisms on term and preterm newborns, with particular attention to the metabolic and thyroid consequences. Metabolic syndrome, higher body mass index and greater waist circumference, seem to be more prevalent in children of TPO-Ab-positive mothers. Maternal hypothyroidism may be associated with higher risk of gestational diabetes and adverse birth outcomes, such as preeclampsia, preterm delivery, fetal death and low birth weight offspring. In adulthood, preterm (< 37 weeks of gestational age) or low birth weight (<2.500 g) newborns seem to be more susceptible to develop gestational diabetes, preeclampsia, type 2 diabetes mellitus and behavioral alterations. (www.actabiomedica.it)

Key words: Thyroid; Pregnancy; Intra uterine growth restriction; Small for Gestational Age; Prematurity

Introduction

Interest on the relationship between prematurity and endocrine diseases is rising, seen the increased incidence of preterm birth and the better survival rate compared to the previous decades. The development of endocrine disorders in offsprings is influenced not only by the gestational age at birth and the consequent duration of hospitalization, but also by pregnancy factors. The restriction of fetal growth during pregnancy, most of times due to placental flux alterations, seems to influence the development of metabolic disorders later in life (obesity, increased risk of hypertension and insulin-resistance) (1). Different authors have investigated whether maternal thyroid function during pregnancy affect thyroid function of the offspring later in life (2,3,4,5,6). Data are often controversial because of different methods for assessing thyroid function, but a link is often described. Although the incidence of persistent hypothyroidism does not appear to differ

from term and preterm infants, the risk of transient hypothyroidism is higher in the latters (7). Aim of our work is to review the most significant reports regarding the relationship between prematurity/dysmaturity and the endocrine/metabolic future in the offspring.

1.Correlation between maternal hypothyroidism and gestational diabetes mellitus

Pregnancy may strongly influence women future health because of the many challenges that gestation presents for several organ systems. During pregnancy thyroid function undergoes physiological changes as the increase of thyroid hormone-binding globulin, thyroid hormones and thyroglobulin concentrations, the increased elimination of iodine through the kidneys, the thyrotropic effect of the rising human chorionic gonadotropin (8). Failure to adapt to physiological changes results in thyroid dysfunction, especially if complicated by the presence of thyroid antibodies.

Thyroid diseases affect approximately 4% of pregnancies (9). Hypothyroidism seems to be associated with an increased risk of perinatal adverse outcomes in both the mother and the fetus (hypertension, anemia, post-partum hemorrhage, spontaneous abortion (10), fetal death (11) and neonatal low birth weight (12), The effects of subclinical hypothyroidism on pregnancy are controversial.

In the last few years, the correlation between maternal thyroid dysfunction during pregnancy and adverse obstetric and perinatal outcomes has been largely investigated. Several epidemiological studies have recently analysed whether the abnormal thyroid function during pregnancy is linked with higher risk of gestational diabetes mellitus (DGM), focusing mainly on the role of anti-thyroid antibodies (TPOAb and TGAb).

GDM can be defined as "any degree of glucose intolerance with onset or first recognition during pregnancy" (13). The prevalence of DGM ranges between 1.7% and 11.6% in industrialized countries (14). GDM may be considered as the most common complication affecting women during pregnancy; several studies have investigated its association with different adverse pregnancy outcomes, such as preterm birth, excessive fetal growth, increased risk of birth trauma and neonatal metabolic abnormalities (15). Furthermore, women with GDM seem to be more susceptible to developing Type-2 Diabetes Mellitus (TDM2) and hypertension later in life (16).

The possible relationship between maternal thyroid dysfunction and GDM was hypothesized in the role of thyroid dysfunction in increasing insulin-resistance, although results seem to be rather conflicting (17).

Casey et al. realized a large prospective study including 17,298 pregnant women, whose thyroid function (TSH, fT4, TPOAb) was analysed during the first trimester of gestation. Women with isolated hypothyroxinemia and euthyroid ones had similar rates of adverse pregnancy outcomes. Compared to the normal cohort, women with SCH (considered as TSH> 3 mU/L) showed a higher incidence of placental abruption (p: 0.03), preterm delivery (p: 0.005 for gestational age lower than 36 weeks) and GDM (p<0.01). These differences were also observed after adjustment for maternal confounding factors such as age, weight, ethnicity and number of previous deliveries (OR 1.47, 95% confidence interval 1.1-2.0). Furthermore, the evaluation of TPOAb did not affect the significant differences among the three groups. On the basis of populations' numbers, authors also created gestational age-specific nomograms for TSH and fT4 during the first trimester of pregnancy (18).

