Mortadha, Endocrinol Metab Syndr 2018, 7:6
DOI: 10.4172/2161-1017.1000291

Endocrinology & Metabolic Syndrome

Research Article Open Access

Diagnosis and Management of Subclinical Hypothyroidism in Pregnancy: A Retrospective Review Study

Ala Hossain Mortadha*

New Fujairah Hospital, Ras Alkhaima Medical University, UAE

Abstract

Back ground: The hormones of thyroid organ play an important role for a normal pregnancy without maternal or fetal complexities. However, using different methods and thyrotropin (TSR) ranges for diagnosis subclinical hypothyroidism (SCH) in different population are challenging. The aim of this study is to clarify the world wide variation in prevalence of SCH, the accurate methods been used for diagnosing (SCH) in pregnant women, main adverse pregnancy outcomes related to (SCH) and the clinical impact of levothyroxine on gestational SCH related complications.

Methods: Meta-analysis of the results of all studies that were investigated the screening methods, adverse pregnancy outcomes and the treatment of SCH during pregnancy which was published in English language during the last two decade including the popular guidelines in this regard.

Results: The studies revealed a strong linear association between preterm delivery, miscarriage and TSH level with more events, if combined with positive thyroid antibodies. The difference in TSH (TSR) ranges among different ethnicity and countries should be considered for diagnosis and treatment.

Conclusion: Early diagnosis and treatment of SCH during pregnancy is cost effective in reducing the preterm labour, miscarriage and its complications. Using specific TSH cut off level for each population is essential for accurate diagnosis and screening should include not only high risk cases but patients in countries with high prevalence of SCH.

Keywords: Subclinical hypothyroidism; Pregnancy; Epidemiology; Adverse pregnancy outcomes; Diagnosis; Management

Abbreviations: AACE: American Association of Clinical Endocrinologists; ACOG: American College of Obstetrics and Gynaecologists; ADHD: Attention-Deficit/Hyperactivity Disorder; APGAR: Appearance Pulse Grimace Activity and Respiration; ART: Assisted Reproductive Techniques; ATA: American Thyroid Association; CI: Confidence Interval; CS: Caesarean Section; ES: Endocrine Society; ETA: European Thyroid Association; FT4: Free Tetraiodothyronin; GDM: Gestational Diabetes Mellitus; GH: Gestational Hypertension; HCG: Human Chorionic Gonadotropin; ICU: Intensive Care Unit.

Introduction

Evaluation of SCH prevalence is varied by geographical location, ethnicity, age, sex and it is highly reported in the women rather than men about 0.9 to 16.9%. There is a significant and positive association between gestational SCH and its adverse impact on the fetal outcomes and moms. To diagnose SCH in different areas or geographical regions in the whole world, the thyrotropin varies. There is a need to have common screen mechanism for the sake of diagnosis and the management of SCH during the pregnancy in order to avoid any kind of harm to both fetus and the mothers. On the other hand, there is still conflict in the data and the information regarding the treatment of this endocrine disorder in the pregnant women.

According to Cleary-Goldman et al. [1], SCH is responsible for many pregnancy complexities, particularly preterm delivery and miscarriage. In addition to this, some researches has demonstrated higher frequency of GDM , preeclampsia and increased caesarean section rates with low intelligence quotient (IQ) level of the offspring. In addition, Negro et al. [2] demonstrated that treatment of SCH with levothyroxine during pregnancy leads to better results.

During pregnancy, numerous physiological changes happened for the most part (hCG) and increment in (TBG) with decrement of TSH and increase the requirement for thyroid hormones by 50%. In addition, there is addition essential for iodine allow by 40-50% securing fetal interest for thyroid hormones, particularly during the first trimester. Along these lines, estimation of thyroid capacity during pregnancy stay testing, and the elucidation of all the talked about things is distinctive for non-pregnant women.

Furthermore, various studies has come to the way that there is a powerful relationship between (TPOAb) or (TgAb) positive and thyroid dysfunction especially SCH , related with more opposing pregnancy comes about. Some looks into has portrayed thyroid antibodies in up to 18 % of pregnant women. Along these lines, the high recurrence of SCH and potential negative impacts on pregnancy, make the right screening of thyroid points of confinement as of now and during early pregnancy has ended up being crucial fundamental. Nevertheless, the cost effectiveness of this problem should be taken into account and still up to date, there is mixed conclusions.

For finding of SCH, the (ATA) address utilized TSH particular (TSR) Stagnaro-Green et al. [3], while The Spanish Society of Endocrinology and Nutrition provoke maternal TSH screening in early pregnancy Vila et al. [4] and the Endocrine Society (ES) supported levothyroxine for SCH during pregnancy [5].

Objectives of study

The main objective of this systematic review is to anlayze the existence of SCH in the pregnant women during their pregnancy in different areas varied by age, sex and ethnicity. The aim is also to evaluate

***Corresponding author:** Mortadha AH, Assistant professor, New Fujairah Hospital, Ras Alkhaima Medical University, UAE, Tel: +971-50-5206883; E-mail: alaamurtatha@hotmail.com

Received September 22, 2018; **Accepted** October 05, 2018; **Published** October 12, 2018

Citation: Mortadha AH (2018) Diagnosis and Management of Subclinical Hypothyroidism in Pregnancy: A Retrospective Review Study. Endocrinol Metab Syndr 7: 291. doi:10.4172/2161-1017.1000291

the outcomes of SCH on the mother and fetus. This study aimed to analyse the cut-off level of TSH in the three trimesters, suggestions for the method of screening and levothyroxine replacement therapy impact on the pregnant women especially in the United Arab Emirates.

Methods and data source

The data used for this investigation are specific to SCH in the midst of pregnancy in different ethnicity and geographical locale. Each and every separated result are from cohort, prospective and randomized controlled examinations which were circulated on the distinctive stages in the English language since the latest twenty years including the declaration of latest standards of ATA, ES and American College of Obstetrics Gynaecologists (ACOG). It gives understanding into the assortment in occurrence in a number of countries, the association among SCH and negative maternal and fetal outcomes, treatment and screening.

Background and Literature Review

Definition of subclinical hypothyroidism during pregnancy

With regards to this examination, and numerous others, the meaning of SCH implies the presence of high TSH (<10 mU/l) with a free thyroxine (FT4) of typical level without indications of hypothyroidism [6]. There is agreement which relies upon the confirmation base of numerous trials done in Europe and furthermore distributed rules by ATA and ES which thought about the TSH (TSR) for the first, second and third trimester as following (0.1-2.5 mU/l), (0.2-3.0 mU/l), (0.3-3.0 mU/l) separately [7].

Prevalence of subclinical hypothyroidism during pregnancy

There is very distinction in the predominance of SCH relies upon the populace, age, sex, race, area, and strategy for TSH estimation .However, it is higher in the women (6% to 10%) than in men (2% to 4%). Thus, we need to have TSH reference range, which should be standardized to that region, and each laboratory should have their appropriate quality control procedure [8].

The (NHANES III) gives information related to the pre-adult and conceptive age demonstrated the SCH and antithyroid antibodies prevalence, which were 4.8% and 3.9% in whites, non-Hispanic and Mexican Americans individually with 1.6% in blacks , non-Hispanic while in other races/ethnicities is 4.0% [9].

In addition, many recent studies in Asian countries had shown variation in prevalence of SCH during pregnancy (Table 1).

Aetiology of subclinical hypothyroidism during pregnancy

The clinical association between thyroid autoimmunity and subclinical hypothyroidism on pregnancy outcomes

Numerous observational and cohort studies thinks about demonstrated that both, the high TSH and TPO antibodies have been related with increment preterm birth, premature birth and poor neonatal unfavourable results. Then again, the majority of the studies found a strong relationship between segregated positive TPO antibodies or (TgAb) and a higher serum TSH contrasted with women without thyroid antibodies and the predominance of auto immune thyroiditis is variable between 2% while in different trials were accounted for up to 17% Abbassi-Ghanavati et al. [7]. Additionally, there is variety in the predominance of auto immune thyroiditis among various racial and people's ethnicities. It has been observed to be more commonness of this thing in Caucasian and Asian women and substantially less among African American women Hollowell et al. [9].

In a prospective trial, Kutteh et al. [18], contemplated connection between TgAb, TPOAb, or both and intermittent pregnancy loss and the outcomes indicated 22.5 % among women with positive contrasted with 14.5 % in healthy control pregnant women (p=0.01). Likewise, Negro et al. [19] considered the connection between TPOAb-positive and TSH level among euthyroid pregnant women and found a straight increment in TSH level with movement of the pregnancy. The expansion is from 1.7 mU/L during first trimester to 3.5 mU/L when achieving full term with up to 19%, their TSH level was surpassing the upper ordinary farthest point.

Comparative study was directed by Ghafoor et al. [20] and 1500 euthyroid women were incorporated. He examined the connection between TPOAb-positivity and preterm delivery and the outcome, which had been gotten demonstrated 26.8% preterm delivery among positive TPOAb contrasted with 8.0%, in women who were TPOAb negative (p<0.01).

Another study by Cleary-Goldman et al. [21], a total of 10,990 pregnant women were enrolled and SCH was identified in 3% patients during 1st and 2nd trimester, respectively , 39% of them had thyroid antibodies. Patients with SCH were compared to healthy controls and thyroid Abs +ve were compared to those without. In the 1st trimester, SCH was associated with abruptio placenta (p=0.01) and positive thyroid antibodies were associated with preeclampsia, (PROM) and macrosomia with p=0.009, p=0.004, and p=0.02, respectively. However, in the 2nd trimester, SCH was associated with (GDM) (p=0.03) but antibodies were not associated with adverse outcome.

Iravani et al. [22], contemplated the relationship between the positivity of TgAb or potentially TPOAb and rehashed pregnancy loss and he discovered TgAb and additionally TPOAb positive women had higher frequency with (OR 2.24; 95% CI 1.5–3.3).

In a meta-examination of eight case–control studies, Chen and Hu [23], considered the relationship between thyroid antibodies and pregnancy loss and inferred that pregnancy loss was altogether high in thyroid autoimmune positive (OR 2.55; 95% CI, 1.42-4.57; P=0.002) contrasted with negative thyroid antibodies (OR 2.31, 95% CI, 1.90-2.82; P<0.00001). Likewise, Boogaard et al. [24], examined this relationship among 460 patient contrasted with 1923 controls and determined that recurrent pregnancy loss among thyroid Abs positive pregnant ladies was fundamentally high (OR 2.3 ,95% CI 1.5–3.5). In another meta-analysis led by Negro [25], seven investigations with 23,000 pregnant women were incorporated and reach to the fact that there is a relationship between thyroid antibodies and higher preterm deliveries (OR 1.6, 95% CI 1.44–1.94).

Moreover, He et al. [26] had examined the relationship between thyroid antibodies and higher preterm deliveries in eleven prospective cohorts with an aggregate (35,467) pregnant women were incorporated and the outcomes uncovered a relative risk (RR) 1.41(95% CI 1.08–1.84). Be that as it may, for another case control study, the predominance of thyroid antibodies and recurrent loss of pregnancy was 31% contrasted with 18% in healthy control ladies without history of recurrent pregnancy loss p=0.031.

In a cohort study of 395 pregnant ladies, Kumru et al. [27] found higher preterm deliveries in euthyroid with positive thyroid antibodies (OR 2.5, 95% CI 1.06–5.89). Likewise, comparable affiliation was found in five cohort studies about with an aggregate of 12,566 pregnant women (OR 2.907, 95% CI 1.17–3.68) [28].

Additionally, Negro et al. [19] discovered euthyroid women with positive thyroid antibodies conveyed a higher risk of unexpected labour

Country	Author & year	Study	Participants	Number of cases with SCH	% TPOAb +ve among SCH	Prevalence	Conclusion
North India	Dinesh et al. (2013) [10]	Prospective observational	1000 pregnant women during 1st trimester were enrolled	135	18.5%	13.5%	SCH is common in North Indian women during first trimester and need universal screening
Iran (Tehran)	Ali et al. (2014) [11]	Cross sectional	3158 pregnant women irrespective of gestational age	131	Not done	4.1%	It is fundamental to check TSH during pregnancy because of watched pervasiveness of SCH
India	Pavanagan ga et al. (2015) [12]	Observational study	1663 pregnant women irrespective of gestational age	156	17.9%	9.3%	Screening and treatment of SCH before & during pregnancy can prevent adverse pregnancy outcome
India , Bangalore	Nataraj et al. (2015) [13]	Prospective study	150 pregnant in 1st trimester	20	Not done	13%	Universal screening of thyroid disorder is necessary during pregnancy to prevent fetal and maternal morbidity associated with SCH
South Bengal	Mandal et al. (2016) [14]	Cross sectional	510 pregnant women during 1st trimester were enrolled	168	33.93%	32.94%	High pervasiveness of SCH in South Bengal make routine thyroid screening during antenatal visit basic to diminish the social and budgetary weight of SCH
Kashmir ,India	Beenish et al. (2017) [15]	Cohort study	902 pregnant women	114	Not done	(12.6%)	High prevalence of SCH in pregnancy sound for prenatal and early pregnancy screening & treatment
Saudi Arabia	Shatha et al. (2018) [16]	Cross-sectional study	384 (127randomly screened pregnant women were 3 times more to have SCH compared to 257 screened based on their physician's judgment (OR: 3.1; 95% CI : 1.182 - 8.704, p=0.022)	50	Not done	13%	Random screening of pregnant women showed a higher prevalence of SCH compared to screened physician referrals

Table 1: Worldwide prevalence of subclinical hypothyroidism during pregnancy.

22.4% contrasted with 8.2% in thyroid antibodies negative women p<0.01 and on randomization of the thyroid Abs positive gathering to either levothyroxine or without, discovered preterm delivery in levothyroxine was 7% contrasted and 22.4% in non-treated p<0.05.

Likewise, prospective cohort studies were seen in planned companion think about for 3315 pregnant women, screened for TPO Abs during first trimester and contrasted with euthyroid women. Premature births were 7.1% versus 2.2% with (OR 3.40, CI 1.62-7.15; p=0.002), thyroid autoimmunity (TAI) (5.7% versus 2.2%, OR 2.71 [CI 1.43-5.12]; p=0.003), SCH+TAI (10.0% versus 2.2%, (OR 4.96, CI 2.76-8.90) and reasoned that early pregnant women with SCH and TAI conveyed the most noteworthy hazard for abortion [29].

One more prospective study for 10,990 pregnant women were screened for TPO Abs and detailed positive in 15% and 14 % during first and second trimester individually, were related with higher (PROM) with (P=0.002 and P<0.001, separately) [1]. Additionally, in a Cohort study of 2497 Dutch women, TPO Abs and FT4 were estimated during early pregnancy. The foetal loss was strongly related to higher maternal TSH and positive TPO Abs with expanded hazard by 60 % (OR=1.60, 95% CI: 1.04-2.47) [30]. The outcomes indicated high TSH with positive thyroid antibodies during early pregnancy were related with expanded hazard for (GDM) (RR 4.3, 95% CI 2.1-8.9) and (LBW) (RR 3.1, 95%CI 1.2-8.0) while detached thyroid Abs positive was related with unconstrained preterm delivery (RR 1.7, 95% CI 1.1-2.8) [31]. Another huge prospective study for 5622 members indicated a powerful relationship between positive TPO Abs during early pregnancy and unfavourable pregnancy results. It may result in 1.7 times expanded risk of unexpected labour (P=0.01), a 2.1 times expanded risk of unconstrained unexpected labour (P=0.02), and a 2.5 times expanded risk of extremely unexpected labour (P=0.04) and these expanded risks were independent of thyroid function [32].

Thangaratinam et al. [33], assessed 30 articles and 31 studies about (19 cohorts and 12 case controls) with add up to 24,692 members were incorporated and the clinical effect of thyroid antibodies on pregnancy results was assessed. Twenty eight studies showed higher abortion among TPO Abs positive (OR 3.90, 95% CI 2.48 - 6.12; P<0.001) in cohort studies and comparable affiliation was found in the case-control studies (OR 1.80, 95% CI 1.25 - 2.60; P=0.002). In addition to this, women with positive thyroid Abs had expanded unexpected labour (OR 2.07, 1.17-3.68; P=0.01) .In addition, the meta-analysis of two randomized trials utilizing LT4, there is 52% decrease in abortion in both trial (RR 0.48, 0.25 - 0.92; P=0.03). Additionally, treatment with LT4 in one trial indicated 69% lessening in unexpected labour (RR 0.31, 0.11 - 0.90) while [31-34], did not discover any distinction in unexpected labour between pregnant women with positive thyroid antibodies contrasted with negative.

