

Hypothyroidism in pregnancy

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Abstract: Thyroid hormones of the fetus exclusively comes from mothers in early pregnancy, indicating that maternal hypothyroidism has a close-knit relationship with fetal growth and neuropsychological development. Hypothyroidism is one of the most common endocrinopathies during pregnancy with an estimated prevalence of 3–5% among pregnant women. Emerging evidence suggests that maternal overt hypothyroidism is associated with adverse maternal, obstetrical and neonatal outcomes, but, although there is still no consensus on the association of subclinical thyroid disorders or increasing thyroid antibodies with complications of pregnancy and childhood cognition. Data available are inconclusive regarding the benefits of treatment of subclinical hypothyroid pregnant women for both fetomaternal outcomes and even neurocognitive development of the children of affected women. In this review we aimed to address pregnancy outcomes of mothers affected by overt and subclinical hypothyroidism, psychosocial development of neonates affected by overt and subclinical maternal hypothyroidism and the beneficial effects of treatment.

Keywords: Hypothyroidism; pregnancy adverse outcome; review; subclinical hypothyroidism (SCH)

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Introduction

Function of the thyroid gland is affected by pregnancy is associated with maternal/fetal health (1). In the first trimester of pregnancy, human chorionic gonadotropin (hCG) stimulates a transient elevation in maternal serum concentration of free thyroxine (fT4), which is reflected by a decrease in levels of thyroid stimulating hormone (TSH); during this trimester, maternal serum TSH concentrations are significantly lower than pre-conception levels. Following, serum levels of fT4 decrease by 10%, and maternal level of TSH gradually increases to normal values. In addition, mid-gestation rise in serum concentrations of thyroxine binding globulin (TBG) leads to significant increase in both total thyroxine (T4) and triiodothyronine (T3) in the second and third trimesters of pregnancy (2-4). In this context daily iodide consumption increased along with a reduction in TSH levels (5) and immunosuppression

inherent throughout pregnancy, leads to decrease in level of maternal thyroid autoantibodies levels (6).

Hypothyroidism is one the most common endocrinopathies during pregnancy (7). Emerging evidence suggests that maternal hypothyroidism is associated with adverse maternal, fetal and obstetrical outcomes, including preeclampsia, gestational hypertension, low birth weight, abortion, and premature delivery (8).

However, complex physiological changes in thyroid hormones functional levels makes it more difficult to diagnose hypothyroidism in pregnancy. In addition, signs and symptoms of thyroid disease can be hidden by normal physiological changes of pregnancy, making diagnosis of maternal thyroid dysfunction difficult, indicating that all thyroid function tests in women who are pregnant must be interpreted differently to those of women who are not. However, whether to use the targeted high-risk case findings or the universal screening approach for thyroid

dysfunctions during pregnancy remains controversial over the past decades (9,10).

Although, there is a consensus on the diagnosis and treatment of overt hypothyroidism (OH) during pregnancy, ongoing debate continues regarding the diagnosis of subclinical hypothyroidism (SCH) as its symptoms are non-specific and the exact diagnostic reference threshold for TSH is arbitrary. Moreover, the need for treatment in SCH and its effects on maternal and fetal outcomes are insufficient and controversial (11-14).

In this review, however, we aimed to address both the screening approaches for hypothyroidism and their benefits and drawbacks, diagnostic reference threshold for TSH in clinical and SCH, adverse pregnancy outcomes and the psychosocial development of neonates affected by maternal SCH.

Changes in thyroid functional hormones during pregnancy

It is well documented that normal pregnancy is associated with an elevation in urinary iodine excretion as well as increase in TBG and thyroid functional hormones induced by hCG which followed by subsequent decrease in serum concentration TSH values (15). All of these factors influence thyroid function tests in the pregnant women (16); responses of the maternal thyroid gland to these changes make through alteration in thyroid metabolism. Hence serum concentrations of thyroid hormones especially TSH and fT4 are significantly different from non-pregnant female populations. However, its amount gradually increases later in pregnancy, but does not reach the pre-conception level (17).