Tudela et al found similar results enrolling 24,883 pregnant women, whose thyroid function was evaluated. The development of GDM increased with increasing levels of TSH (p: 0.002). Moreover, TSH persisted as a significant predictor of GDM when logistic regression model was used (p: 0.001). Furthermore, the risk of GDM appeared higher in the cohort with subclinical hypothyroidism than in the cohort with normal thyroid function, although the significance was borderline after adjustment for confounding factors (p 0.056). A potential limit of Tudela's study is the disproportion observed in the distribution of ethnic groups with greater prevalence of African-American and Hispanic ethnics (19).

Karakosta et al found that the risk of GDM was 4-fold increased if high levels of TSH were associated with thyroid-positive autoimmunity (RR 4.3, 95% CI 2.1-8.9), although there was no data on maternal

treatments that may affect thyroid function (e.g: amiodarone) (20).

On the contrary, Männistö et al described different results, finding that maternal thyroid dysfunction during pregnancy and the positivity for anti-thyroid antibodies seem not to be associated with pregnancy complications themselves, but with later thyroid disease and higher risk of diabetes. In fact, overt hypothyroidism during pregnancy was found to be associated with the development of TDM2 [HR (95% CI), 6.0 (2.2-16.4)] and thyroid disorders [HR (95% CI), 17.7 (7.8-40.6)] in women later in life. Authors underline how women with thyroid disease are generally older and heavier than euthyroid ones and this could have been one of the main bias of previous studies detecting association between alteration of thyroid function and complications during pregnancy. Older age and higher Body Mass Index (BMI) could also promote the onset of glucose metabolism alterations and this could also explain in a certain way the association between GDM and hypothyroidism (21).

Agarwal et al supported the absence of a relationship between risk of developing GDM and thyroid dysfunction with or without autoantibody positivity during pregnancy. However, the population studied was rather small (301 women) (22). Chen et al found the same conclusions but their study was burdened by two main limitations: lack of information about anti-thyroid autoimmunity and data were only from a single centre (23). Plowden et al also did not find any relationship between maternal thyroid disease and GDM although, interestingly, authors showed available data on the thyroid status before conception (24). According to Cleary-Goldman et al, subclinical hypothyroidism is not related to an increased risk of complications during pregnancy. Nevertheless, maternal hypothyroxinemia seems to be associated with preterm birth (aOR 1.62; 95% CI 1.00-2.62) and macrosomia (aOR 1.97; 95% CI 1.37-2.83) in the first trimester and to GDM (aOR 1.7; 95% CI 1.02-2.84) in the second trimester. The study includes more than 10,000 patients, although women with thyroid hypo-function represented only a small group (25).

All the mentioned studies have delivered conflicting results, and several meta-analyses have not been able to find a common thread by increasing statistical power. Meta-analyses by Yang et al is so far the most useful to clarify the diatribe about the relationship between GDM and maternal thyroid dysfunction by focusing on the role of anti-thyroid antibodies. 167 potentially relevant publications were identified and 20 were included in the meta-analysis, suggesting a significant, but not strong, relationship between anti-thyroid antibodies and risk of GDM (overall combined RR 1.12; 95% CI 1.03-1.22); furthermore, it only applies to women with thyroid dysfunction (pooled RR 1.35, 95% CI 1.06-1.71). Euthyroid women do not present increased risk of GDM even if their anti-thyroid antibodies are positive. The strength of Yang meta-analyses is the kind of studies included, not only case-control studies but also prospective cohort studies (26). We may identify a limitation due to the fact that prevalent ethnical group was Chinese reducing the possibility of generalizing the results. However, meta-analyzes by Toulis et al reached the same conclusions about the different role of anti-thyroid antibodies according to maternal thyroid status (27).

2.Short term effects of maternal hypothyroidism during pregnancy on newborns

During the first half of pregnancy, fetal thyroid is not yet able to produce hormones by itself, making the fetus entirely dependent on maternal production. Fetal thyroid gland begins to develop around the 10-12 weeks of gestation and only completes at the end of pregnancy; moreover, fetal secretion of fT4 begins at 18-20 weeks (28). Maternal thyroid hormones cross the placenta and play a pivotal role in fetal neurodevelopment, influencing several parameters in fetal brain. In healthy pregnancies, infant neurodevelopment correlates directly with maternal plasma fT4 levels during the first trimester (29). Maternal hypothyroidism during pregnancy is associated with impaired cognitive and motor function in children (30). Moreover, it is well documented how neonatal overt hypothyroidism is associated with abnormal neurological development and, if not treated, could lead to mental retardation due to the fact that thyroid hormone regulates most stages of neuronal and glial cell development.