A few examinations were accounted for that SCH might influence barrenness in women. Lincoln et al. [35] tried the connection amongst infertility and the serum TSH focus and found no distinction contrasted with barrenness in the people. Same outcomes were accounted in another prospective study by Poppe et al. [36] with a median TSH 1.3 in the infertile women compared to 1.1 mU/L in controls. On the other hand, Abalovich et al. [37] led a retrospective study and discovered 13.9% of fruitless women had SCH contrasted with 3.9% in fertile women, which propose an impact of high TSH on fertility of women and these results were supported by another retrospective study indicated effective pregnancy with the utilization of LT4 treatment in 84.1% of barren women with SCH [38].

Likewise, Seungdamrong et al. [39], led secondary analysis from two multicentre and randomized controlled trials looking by at the adverse pregnancy results in TPO Abs positive women with SCH to TPO Abs negative gathering, 21.9% of the included members had TSH ≥ 2.5 mIU/L with 8.6% positive TPO Abs and found the rate of abortion in TPO +ve was 43.9% contrasted with 25.3% in TPO Abs –ve , P=0.02 and the live deliveries was 17.1% in TPO Abs +ve contrasted with 25.4% in TPO negative.

In a prospective study, Bhattacharyya et al. [40] had enlisted 400 pregnant ladies during first trimester and were screened for their thyroid

profile and followed-up to 3 months postpartum. Those with irregular thyroid profile were evaluated every 2 months up to one year postpartum and the outcomes demonstrated 11.5% of the subjects were positive for TPO-Ab with TSH level of 2.31 μIU/ml, which was fundamentally higher than negative TPO-Ab (1.73 μIU/ml) with P=0.0001 with higher abortion rate in TPO-Ab positive ladies contrasted with negative while postpartum thyroid dysfunction created in 4.7% cases at 3 months and among them, antibody positivity was seen in 81.25% of subjects and 18.75% moms who were positive for TPO-Ab, the thyroid dysfunction prevails up to a year postpartum and inferred that positive TPO-Ab in early pregnancy can foresee pregnancy difficulties and later maternal thyroid dysfunction.

One more prospective study from Iran, Saki et al. [41], had analysed the thyroid autoimmunity and adverse pregnancy outcomes in about 600 pregnant women and the results exhibited prevalence of TPO-Ab and Tg-Ab was 12.8% and 8.5% respectively and were connected with a higher risk of preeclampsia (p=0.019), preterm delivery (p<0.001), IUGR (p<0.001), and low Apgar score (p<0.001). This association was free of thyroid dysfunction for preterm deliveries (R=5, p<0.001), and low Apgar score neonates (RR=8.8, p<0.001), however this relationship for preeclampsia was a result of thyroid dysfunction (RR=3.7, p=0.003). In any case, IUGR in either TPO or Tg-Ab positive moms, resulted from the synergistic effect of thyroid dysfunction and thyroid autoimmunity (RR=8.3, p<0.001). Caesarean section was significantly higher in abnormal TSH with positive anti-Tg mothers (p=0.045) and established that thyroid autoimmunity free of thyroid dysfunction could have basic ominous outcomes to the mother and foetus.

At last, the clinical effect of SCH on pregnancy results was researched in women experiencing (IVF) or (ART) and the greater part of the studies found no distinction whether the basal TSH level was increasingly or <2.5 mU/L as condensed in (Table 2).

Authors and year	Study design	Participants for IVF	Results	Conclusion
Baker et al. (2006) [42]	Retrospective cohort	195 cycles, 36% of which had TSH level >2.5 ,remaining ≤ 2.5 μIU/ml	GA and mean BW at delivery for those with TSH ≤ 2.5 μIU /ml was higher than for cycles with TSH >2.5, *P* 0.012	Pre-conception TSH >2.5 ml U/L is linked with a lower GA & LBW in women undergoing IVF
Reh et al. (2010) [43]	Retrospective cohort trial	1055 women with IVF	No distinction in pregnancy results in term of fetus removal , preterm delivery and pregnancy rate between pregnant women with TSH <2.5 mU/L contrasted with TSH <4.5 mU/L	Presenting stricter TSH cut-off esteems does not appear to affect IVF results.
Konstantinos et al. (2011) [44]	Cohort	1,231 women pursuing ART	23% with preconception TSH (2.5–4.0 μIU/mL)	Preconception high TSH was linked with low ovarian reserve but without affecting ART or pregnancy outcomes.
Fumarola et al. (2013) [45]	Retrospective cohort	164 women with IVF	The pregnancy rate was 22% in those with TSH ≤ 2.5 appeared differently in relation to 9% with TSH >2.5 mU/L p = 0.045 .Also ,no pregnancy occurred in TPO Abs +ve , while pregnancy occurred in 23.9% of cycles TAI (P = 0.02)	Additionally thinks about are expected to test the relationship amongst fruitlessness and thyroid dysfunction.
Jatzko et al.(2014) [46]	Retrospective Cohort study	540 women underwent Intrauterine Insemination	LT4 treatment for TSH levels > 2.5 μIU / ml is a predictive factor for higher pregnancy rate (OR 3.31, 95% CI 1.31-8.35)	Patients with initial TSH levels >2.5 μIU/ml and received LT4 achieved higher pregnancy rate
Aghahosseini et al.(2014) [47]	Cohort study	816 fruitless patients ordered to cluster with check TSH level ≥ 0.5 to < 2.5 mIU/L and other get-together with TSH ≥ 2.5 ≤ to < 4.5 mIU/L.	The HCG rise was happened in 30.4% of the subjects with TSH level < 2.5 mIU/L versus 26.3% of the subjects with TSH ≥ 2.5 mIU/L (p value= 0.2) Moreover, pregnancy rates in patients with TSH < 2.5 mIU/L and those with ≥ 2.5 mIU/L were 27.1% and 23.9% separately (p value= 0.3)	No relationship between TSH level in the level of 0.5-4.5 mIU/L and IVF result
Chai et al. (2014) [48]	Retrospective study	627 women experiencing IVF with predisposition TSH >4.5 mU/L	No distinction in abortion and pregnancy rate	The live birth rate and abortion rate of women with TAI as well as SCH following IVF were not disabled
Katherine et al.(2015) [49]	Retrospective analysis	1599 exchange cycles were incorporated for investigation to distinguish the ideal TSH run for patients endeavoring origination through IVF and results for people on thyroid hormone and those not requiring supplementation were assessed.	No distinction in live birth (p = 0.36), implantation (p = 0.56), or fetus removal rates (p = 0.10) between TSH bunches ≤2.5 mIU/L .Also, live birth rates for patients requiring thyroid hormone supplementation and those not taking drugs were comparative (p = 0.86)	The prescribed TSH run for pregnancy (≤2.5 mIU/L) might be connected to fruitless patients endeavoring origination without a requirement for promote change
Weghofer et al. (2015) [50]	Case–control study	77 women presented with TSH levels ≤ 2.5 μIU/mL & 21 with TSH > 2.5 μIU/mL. TAI was present in 17.3 % and more often with high normal TSH levels (P = 0.015 and P = 0.003, respectively).	No difference in pregnancy rate between TSH 0.45–2.5 mU/L compared to 2.5–4.5 mU/.	In women with TSH ≤2.5 μIU/mL, TPO antibodies negatively affect embryo quality. In women with high-normal TSH levels, increasing TSH levels & TPO antibodies impair embryo quality.
Yun Ying et al. (2017) [51]	Prospective Cohort study	270 SCH patients treated with levothyroxine	Treated women with basal TSH level 0.2-2.5mIU/L exhibited an equivalent rate of clinical pregnancy (47.4% versus 38.7%, P = 0.436), unsuccessful work (7.4% versus 16.7%, P = 0.379) and live birth (43.9% versus 32.3%, P = 0.288) showed up differently in association with women with a basal TSH level between 2.5-4.2 mIU/	Totally controlled TSH <2.5 mIU/L before IVF have no effect on pregnancy rate in LT4 treated SCH women

Table 2: Association of clinical pregnancy rate with regard to SCH in women undergoing IVF.

The clinical impact of iodine deficiency on SCH during pregnancy

Iodine is vital for thyroid hormones synthesis and ordinary foetal improvement and nourishing deficiency in various regions of the world is yet a matter of concern [52]. Clinically, iodine deficiency related SCH is all around universally with 45% expanded prerequisite all through pregnancy in view of expanded breakdown and discharge, foetal take-up, and expanded (TBG) Mandel et al. [53]. Therefore, diagnosis and treatment of iodine deficiency is imperative in developed and developing nations to avoid the thyroid dysfunction and adverse pregnancy results.

The existence of iodine deficiency is variable and influenced by geographic region and sort of eating and as per the NHANES 2005-2010; Hispanic dark pregnant ladies had low urinary iodine concentration (UIC) than non-Hispanic whites or Hispanics [54].

During the first trimester, the foetal mind development is absolutely relying upon maternal thyroid hormones. Thus, iodine deficiency during pregnancy may influence the psychological functions and in extreme insufficiency case, may cause serious foetal intellectual dysfunction, which can be averted if treated adequately [55]. Therefore, mild to moderate iodine deficiency is related with impeded psychological capacities, little placenta and head, low birth weight and hyperactivity disorders [56]. The UIC >100 μg/L is viewed as ordinary while 50-99 μg/L, 20-49 μg/L and <20 μg/L are meant to mild, moderate and serious iodine insufficiency individually. For pregnant women, 149-249 μg/L is worthy as satisfactory iodine consumption [57].Thus, revision of iodine inadequacy before pregnancy and amid first trimester can enhance psychological functions of kids contrasted with non-treated women [58].

O'Donnell et al. and Berbel et al. [58,59] evaluated the impact of iodine correlation in mild to moderate iodine lack during first trimester through two randomized trials and discovered loss of constructive outcome of iodine on psychological improvement when begun following 10-20 weeks. The United States (IOM) instructed daily iodine consumption regarding 150 μg/day for arranged pregnancy and 220 μg/day during pregnancy [60].

Maternal and foetal consequences of subclinical hypothyroidism during pregnancy

Confusion proliferates with respect to the correct mechanism of how SCH induces foetal neurologic deficits .One potential clarification is the presence of anti-thyroid antibodies, which could possibly associate with the placenta or foetal thyroid specifically. Haddow et al. [61], revealed an expanded rate of placental abruption placenta (OR 2.2, 95% CI, 1.21-3.99) among euthyroid women who were TPO-positive.

In a prospective study, Casey et al. [62], recruited 17,298 pregnant women at <20 weeks gestation and pregnancy complications with SCH were studied. A total of 404 women with SCH were compared with control subjects and found no differences in gestational hypertension, preeclampsia, birth weight, or in foetal and neonatal death. After adjustment for age and race, patients with SCH had significant higher abruption placenta (RR 3; 95% CI, 1.1- 8.2), more preterm birth (RR 1.8; 95% CI, 1.1-2.9) and excess respiratory distress (RR 1.8; 95% CI, 1.0-3.3).

A meta-analysis for 18 cohort studies was composed by Maraka et al. [63], and the adverse impact of SCH on pregnancy comes was considered. The outcomes indicated more placental separation (RR 2.14, CI 1.23-3.70), (PROM) (RR 1.43, CI 1.04-1.95) and higher neonatal loss (RR 2.58, CI 1.41-4.73) compared with euthyroid women.

Van et al. [64], analysed the pregnancy intricacies identified with SCH compared to euthyroid pregnant ladies in another meta-examination of 38 articles and discovered huge higher pre-eclampsia (OR 1.7; 95% CI 1.1-2.6) and more perinatal mortality (OR 2.7, 95% CI 1.6-4.7). Moreover, the presence of positive TPO Abs expanded the infertility (OR 1.5, 95% CI 1.1-2.0) and abortion (OR 1.5, 95% CI 1.1-2.0). Likewise, higher recurrent abortion, preterm deliveries and postpartum thyroiditis with (OR 2.3, 95% CI 1.5-3.5), (OR 1.9, 95% CI 1.1-3.5) and (OR 11.5, 95% CI 5.6-24) separately compared with TPO negative patients.

Negro et al. [2] contemplated the relationship between TPO Abs and unfavourable pregnancy results during the first trimester in women with ordinary thyroid capacity. Two hundred and forty five euthyroid women with (TSH<2.5 mIU/l) and positive TPO Abs in the first trimester and the outcomes were contrasted with 3348 pregnant euthyroid women with negative TPO. The outcomes demonstrated higher preterm birth 4.5% among TPO +ve contrasted with 1.8% in TPO negative gathering with P=0.003 and higher respiratory distress 3.3% among TPO +ve contrasted with 1.2% in TPO –ve with P=0.005. These outcomes were bolstered by Liu et al. [29], who discovered this strong relationship between TPO Abs and the inclination to have expanded risk of pregnancy complication at lower TSH contrasted with TPO negative women.

Haddow et al. [65], contemplated the antagonistic impact of untreated SCH during pregnancy on the cognitive functions of the off spring and discovered 15 % youngsters at age 5 years have a place with moms with high serum TSH. During second trimester had brought to down IQ score contrasted with 5% among kids have a place with euthyroid women p=0.06. Similar outcomes were seen by Williams et

Author and year	Study	Results	Conclusion
Chen et al.(2015) [67]	A prospective study	The Neurodevelopment of babies destined to 106 women with SCH contrasted with 106 new-born children of euthyroid women, utilizing five improvement subscales, including: Gross motor progress (P = 0.773), fine motor progress (P = 0.070), language development (P = 0.090), adaptive skills (P = 0.694) and individual social abilities (P = 0.406).	No perceivable neurodevelopment deficiency was seen in posterity up to two years old from moms who had gestational SCH.
Hershman et al.(2017) [68]	2 parallel, multicentre , randomized, placebo - controlled trials to address the thyroxine treatment of SCH and hypothyroxinemia	339 women with SCH got thyroxine contrasted with 338 got fake treatment indicated middle IQ score of 97 in treated gathering versus 94 in fake treatment assemble P=0.71 . 265 hypo-thyroxinemic women got thyroxine contrasted with 261 got fake treatment demonstrated middle IQ score of youngsters in the thyroxine gather was 94 versus 91 in the fake treatment gathering (P=.30)	There is no noteworthy distinction in IQ score of kids through age of 5 years for both treated gatherings with thyroxine contrasted with fake treatment

Table 3: Clinical impact of subclinical hypothyroidism in pregnancy on IQ score of offspring.