Epidemiology of hypothyroidism

Hypothyroidism is one of the most common thyroid dysfunctions during pregnancy, although its prevalence varies between among different nations, depending on screening approaches, cut off values for TSH, and assays used for assessment of T4. Besides there are significant differences according to various ethnicities or iodine sufficiency status of countries (18-22). Moreover, the prevalence of thyroid dysfunction in pregnancy is strongly influenced by specific characteristics of the population under study, for instance hypothyroidism in infertile women and those with recurrent pregnancy loss is much more common than in healthy populations (23).

In a community based large scale study of 502,036 pregnant women, aged 18 to 40 years, Blatt *et al.* showed that 15.5% of them had positive screening test for gestational hypothyroidism; of these 2.4% had OH and 97.6% had SCH (24). Using the universal screening approach, Nazarpour *et al.* in a cross-sectional prospective study conducted on 1,600 Iranian pregnant women, OH and SCH were observed in 1.1% and 30.1% participants, respectively (25). In another cross-sectional study from India, conducted on 461 pregnant women, Rajput *et al.* reported the prevalence of overt hyperthyroidism and sub-clinical hyperthyroidism to be 1.3% and 21.5%, respectively (26). Using a cut-off TSH level of 4.5 μ IU/mL, Dhanwal *et al.* showed that 14.3% women attending tertiary centers in India suffered from hypothyroidism, with most of these women having sub-clinical hyperthyroidism (27). Another study of 500 pregnant women attending two hospitals in Chennai, the prevalence of SCH was around 2.8%, and thyroid peroxidase (TPO) antibodies positivity was seen in 57.1% (28). In another study, Sahu *et al.* performed the thyroid screening test at second trimester in 633 high risk pregnant women and reported that 6.47% of them had SCH and 4.58% suffered from OH (29).

Despite these variations, hypothyroidism is a common disorder in pregnancy that needs to be addressed appropriately.

Screening of thyroid disorders during pregnancy

While the maternal and fetal complications of overt hyperthyroidism are well known (30-32), there is still no consensus on the association of subclinical thyroid disorders or increasing thyroid antibodies with complications of pregnancy and childhood. Hence, there is no consensus regarding universal thyroid screening or case-finding screening approach during pregnancy; besides different risk factors have been introduced for consideration in the case finding approach and varies significantly among diverse racial and ethnic groups (33).

In this respect the American College of Obstetrics and Gynecology, the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists recommend the targeted case findings screening for thyroid disorders (34-36). However, there are some well-designed investigations showed that the case finding screening strategy may approximately miss 30-90% of the hypothyroid patients, even overt hypothyroid ones (9,25,33,37,38). Moreover, data on the cost-effectiveness of

universal screening approaches compared to no screening and targeted screening is not conclusive (35). The clinical signs/symptoms of hypothyroidism such as weight gain, anxiety, fatigue and constipation may be attributed to the pregnancy (39).

To the best of our knowledge, supporting evidence for both screening approaches is inconclusive and further evidence regarding the impact of SCH on pregnancy outcomes, beneficiary effect of LT4 treatment, well defined risk factors and trimester specific reference range for TSH, FT4, TPO autoantibody (TPOAb) is essential for making a recommendation for or against routine pregnancy screening for thyroid dysfunction.

OH: adverse maternal and neonatal cognitive development complications

Overt maternal hypothyroidism (elevated serum concentrations of TSH with decreased serum concentrations of free T4 values) is prevalent during pregnancy, a prevalence rising with increase in advanced maternal age worldwide (40), making it an important public health concern. The main risk factors for maternal hypothyroidism during pregnancy are iodide deficiency and autoimmune thyroid disorder, with TPOAb positivity (8,41).