An adequate fetal supply of fT4 is also important for the development of pituitary-thyroid axis and the physiological cardiovascular homeostasis in uterus (31). Pickard et al suggested that consequences of hypothyroidism during pregnancy may be characterized by abnormal fetal-placental glucose metabolism and abnormal fetal growth. In detail, the more severe the hypothyroidism, the lower fetal weight and volume of brain and liver is registered. An abnormal fetal-placental glucose metabolism has been supposed because the fetuses of hypothyroid mothers have decreased hepatic glycogen stores (32). Moreover, Karakosta et al found that high TSH levels during pregnancy were associated with an increased risk of low birth weight (LBW – birth weight lower than 2500 grams) (RR 2.6, 95% CI 1.1-5.9), and the risk increased of 3-fold if thyroid-positive autoimmunity was present (RR 3.1, 95% CI 1.1-2.8) (20).

Newborns from women affected by SCH presented higher rate of LBW (P<0.001; adjusted OR, 2.919; 95% CI, 1.650-5.163) than newborns to euthyroid mothers. However, Plowden et al in a prospective cohort study found that SCH was not associated with preterm delivery and preeclampsia (adjusted relative risk, 0.77 [CI 0.40-1.47] and 1.20 [0.71-2.04], respectively). Similarly, no relationship between thyroid antibodies and preterm delivery or preeclampsia was observed (adjusted relative risk, 1.26 [CI 0.65-2.45] and 1.02 [0.54-1.92], respectively) (24). Instead, Su et al assessed that SCH is associated with an increased likelihood of preterm delivery and fetal distress (OR 3.32, CI [1.22–9.05], OR 3.65 CI [1.44 –9.26], respectively). Hypothyroidism appeared associated with higher risk of fetal loss, LBW, and congenital circulation system malformations (OR 13.45 [2.54 –71.20], 9.05 [1.01– 80.90], and 10.44 [1.15–94.62], respectively) (12).

Maternal thyroid dysfunction may compromise neonatal thyroid function. A valid method to identify neonatal hypothyroidism is TSH screening, performed at 2-3 days of life. Rovelli et al (2010) analyzed the thyroid function of 129 neonates born from mothers with autoimmune thyroiditis due to TPOAb. They found that 23,2% of newborns presented a pathologic TSH value (median value: 11.86 mU/L, range 8,54 – 35,37 mU/L) at the 3rd – 4th day of life. However, only 2.2% of them required replacement therapy for persistent hypothyroxinemia, suggesting that thyroid dysfunction is usually transitory (33,34). Ozdemir et al (2013) showed that newborns of mothers with thyroid disorders (autoimmune hypothyroidism or hypothyroidism without TGAb and TPOAb) had a higher recall rate to repeat TSH screening (p=0.002) and increased risk of transient thyroid dysfunction in the first 8 weeks of life (35). Dussault and Fisher reported that the prevalence of neonatal transient hypothyroidism was higher in the infants whose mothers were affected by autoimmune thyroid disease compared to newborns with healthy mothers (27% vs 15%; p=0.04). Offspring of women with Graves disease could have higher risk of both hypothyroidism and hyperthyroidism through the trans-placental transfer of synthetic anti-thyroid drugs or maternal TRAbs, respectively (36). Banigè et al analyzed retrospectively the offspring of 417 women with Graves disease and positivity for TRAbs during pregnancy. They found that TRAbs levels may be considered the strongest independent predictor of fetal and neonatal dysthyroidisms. Cut-off of maternal TRABs predictive of neonatal dysthyroidisms seems to be 5.9 UI/L, instead cut-off of neonatal TRABs suggestive of neonatal thyroid disease is 6.8 UI/L. Fetal thyroid gland ultrasound could be useful for predicting the risk of neonatal thyroid disease, even though it presents few limitations, such as that it can be performed only after 22 days of post-conceptional age, and that a cutoff of maternal TRABs to recommend fetal thyroid ultrasound is not yet available (37).