Country, Year and authors	Thyroid Test FreeT4(FT4) Total T4(TT4)	Methods/Instrument	First Trimester	Second Trimester	Third trimester	Number of participants
Malaysia, 2009	TSH MIU/L	Abbott AxSYM immunoassay platform.	1.04 ± 0.08	1.82+0.07 mIU/L	1.92+0.06	626
Mean ± SD						
Mean ± SD	FreeT4 pmol/L		13.86 ± 5.9	9.35+2.07	8.40+1.30	
Mean ± SD	Total T4 nmol/L		143.56 ± 38.26	140.89+26.99	138.03+22.79	
Mean ± SD	Total T3 nmol/L		1.18 ± 0.38	1.29+0.24	1.29+0.30	
New Delhi, India, 2008 5th–95th centile	TSH µIU/mL	ECL/Elecsys 1010 analyzer	0.6-5	0.435-5.78	0.74-5.7	541
5th–95th centile	FreeT4 pmol/L		12-19.45	9.48-19.58	11.3-17.71	
Basrah, Iraq, (2016)		ECL/*cobas e411* analyzer				540
5th–95th centile	TSH µIU/mL		0.04-3.77	0.30-3.21	0.6-4.5	
Mean ± SD			1.51 ± 1.16	1.58 ± 0.94	1.87 ± 1.11	
5th–95th centile	FreeT4 ng/dL		0.8-1.53	0.70-1.20	0.70–1.20	
Mean ± SD			1.15 ± 0.23	0.97 ± 0.16	0.90 ± 0.16	
5th–95th centile	Total T4 µg/dL		7.31-15.0	8.92-17.38	12.43 ± 3.0	
Mean ± SD			11.07 ± 2.62	13.02 ± 2.59		
5th–95th centile	Total T3 ng/mL		0.90-2.51	1.30-2.87	1.20-2.70	
Mean ± SD			1.62 ± 0.47	1.99 ± 0.47	1.99 ± 0.44	
North Kolkata, West Bengal, India, 2014	TSH µIU/mL	ELISA	0.25-3.35	0.78-4.96	0.9-4.6	402
Mean ± SD						
Mean ± SD	FreeT4 ng/dL		0.64-2.0	0.53-2.02	0.64-1.99	
Tabriz, Iran, 2005		Radio immunoassay/Gammamatic II gamma counter (Contron, Switzerland)				229
Mean+SD	TSH µIU/mL		1.71+1.38	1.89+1.24	2.12 ± 0.77	
Mean+SD	FreeT4 pmol/L		14.90 ± 4.67	13.07 ± 3.06	6.91+3.20	
Mean+SD	Total T4 nmol/L		87.98+40.87	94.30 ± 41.70	123.80+50.50	
Mean+SD	TT3 nmol/L		2.54+1.41	3.15+1.76	2.90 ± 1.5	
Korea, 2012		ECL/Elecsys thyroid tests, Roche Diagnostics				531
Mean+SD	TSH µIU/mL		0.01-4.10	0.01-4.26	0.15-4.57	
Mean+SD	FreeT4 ng/dL		0.83-1.65	0.71-1.22	0.65-1.13	
Jiangsu, China, 2010		Electrochemistry immunoassay (ECL)/COBAS e601			0.44-5.04	301
2.5th–95thcentile	TSH µIU/mL		0.02-3.65	0.36-3.46		
2.5th–95thcentile	FreeT4 pmol/L		11.85-21.51	9.45-6.26	9.30-17.14	
Australia, 2013		Beckman Dxl 800 analysers				130
5th–95th centile	TSH µIU/mL		0.05-2.33	0.47-2.71	0.42-2.65	
Mean+SD	FreeT4 pmol/L		5.9-15.5	4.9-11.3	4.5-11	
Shanghai, China, 2013		Beckman Coulter UniCel™ DxI 600.			0.15-5.02	2743
2.5th–95thcentile	TSH mIU/L		0.06-3.13	0.07-4.13		
2.5th–95thcentile	FreeT4 pmol/L		8.72-15.22	7.10-13.55	6.16-12.03	
Tehran, Iran, 2013	TSH µIU/mL	Immunoenzy mometric assay (IRMA) /Wizard, Wallac Oy, Turku, Finland).	0.2-3.9	0.5-4.1	0.6-4.1	152
5th–95th centile						
5th–95th centile	Total T4 (µg/dL)		8.2-18.5	10.1-20.6	9.0-19.4	
5th–95th centile	Total T3 (ng/dL)		138-278	155-328	137-324	
United state	TSH µIU/mL		0.1-2.5	0.2-3	0.3-3	
Mixed(Dutch, Turkish, Moroccan, Surinamese)					Not mentioned	
	TSH µIU/mL		0.06-4.51	Not mentioned		

Table 4: Trimester specific reference (TSR) of thyroid function tests in different regions [71].

al. [66], who noticed that women with preterm deliveries and SCH, the neurodevelopmental result of their kids was surveyed at 5.5 years old and discovered impedance in psychological, verbal and discernment capacities which was linearly in relation with expanded TSH during pregnancy.

Likewise, another two late examinations inspected the impact of SCH in pregnancy on IQ as explained in the below (Table 3).

Screening

Screening of subclinical hypothyroidism during pregnancy

The information from various studies indicated debate whether universal screening for the thyroid dysfunction and specifically, SCH during pregnancy is ought to be focused on high hazard patients.

In cross-sectional prospective study, Nazarpour et al. [69],

enlisted 1600 pregnant women during first trimester, 44.3 % had no less than one hazard factor for thyroid dysfunction and considered as focused high hazard patients, the staying 55.7% were without risk and considered low risk. By utilizing general screening 65.8% was ordinary thyroid status and 34.2% with thyroid dysfunction. 64.4% of women with thyroid dysfunction were in the high-chance gathering and 35.6% were in the generally safe gathering (P<0.0001) which implies 33% of cases with thyroid dysfunction was missed when screening was viewed as just for high hazard gathering.

Hye et al. [70], had conducted across sectional study and his main objective was testing of the normal reference of TSH during 1st trimester which can be used later to diagnose the SCH among pregnant Korean women with TSH >2.5 mIU/L. A total of 492 pregnant women and 984 non-pregnant age-matched women were included and the median TSH values in each trimester were compared to the non-pregnant. TSH >2.5 mIU/l, showed decrease in the rate of SCH diagnosis when the trimester TSH measurements consider the diagnosis rate of SCH. SCH significant decreases with increasing gestational age (25% in 3+0 to 6+6 weeks, 13% in 7+0 to 7+6 weeks, and 9% for 8+0 to 13+6 weeks,

Author, year and country	Number of participants	TSH, FT3, FT4, Anti-TPO, and Anti-TG	Result	Conclusion
Maji et al. (2014), India [73]	402 strong pregnant women were enrolled and the (RIs) of TSH and fT4 were settled in by (ELISA) in the wake of parceling them into three trimesters while, the reference masses was 610 pregnant females.	(RIs) for TSH were 0.25-3.35; 0.78-4.96 and 0.89-4.6 µIU/ml for to begin with 1st, 2nd & 3rd trimester independently. In like manner, the (RIs) for fT4 during 1st ,2nd and 3rd trimesters were 0.64 -2.0, 0.53-2.12 & 0.64-1.98 ng/dl separately	In contrast with the acquired (RIs), the reference information from unit producer under analyzed both SCH and hyperthyroidism inside pregnant reference populace	There should be a specific regional TSH (TSR) ranges and the reference data from kit manufacturer should be adapted to that population
Zhang et al. (2015), china [74]	2743 were eligible for analysis set reference intervals. TSH, FT4, and TPOAb levels were analyzed with Beckman Coulter UniCel DxI 600 immunoassay system	Establishment of method- and trimester-specific TSH and FT4 (RIs) in pregnant Chinese women using the Beckman Coulter UniCel™ DxI 600.	The calculated (RIs)for the 1st, 2nd, and 3rd trimesters were TSH: 0.06-3.13, 0.07-4.13 and 0.15-5.02 mIU/L, respectively , and FT4: 8.72-15.22, 7.10-13.55 and 6.16-12.03 pmol/L, respectively	RIs for TSH and FT4 are distinct from the ranges reported in DxI 600 instruction manual, confirming the value of method-specific (RIs)
Rajesh et al. (2016) , India [75]	1430 pregnant women	Reference masses was recognized to process serum (FT3), (FT4) and (TSH) for each trimester	The 2.5– 97.5th percentiles for FT3, FT4, and TSH were : In the primary trimester 2.53– 4.54 pg/ml, 0.88– 1.78 ng/ml and 0.37– 3.69 µIU/ml In the second trimester 2.0– 4.73 pg/ml, 0.91– 1.78 ng/ml and 0.54– 4.47 µIU/ml In the third trimester 2.01– 4.01 pg/ml, 0.83– 1.73 ng/ml, and 0.70– 4.64 µIU/ml	It is fundamental to have foundation of (RIs) in every district in light of the fact that current outcomes for TSR interims for thyroid hormones are conflicting
Tarun et al. (2016), India [76]	86 normal pregnant women during 1st trimester were selected for setting (RIs) compared to 124 normal nonpregnant.	(TSH), (FT4), (FT3) and hostile to TPO were estimated. The 2.5th and 97.5th percentiles were determined as the thyroid hormone (Ris) during each trimester	The (RIs) in first, second and third trimesters for: TSH (0.09-6.65, 0.51-6.66, 0.91-4.86 µIU/mL) FT4 (9.81-18.53, 8.52-19.43, 7.39-18.28 pM/L) FT3 (3.1-6.35, 2.39-5.12, 2.57-5.68 pM/L) separately.	The thyroid tests TSR intervals have been established for Indian pregnant using 2.5th – 97.5th percentiles.
Akarsu et al. (2016) Turkey [77]	TFT (TSR) ranges was tested in 2460 pregnant women (945 in the 1st trimester, 1120 in the 2nd trimester, and 395 in the 3rd trimester compared to 220 non-pregnant women	There is increase in TSH level from 1st to 3rd trimester While FT4 and FT3 level remain same during pregnancy	There is different TSH (TSR) intervals levels : 0.49-2.33 mIU/L ; 0.51-3.44 mIU/L and 0.58-4.31 mIU/L in the 1st, 2nd and 3rd trimester respectively while the ranges of FT4 and FT3 were same during the three trimesters	Gestational TSH (RIs) can help in the diagnosis & appropriate treatment of thyroid dysfunction during pregnancy to prevent adverse pregnancy outcomes
Veltri, et al. (2017) Belgium [78]	1683 **pregnant** women (481 women with sub-Saharan (28.6%), 754 North African (44.8%) and 448 Caucasian (26.6%)	(TPO Abs), TSH and FT4 were measured.	Median TSH was significantly lower in sub-Saharan & North African groups compared with Caucasian group (1.3 and 1.4 versus 1.5 mIU/L; P=0.006 & 0.014, respectively). The prevalence of SCH was comparable between all groups when 2.5 mIU/L was used as cut-off, but when 4.0 mIU/L or the institutional cut-off 3.74 mIU/L was used, it was significantly higher in the Caucasian group vs North African group (5.4% vs 2.1% and 7.1% vs 3.3%, P=0.008 & 0.013, respectively)	The use of ethnicity-specific TSH cut-offs in early pregnancy was not more specific for the diagnosis of SCH as compared to the use of the institutional cut-off.
Liu, et al. (2017), China [79]	947 pregnant women were accumulated by two methodology :The central system included division by trimester: stages T1, T2, and T3 and the second procedure included isolating T1, T2, and T3 stages into two stages each: T1-1, T1-2, T2-1, T2-2, T3-1, and T3-2	Estimated by three recognition frameworks	No noteworthy complexities were found in TSH regards between T1-1 gathering and the non-pregnant women assembling .The TSH estimation of the T1-1 collect was higher than that of T1-2 total (P < 0.05). The TSH regards in sort out T3-2 extended inside and out appeared differently in relation to those in organize T3-1 evaluated by three various looks at (P < 0.05). FT4 and FT3 regards lessened out and out in the T2-1 and T2-2 stages appeared differently in relation to the past stage (P < 0.05). The serum levels of Anti-TPO and Anti-TG were not having imperative differentiations between the six stages.	The finding & treatment of thyroid dysfunction during pregnancy should base on pregnancy and system specific (RIs)

Table 5: Thyroid function references intervals (RIs).

P<0.001). The rate of SCH was 5% in all gestational ages P=0.995 when gestational age specific cut off value was used.

Another examination from Iraq was conducted by Ammar et al. [71] who attempted to discover TSR for total tetraiodothyronin (TT4), free T4 (fT4) and total tri-iodothyronine (TT3) and TSH among Iraqi individuals who had been utilizing electro-chemiluminescence procedures. Six hundred and forty three pregnant women were combined and tested for anti TPO. Out of this total, 103 women were positive, the remaining 540 were negative and distributed as following (123 in the primary trimester; 246 in mid trimester and 171 in the third trimester) and concluded that the established (TSR) ranges for each thyroid function test and thyroid antibody status in Iraq are different from previous studies outside Iraq relying upon various territories and the sorts of reference packs utilized as abbreviated in (Table4).

During the first trimester, a few hormonal changes play a manage in the lessening of TSH for the most part due expanded hCG which has comparative impact to TSH and lead to expanding thyroid hormone production and diminishing TSH .Yet later , there will be gradual increase of TSH level during subsequent trimesters but remain lower than non-pregnant [72].

There are numerous elements influencing the TSH references extend and on its highest point is TPO antibodies and lacking iodine intake with some distinction additionally identified with ethnicity and topographical appropriation.

Also, there was several studies support the establishment of regional thyroid function references intervals (RIs) compressed in (Table 5).

The vast majority of the trials which were done in western nations including United States reach to a typical finish of keeping the maximum furthest reaches of TSH 2.5 mU/l and 3.0 mU/L during the first and both the second and third trimesters separately [80].

Additionally, the impact of TPO Abs on TSH level was thought about between 137 pregnant women (17.2% were TPOAb +ve) to 107 non-pregnant (13.1% were TPOAb +ve) as control. The upper reference utmost of TSH was reliably higher: 0–2.2 times in the non-pregnant women, 2.01–2.78 times in the primary trimester, 3.18–4.7 times in the second and 1.05–1.42 times in the third without influencing lower TSH reference confine. Along these lines, for building up pregnancy-particular reference ranges, TPOAb-positive subjects ought to be prohibited from the study [81].

As per Korevaar et al. [32], the majority of the studies which had been done in south Asia including India and Netherlands indicated gentle diminishment in upper TSH reference restrict.

Li et al. [82], considered the TSH references during first trimester and 4800 Chinese pregnant women were incorporated. The outcomes demonstrated descending movement in the TSH reference run began from weeks 7-12 with gentle lessening in the upper reference confine from 5.31 to 4.34 mU/L. Different studies which were done in India and Korea reach to a comparative finding of a modest reduction in the primary trimester upper TSH cut-off of 0.5-1.0 mU/L. The greater part of the research facilities by utilizing indirect simple immunoassays for estimating FT4 resulted by effortlessness and fast outcomes acquired however ,the precision is diminished during pregnancy due to the adjustment in temperature , buffer composition , affinity and concentration of the reagent and binding capacity of T4 . In addition, the decrease in albumin and increment TBG contrasted with sera of non-pregnant, make the aftereffects of FT4 analogue immunoassays during pregnancy inaccurate [83].

There are numerous techniques for measuring free thyroid hormones with a few cons and geniuses for every strategy. Dialysate is one of them which is exorbitant and tedious that also make it hard to be the real with the passage of time. Other structure is direct equilibrium dialysis and liquid chromatography tandem mass spectrometry (LC/MS/MS), in which the 95% FT4 reference interims was lessened unendingly with progressing gestational age [84].

LC/MS/MS is viewed as the highest quality level technique, which is utilized by most labs for estimation of FT4 and relates precisely with the established balance dialysis yet with FT4 immunoassay, the relationship is less exact [85]. Although, the isotope dilution LC/MS/MS is a decent reference for estimating serum FT4 but since of the cost and methodology trouble, the utilization of this strategies is constrained for specific research facilities [86].

In another study, Chrysoula et al. [87] tried the cost viability of universal TSH and thyroid antibodies screening during first trimester and the outcomes demonstrated noteworthy cost saving for TSH screened pregnant women contrasted and no screening. Additionally, screening for TPO Abs contrasted and TSH screening indicated incremental cost-viability proportion of $15,182 for every quality-balanced life year and reasoned that universal screening of early pregnant women for immune system thyroid infection is cost-effective compared with no screening. Likewise, Stephen et al. [88] got comparable outcomes and the cost viability of screening SCH during pregnancy by contrasting between the standard technique without screening and routine screening of TSH level was computed. For routine screening, levothyroxine was utilized for all SCH pregnant women to enhance the IQ of children and the fundamental goal was estimation of cost per quality-balanced life year (QALY) and found that by diminishing SCH commonness to 0.25%, $ 21,664/QALY was picked up which bolster the cost adequacy for screening SCH during pregnancy.

Also, Jouyandeh et al. [89] completed a meta-analysis and accepted that case-based screening can miss up to 49 % of pregnant women with thyroid dysfunction which make sound for the importance of comprehensive screening systems for thyroid issue in pregnancy, compressed in (Table 6).

SCH and Adverse Pregnancy Outcomes

Adverse effects of subclinical hypothyroidism on pregnancy outcome and intellectual development of the fetus

Subclinical hypothyroidism has been associated with neurodevelopmental disorders in foetuses and infants with several adverse maternal outcomes, including GDM, preeclampsia, placental abruption, pregnancy loss and preterm delivery.

In a cohort study, Foster and Warren [99] enrolled 16,093 pregnant women with less than 20 weeks of gestation. The results showed that 404 women had SCH having three times more likely to have placental abruption and 2 times higher preterm birth than those without SCH. However, the weight of infants belong to SCH did not differ from those without SCH. Respiratory distress was twice as likely in infants delivered by women with SCH. There was no difference for major malformations, foetal death or neonatal death. This study concluded that SCH was associated with increased risk of adverse pregnancy complicated by placental abruption, preterm birth with more respiratory distress admission to the neonatal intensive care.