Clinical diagnosis of OH in pregnancy is particularly challenging as pregnancy per se may mimic some of the clinical manifestations of hypothyroidism, including weight gain, anxiety, fatigue, muscle cramps and constipation (41,42). In addition, increased metabolism during pregnancy may hide the symptoms of hypothyroidism (41). Moreover, normal changes of thyroid functional tests during pregnancy may be misinterpreted as hypothyroidism.

In the last two decades, emerging evidence has been documented on the adverse consequences of maternal hypothyroidism on pregnancy outcomes and child development. Infertility is more common among women with OH (43,44); even if they conceive, risk of abortion and stillbirth (34,45,46), anemia and postpartum hemorrhage (47), abruptio placenta (48), gestational hypertension and preeclampsia (29,49,50), gestational diabetes (51,52), low birth weight (34,53), and preterm births (48,54,55) are increased. A meta-analysis by Sheehan *et al.* demonstrated that the odds ratio (OR) of preterm delivery for women with OH in comparison to euthyroid women was 1.19 (95% CI, 1.12–1.26; $P < 0.00001$) (48). In another meta-analysis, Gong *et al.* indicated that the risk of gestational diabetes was significantly increased in hypothyroidism during pregnancy

(OR 1.892; 95% CI, 1.679–2.132, $P < 0.001$) (56).

Moreover, overt maternal hypothyroidism is a well-known cause of cretinism, which reflects that the placental transfer of maternal thyroid hormones to the fetus regulate fetal brain development (57). Data shows that levothyroxine treatment is crucial for women with OH and therapy should be initiated as early as possible to yield optimal fetal neurodevelopment (58–60). In 1999, Haddow *et al.* in a large case control study reported that untreated maternal hypothyroidism leads to a seven-point reduction in their child IQ, delays in motor-skill and language neurodevelopment as well as attention deficiency at 7–9 years of age compared to children born from euthyroid mothers (61). Fetene *et al.* in a systematic review concluded that maternal thyroid dysfunction and autoimmune thyroiditis during the first trimester of pregnancy were associated with some child behavioral and psychiatric problems including epilepsy and seizure, attention deficit hyperactivity disorder (ADHD) and autism (62).

Pregnancy outcomes in women with SCH

SCH is defined as an elevated thyrotropin (TSH) concentration with normal serum levels of thyroxine (T4). Despite the clear evidence for adverse pregnancy and neonatal outcomes of OH, the impact of SCH on pregnancy is unclear and controversial (35).

While several observational studies have reported an association of SCH with an increase in the risk of adverse pregnancy and neonatal outcomes, including miscarriage, preterm delivery, preeclampsia, intrauterine growth retardation, low birth weight, gestational diabetes, gestational hypertension, placental abruption and low Apgar score (63–65), other observational studies, however, do not report any increase in risk in their outcomes in pregnant women with SCH (30,40,66). Data are inconclusive regarding the treatment pregnancy benefits of SCH women. To date, four randomized trials have investigated the effect of levothyroxine (LT4) in such women, of which two were conducted among TPOAb+ women (14,67); one trial pooled both TPOAb+ and TPOAb– subjects (68) and one in TPOAb– pregnant women (14).

In first study, Negro *et al.* randomized 4,562 women using thyroid universal screening and case finding approach and further medication in abnormal cases. They reported a reduced risk of adverse pregnancy outcome in terms of preterm delivery and abortion among those SCH-TPOAb+ who women received levothyroxine (LT4) (67).

The Tehran Thyroid Study also reported a 70% reduction in preterm delivery rate in LT4-treated TPOAb+ women (14). Ma *et al.* observed 66% and 54% reduction in rates of abortion and macrosomia in LT4-treated TPOAb+ pregnant women (68). A randomized clinical trial among SCH-TPOAb- women of Tehran Thyroid Study revealed that considering a TSH cut-point of 2.5 mIU/L, LT4 therapy have not had beneficiary effect in terms of adverse pregnancy outcomes, however secondary subgroup analysis of data using the ATA currently recommended cut-point of 4.0 mIU/L, decrease the rate of preterm delivery by 62% in those SCH-TPOAb- women received LT4 (14). In addition, in recent study, Casey *et al.* randomly assigned 677 women with SCH and 526 with hypothyroxinemia to receive levothyroxine or placebo; results of the study showed that early treatment (8–20 weeks of gestation) for SCH or hypothyroxinemia did not result in significant improvement in cognitive outcomes of children aged 5 years (69).