3.Alteration of thyroid function during pregnancy and its effect during childhood, adolescence and adulthood

Metabolic and cardiovascular effects

During pregnancy, maternal thyroid hormones seem to affect metabolic and cardio-vascular assessment of the offspring. However, little is known about the long-term effects of the offspring exposed to maternal thyroid abnormalities during fetal life. An experimental animal study showed that thyroid hormones may affect cardiovascular and metabolic

function both directly by acting on the tissues (heart, skeleton, fat) and indirectly by acting on hypothalamic regulatory center. Therefore, pregnancy thyroid disease might represent an epigenetic risk factor for the development of cardiovascular pathologies (38). Vujovic et al have suggested the importance of the maternal thyroid hormones in susceptibility of developing metabolic diseases in adulthood. Mice expressing the mutant thyroid hormone receptor TRalpha1R384C had a 10-fold reduced affinity to the ligand T(3), showing increased metabolism (39). Maternal thyroid status during pregnancy could affect liver phenotype in adulthood. Two interesting studies have been presented on the relation between maternal thyroid status and the development of metabolic consequences in the offspring later in life (40,41). Rytter et al showed a link between subclinical hypothyroidism during pregnancy and increased blood pressure at the age of 20 years (difference in systolic blood pressure: 3.7, 95% CI: 0.6, 6.8 mmHg and difference in diastolic blood pressure: 2.5, 95% CI: 0.2, 4.9 mmHg compared to offspring of euthyroid mothers). The study was based on a large Danish population born between 1988-1989 and followed up in 2008-2009, with 425 young adults who underwent blood pressure evaluation. The same result was also observed in the offspring of women with subclinical hyperthyroidism, although the sample size was too small (only 13 patients). The same association between maternal thyroid function and adiposity at 20 years of age was not found, although information on the anthropometric data were self-reported (40). Godoy et al reported no association between maternal subclinical hypo/hyperthyroidism and adiposity and blood pressure in offspring at the age of 6 years. It was observed that lower TSH levels were associated with lower Body Mass Index (BMI) and lower diastolic blood pressure in the offspring at the age of 6 years. Although thyroid function was studied in 5961 mothers, the group of mothers with thyroid disease was small. The relative short term follow-up, especially if compared with to the study of Rytter and coauthors, may have influenced the results (41). A recent 2017 study investigated the relationship between maternal or Ab positive thyroid dysfunction during pregnancy and the development of cardio-metabolic risk factors in children at the age of 16 years. Heikkinen et al. found that TPO-Ab-positive mothers had more often children with increased waist circumference or overweight (OR, 1.69; 95% CI, 1.14 to 2.50 and OR, 1.56; 95% CI, 1.04 to 2.34, respectively), both factors suggestive of increased cardio-metabolic risk. No association between maternal thyroid dysfunction or Tg-Ab positivity and cardio-metabolic risk factors in children was observed (42).

Endocrine effects

Cuestas et al investigated whether transient neonatal hypertirotropinemia (TNH) affects neurodevelopment, growth and/or promote the onset of permanent hypertirotropinemia (PH) in childhood. Through a relatively large, randomized, longitudinal cohort study, 65 children were evaluated at the age of 6 years through their thyroid function, linear growth and cognitive development. The authors found that children with TNH had a higher risk of developing PH later in childhood (RR 5.7, 95% CI 1.5-22.1, p = 0.00114). No effects on linear growth was observed. The use of specific questionnaires revealed that children with a history of TNH were more susceptible to the developing of "suspected developmental delay". Some studies presented similar results on the risk of developing PH later in life. However, Cuestas showed a lower prevalence of PH in children with a history of TNH than the other authors. These differences may be explained by the different methods for assessing thyroid function and different upper limits of confidence intervals (2). Päkkilä et al found that hypothyroid mothers more often had hypothyroid children (OR [95% CI] 3.4 [1.8-6.5]) and hyperthyroid mothers more often had hyperthyroid children (OR [95% CI] 4.1 [1.7-9.8]). Moreover, TPO-Ab-positive mothers more often had children with positive thyroid autoimmunity, mostly if boys (p = 0.021) (6).

Neuropsychiatric effects

Haddow et al investigated prospectively the intellectual development of 8-10 years old children born to mothers with thyroid disease (different degrees of hypofunction). They found out that the study population had an IQ 4 points lower than the control group.