In a meta-analysis of eighteen cohort studies, Maraka et al. [63] discovered huge pregnancy loss in women with SCH contrasted with pregnant women with ordinary thyroid capacity (RR 2.01,95% CI 1.66–

Author & year	Study & number of participants	Thyroid dysfunction	% of instances of hypothyroidism missed by case-discovering screening
Vaidya et al. (2007) [90]	Single-centre cohort (1,560)	Low risk: 1 % raised TSH High risk: 6.8 % raised TSH	30 %
Horacek et al. (2010) [91]	Cross sectional 400	10.3 % raised TSH 16.3 % at least one abnormality	55 %
Matuszek et al. (2011) [92]	Case–control (270)	Hypothyroidism: 10.4 %	46.4 %
Goel et al. (2012) [93]	Prospective case–control (1,020)	Hypothyroidism: 6.3 %	32 %
Jiskra et al. (2011) [94]	Prospective Cross sectional 5220 (200 positive in screening)	21 % transient gestational hyperthyroidism, 5 % unmistakable hypothyroidism, 38 % SCH, 3.5 % hyperthyroidism, 33 % euthyroid.	(47 %)of the decidedly screened pregnant women can be named high hazard
Chang et al. (2011) [95]	Review study (983) pregnant women were incorporated, 56 of the 932 women had a lifted TSH.	Of these 56 women, nine had a past loaded with thyroid ailment; two had a foundation set apart by type 1 diabetes. In perspective of current Endocrine Society case-finding rules, only these 11 women with a raised TSH were experienced thyroid testing in pregnancy while other 80.4% of women with a lifted TSH in pregnancy would not have been attempted.	Coordinated thyroid testing in simply high-chance patients would have missed 80.4% of pregnant women with hypothyroidism.
Gudala et al. (2013) [96]	Ameta-analysis of total 5 studies for thyroid dysfunction during pregnancy	For the effectiveness of universal screening, pooled odds ratio was found to be 2.87 (95% CI, 1.60-4.94, p=0.00).	Targeted thyroid function testing of only the high-risk group would miss about one third of pregnant women with overt/ subclinical hypothyroidism.
Yang et al. (2014) [97]	Prospective study (3882)	3882 Chinese women during the 1st and 2nd trimester of pregnancy were divided into high risk and non-high risk groups. TSH, FT4 and TPO Abs were measured.	High risk screening strategy failed to detect the majority of pregnant women with thyroid disorders and universal screening of TSH, FT4 & TPOAb during 1st and 2nd trimester was recommended.
Norman et al. (2016) [98]	Prospective observational study (1069)	103 had SCH with TSH levels >2.5mIU/l, 87 women had TSH levels > 2.5 and ≤5 mIU/l. Of these, 36 patients were sure for TPOAb. 12 had a TSH >5 and ≤10 mIU/l with 8 patients positive for TPOAb. 4 patients had a TSH level >10 mIU/l with 2 patients positive for TPOAb .TAI were distinguished in 258 patients (24.13%).	A high prevalence of SCH and TAI is pointing for a strong indication for universal screening with TFT and TAI testing for all Australian pregnant women
Nazarpour et al. (2016) [69]	Cross-sectional prospective study (1600)	1600 pregnant women in their first trimester were enlisted and TSH, FT4 and TPO Abs were assessed. Of women with thyroid dysfunction, 64.4% were in the high-chance get-together and 35.6% were in the all-around safe social gathering (P<0.0001).	Coordinated high-chance case finding approach disregards around 33% of pregnant women with thyroid dysfunction

Table 6: Widespread versus case-discovering screening of thyroid dysfunction during pregnancy.

2.44), placental abruption (RR 2.14, CI 1.23– 3.70), PROM (RR 1.43 ,95% CI 1.04–1.95), and neonatal demise (RR 2.58, 95% CI 1.41–4.73).

In another meta-examination of 38 articles, Van et al. [64], analysed the pregnancy complications identified with SCH contrasted and euthyroid pregnant ladies and discovered noteworthy higher pre-eclampsia (OR 1.7; 95% CI 1.1-2.6) and more perinatal mortality (OR 2.7, 95% CI 1.6-4.7). Additionally, the presence of positive TPO Abs expanded the infertility (OR 1.5, 95% CI 1.1-2.0) and abortion (OR 1.5, 95% CI 1.1-2.0). Additionally, higher recurrent abortion, preterm deliveries and postpartum thyroiditis with (OR 2.3, 95% CI 1.5-3.5), (OR 1.9, 95% CI 1.1-3.5) and (OR 11.5, 95% CI 5.6-24) separately contrasted and TPO negative patients.

Another prospective study inspected the adverse pregnancy results of SCH during pregnancy and 8012 Chinese pregnant women were enrolled; 371 women had SCH and the staying 7641 had typical thyroid capacity. The women with SCH contrasted with pregnant women with ordinary thyroid capacity had critical more rates of gestational hypertension (GH) (3.504% versus 1.819% P=0.020); IUGR (2.965% versus 1.008% p<0.001; (PROM) (8.625% versus 4.973%, P=0.002; LBW ≤ 2500 g) (4.582% versus 1.885%, P<0.001) [100].

In another vital survey of 9 cohort studies by Yibing et al. [101], the threatening impacts of SCH before 20 week of advancement was emerged from pregnant women with ordinary thyroid utmost and found the non-treated SCH had a higher miscarriage (RR=1.90, 95% CI 1.59–2.27, P<0.01). Compared to isolated SCH women, the abortion risk of SCH patients with thyroid antibodies was obviously higher (RR=2.47, 95% CI 1.77– 3.45, P<0.01), and isolated SCH patients had also a higher prevalence of abortion than euthyroid women (RR=1.45, 95% CI1.07–1.96, P=0.02). Therefore, SCH is a danger factor for abortion in women before 20 weeks of pregnancy.

In another prospective cohort, 400 pregnant women were followed from second trimester until the full term. The gestational complexities of SCH in pregnant women were compared with normal thyroid and found a higher rates of preeclampsia 22.3% versus 7.8%, spontaneous abortion (5.5 versus 2.39%), preterm birth (11.2 versus 5.8%), LBW (25 versus 12.11%), and IUGR (8.4 versus 4.9%) [102].

The IQ of the posterity was inspected in a cohort study of 64 pregnant women with high TSH and of this number; levothyroxine was not given for 48 women and found the IQ of children for these women was seven points less compared with the offspring of the 128 controls [65]. Another examination attempted the effect of levothyroxine use on the IQ of the offspring in pregnant women with SCH. In this unavoidable multi-nation randomized controlled trial in Europe, 21,846 women with a TSH >97.5th centile or free thyroxine <2.5 centile (or both) were joined. The outcomes showed that children's IQ <85 at 3 years old was not different between treated and untreated mothers [103].

In a cohort prospective study from Finland, the relationship between maternal high TSH and TPO positivity during early pregnancy and deficiency/hyperactivity issue (ADHD) was studied among their kids. For that 9362 pregnancies and 9479 new born children were incorporated. The outcomes demonstrated critical higher combined ADHD manifestations (OR 1.39, 95% CI 1.07–1.80) among young women as opposed to young men with increment maternal TSH focuses ,however no relationship with TPO Abs [104]. Another, two cohort studies from Danish and Spanish populace, found no impact of SCH on advancement of kid during follow up for 30 months Henrichs

Author and year	Number of pregnant women	Type of study	Results	Conclusion
Casey et al. (2003) [109]	404 women with SCH , and 15,844 women with TSH	Prospective	Preterm deliveries (PT) happened in 18 (4%) in SCH contrasted with 428 (2.7%) with typical TSH levels (P = 0.03) and this hazard persevered after modification for age and race (OR 1.7; 95% CI, 1.07-2.81	Subclinical hypothyroidism is significantly associated with preterm birth.
Wilson et al. (2011) [110]	25,687 (22,223 (86%) euthyroid , 1,934 (7%) with subclinical hyperthyroidism, and 1530 (6%) with SCH	Prospective	PT happened in 18 (4%) in SCH contrasted with 428 (2.7%) with typical TSH levels (P = 0.03) and this hazard persevered after modification for age and race (OR 1.7; 95% CI, 1.07-2.81	Hypertension during pregnancy and severe preeclampsia are more common in women with SCH
Wang et al. (2012) [111]	756 pregnant women during the 1st trimester were enrolled	Prospective	unconstrained premature births in the SCH amass was higher than the ordinary TSH gathering (15.48% vs 8.86%, p =0.03)	Unconstrained fetus removal in pregnant women with SCH increments in early pregnancy and no noteworthy affiliation was seen amongst SCH and other obstetrical difficulties
Fionnuala et al. (2013) [112]	953 primigravid women	Cohort	Positivity of TAI connected with SCH status (P = 0.02). Placental unexpectedness was watched all the more normally in the setting of either SCH or detached maternal hypothyroxinaemia when contrasted and euthyroid controls (P = 0.02 and 0.04, separately).	SCH and confined maternal hypothyroxinaemia are related with placental suddenness.
Suhitha et al. (2016) [113]	One Hundred (50 SCH and 50 euthyroid) and SCH women are treated with levothyroxine	Observational, prospective, cohort study	pregnancy outcomes between cases and controls, TPOAb positive and negative cases are similar with significant increase of PT deliveries (10% versus 0) and CS (36.73% versus 15%) in cases when compared to TPOAb negative controls and PIH (6.67% versus 0) is significantly higher in TPOAb positive controls when compared to TPOAb negative controls	Unfavourable pregnancy comes about are not in a general sense higher in treated SCH compared to euthyroid women, and TPO -Ab status have not influenced the results in SCH with noteworthy higher PT deliveries and CS in SCH contrasted with TPOAb negative euthyroid women. Euthyroid women with TPOAb are related with essentially higher risk of PIH.
Myrthe et al. (2016) [114]	848 ladies; 20 (2.4%) had SCH; 818 ladies (96%) had euthyroidism; and 10 (1.2%) had clear hypothyroidism	Cohort study	The live birth rate was 45% in SCH ladies and 52% in euthyroid ladies (OR 0.69, 95% CI 0.28 to 1.71) and steady pregnancy rate was 65% versus 69% (OR 0.82, 95% CI 0.32 to 2.10) and miscarriage rate was 35% versus 28% (OR 1.43, 95% CI 0.56 to 3.68), separately.	No capabilities were found in live birth, incessant pregnancy and unforeseen work rates between women with SCH and euthyroid ladies.
Plowden et al. (2017) [115]	1193 with 1–2 previous pregnancy losses	Prospective cohort	No relationship between pregestation TSH level >2.5 versus ≤ 2.5 mIU/L and (PT) deliveries (balanced RR, 0.77; 95% CI, 0.40– 1.47), GDM (CI, 0.54– 3.04), or preeclampsia (balanced RR , 1.20; 95% CI, 0.71–2.04).Also, among women with thyroid antibodies, there was no improve in the probability of PT (RR , 1.26; 95% CI, 0.65– 2.45), GDM (RR, 1.33; 95% CI, 0.51–3.49), or preeclampsia (RR, 1.02; 95% CI, 0.54– 1.92), contrasted and women without antibodies.	SCH and TAI were not related with an expanded risk of PT, GDM and preeclampsia.
Li et al. (2017) [116]	1,896 pregnant women with SCH	15 cohort studies	SCH in pregnancy was fundamentally connected with kid's knowledge (P = 0.0007), engine improvement (P < 0.00001) and essentially connected with the kid's weight. Four studies explained results including 222 women (P = 0.02) and maternal SCH, a hazard factor for fetal development confinement with a joined RR 2.4 (95% CI: 1.56, 3.7), critical relationship with unexpected labor, RR 1.96 (95% CI: 1.34, 2.88) and a huge impact on fetal misery in utero (P = 0.003).	Maternal SCH in pregnancy is related with expanded risk of neonatal postponed scholarly and engine advancement, low birth weight, unexpected labour, fetal pain and fetal development confinement

Table 7: Subclinical hypothyroidism during pregnancy and adverse pregnancy outcomes.

et al. and Julvez et al. [105,106] and another Scottish study found no relationship between maternal TSH level and neuropsychological formative at 5.5 years old for youngsters born after 37 weeks [66]. Additionally, Männistö et al. [107], contemplated the clinical effect of SCH on pregnancy results and for that 223, 512 pregnant women were incorporated into a retrospective electronic chart analysis and discovered that SCH is the reason behind the higher number of GDM, preterm birth, increment caesarean segment with more maternal admission to ICU because of higher intricacies, mostly abruption placenta and breech position.

In another study, an aggregate of 2497 Dutch women was enrolled and the connection between high TSH and foetal loss was tried. The outcomes demonstrated a flat out hazard for foetal loss 0.8% in women with TSH 0.54mU/L and expanded to 2.2% in women with TSH 3.13 mIU/L [30]. Recently, another Japanese retrospective study of 167 women less than 20 weeks of gestation with TSH >3 and <10mIU/L were analysed. 27 out of 167 cases with thyroid antibodies were included and the adverse pregnancy outcomes was compared with 578 euthyroid control and without thyroid antibodies .The result showed GDM was significantly higher in SCH group (p<0.01) but there is no difference in adverse maternal and neonatal outcome with p=0.19 and p=0.50, respectively. Also there is no difference between SCH with antibodies and controls (p=0.64 and p=0.50, respectively) [108].

Additionally, the data from many other studies showed the relationship amongst SCH and or TAI and adverse pregnancy outcomes were compressed in (Table 7).

Also, such relationship amongst SCH and antagonistic pregnancy results was bolstered by information from other fifteen studies, outlined (Table 8).

Treatment

Treatment of subclinical hypothyroidism during pregnancy and its consequences on mother and foetus

There is controversy regarding treatment benefit of SCH during pregnancy despite the way that the perils for pregnancy complexities and foetal neurologic mischief are far from clear, accessible confirmation recommends a conceivable hazard for unfavourable results. Studies have recorded that satisfactory thyroid hormones is required for regular insightful and mental components of the descendants exceptionally in

Authors	Year & Country	SCH (number)	Study type	trimester	SCH	Eclampsia	Fetal death	LBWT	HTN	Abortion	GD	Preterm birth	Placental abruptio
Allan et al. (2000) [117]	2000 US	209	Retrospective	2nd	>6.0		**S**						
Casey et al. (2005) [62]	2005 US	404	Prospective	2nd	2.74-5.09	NE	NE	NE	NE	NE	NE	**S**	**S**
Clearly-Goldman et al. (2008) [1]	2008 US	240	Prospective	1st & 2nd	4 & 4.3	**NS**	NE	NE	**NS**	NS	**NS**	**NS**	**NS**
Männistö et al. (2009) [34]	2009 Finland	224	Prospective	1st	>3.6	NE	**NS**	**NS**	NE	**NS**	NE	**NS**	NE
Sahu et al. (2010) [118]	2010 India	41	Prospective		>5.5	NE	NE	**NS**	NS	NE	NE	**NS**	NE
Mainnisto et al. (2010) [119]	2010 Finland	224	Prospective	1ST	>3.6	NE	NE	NE	**NS**	NE	**NS**	NE	**NS**
Negro et al. (2010) [2]	2010 Italy	642	Prospective	1ST	2.5-5	NE	NE	NE	NE	**S**	NE	**NS**	NE
Goel et al. (2012) [93]	2011 India	34	Prospective	ALL 3	>5	**NS**	NE	NE	**NS**	NE	NE	**NS**	**NS**
Su et al. (2011) [120]	2011 China	41	Prospective	1ST & 2ND	>4.3	NE	**NS**	NE	NE	**NS**	NE	S	NE
Wilson et al. (2012) [121]	2012 US	528	Prospective	1ST &2nd	>4.1	**S**	NE	NE	**S**	NE	NE	NE	NE
Tudela et al. (2012) [122]	2012 US	528	Prospective			NE	NE	NE	NE	NE	**S**	NE	NE
Schneuer et al. (2012) [123]	2012 Australia	152	Retrospective	1st & 2nd	>4.1	**NS**	**NS**	NE	NE	**S**	NE	**S**	NE
Karakosta et al. (2012) [31]	2012 Greece	79	Prospective	1st & 2nd	2.5& 2.7	NE	NE	**S**	NE	NE	**S**	**NS**	NE
Korevaar et al. (2013) [32]	2013 Netherland	188	Prospective	1st&2nd	4.04	NE	NE	NE	NE	NE	NE	**S**	NE

S : Significant association found

NS: No significant association found

NE : Association between SCH and complications during pregnancy is not evaluated

GD : gestational diabetes

LBWT: Low birth weight

SCH: Subclinical hypothyroidism (mIU/L)

Table 8: Subclinical hypothyroidism and adverse pregnancy outcomes

the initial 12 weeks of pregnancy, during which the headway of foetal central nervous system is totally reliant on maternal thyroid hormones [124].