Several meta-analyses have been conducted to assess the impact of SCH on preterm deliveries. Maraka *et al.* included 18 cohort studies at low to moderate risk of bias and reported that compared to euthyroid women, pregnant women with SCH were at higher risk for pregnancy loss [relative risk (RR) 2.01; 95% CI, 1.66–2.44], placental abruption (RR 2.14; 95% CI, 1.23–3.70), premature rupture of membranes (RR 1.43; 95% CI, 1.04–1.95), and neonatal death (RR 2.58; 95% CI, 1.41–4.73). Despite the fact one interventional study found no significant decrease in the rate of pregnancy loss, preterm delivery, gestational hypertension, low birth weight, or low Apgar score in SCH pregnant women who received levothyroxine in comparison to those who did not (12). Contrary to these results, another meta-analysis including 14 cohort studies and one case control study involving 2,532,704 participants showed that SCH and isolated hypothyroxinemia, in comparison to their euthyroid complication, had no significant increase in OR of preterm delivery (48).

van den Boogaard *et al.* (70) in a systematic review of 38 studies [case-controls, cohorts, randomized control trials (RCTs)] reported that women with SCH, compared with euthyroid ones, had increased risk of pre-eclampsia (OR 1.7; 95% CI, 1.1–2.6) and perinatal mortality (OR 2.7; 95% CI, 1.6–4.7).

The main problems of these meta-analyses were their significant heterogeneity and elimination of the positive findings after excluding the observational studies. It seems there is inadequate insight into the clinical significance of subclinical thyroid dysfunction and thyroid autoimmunity

in early pregnancy; as a result, treatment intervention in these women need to be justified.

Maternal SCH and child cognition

The initial development of the fetal brain in the first trimester of pregnancy, when the embryo's thyroid still is not fundamental and is completely dependent on the mother's thyroid; after that however the mother and fetus both provide this need. Despite the strong evidence on the adverse effects of overt maternal hypothyroidism on neurocognitive development of affected children, there is uncertainty regarding this negative effect in children of women with gestational thyroid dysfunction or autoimmune thyroiditis (71). While some studies report an increased risk of neurocognitive deficits in the offspring of women with SCH (72,73), this adverse effect has not observed in other studies (41,74,75). In one study, Li *et al.* (73) showed that the intellectual and motor development of children at 25–30 months of age is associated with abnormalities of maternal thyroid at 16–20 weeks gestation; also, maternal SCH or euthyroidism with elevated TPOAb titers were predictors of lower motor and intellectual development. Ghassabian *et al.* (72) showed that higher titers of TPOAbs during pregnancy associated with an increase in children's risk of attention deficit/hyperactivity. However, this adverse effect has not been observed in the Controlled Antenatal Thyroid Screening (CATS) study (41,74) that investigated treatment for SCH on childhood cognition and found no difference in IQ at 3 or 9.5 years between children of treated and untreated SCH mothers. However, a 24% follow-up loss of the initial cohort was a limitation for their intention-to-treat analysis. Additionally, Casey *et al.* (69) reported similar findings to the CATS study in terms of neurocognitive function of SCH affected children. Despite a 90% 5-year follow-up rate, their results need to be interpreted with caution due to the late initiation of replacement therapy (on average 17 weeks). Also, in a prospective study conducted by Chen *et al.* (75) to compare the neurodegenerative development of infants born to mothers with gestational SCH and those born to euthyroid mothers, they found that both groups had similar scores according to the Gesell development test and there was no detectable neurodevelopment deficit in offspring up to 24 months of mothers who had gestational SCH. In another study conducted by Behrooz *et al.* (42) resulted showed that the total IQ, performance IQ, and verbal IQ of children of mothers with gestational