Moreover, cases performed poorer on attention, language, intelligence, reading, motor and visual-spatial performances. Interestingly, the lower intellectual and academic performances were also associated with a mild and asymptomatic maternal hypothyroidism. The most common cause was an autoimmune maternal thyroid disease (30). Pop et al investigated the neurological development of 22 children born to mothers with low-normal T4 concentrations during early pregnancy (<10.4 pmol/L). Their performances, assessed at 22 months by using the Bayley Psychomotor Developmental Index (PDI), was lower than the control. These two studies stated that maternal thyroid hypofunction during early pregnancy, even if mild and asymptomatic, may be associated with abnormalities of neurological development in the offspring. 20% of preterm neonates have a condition of transient hypothyroidism (29).

4. Effects of intra uterine growth restriction on thyroid function

Neonates Small for Gestational Age (SGA) and thyroid function

Physiologically, at birth the exposure to colder temperatures than the intra-uterine, promotes the increase of TSH levels that stimulates the production of thyroid hormones. During the first week of life, fT4 reaches the highest levels in life. fT3 levels continue to increase during the first 28 days because of both increased levels of TSH and increased postnatal expression of deiodinase D1. Approximately 30 minutes after birth, a significant increase in serum TSH levels (up to 60-70 μU/L) occurs.

A neonate is defined "Small for Gestational Age" (SGA) if his/her weight and/or length are below the average of the general population of at least less than 2 Standard Deviations (SD) (corresponding to the 2.3th percentile) (43). Genetic factors, nutritional maternal status, placental function, intrauterine hormones may affect fetal growth (44). Several studies suggested a relationship between the restriction of fetal growth and the development of metabolic disorders later in life (obesity, increased risk of hypertension and type 2 diabetes) (1). Few studies investigated neonatal thyroid function by comparing AGA infants to SGA neonates. Moreover, results are often contrasting because of different methodology and timing. Studies conducted on animal models showed that SGA fetuses were characterized by lower T3, T4 and fT4 levels compared to AGA fetuses, while TSH levels overlapped. Some studies investigated human fetal thyroid function through cordocentesis by concluding that SGA infants had lower T4 and fT4 levels. Results related to TSH levels were rather controversial. Authors suggested that SGA infants had no significantly higher TSH levels compared to AGA ones (45,46,47). Rashmi et al found no relation among cord blood TSH levels, IUGR and gender, but amounts of TSH seemed to be negatively influenced by gestational age and birth weight (46). According to Nieto-Diaz et al, compared to AGA newborns, SGA neonates showed at birth significantly lower cord blood levels of TSH and IGF-1 (48). Hypothalamic-pituitary-thyroid axis response to TRH stimulation seem to be similar in SGA and AGA infants (49). Radetti et al studied 40 children at the age of 6.7±1.7, SGA both preterm (n=26) and full-term (n=14). Control group was composed of children, born AGA, matched for age and gender. Children born SGA had higher TSH and FT3 levels compared to AGA ($p < 0.0001$). No difference was observed for T4, RT3 and FT3/RT3 ratio. Thyroid ultrasound was normal for all the children as well as urinary iodine excretion. Moreover, no difference in insulin sensitivity was observed later in life between SGA and AGA children (50). Cianfarani et al investigated insulin sensitivity by comparing children born SGA (n=26) with children born AGA (n=26) at the average age of 8.6±3.5, matched for age, gender, height, BMI and pubertal stage. SGA were divided into two subgroups according to whether or not they had a full catch-up growth: 1) catch-up growth group (CG, children with correct height with at least 0 z-score) and no-CG (children with correct height less of 0 z-score). SGA showed no differences in insulin sensitivity compared to AGA but had significantly lower blood glucose levels ($p<0.005$). No-CG group had higher TSH levels than the CG group ($p=0.002$) (51). Bagnoli et al investigated the relationship between IUGR and thyroid function in the first week of life. They found that SGA neonates (both preterm and full-term) showed