In an interventional retrospective cohort utilizing levothyroxine treatment for pregnant women with SCH, the safety and effectiveness in decreasing antagonistic pregnancy results was tried and 5405 pregnant women with SCH were enrolled and ordered into 2 gatherings; the first gathering of 843 women had a mean TSH 4.8 mIU/L and were subjected for levothyroxine treatment while the second gathering of 4562 with a mean standard TSH centralization of 3.3 mIU/L were not treated. The outcomes demonstrated a striking lessening in pregnancy loss in the treated gathering 10.6% (OR 0.62, 95% CI 0.48-0.82) contrasted and 13.5% in untreated gathering, P<0.01. This positive useful impact was seen just when pre-treatment TSH fixation was 4.1-10 mIU/L and (OR 0.45, 0.30 - 0.65) yet not when the pre-treatment TSH was 2.5-4.0 mIU/L (OR 0.91, 0.65-1.23) (P<0.01) .However, the present rules instruct a limit concerning 2.5 mIU/L for treating SCH when there is no territorial populace references [125].

In like manner, Negro et al. [126] chose 4,562 pregnant women and indiscriminately subjected into comprehensive screening or case finding tradition .Then, furthermore isolated into high and low risk depend upon history and examination. Levothyroxine was given for patients with TSH>2.5 mU/l with positive TPO Abs and the results showed no difference in the outcomes among universal and case finding group.

Another Interventional study done by Lazarus et al. [127] tried the clinical impacts of levothyroxine treatment during the first trimester for both overt and SCH related scholarly elements of youngsters. The outcomes demonstrated that the mean IQ at age 3.5 years and the level of kids with IQ <85 was essentially diminished in the agreeable gathering with levothyroxine treatment.

There are numerous examinations analysed the control of thyroid hormone trade for accomplishing successful pregnancy in women experiencing IVF and the (ES) exhorted thyroid capacity screening for barren women. In a randomized report, 64 women with SCH (TSH >4.5 mU/L) were incorporated and for whom IVF was done, 50 µg/d was begun at time of ovarian incitement and the measurement was raised to keep TSH <2.5mU/L during the underlying 12 weeks of pregnancy contrasted with fake treatment. The outcomes indicated more fruitful pregnancy rate, not so much premature births, but rather more delivery rates in treated gathering [128]. Comparative outcomes were gotten in another prospective, randomized study, inspected the thyroxine substitution treatment in 64 fruitless women with SCH , for whom 64 IVF cycles were done and were randomized into either the LT4 treatment gathering (n=32) or control gathering (n=32). Contrasted and fake treatment, utilizing a measurement of 50 µg/day brought about more effective rate of pregnancy and live births with less death rates in the treated gathering [129].

A meta-analysis by Negro et al. [130], examined the rule of levothyroxine treatment on ART in women with normal thyroid function and +ve TPO Abs and found no effect on clinical pregnancy rates with (RR 1.75 ,95% CI 0.90–3.38) but resulted in a higher delivery rate (RR 2.76 ,95% CI 1.20–6.44).

Although, levothyroxine treatment is relatively cheap, safe, widely available, and well tolerated, ACOG Committee [131], recommends against screening and treating SCH in pregnancy. It does not directly address the situation if it is found incidentally or by means of risk factors while other endocrine organizations, such as ES, and the AACE, advised treatment for SCH in pregnancy [132].

Nazarpour et al. [133], made a randomized clinical trial with an aggregate 1746 pregnant women were picked, 393 of them had SCH and were self-unequivocally consigned to treatment with thyroid

Author & year	Study design	Number of participants	Levothyroxine dose /day	Results	Conclusions
Yu et al. (2013) [138]	Prospective	56 SCH pregnant women were isolated into three subgroups(A,B and C) in setting of the measure serum TSH levels	**A** : (n = 29,TSH 2.5-5.0 mIU/L, got 50 µg/day; **B** :(n = 17, TSH 5.0 - 8.0 mIU/L got 75 µg/day; and **C** :(n = 10, TSH >8.0 mIU/L got 100 µg/day with estimation change as per keep TSH 0.13– 2.5 mIU/L for first trimester, 0.26– 3.0 mIU/L for second , and 0.42– 3.0 mIU/L for third trimester	**A Group:** the last estimations of 23 patients (79.3 %) was 50 µg/day and that of six patients (20.7 %) was 75 µg/d. **B Group**: the last estimations for 14 patients (82.4 %) was 75 µg/d. One patient (5.9 %) was at 100 µg/d, one patient (5.9 %) was at 50 µg/d, and one (5.9 %) was at 25 µg/d. **C Group:** the last estimation of nine patients (90.0 %) in total C was 100 µg/day and that of 1 steady (10.0 %) was 75 µg/d.	LT4 estimations can be picked by the check TSH levels of SCH pregnant women. The expected LT4 estimation can keep up serum TSH levels of 79.3–90 % patients in the ideal range
Abalovich et al. (2013) [139]	Retrospective analysis	64 SCH pregnant women were into collect 1a:TSH >2.5 first trimester or >3 - 4.2 mIU/L (second or third trimester) and get-together 1b: TSH >4.21– 10 mIU/L	The estimation is to keep TSH of ≤ 2.5 mIU/L in first trimester and ≤ 3 mIU/L during second and third trimesters	**Group1a** required lower estimation (p <0.014) than **Group1b:**1.20±0.39 versus1.42±0.31 µg/kg/d. In 57 women, LT4 estimations orchestrated with the basic dose and estimations modification was required in 11% and 23% independently.	In pregnant women with SCH ,the starting LT4 estimations: 1.20 µg/kg/day with TSH ≤ 4.2 mIU/L and 1.42 µg/kg/day with TSH >4.2– 10 were securely capable euthyroid status
Penin et al. (2014) [140]	Prospective	116 pregnant women with TSH levels > 4.5 mUI/ml were enrolled	75µg	All patients were treated with settled dose 75µg and thyroxine levels were assessed at two, four, and half year , and estimation was balanced if TSH level<0.3or > 4.5mUI/ml.	Settled every day estimations of thyroxine 75µg considered accomplishing target TSH levels in a generous piece of our pregnant women with SCH, paying little personality to their weight and illustration TSH level.
Chakraborty et al. (2016) [141]	Prospective	42 clearly typical pregnant women	Mean dosage during first trimester was 40.18 ± 13.78 75µg and mean measurement during third trimester was 58.25 ± 18.57 µg	81.25% of subjects achieved euthyroidism with huge increment in the mean measurements of levothyroxine required in the third trimester when contrasted with the primary trimester , P = 0.0012)	Critical change in the thyroid capacity as demonstrated by higher extent of patients accomplishing typical TSH esteems with huge increment in the mean levothyroxine measurements utilized over the span of treatment.

Table 9: Optimal levothyroxine treatment dose for subclinical hypothyroidism in pregnancy.

hormone or without treatment. The treated group with initial TSH >4.0 mIU/L had less premature deliveries than untreated women did. Further analysis among untreated women with SCH, the risk for preterm delivery was lower with baseline TSH <4.0 mIU/L (RR, 0.44; 95% CI, 0.2–0.97). In addition, no difference found whether the (UIC) was more or <150 µg/L and this study concluded that there was no benefit of thyroxine replacement for prevention of premature delivery in TPOAb-negative pregnant women with baseline TSH >2.5 mIU/L. However, in secondary analyses, there was a benefit of treatment for TPOAb-negative with a baseline TSH ≥ 4.0 mIU.

Another prospective observational study, 1025 pregnant women were incorporated. 10.1 % were determined to have SCH and 18.2 % were sure for thyroid antibodies, treated with thyroxine to keep TSH <2.5 mIU/L and found no distinction in pregnancy complications results compared with ordinary thyroid capacities [134].

Brian et al. [135] directed two multicentre, randomized, placebo-controlled trials explaining the impact of thyroxine substitution treatment on IQ score of posterity in 97 pregnant women with SCH contrasted and 94 fake treatment gathering. The outcomes demonstrated no critical distinction in the median IQ score of the posterity of treated gathering (95% CI, 94-99) contrasted with fake treatment gathering (95% CI, 92-96), (P=0.71). This examination did not yield any distinction in term of intellectual capacities or antagonistic pregnancy results but this has helped in understanding the aftereffects of a few studies that include treating of SCH during second trimester, which is not about preferable psychological capacities over no treatment. We expect any advantage from thyroid hormone substitution, such treatment ought to be begun assumption or early pregnancy however not later to enhance pregnancy results.

Protocol of levothyroxine treatment for subclinical hypothyroidism during pregnancy

There is still some debate about the treatment of SCH during pregnancy and that is identified with clashing outcomes about upsides and downsides of thyroid hormone treatment, the TSH (TSR) run at which, the treatment ought to be begun and trimester timing. There is understanding amongst (ATA) and (ES) rules to give thyroid hormone substitution for SCH during pregnancy while the announcement of ACOG is against that because of lack of enough information with respect to the protected dosage of levothyroxine that can be utilized during pregnancy [80].

In a prospective interventional trial by Yu et al. [136] the required measurements of levothyroxine for SCH during pregnancy were tried and 56 pregnant women with SCH were enrolled. The beginning measurements of thyroxin for various TSH focuses: TSH 2.5-5.0 mIL/U, TSH 5.0-8.0 mIU/L and TSH >8.0 mIU/L were 50 µg/day; 75 µg/day and 100 µg/day individually and inferred that utilizing these doses identified with TSH fixations accomplish >80% control of SCH without requirement for assist acceleration of dosage during pregnancy. Another review thinks about that included 64 members, diverse dosages of levothyroxine had been utilized as a part of various TSH fixation for treating SCH during pregnancy and the point was to keep TSH <2.5 mIU/L during first trimester and <3.0 mIU/L during second and third trimester. The underlying measurement of thyroxine was 1.20 µg/kg/day for TSH 2.5-4.2 mIU/L and 1.42 µg/kg/day for TSH 4.2-10.0 mIU/L and presumed that these underlying levothyroxine dosages were not altered and keeping the TSH level with in the acknowledged range in over 89% of women during pregnancy [137]. Additionally, the ideal dosage of levothyroxine in SCH during pregnancy was tried in

numerous studies and the wellbeing and viability of the hormonal pay were taken in thought as abridged (Table 9).

Monitoring of levothyroxine in pregnant women with SCH

A large portion of the rules considered thyroxine treatment during pregnancy, if the underlying TSH focus is >2.5 mIU/L with typical FT4 and TPO-Ab positive. At the same time, there is no enough information about clinical adequacy when utilized as a part of TSH >2.5 mIU/L with TPO-Ab negative pregnant women and encourage rehashing the TSH at regular intervals during first and second trimesters and once during the third trimester [3]. The (ES) exhorted the treatment with levothyroxine for any pregnant women with SCH, if the underlying TSH during first trimester is >2.5 mIU/L regardless of their TPO Abs condition with consistent follow up by estimating TSH fixation every 4-6 weeks during pregnancy [80].

As showed by current affirmation, levothyroxine treatment for SCH during pregnancy using the going with estimations 50 μg, 75 μg, and 100 μg consistently for the going with TSH level 2.5-5.0 mIU/L, 5.0-8.0 mIU/L, and >8.0 mIU/L independently were shielded, suitable and practical [136].

Treatment of SCH with iodine during pregnancy

(UIC) <100 μg/dL is showing potential iodine require and <50 μg/dL is seen as surprising deficiency [142]. The U.S. (IOM) showed signifies all around requested estimations concerning iodine before pregnancy is 150 μg/day and 220 μg/d for pregnant women. WHO consider the estimations 250 μg/d for pregnant and lactating women [143]. There is affirm which reinforce this estimation worked out obviously in the light of an examination for >7000 pregnant Chinese women and found SCH was uncommon, if the (UIC) was 150-249 μg/L [144].

Data from UAE regarding the prevalence of SCH during pregnancy, diagnostic test and treatment protocol

In UAE, in spite of announcing a high number of SCH in pregnancy because of positive TPO-Abs or potentially iodine deficiency, there is no information about the predominance of SCH and how much its clinical effect on pregnancy results. Also, the management of SCH during pregnancy is predominantly relying upon the rules of the (ATA) and the (ES) [80,132], taking in consideration the decision of treating physician and the willing of patient with SCH for treatment with levothyroxine during pregnancy as follow:

• Treatment is prescribed if TSH is above (TSR) or >4.0 mU/L and (TSR) is difficult to accomplish, free of (TPO) Abs status.

• Treatment is prescribed if a TSH (2.6-4 mU/L), positive TPO Abs, and there is history of recurrent miscarriage.

• In case TSH (2.6-4 mU/L) and no prior history of abortion, the decision of treatment is individualized in light of the existence of TPO antibodies and patient preference.

• A couple of endocrinologists offer levothyroxine 50 mcg/ dependably for positive TPO Abs women having TSH >2.5 mU/L. Others considered treatment of pregnant women with TPO Abs, paying little regard to the TSH level.

• In pregnant women with TSH (2.6-4 mU/L) and not taking treatment, TSH ought to be reassessed monthly during the primary trimester and once during second and third trimester but in case TSH increase above the regional (TSR) of upper normal or >4 mU/L, levothyroxine ought to be begun.

• For TSH between the trimester-specific lower limit of normal and 2.5 mU/L, women are euthyroid and don't require T4 treatment. However, if there is a prior history of recurrent abortion, TPO antibodies have typically already been assessed, thyroxine treatment with 50 mcg/ daily should be began.

• The ATA guidelines considered the positivity of TPO Abs on treating SCH during pregnancy Alexander et al. [132]:

- Positive TPO antibodies with TSH >2.5 mU/L and or if TSH is above the population and trimester-specific upper limit of normal (4.0 mU/L), thyroid hormone should be started.
- Negative TPO antibodies: Thyroid hormone should be considered if the TSH is above masses and trimester-specific most removed purpose behind control of normal yet <10 mU/L.

Some hospitals in UAE are using the following treatment protocol and monitoring for thyroid dysfunction before and during pregnancy, condensed as following:

1. Women on levothyroxine with as of recently settled inclination TSH >1.2 to <2.5 mIU/L, once pregnancy is affirmed, the dose of thyroxine is increased initially by 25 % with monthly checking of TSH level to keep it <2.5 mIU/L.

2. For women on levothyroxine before pregnancy with early settled inclination TSH <1.2 mIU/L and once pregnancy is affirmed, TSH ought to be checked every 4-6 weeks

3. For untreated pregnant women and their first trimester TSH >2.5 mIU/L with or without TPO-Abs. Beginning estimations of levothyroxine were as follows

- 50 μg /day for TSH 2.5-5 mIU/L

- 75 μg /day for TSH 5-8 mIU/L

- 100 μg /day for TSH >8 mIU/L

4. TSH ought to be observed each month during the starting three month of pregnancy, by then once during second trimester and third trimester.

5. Postpartum TSH monitoring should every 6 weeks with reducing the estimation of levothyroxine to pre-pregnant level.

Results

After reviewing the various studies carried out in the past related to ATA and ES guideline, there is evidence that SCH is very common in the women importantly in those countries where the people have deficiency of iodine and high autoimmune thyroiditis. The study has reach to the point that the pregnancy loss and the premature births are very frequent in number in such countries where the SCH is very common in women. This thorny of on thyroid dysfunctions is also supported by ATA systematic review and found the risk of pregnancy-specific complications was apparent in women who had positive TPOAb and TSH >2.5 mU/L but was not consistently apparent in TPO-negative women until TSH values exceeded 5 to 10 mU/L [132].

Additionally, the data from the previous reviewed studies is pointing to a strong association between higher serum TSH level and positive thyroid antibodies. There is a same relationship between positive thyroid antibodies, higher abortion rate and preterm labour, which make screening of TPO +ve for women essential during early pregnancy. Thus, to reduce pregnancy loss, the measurement of TSH is recommended by ATA for any euthyroid pregnant women with positive

thyroid Abs at time of pregnancy and to be monitored every month for initial four months. Likewise, there are more chances of pregnancy loss and prematurity births where pregnant women have SCH and positive TPO Ab, this thing need to pay a proper attention for monitoring (TFT) during pregnancy. There is a conflict in the outcomes of the studies done in the past about the SCH prevalence in the pregnant women during pregnancy with cognitive development, gestational diabetes, gestational hypertension, and eclampsia and offspring development [100].