hypothyroidism were similar to euthyroid ones; cognitive performance tests were also similar in both groups. The results of studies on the effect of maternal autoimmune disorders on cognitive development in children are also controversial. Pop *et al.* (43) reported that the scores of neurocognitive function of children of TPOAb-positive mothers at age 32 years are significantly lower than offspring of TPOAb-negative mothers, Williams *et al.* (44) showed no association between maternal TPOAb and TSH levels and neurodevelopmental outcomes of offspring.

A recent meta-analysis including 39 articles (37 observational studies and 2 RCTs) showed that maternal hypothyroidism and hypothyroxinemia are associated with intellectual disability in offspring (OR 2.14; 95% CI 1.20–3.83, $P=0.01$ and OR 1.63; 95% CI, 1.03–2.56, $P=0.04$, respectively); these thyroid dysfunctions were not associated with ADHD and their effect on autism was unclear (46). Subgroup analysis of RCTs revealing no association between maternal hypothyroidism and hypothyroxinemia and intellectual disability and showing no beneficial effects for levothyroxine treatment of these conditions. Another recent meta-analysis conducted by Levie *et al.*; it included 9,036 mother-child pairs from three birth cohorts: INMA (Spain), Generation R (The Netherlands) and ALSPAC (United Kingdom) (45). They found that FT4 <2.5th percentile was associated with a 3.9 (95% CI, 2.2–5.7) point lower non-verbal IQ and a 2.1 (95% CI, 0.1–4.0) point lower verbal IQ; they also reported a significant positive association between FT4 >97.5th percentile with risk of autistic traits (OR 1.9; 95% CI, 1.0–3.4). They observed no significant independent association between child neurodevelopment with maternal serum concentration of TSH (45).

Management of maternal hypothyroidism

Several studies confirm the detrimental effects of OH on both maternal and fetal health. In addition, data available support the beneficial effect of treating OH during pregnancy (35,76). The recommended treatment of maternal hypothyroidism is administration of oral LT4 (35). The biochemical target of treating hypothyroidism in pregnant women is obtaining the TSH concentrations <2.5 mU/L (35,76).

In addition, pregnancy increases the likelihood demand for LT4 during pregnancy among treated hypothyroid reproductive aged women. In this respect, if these women are planning to become pregnant, serum concentration of TSH must be measured preconception, and the LT4 dose

adjusted to obtain a TSH value between the lower reference limit and 2.5 mU/L (35,76).

If pregnancy is confirmed among hypothyroid patients receiving LT4 treatment, dose of LT4 should be increased by 20–30% (35,76) to maintain the preconception serum TSH level. ATA recommends that, following delivery, LT4 should be decrease to the patient's preconception dose and followed with additional thyroid functional testing at 6 weeks postpartum (35,76).

However, due to the lack of sufficient randomized controlled trials in pregnant women with SCH, there is insufficient evidence to recommend for or against universal LT4 treatment (35,76), however they should be monitored for potential increase serum concentration of TSH in pregnancy every 4–6 weeks (76). There is insufficient data for making a precise recommendation for or against LT4 treatment among euthyroid TPOAb+ women (35,76).

Conclusions

Maternal hypothyroidism, a common endocrine problem during pregnancy is associated with adverse obstetrics, maternal and neonatal outcomes. While several observational studies have reported an association of SCH and adverse pregnancy and neonatal outcomes, some others did not confirm these associations. Also, data are inconclusive regarding the treatment pregnancy benefits of SCH women. Supporting evidence for both screening approaches is insufficient and controversial. To date the case-finding screening approach is recommended by international professional societies, even though the well-defined risk factors and trimester specific reference range for TSH, FT4 and TPOAb are not precisely specified.

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