lower T4 serum levels perhaps because of increased ACTH levels and decreased cortisol concentrations, and/or reduced availability of phenylalanine and tyrosine. TSH concentrations, instead, were significantly higher only in full-term SGA newborns. Furthermore, cases of congenital hypothyroidism were observed only among AGA infant, suggesting that hypothyroxinemia found in SGA babies is a transient condition destined to disappear (52). Interestingly, T3 seems to promote the production of 17β-estradiol and EGF (Epidermal Growth Factor), by playing a role in trophoblast development and growth, disrupted in pregnancies complicated by IUGR (53). Compared to physiological pregnancies, the amounts of placental thyroid receptors (β1, β2, β3) seem to be increased in pregnancies complicated by IUGR. The condition characterized by lower circulating thyroid hormones is counterbalanced by a higher expression of placental thyroid receptors (54). Setia et al suggest a possible role played by transthyretin (TTR) in the restriction of fetal growth. TTR is involved in the placental uptake of maternal thyroid hormones and retinol binding protein (RBP) (55). RBP seems to play a role in insulin resistance by promoting down-regulation of GLUT4 in adipocytes (56,26). An abnormal production of TTR could be associated with a reduced placental passage of maternal thyroid hormones and RBP in IUGR fetuses by resulting in hypothyroidism and increased insulin sensitivity. Setia et al investigated the relationship among thyroid function, insulin level and insulin sensitivity at birth in term IUGR neonates (n=50) compared to maternal age and parity matched term healthy newborns. Insulin sensitivity was expressed as cord blood glucose to insulin ratio (G/I). No significant difference in T3 was found in the 2 groups. Respect to healthy term neonates, IUGR newborns showed lower T4, plasma glucose and insulin levels ($p=0.009$, $p<0.001$, $p<0.001$, respectively) and higher TSH concentrations and G/I ($p<0.001$ and $p<0.001$, respectively). These differences persisted even if maternal factors (such as pregnancy induced hypertension, heart disease and malnutrition) were considered through logistic regression analysis. Stepwise linear regression analysis identified TSH and T4 as a possible predictor of G/I in IUGR neonates. These results should be considered with caution. G/I is used as kind of surrogate to measure insulin sensitivity and secretion. Moreover, free T4 and free T3 have not been evaluated. In conclusion, only few studies investigate thyroid function in SGA neonates during the first days of life. Other case-control studies are necessary to evaluate the necessity of replacement therapy in SGA neonates (55).

5.Effects of prematurity on thyroid function

Prematurity and thyroid function

Thyroid hormones are important for the intrauterine homeostasis of the fetus, and cooperate with the adrenal hormones during the perinatal period to determine a physiological adaptation to the extrauterine life (57). In the fetus, thyroid gland appears complete at 10-12 weeks of gestational age (GA); blood levels of thyroxine (T4) and triiodothyronine (T3), which start to be measurable at that time, increase gradually during pregnancy (58). Fetal hypothalamic-pituitary-thyroid axis begins to work after the first trimester of pregnancy and its development appears complete at the end of gestation. For this reason, thyroid dysfunction is a common condition in preterm infants and can be linked to several factors. First, there are physiological conditions related to prematurity, that include immaturity of the hypothalamic-pituitary-thyroid axis, impairment of thyroid ability to concentrate and synthesize iodine, and immaturity of the metabolic pathways in the thyroid. Then, preterm newborns have greater demand for thyroid hormones for thermogenesis and dealing with diseases related to prematurity. Williams et al showed that typical diseases of preterm, e.g. respiratory distress syndrome (RDS), sepsis, intra ventricular hemorrhage (IVH), may alter thyroid function through inflammatory response. Transient thyroid dysfunction that affects newborns admitted to the NICU can be also a consequence of drugs as dopamine and steroids, often used during the recovery of preterm infants (59). Finally, also iodine insufficiency and iodine excess can influence preterm thyroid function (60). Iodine request in the preterm infant is about 30-40 mcg/Kg/die; neonatal thyroid gland is sensitive to both deficit and excess of iodine. This latter can be a consequence of the use of iodinated contrast media and iodinated

skin disinfectants. Due to the unknown amount of iodine contained in the sources of exposure and in the urine, and the unavailability of any information about renal function, the effect of iodine exposure on preterm babies was not clear. Studying the mechanisms that underlie the predisposition of the preterm infant for thyroid dysfunction, Ogilvy-Stuart AL et al reported that the site of immaturity seems to be the hypothalamus, because of a normal response of TSH and T4 to THR found in preterms (61). Furthermore, blood levels of T4 are lower in extreme preterms than in fetus with same gestational age (62). In most cases, it is a transient dysfunction that normalizes itself with the maturation of the thyroid gland and the mechanisms that underlie its functioning. Rarely, the dysfunction remains persistent and requires pharmacological treatment.