Likewise, we saw in screening of SCH during pregnancy that there is a decrease in the diagnosis rate of SCH with progression of gestational age when fixed cut-off values of TSH are adopted, which means, we have to do more randomised studies in different populations to adjust new optimal cut-off values of TSH according to the geographical distribution and ethnicity to avoid over estimate or underestimate diagnosis of SCH during pregnancy. Also, the results of thyroid function tests showed that indirect analogue immunoassay is commonly used for measuring serum FT4, but the accuracy of the results is affected by gestation and depending on the manufacturer. Therefore, during pregnancy, we ought to determine the technique been connected and utilizing (TSR) ranges. Also, we can gauge FT4 precisely by estimating FT4 list giving, we should utilize strategy particular and in addition trimester-particular extents in view of inconstancy in FT4 references during pregnancy relying upon the technique been utilized [145].

Another framework which is viewed as uncommonly revise for assessing serum FT4 and for that, the use of isotope dilution LC/MS/MS for surveying T4 in the dialysate from concordance dialysis of serum is useful. For nations without contiguous TSH reference, the utilization of the thyrotropin (TSR) with reducing lower reference degree of TSH by 0.4 mU/L for the (ATA) proposes during first trimester. While the upper reference grow is diminished by around 0.5 mU/L which diverge from a TSH upper reference motivation behind control of 4.0 mU/L, by then powerfully, return back to non-pregnant range in the second and third trimesters providing thyroid Abs, iodine deficiency and thyroid diseases are ruled out [132].

ATA, ES and ACOG lean toward a focused on way to deal with screening high hazard pregnant women on the off chance that they have on or a greater amount of the accompanying danger factors:

- Living in geographical region with high risk of iodine insufficiency
- Symptomatic hypothyroidism
- Past history of individual and family thyroid issue
- Positive TPO antibodies, goiter, age >30 years ,Type 1 diabetes, past history of head and neck radiation, repetitive abortions and preterm deliveries, multiple pregnancies, obesity, barrenness , past thyroid surgery, recent utilization of medicines, or intake iodinated radiologic contrast agents which cause thyroid dysfunctions.

Also, Jouyandeh et al. [89], found in ameta-analysis of several studies that targeted high-risk case finding might miss the diagnosis of SCH up to 49 % of pregnant women and recently, Blumenthal et al. [90], reported 9.6% of cases of SCH have been missed by depending on targeted screening which points for importance of the universal screening of thyroid disorder before and during 1st trimester of pregnancy but yet, it is not recommended by recent ATA guidelines [132].

Likewise, the outcomes demonstrated a reasonable confirmation that the rectification of iodine lack previously and during early pregnancy will forestall thyroid dysfunction during pregnancy and enhance fruitful pregnancy and typical foetal improvement [56].

Concerning treatment of SCH during pregnancy with levothyroxine, indicates the clear confirmation that this treatment is safe and not costly especially when utilized as a part of first trimester to keep up focus on TSH <2.5 mU/L. It is altogether lessening the gestational loss, and prematurity. The (ATA) featured the amassing proof recommending that unfavourable obstetric results may happen at a lower TSH threshold in (TPO) positive women. Likewise, therapy is recommended for all women with gestational TSH level range >4 and <10 mIU/L and for positive TPO Abs during gestation with TSH >2.5 and <4 mIU/L, meanwhile treatment is no longer recommended for TPO negative women with serum TSH values <4.0 mIU/L [132]. This concentration is agreed with ATA proposition for treatment of SCH during pregnancy and these recommendations were supported recently by Maraka et al. [125], for unnecessarily over-treatment of women with TSH levels of 2.5-4.0 mIU/L.

In addition, the data from these examinations suggest that SCH affects (ART) and escalates as TSH rise. Thus, it is prescribed to treat SCH women with TSH >2.5 mU/L before endeavoring (ART) yet, for barren women with SCH and negative thyroid Abs who are endeavoring gestation however not experiencing (ART), there is no confirmation whether to give thyroxin substitution treatment or not [80].

There is proving of unmistakably point to the connection between untreated SCH and expanded gestational difficulties for both the foetus and the mother. In any case, few studies of little size example with poor randomization did not show such antagonistic outcomes.

Additionally, this examination showed that in United Arab Emirates and other gulf countries, trials on the relationship of SCH and pregnancy complication with its outcomes are very rare. This is the main gap which needs to be filled through the use of regional thyrotropin cut-off TSR ranges and have a local screening in order to arrange a suitable treatment for the pregnant women in those countries.

Discussion

The prevalence of SCH is extending word wide yet more in South Asia, India, China and Middle East, generally due to iodine deficiency and autoimmune thyroid disease. In western nations, the prevalence of SCH in pregnancy is 2-3% Klein et al. [147] and late examinations indicated higher figures while in India , extending between 4.8-11% Sahu et al. [118] and in north India 14.3%, mainly during 1st trimester [148]. In china, Wang et al. [149] found a higher prevalence of SCH (10.9%) among patients with high risk compared with (7.0%) in low risk, p=0.008.

The commonness of thyroid antibodies is diverse among various ethnicity and topographical locales, extending between 3-8% and it is higher among women and expanding with age. Likewise, iodine insufficiency was more, particularly in Middle East and south Asia. Different reasons for plain and subclinical hypothyroidism incorporate medications like lithium and amiodarone [150].

Likewise, the examinations indicated adverse pregnancy outcomes if SCH was not treated during pregnancy, mainly premature births, abortions, preterm labour, higher rate of transformation to unmistakable hypothyroidism and low IQ of posterity and that bring up the issue of cost effectiveness of screening SCH during pregnancy [62,65,151,152].

Another meta-analysis by Tong et al. [153], exhibited that (IUGR) was higher in SCH in the midst of pregnancy (OR=1.54; 95% CI, 1.06-2.25) however not in TPOAb positive (OR=1.57; 95% CI, 0.77-3.18).

(A)Categorization of thyroxine treatment in SCH during pregnancy and clinical outcomes for TPO +ve patients			
TSH concentration	**Advised treatment**	**Advantages of treatment**	**Disadvantages of treatment**
TSH 4.0–10.0 IU/L	Strongly advised	Diminishment of unsuccessful labors, preterm deliveries and movement to symptomatic hypothyroidism: confirm from the vast majority of extensive and all around randomized studies	Consistent checking of TFT is expected to maintain a strategic distance from over treatment
TSH 2.5–4.0 IU/L	May be advised	For patients with barrenness, experiencing ART and previous history of intermittent fetus removal	Risk of over treatment and no proof of viability for GDM, gestational hypertension and IUGR
TSH <2.5 IU/L	Not advised	Treatment can be individualized per case with previous history of repetitive premature births, fruitlessness and ART	There is no adequate information or clear proof to lessen unfavorable pregnancy results in pregnant women with typical TFT
(B) Categorization of thyroxine treatment in SCH during pregnancy and clinical outcomes for TPO – ve patients			
TSH concentration	**Advised treatment**	**Advantages of treatment**	**Disadvantages of treatment**
TSH 4.0–10.0 IU/L	Strongly advised	Lessening of premature birth, preterm deliveries and future symptomatic hypothyroidism	Low quality confirmation with feeble suggestion
TSH 2.5–4.0 IU/L	Not advised	Can be utilized as a part of little measurements for ART to keep TSH <2.5 IU/L	No enough information about the viability of thyroxine for enhancing barrenness
TSH <2.5 IU/L	Not advised	No any advantages	High risk of development confinement and irregular mind morphology in posterity
(C) Intellectual and cognitive functions			
TSH 4.0–10.0 IU/L	Strongly advised	Substitution treatment during first trimester can enhance subjective capacities	There is uncertain impact for thyroxine substitution on results of psychological capacities
TSH 2.5–4.0 IU/L	Not advised	No advantages	Potential risk of over treatment and no proof of advantage for intellectual capacities
TSH <2.5 IU/L	Not advised	No advantages	There is risk of development limitation and irregular cerebrum conduct with thyroxine substitution, along these lines treatment is Strongly not exhorted in this gathering

Table 10: Recommendations for thyroid screening in pregnancy in different specialist societies [159].

Likewise, another a meta-analysis by Gong et al. [154], found the relative risk of (GDM) was extended in SCH (OR 1.558, 95% CI 1.292-1.877, p<0.001).

Toulis et al. [155], recognized the relationship among GDM and SCH in a six cohort studies, with a total of 35,350 pregnant women joining 1,216 women with SCH. Pregnant women with SCH exhibited a higher threat of GDM with pooled unadjusted (OR 1.35, 95% CI: 1.05-1.75) and remain high with pooled adjusted (OR: 1.39, 95% CI: 1.07-1.79).

Another meta-analysis by Van den et al. [156] inspected the pregnancy difficulties results in early pregnant women with SCH contrasted and euthyroid women. He discovered higher risk of abortion (OR 1.7, 95% (CI) 1.1-2.6) and higher mortality (OR 2.7, 95% CI 1.6-4.7). On the other hand, there is higher subfertility (OR 1.5, 95% CI 1.1-2.0), abortion (OR 3.73, 95% CI 1.8-7.6), recurrent abortion (OR 2.3, 95% CI 1.5-3.5), preterm delivery (OR 1.9, 95% CI 1.1-3.5) and post-partum thyroiditis (OR 11.5, 95% CI 5.6-24) in pregnant women with +ve thyroid Abs compared with negative one.

Nelson et al. [157] distinguished the antagonistic pregnancy results between 6,985 pregnant women included 3.3% with previous history of SCH contrasted with 6,645 with typical capacity and noted higher risk of GDM (adjusted OR 1.58, 95% CI 1.04 - 2.40, p=0.032) and stillbirth (adjusted OR 3.41, 95% CI 1.01 - 11.49, p=0.048) during an ensuing pregnancy. Mannisto et al. [119] completed a prospective population-based cohort study examine in light of pregnant women with thyroid dysfunction including SCH and positive thyroid antibodies and didn't found any relationship between SCH with thyroid antibodies and unfavourable pregnancy results.

For assessment of thyroid capacity during gestation, there is a suggestion from the global rules of the European Thyroid Association (ETA) for utilizing TFT (TSR) with particular test techniques for every populace [80,158]. TSH reference intervals of 0.1-2.5mU/L, 0.2-3.0mU/L and 0.3-3.0mU/L for the first, second and third trimester separately are acknowledged by the universal rules, if populace-based (TSR) are not accessible independent of lab techniques [3]. Likewise, the majority of the TSH references from populace–based studies demonstrated higher upper references breaking point of TSH contrasted with settled cut - off (2.5 and 3.0 mU/L) and that means , there will be over determination and superfluous treatment of ordinary thyroid capacity in women, which implies the utilization of populace–based TSR is clinically essential. Also, estimating fT4 should be by utilizing dialysate or ultra-filtrate of serum tests, fluid chromatography or tandem mass spectrometry and if that is not accessible, strategy and trimester-particular reference interims for fT4 must be utilized [3].

Additionally, there is distinction in recommendation for thyroid screening in pregnancy between various master social orders, abridged in (Table 10) [159].

As per late ATA rules, there is no proof for or against all-inclusive screening for thyroid function tests previously or during early gestation. Be that as it may, TSH screening is suggested for ladies arranging ART or those known to have positive autoimmune thyroid disease by estimating serum TSH , FT4 and TPO-Ab, utilizing the (ATA) and (ES) TSH (TSR) if the neighbourhood TSH trimester level isn't accessible. In addition, targeted, high-risk group need screening preconception or during the 1st trimester of pregnancy and these recommendations are supported by ETA for TSH measurement in a targeted population. In addition, for different FT4 assay, we should consider (TSR) ranges and specific methods should be used [3].

Casey et al. [62] had studied mothers with SCH compared to matched controls and found a three-fold increase in risk of placental abruption and a two-fold risk of preterm delivery before 32 weeks; in mothers with SCH compared to matched controls delivering at term.

Wilson et al. [121], found a relationship between SCH in pregnancy and higher occurrence of preeclampsia with 8.5% and 10.9% in the

(A)Categorization of thyroxine treatment in SCH during pregnancy and clinical outcomes for TPO +ve patients			
TSH concentration	**Advised treatment**	**Advantages of treatment**	**Disadvantages of treatment**
TSH 4.0–10.0 IU/L	Strongly advised	Diminishment of unsuccessful labors, preterm deliveries and movement to symptomatic hypothyroidism: confirm from the vast majority of extensive and all around randomized studies	Consistent checking of TFT is expected to maintain a strategic distance from over treatment
TSH 2.5–4.0 IU/L	May be advised	For patients with barrenness, experiencing ART and previous history of intermittent fetus removal	Risk of over treatment and no proof of viability for GDM, gestational hypertension and IUGR
TSH <2.5 IU/L	Not advised	Treatment can be individualized per case with previous history of repetitive premature births, fruitlessness and ART	There is no adequate information or clear proof to lessen unfavorable pregnancy results in pregnant women with typical TFT
(B) Categorization of thyroxine treatment in SCH during pregnancy and clinical outcomes for TPO – ve patients			
TSH concentration	**Advised treatment**	**Advantages of treatment**	**Disadvantages of treatment**
TSH 4.0–10.0 IU/L	Strongly advised	Lessening of premature birth, preterm deliveries and future symptomatic hypothyroidism	Low quality confirmation with feeble suggestion
TSH 2.5–4.0 IU/L	Not advised	Can be utilized as a part of little measurements for ART to keep TSH <2.5 IU/L	No enough information about the viability of thyroxine for enhancing barrenness
TSH <2.5 IU/L	Not advised	No any advantages	High risk of development confinement and irregular mind morphology in posterity
(C) Intellectual and cognitive functions			
TSH 4.0–10.0 IU/L	Strongly advised	Substitution treatment during first trimester can enhance subjective capacities	There is uncertain impact for thyroxine substitution on results of psychological capacities
TSH 2.5–4.0 IU/L	Not advised	No advantages	Potential risk of over treatment and no proof of advantage for intellectual capacities
TSH <2.5 IU/L	Not advised	No advantages	There is risk of development limitation and irregular cerebrum conduct with thyroxine substitution, along these lines treatment is Strongly not exhorted in this gathering

Table 11: Indication for treatment of SCH with levothyroxine during pregnancy [132].

Author & year	Study	Treatment with thyroxine	Results	Conclusions
Vissenberg et al. (2012) [170]	Meta-analysis	All members in the trials were pregnant women with SCH as well as with positive TAbs ,tried for impact of treatment with thyroxine on pregnancy results	pregnant women with just SCH, there is diminish in abortions and preterm deliveries while those with thyroid antibodies , there is diminish in preterm deliveries however the miscarriage rate was not critical	There is deficient confirmation for treating SCH and TAbs with thyroxine
Yan et al. (2012) [171]	Prospective Non-randomised	53 pregnant women with TPO Ab (+) and history of rehashed fetus removal, contrasting treated (17 pregnancies) with (36 untreated)	There is no distinction in term of live birth rate	Treatment of TPO Abs +ve pregnant women with levothyroxine didn't demonstrate any change
Lepoutre et al. (2012) [172]	Retrospective	96 TPO Ab (+) pregnant women were incorporated and contrasted treated gathering and no treatment	There is a reduction in the fetus removal rate	There is advantage for pre and early pregnancy screening and there is put for thyroxin treatment in pregnant women with TAs +ve
Reid et al. (2013) [173]	Meta-analysis	All members were pregnant women with SCH	There is a lessening in preterm deliveries and no impact on pre-eclampsia	Potential decrease in premature birth rate yet factually isn't huge
Velkeniers et al. (2013) [167]	Meta-analysis	All members were women with SCH and experiencing ART , were treated with thyroxine	Increment in fruitful pregnancies and decline the fetus removal rate	Lacking proof for run of thyroxine in decreasing preterm deliveries or preeclampsia in women experiencing ART
Bernardi et al. (2013) [174]	Prospective Non-randomised	Looking at pregnancy results between 24 treated women with SCH and history of REPL versus 15 untreated women	No distinction in the rate of live birth between the two gatherings	Among the women with REPL, the predominance of SCH was 19 %
Bartáková et al. (2013) [175]	Prospective Non-randomised	Looking at cost-viability of thyroxin substitution after unconstrained premature birth between treated group(73 with SCH as well as TAbs) and untreated (38 SCH as well as TAbs)	Increment in finished and fruitful future pregnancies	Thyroxine treatment in women with SCH and previous history of unconstrained premature birth is cost effective and connected with more fruitful future pregnancies
Lata et al. (2013) [176]	Prospective Non-randomised	The thyroxin impact in women with history of rehashed fetus removal with SCH or thyroid antibodies contrasted and sound women without history of premature birth	No distinction in fetus removal rates between treated TPO Abs +ve SCH women and typical thyroid capacity	Contrasting and healthy euthyroid pregnant women , there is higher pervasiveness of thyroid Abs among women with repetitive miscarriages
Jayaraman et al. (2013) [177]	Uncontrolled, prospective cohort study	98 women with SCH were followed up until the finish of pregnancy. TPO antibodies status was performed for 59 women (positive 20, negative 39).	TPO immune response was noted in 34% of women with adverse pregnancy results (4 unconstrained premature births, 4 preterm deliveries, 3 PIH) with no noteworthy contrast between the gatherings	No distinction in unfavorable pregnancy results between satisfactory LT4 supplanting for pregnant women with SCH focusing on TSH in euthyroid go, regardless of thyroid autoimmunity status.