Transient hypothyroxinemia of prematurity

While the incidence of persistent hypothyroidism does not differ from term and preterm infants, transient hypothyroidism is significantly more frequent in preterm ones (7). Transient hypothyroxinemia of prematurity (THoP), a transient reduction of the fT4 values despite normal levels of TSH, affects about 20% of newborns with gestational age < 34 weeks and up to 29% of VLBW newborns with gestational age < 32 weeks (63,64). THoP seems to resolve spontaneously within 6–8 weeks (65). The benefits of thyroid hormone supplementation in transient hypothyroxinemia of prematurity remain unknown, and clinical studies report no improvement in mortality, morbidity and neurological disability in preterm prophylaxis supplementation (66).

Transient hyperthyrotropinemia

As THoP, also transient hyperthyrotropinemia (TNH) with elevated thyroid-stimulating hormone and normal values of fT4 is common in preterm infants. While the increase of TSH with a peak at about 36 hours of life can be considered a physiological consequence of stress and environmental factors linked to birth, transient neonatal hyperthyrotropinemia is defined as an increase of TSH that occurs after 48 hours of life, and that returns to normal after 2 weeks. Newborns with a rise in TSH may have transient or persistent hyperthyrotropinemia, but may also develop transient or permanent hypothyroidism. The effects of TNH on child's metabolic future later in life are controversial. While some studies have shown that TNH is a transient condition that does not lead to long-term effects on thyroid function, other reports recommend to check these patients over time, to rule out the possibility of developing a persistent form. Cuestas et al evaluated after 6 years 65 newborns with TNH and 185 newborns with TSH < 10 mUI/ml at birth, comparing auxological parameters, thyroid function and developmental assessment later in life. They found an increased risk of developing persistent hyperthyrotropinemia in patients with TNH (RR 5.7, 95% CI 1.5–22.1, p=0.0114), with no alteration on growth but with an impairment on development status identified through PEDS questionnaire (Spanish adaptation of Parents' Evaluation of Developmental Status). Moreover, they found higher mean values of TSH in children who previously had a physiological rise after birth, making the hypothesis that in these children thyroid function even in the normal range is not completely normal (2). Therefore, they suggest to treat these patients until to TSH levels in normal range, suspending therapy two years later to re-evaluate the need.

Another condition that can develop in premature infants is the so called **"delayed TSH elevation" (dTSH)** which is characterized by a rise in TSH at the second screening after a first normal screening. This condition occurs predominantly in preterm infants, in low birth weight newborns and in newborns admitted to NICU. The period of time in which it occurs is variable, usually between 2 and 6 weeks of life. The etiology of this condition is heterogeneous; among the causes, there could be iodine excess or iodine deficiency. Zung et al. studied the risk factors that can determine dTSH in newborns admitted to NICU, concluding that both gestational age and birth weight are less important than the severity of the clinical conditions, to determine dTSH (67). Cavarzere P. et al. carried out a retrospective study to evaluate the incidence of dTSH in LBW neonates, showing that 57.5% of newborn with a weight lower than 2500 grams presented dTSH. They concluded that a second screening performed at 15 days of life in preterm infants is essential to identify dTSH (68).

Conclusions

In summary, we can affirm that in literature it has been shown an association between maternal thyroid dysfunction and an increased risk of adverse effects, not only during pregnancy (such as GDM, preeclampsia and preterm delivery), but also in siblings. In particular, during fetal and perinatal period, maternal thyroid dysfunction seems to be associated with an impairment of fetal-placental glucose metabolism, that may predispose to fetal hypoglycemia and growth retardation by increasing the risk of LBW. Moreover, maternal thyroid dysfunction may compromise neonatal thyroid function and it can alter neonatal metabolic screening. Maternal thyroid dysfunction during pregnancy may also affect offspring later in life, by increasing metabolic and cardiovascular risk, impairment of thyroid function and neuropsychiatric effects. At the same time, prematurity and dysmaturity may compromise neonatal thyroid function, leading to transient or permanent thyroid dysfunction, and to metabolic and cardiovascular disorders. Other studies are needed to better understand the endocrine and metabolic effects of maternal thyroid dysfunction and prematurity on offspring in order to prevent and treat properly these conditions.

Conflicts of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Correspondence:
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Prof. Lorenzo Iughetti, MD, PHD
Department of Medical and Surgical Sciences of the Mother, Children and Adults
University of Modena and Reggio Emilia
Via del Pozzo, 71 – 41124 Modena
Italy, Phone: +39 059 422 5382
Fax: +39 059 422 4583
E-mail: iughetti.lorenzo@unimore.it