Author & year	Study	Treatment with thyroxine	Results	Conclusions
Ma et al. (2016) [178]	Prospective Non-randomised	Clinical effect of thyroxine on pregnancy results in 105 pregnant women with SCH contrasted with control gathering (252), for whom not treatment was given	Abatement premature births Abatement in number of cases with macrosomia Increment in cases that need Caesarean area	Early checking of thyroid capacity tests and thyroxine substitution help in diminishing the rate of premature births ,however there is no impact on other adverse pregnancy results
Maraka et al. (2016) [179]	Retrospective	The impact of thyroxine in 82 pregnant women with SCH contrasted & untreated (284 women with SCH)	There is diminish in the rate of LBW and change of Apgar score	There is no distinction in other pregnancy results between the two gathering
Negro et al. (2016) [180]	Prospective Randomised	The impact of thyroxine in 198 euthyroid pregnant women with TAbs +ve was contrasted with two other gathering :195 untreated euthyroid amass with comparable criteria and to untreated 197 euthyroid pregnant women with negative TAbs	There is no distinction in rate of fetus removal or preterm work between the three gathering	In TAbs +ve pregnant women with ordinary thyroid capacity ,thyroxine treatment didn't diminish miscarriages or preterm deliveries
Casey et al. (2016) [181]	Multicentre study of two randomized double-masked placebo controlled trials run in parallel	97,226 pregnant women , (3.1%) with SCH (TSH ≥ 4.0 mU/L) , (2.9%) with low thyroxine randomized to thyroxine substitution or fake treatment	Treated women with SCH and lowLT4 during first 50% of pregnancy did not bring about enhanced psychological result in posterity at 5 yrs. age with P 0.76 and 0.3 individually	Treatment of women with either SCH or low LT4 during first 50% of pregnancy didn't bring about enhanced psychological result in posterity at 5 years old
Ju et al.(2016) [182]	Randomised controlled study	457 pregnant women with affirmed SCH were separated into treatment (N = 184) and control (N = 273) bunches TSH level ought to be < maximum point of confinement of the (TSR) run	Inconveniences in charge amass was more than in the treatment gathering (P < 0.05). After LT4 treatment, the occurrences of (PROM), GDM, fetal macrosomia, and PPH in the treated gathering term < 4 wks were essentially < the gatherings with 4-8 and 8 wks. Treatment length (P < 0.05).	LT4 is viably decrease the frequency of adverse pregnancy results in pregnant women with SCH giving treatment ought to be opportune and achieve treatment objectives as fast as could be expected under the circumstances
Korevaar et al. (2016) [183]	Retrospective study	366 women with SCH, (82) got LT4 and had a higher BMI (29 versus 27), a higher mean TSH (4.9 versus 3.5 mU/L and a higher pregestational thyroid affliction (21% versus 7%) and more slanted to be TPOAb-positive (46% versus 29% .These women were apportioned into treated and counterfeit treatment gathering. Treatment point was to keep TSH <2.5 and <3 mU/L in the first and second trimester independently.	Treatment was connected with a 59% lower risk of pregnancy mishap (P = 0.12), a 67% lower peril of preterm delivery (P = 0.06), and a 70% lower threat of GDM. (P = 0.07). Youths from treated women were less disposed to have an Apgar score underneath 8 (0% versus 7.0%; P <0.001) and 94% lower threat of having a birth weight <2500 gram (1.3% versus 10.0%, P<0.001)	There is perfect effects of treatment with L-T4 in women who were found to have a TSH >2.5 mU/L in the fundamental trimester, or >3.0 mU/L in the second trimester using a high-risk case– finding approach
Peaceman et al. (2016) [184]	Multicentre study consisting of two randomized, double -masked, placebo controlled trials	677 pregnant women < 21 week with SCH were randomized to treatment and fake treatment bunch as were 526 women with low thyroxine	No distinction in maternal intricacies between the treatment and fake treatment gatherings and no critical contrasts in delivery before 34 weeks, delivery course, and occurrence of placental suddenness or clinical chorioamnionitis seen with treatment in either gathering	LT4 did not influence the rate of pregnancy inconveniences in women with either SCH or with low thyroxine
Nazarpour et al. (2017) [133]	Prospective Randomised	Viability of thyroxin in diminishing pregnancy unfavorable results between (65) TPO Ab +ve pregnant women was contrasted with other two gathering : untreated gathering of 66 TPO Abs +ve and untreated 131 members of TPO Ab – ve	There is huge reduction in rate of preterm labour	The number expected to treat for preterm birth was 1.7
Maraka et al. (2017) [125]	Retrospective	Viability of thyroxin substitution in treated gathering 843 pregnant women with SCH was contrasted with untreated gathering of 562 pregnant women with SCH as control	Reduction in gestational loss and increment in gestational diabetes , preterm work and preeclampsia	Critical lessening in gestational loss in treated gathering than non-treated if the underlying TSH was 4.1– 10 mIU/L
Blumenthal et al. (2017) [185]	Prospective observational study	1025 pregnant women were selected during first trimester, 10.1% had SCH mIU/L and 18.2% had no less than one raised thyroid immune response level.	Contrasted and euthyroid work, no distinctions in unfavorable pregnancy results aside from SGA was diminished altogether in the thyroxine treatment gathering (1.3% versus 10%; p <0.001)	No distinction in pregnancy antagonistic results in treated gathering with SCH contrasted with euthyroid patients. Likewise, no association with TAbs and adverse pregnancy results in the two gatherings

Author & year	Study	Treatment with thyroxine	Results	Conclusions
Li et al. (2017) [186]	a meta-analysis of randomized controlled trials (RCTs)	14 RCTs(SCH in 8 studies, hypothyroidism in 5 studies, and TPOAb-positive status in one examination including (1918) fruitless women who had SCH or were TPO immune response positive and randomized into mediation assemble with LT4 supplementation and control fake treatment gathering group	Differentiated and control gathering, LT4 in a general sense extended the movement (RR = 2.21; 95% CI, 1.39-3.51; P = .001), clinical pregnancy (RR=1.43; 95% CI 1.04-1.97; P=.026),, and arrangement rates e (RR = 2.06; 95% CI, 1.30-3.26; P=.002) . Also, lessened the unnatural birth cycle rate (RR = 0.49; 95% CI, 0.30-0.80; P = .004), GDM s (RR = 0.50; 95% CI, 0.36-0.69; P < .001), and PIH (RR = 0.60; 95% CI, 0.43-0.84; P = .003), however not preeclampsia (RR=0.84; 95% CI, 0.42-1.70; P=.636). There is less preterm deliveries (RR = 0.44; 95% CI, 0.27-0.71; P=.001), birth weights <2500 gm. (RR=0.26; 95% CI, 0.14-0.48; P < .001), passing (RR=0.18; 95% CI, 0.07-0.51; P =.001) and inborn changes (RR = 0.19; 95% CI, 0.07-0.51; P = .001)	LT4 supplementation indicated useful impacts in pregnancy results among patients with thyroid dysfunction. In this way, LT4 ought to be prescribed to enhance clinical pregnancy results in women with thyroid dysfunction.

Table 12: The clinical effect of thyroxine in pregnant women with subclinical hypothyroidism and/or thyroid antibodies.

euthyroid and SCH groups separately, when balanced (p=0.016) and this affiliation stay important in the wake of altering different elements (OR 1.6, 95% CI 1.1-2.4; p=0.03).

Also, Tudela et al. [122], found that the higher TSH during pregnancy, the more incidence of GDM and more progression to clinical hypothyroidism with annual rate of 2-5%. In addition, Wier and Farley [160], found higher incidence of pre-eclampsia, eclampsia and gestational hypertension with (15%) in SCH group compared with (7.6%) in the general population. In addition, Van et al. [161], found higher SCH (19.6%) among pregnant women with history of vascular complicated pregnancy ended prematurely (p=0.008). Haddow et al. [65], studied intellectual functions of offspring for mothers who had SCH at pregnancy and discovered 7-point lessening in insight remainder in kids matured 7-9 years contrasted and offspring of euthyroid moms.

Finally, Casey et al. [62] noticed increase in neonatal respiratory distress and death belong to pregnant women with SCH with (RR 1.8; 95% CI 1.1- 2.9%).

To reduce SCH during pregnancy and specifically in iodine deficit regions, 150μg iodine should be provided before pregnancy and 250 μg iodine during pregnancy with thyroid function screening before and during 1st trimester [3]. The aim of treatment is keeping TSH during pregnancy with in TSR range for that region, but if it is not available , the (USPSTF) advise to use TSH level (0.1-2.5 mIU/L) during 1st trimester, (0.2-3.0 mIU/L) during 2nd trimester and (0.3-3.0 mIU/L) during 3rd trimester [162]. However, women treated for (SCH) during pregnancy are less likely to have pregnancy loss and preterm deliveries and this evidence including other uncertainty behind treatment should be clearly explained to the patient when such decision is taken.

In a randomised study conducted by Negro et al. [163], on 115 pregnant women with TPO Ab +ve and compared levothyroxine treated group with no treatment. There is non-significant reduction in pre-eclampsia (RR 0.61; 95% CI 0.11-3.48); GDM (RR 0.65; 95% CI 0.22-1.92) and placental abruption (RR 0.30; 95% CI 0.01-7.29). On the other hand, there is significantly reduced preterm birth by 72% (RR 0.28; 95% CI 0.10-0.80) and reduced preterm birth rate by 7.2% compared to 26% with risk difference -0.19 (95% CI -0.33 to -0.05 and reduced risk of miscarriage (P=0.07)

The recommendation of (ES) and (ETA) guidelines is to provide thyroxine treatment for all pregnant women with SCH regardless the presence of TPO Abs, with weaker recommendation for negative TPO Abs [158].

The current ATA rules encourage checking the thyroid antibodies in pregnant women with TSH >2.5mIU/L and thyroxine ought to be given if the TPO Abs is certain in presence of TSH over the TSR extend. However, it might be considered with frail suggestion and direct quality confirmation at whatever point TSH >2.5 IU/L and beneath the maximum furthest reaches of the TSR range.

Another prospective trial conducted by Negro et al. [126], examined the thyroxine replacement in TPO Abs positive pregnant women with SCH. This study found reduced risk of at least one of the following (miscarriage, hypertensive disorders, gestational diabetes, placental abruption, caesarean delivery, congestive heart failure, preterm labour, respiratory distress, neonatal intensive care unit admission, aberrant birth weights, preterm delivery, low Apgar score, or perinatal death. On the other hand, Lazarus et al. and Casey et al. [103,164], investigated the effectiveness of thyroxine treatment in improving cognitive function in children of pregnant mothers with SCH and both studies failed to prevent adverse cognitive outcomes and negative rather than positive results might be related to late starting of treatment [165].

Overall, from the above studies and depending on outcomes of results, the indication for treatment of SCH with levothyroxine during pregnancy is summarized (Table 11).

On strict screening of common euthyroid individuals, the TSH level was seen to keep running in the range of 0.4 and 2.5 mIU/L. Thus, for the future, the ATA may consider a reduced upper limit of serum TSH euthyroid reference range to 2.5 mIU/L for all adults and this concept was supported by National Association of Clinical Biochemistry [166].

Overall, the results of reviewed studies and the new guide lines of (ATA) are highlighted the accumulating evidence suggesting that adverse obstetric outcomes may occur at lower TSH thresholds in (TPO) positive women and treatment is no longer recommended for TPO negative women with serum TSH values <4.0 mIU/L. The most of the examinations noticed the antagonistic pregnancy difficulties with in these extents .Thus, checking of TSH levels and modification of thyroxine measurements are fundamental every 4 - 6 weeks to keep the TSH beneath the (TSR) ranges [132]. Likewise, numerous current studies analysed the results of the impact of thyroxine on women with SCH experiencing ART and demonstrated enhanced pregnancy results by keeping TSH <2.5 mIU/L [132,167,168].

As per the current ATA rules and before considering levothyroxine treatment in instances of SCH, there ought to be all around characterized and acknowledged TSH (TSR) which is changed in accordance with populace and ethnicity with screening for thyroid antibodies. For areas lack TSH (TSR) extend, treatment of SCH can be begun for TSH

>4 IU/L and for TSH >2.5 IU/L with +ve TPOAb and the prescribed beginning measurements is 50 micrograms/day with TSH checking each month with heightening the dosage to keep TSH<2.5 mIU/L [158,169]. Then again, the (AACE) and the (ES) considered TSH level of 4.5 mIU/L as upper typical farthest point [8].

Some interventional studies about in pregnant women with SCH, levothyroxine offered great finding in decreasing unfavourable pregnancy result (Table 12).

At long last, finished treatment of levothyroxine in SCH isn't without reaction and ought to be individualized relying upon prove base to lessen the superfluous maternal and foetal results [187,188].

Conclusion

There is a significant variation in the endocrinal disorder of SCH during pregnancy in all over the world based upon the age, ethnicity and other regional factors. For the significant improvements to tack the common endocrinal disorder, early diagnosis can play a vital role. Early examination and treatment will provoke an important change in the pregnancy comes about. Adequate iodine supplement already and during pregnancy in iodine lacking district may upgrade the pregnancy and foetal outcome. Most powerful studies have demonstrated a confirmation for the relationship among SCH in pregnancy, abortion and preterm deliveries but such association between gestational hypertensive disorders, impaired cognitive development and SCH was not seen.

In addition, screening should be done, once pregnancy is confirmed in women with symptoms or risk factors for hypothyroidism, using trimester-specific TSH ranges and universal screening may be considered in the future for region with high prevalence of SCH as several studies showed significant number of SCH were missed, if considering the high risk case targeting rather than universal screening . Additionally, there is a healthy proof that TPOAb +ve pregnant women with a TSH >2.5 mIU/L ought to be treated with levothyroxine focused to the lower half of (TSR) TSH range and TPO-Ab negative women ought to be dealt with just if TSH >4 mIU/l. In addition, this systematic review study demonstrated noteworthy advantage of thyroid hormone treatment for SCH during pregnancy to diminish preterm delivery and pregnancy loss, an occasion most regularly happening in early pregnancy. Also, this study revealed a deficient in the data of SCH in pregnancy with lack of regional TSH (TSR) in Arabic countries and this issue needs a serious attention for doing a randomised controlled study taking in consideration the Arabic ethnicity and the commonness of iodine deficiency and autoimmune thyroiditis.

Finally, in this examination there is demonstrate for favourable position of early screening of thyroid limit tests and evaluation thyroid antibodies for diagnosing SCH pregnant women, confirming pregnancy complexities, and thyroid tests considerations in unproductive women including treatment convention. This will help in clinical basic leadership in the management of SCH in pregnant women to diminish the adverse pregnancy outcomes and to accomplish sheltered and ideal care.

Reflection

This study is the 1st retrospective study which is extensively reviewing all popular and powerful studies which were published in English language over the last two decades were investigated the screening methods, adverse pregnancy outcomes and the treatment of SCH during pregnancy, including recent published guidelines from Spanish Association of Endocrinology and Nutrition, ATA, ES, ACOG, AACE, ITS and ETA . This study clarifies several important points that the predominance of SCH is expanding everywhere throughout the world more than the current figures. Numerous nations do not have their own populace – based TSR and extraordinary change will happen with critical more number of SCH will be analysed if a universal screening was utilized. Moreover, the viability of thyroid hormonal supplanting in pregnant women with SCH should take inconsideration-adjusted criteria for TSR extents and strategies utilized for estimating thyroid capacities, which is particular to that populace. The exactness in deciphering strange thyroid capacity tests with the incorporation of thyroid dysfunction as a reason for some adverse pregnancy results and to have joined advisory group amongst obstetrician and endocrinologist to go after a common assertion and universal guidelines.

Acknowledgements

I would like to thank Professor Atul Kalhan for his kind help and giving me his time, commitment and feedback that supported me unfailingly and unconditionally through this process and without his support, opinion and hand in its completion, this thesis will not see the light.

References

1. Cleary-Goldman J, Malone FD, Lambert-Messerlian G, Sullivan L, Canick J, et al. (2008)Maternal thyroid hypofunction and pregnancy outcome. Obstet Gynecol 12: 85-92.
2. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, et al. (2010) Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy. J Clin Endocrinol Metab 95: E44-48.
3. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, et al. (2011) Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 21: 1081-1125.
4. Vila L, Velasco I, González S, Morales F, Sánchez E, et al. (2012) Detection of thyroid dysfunction in pregnant women: universal screening is justified. Endocrinol Nutr 59: 547-560.
5. Rosario PW, Purisch S (2011) Thyroid dysfunction in pregnancy: definition of TSH cut-off should precede the decision of screening in low-risk pregnant women. Gynecol Endocrinol 27: 205-208.
6. Lee YJ, Kim CH, Kwack JY, Ahn JW, Kim SH, et al. (2014) Subclinical hypothyroidism diagnosed by thyrotropin-releasing hormone stimulation test in infertile women with basal thyroid-stimulating hormone levels of 2.5 to 5.0 mIU/L. Obstet Gynecol Sci 57: 507–512.
7. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC (2000) The Colorado thyroid disease prevalence study. Arch Intern Med 160: 526-34.
8. Surks MI, Goswami G, Daniels GH (2005) The thyrotropin reference range should remain unchanged. J Clin Endocrinol Metab. 90: 5489–5496.
9. Hollowell J, Staehling N, Flanders W, Hannon W, Gunter E, et al. (2002) Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 87: 489-499.
10. Dhanwal DK, Prasad S, Agarwal AK, Dixit V, Banerjee AK (2013) High prevalence of subclinical hypothyroidism during first trimester of pregnancy in North India. Indian J Endocrinol Metab 17: 281-284.
11. Yassaee F, Farahani M, Abadi AR (2014) Prevalence of subclinical Hypothyroidism in Pregnant Women in Tehran-Iran. Int J Fertil Steril 8: 163-166.
12. Pavanaganga A, Rekha BR, Sailakshmi MPA, Nagarathnamma R (2015) Observational Study of Subclinical Hypothyroidism in Pregnancy Indian Journal of Obstetrics and Gynecology Research 2: 255-260.
13. Nataraj HG, Sreelatha S, Ramya S (2015) Prevalence of Sub Clinical Hypothyroidism in First Trimester of Pregnancy Journal of Evidence Based Medicine and Healthcare 2: 2292 -2295.
14. Mandal RC, Bhar D, Das A, Basunia SR, Kundu SB, et al. (2016) Subclinical Hypothyroidism in Pregnancy: An Emerging Problem in Southern West Bengal: A cross-sectional Study. J Nat Sci Biol Med 7: 80-84.

15. Beenish M, Kamili MMA, Ovais H (2017) Prevalence of subclinical hypothyroidism in pregnant females of Kashmir, India. Pulsus Journal of Surgical Research 1: 11-14.

16. Al Shanqeeti SA, Alkhudairy YN, Alabdulwahed AA, Ahmed AE, Al-Adham MS, et al. (2018) prevalence of subclinical hypothyroidism in Saudi Arabia. Saudi Med J 39: 254-260.

17. Abbassi-Ghanavati M, Casey BM, Spong CY, McIntire DD, Halvorson LM, et al. (2010) Pregnancy outcomes in women with thyroid peroxidase antibodies. Obstet Gynecol 116: 381-386.

18. Kutteh WH, Yetman DL, Carr AC, Beck LA, Scott RT Jr (1999) Increased prevalence of antithyroid antibodies identified in women with recurrent pregnancy loss but not in women undergoing assisted reproduction. Fertil Steril 71: 843–848.

19. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, et al. (2006) Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab 91: 2587-2591.

20. Ghafoor F, M Mansoor, T Malik, MS Malik, AU Khan, et al. (2006) Role of thyroid peroxidase antibodies in the outcome of pregnancy. J Coll Physicians Surg Pak 16: 468-471.

21. Cleary-Goldman J, Malone FD, Messerlian G, Sullivan L, Canick J, et al. (2005) Subclinical hypothyroidism and pregnancy outcomes. American Journal of Obstetrics and Gynecology 193: S3.

22. Iravani AT, MM Saeedi, J Pakravesh, S Hamidi, M Abbasi (2008) Thyroid auto -immunity and recurrent spontaneous abortion in Iran: a case-control study. Endocr Pract 14:458–464.

23. Chen L, Hu R (2011) Thyroid autoimmunity and miscarriage: a meta-analysis. Clin Endocrinol (Oxf) 74: 513-519.

24. Van den Boogaard E, Vissenberg R, Land JA, van Wely M, van der Post JA, et al. (2011) Significance of subclinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. Hum Reprod Update 17: 605-619.

25. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, et al. (2011) Thyroid antibody positivity in the first trimester of pregnancy is associated with negative pregnancy outcomes. J Clin Endocrinol Metab 96: E920-E924.

26. He X, Wang P, Wang Z, He X, Xu D, et al. (2012) Thyroid antibodies and risk of preterm delivery: a meta-analysis of prospective cohort studies. Eur J Endocrinol 167: 455–464.

27. Kumru P, Erdogdu E, Arisoy R, Demirci O, Ozkoral A, et al. (2015) Effect of thyroid dysfunction and autoimmunity on pregnancy outcomes in low risk population. Arch Gynecol Obstet 291:1047-1054.

28. Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, et al. (2011) Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. BMJ 342: d2616.

29. Liu H, Shan Z, Li C, Mao J, Xie X, et al. (2014) Maternal subclinical hypothyroidism, thyroid autoimmunity, and the risk of miscarriage: a prospective cohort study. Thyroid 24:1642-1649.

30. Benhadi N, Wiersinga WM, Reitsma JB, Vrijkotte TG, Bonsel GJ (2009) Higher maternal TSH levels in pregnancy are associated with increased risk for miscarriage, fetal or neonatal death. Eur J Endocrinol 160: 985-91.

31. Karakosta P, Alegakis D, Georgiou V, Roumeliotaki T, Fthenou E, et al. (2012) Thyroid dysfunction and autoantibodies in early pregnancy are associated with increased risk of gestational diabetes and adverse birth outcomes. J Clin Endocrinol Metab 97: 4464-4472.

32. Korevaar TI, Schalekamp-Timmermans S, de Rijke YB, Visser WE, Visser W, et al. (2013) Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: The generation R study. J Clin Endocrinol Metab 98: 4382-4390.

33. Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, et al. (2011) Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. BMJ: British Medical 342: d2616.

34. Männistö T, Vääräsmäki M, Pouta A, Hartikainen AL, Ruokonen A, et al. (2009) Perinatal Outcome of Children Born to Mothers with Thyroid Dysfunction or Antibodies: A Prospective Population-Based Cohort Study. J Clin Endocrinol Meta 94: 772-779.

35. Lincoln SR, Ke RW, Kutteh WH (1999) Screening for hypothyroidism in infertile women. J Reprod Med 44: 455-457.

36. Poppe K, Glinoer D, Van Steirteghem A, Tournaye H, Devroey P (2002) Thyroid dysfunction and autoimmunity in infertile women. Thyroid 12: 997-1001.

37. Abalovich M, Mitelberg L, Allami C, Gutierrez S, Alcaraz G, et al. (2007) Subclinical hypothyroidism and thyroid autoimmunity in women with infertility. Gynecol Endocrinol 23: 279-283.

38. Yoshioka W, Amino N, Ide A, Kang S, Kudo T, et al. (2015) Thyroxine treatment may be useful for subclinical hypothyroidism in patients with female infertility. Endocr J 62: 87-92.

39. Seungdamrong A, Steiner AZ, Gracia CR, Legro RS, Diamond MP, et al. (2017) Preconceptional antithyroid peroxidase antibodies, but not thyroid-stimulating hormone, are associated with decreased live birth rates in infertile women. Fertil Steril 108: 843-850.

40. Bhattacharyya R, Mukherjee K, Das A, Biswas MR, Basunia SR, et al. (2015) Anti-thyroidperoxidase antibody positivity during early pregnancy is associated with pregnancy complications and maternal morbidity in later life. J Nat Sci Biol Med 6: 402-405.

41. Saki F, Dabbaghmanesh MH, Ghaemi SZ, Forouhari S, Omrani GR, et al. (2015) Thyroid autoimmunity in pregnancy and its influences on maternal and fetal outcome in Iran (a prospective study) Endocr Res 40: 139-145.

42. Baker VL, Rone HM, Pasta DJ, Nelson HP, Gvakharia M, et al. (2006), Correlation of thyroid stimulating hormone (TSH) level with pregnancy outcome in women undergoing in vitro fertilization. Am J Obstet Gynecol 194: 1668-1674.

43. Reh A, Grifo J, Danoff A (2010) What is a normal thyroid-stimulating hormone (TSH) level? Effects of stricter TSH thresholds on pregnancy outcomes after in vitro fertilization. Fertil Steril 94:2920-2922.

44. Michalakis KG, Mesen TB, Brayboy LM, Yu B, Richter KS, et al. (2011) Subclinical elevations of thyroid-stimulating hormone and assisted reproductive technology outcomes. Fertil Steril 95: 2634-2637.

45. Fumarola A, Grani G, Romanzi D, Del Sordo M, Bianchini M (2013) Thyroid function in infertile patients undergoing assisted reproduction. Am J Reprod Immunol 70: 336-341.

46. Jatzko B, Vytiska-Bistorfer E, Pawlik A, Promberger R, Mayerhofer K, et al. (2014) The impact of thyroid function on intrauterine insemination outcome-a retrospective analysis. Reprod Biol Endocrinol 12: 28.

47. Aghahosseini M, Asgharifard H, Aleyasin A, Banihashemi T (2014) Effects of thyroid stimulating hormone (TSH) level on clinical pregnancy rate via in vitro fertilization (IVF) procedure. Med J Islam Repub Iran 28: 283-286.

48. Chai J, Yeung WY, Lee CY, Li HW, Ho PC, et al. (2014) Live birth rates following in vitro fertilization in women with thyroid autoimmunity and/or subclinical hypothyroidism. Clin Endocrinol (Oxf) 80: 122-127.

49. Green KA, Werner MD, Franasiak JM, Juneau CR, Hong KH, et al. (2015) Investigating the optimal preconception TSH range for patients undergoing IVF when controlling for embryo quality. J Assist Reprod Genet 32: 1469-1476.

50. Weghofer A, Himaya E, Kushnir VA, Barad DH, Gleicher N (2015) The impact of thyroid function and thyroid autoimmunity on embryo quality in women with low functional ovarian reserve: a case-control study. Reprod Biol Endocrinol 13: 43.

51. Cai Y, Zhong L, Guan J, Guo R, Niu B, et al. (2017) Outcome of in vitro fertilization in women with subclinical hypothyroidism. Reprod Biol Endocrinol 15: 39.

52. WHO Secretariat, Andersson M, de Benoist B, Delange F, Zupan J (2007) Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. Public Health Nutr 10: 1606-1611.

53. Mandel SJ (2004) Hypothyroidism and chronic autoimmune thyroiditis in the pregnant state: maternal aspects. Best Pract Res Clin Endocrinol Metab. 18: 2l3-224.

54. Caldwell KL, Pan Y, Mortensen ME, Makhmudov A, Merrill L, et al. (2013) Iodine status in pregnant women in the National Children's Study and in U.S. women (15-44 years), National Health and Nutrition Examination Survey 2005-2010. Thyroid 23: 927-937.

55. de Escobar GM, Obregón MJ, del Rey FE (2007) Iodine deficiency and brain development in the first half of pregnancy. Public Health Nutr 10: 1554-1570.

56. Bath SC, Steer CD, Golding J, Emmett P, Rayman MP (2013) Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). Lancet 382: 331-337.

57. WHO Secretariat, Andersson M, de Benoist B, Delange F, Zupan J (2007) Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. Public Health Nutr 10: 1606-1611.

58. O'Donnell KJ, Rakeman MA, Zhi-Hong D, Xue-Yi C, Mei ZY, et al. (2002) Effects of iodine supplementation during pregnancy on child growth and development at school age. Dev Med Child Neurol 44: 76-81.

59. Berbel P, Mestre JL, Santamaría A, Palazón I, Franco A, et al. (2009) Delayed neurobehavioral development in children born to pregnant women with mild hypothyroxinemia during the first month of gestation: the importance of early iodine supplementation. Thyroid 19: 511-519.

60. Trumbo P, Yates AA, Schlicker S, Poos M (2001) Dietary reference intakes: vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. J Am Diet Assoc 101: 294-301.

61. Haddow JE, McClain MR, Palomaki GE, Neveux LM, Lambert-Messerlian G, et al. (2011) Thyroperoxidase and thyroglobulin antibodies in early pregnancy and placental abruption. Obstet Gynecol 117: 287-292.

62. Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, et al. (2005) Subclinical hypothyroidism and pregnancy outcomes. Obstet Gynecol 105: 239-245.

63. Maraka S, Ospina NM, O'Keeffe DT, Espinosa De Ycaza AE, Gionfriddo MR, et al. (2016) Subclinical Hypothyroidism in Pregnancy: A Systematic Review and Meta-Analysis. Thyroid 26: 580-590.

64. van den Boogaard E, Vissenberg R, Land JA, van Wely M, van der Post JA, et al. (2011) Significance of subclinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. Hum Reprod Update 17: 605-619.

65. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, et al. (1999) Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 341: 549-555.

66. Williams FL, Watson J, Ogston SA, Visser TJ, Hume R, et al. (2013) Maternal and Umbilical Cord Levels of T4, FT4, TSH, TPOAb, and TgAb in Term Infants and Neurodevelopmental Outcome at 5.5 Years . J Clin Endocrinol Metab 98: 829-838.

67. Chen LM, Chen QS, Jin GX, Si GX, Zhang Q, et al. (2015) Effect of gestational subclinical hypothyroidism on early neurodevelopment of offspring. J Perinatol 35: 678-682.

68. Hershman JM (2017) Levothyroxine Therapy of subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy Does Not Improve Cognitive Function in the Offspring .Clinical Thyroidology 29: 132-135.

69. Nazarpour S, Tehrani FR, Simbar M, Tohidi M, AlaviMajd H, et al. (2016) Comparison of universal screening with targeted high-risk case finding for diagnosis of thyroid disorders. Eur J Endocrinol 174: 77-83.

70. Kim HS, Kim BJ, Oh S, Lee DY, Hwang KR, et al. (2015) Gestational Age-specific Cut-off Values Are Needed for Diagnosis of Subclinical Hypothyroidism in Early Pregnancy. J Korean Med Sci 30: 1308-1312.

71. Almomin AMS, Mansour AA, Sharief M (2016) Trimester-Specific Reference Intervals of Thyroid Function Testing in Pregnant Women from Basrah, Iraq Using Electrochemiluminescent Immunoassay Diseases. Diseases 4: 20.

72. Haddow E, Knight GJ, Palomaki GE, McClain MR, Pulkkinen AJ (2004) The reference range and within-person variability of thyroid stimulating hormone during the first and second trimesters of pregnancy. J Med Screen 11: 170-174.

73. Maji R, Nath S, Lahiri S, Saha Das M, Bhattacharyya AR, et al. (2014) Establishment of trimester-specific reference intervals of serum TSH & fT4 in a pregnant Indian population at North Kolkata. Indian J Clin Biochem 29: 167-173.

74. Zhang J, Li W, Chen QB, Liu LY, Zhang W, et al. (2015) Establishment of trimester-specific thyroid stimulating hormone and free thyroxine reference interval in pregnant Chinese women using the Beckman Coulter UniCel™ DxI 600. Clin Chem Lab Med 53: 1409-1414.

75. Rajput R, Singh B, Goel V, Verma A, Seth S, et al. (2016) Trimester-specific reference interval for thyroid hormones during pregnancy at a Tertiary Care Hospital in Haryana, India. Indian J Endocrinol Metab 20: 810-815.

76. Sekhri T, Juhi JA, Wilfred R, Kanwar RS, Sethi J (2016) Trimester specific reference intervals for thyroid function tests in normal Indian pregnant women. Indian J Endocrinol Metab 20: 101-107.

77. Akarsu S, Akbiyik F, Karaismailoglu E, Dikmen ZG (2016) Gestation specific reference intervals for thyroid function tests in pregnancy. Clin Chem Lab Med 54: 1377-1383.

78. Veltri F, Belhomme J, Kleynen P, Grabczan L, Rozenberg S, et al. (2017) Maternal thyroid parameters in pregnant women with different ethnic backgrounds: Do ethnicity-specific reference ranges improve the diagnosis of subclinical hypothyroidism?. Clinical Endocrinology 86: 830-836.

79. Liu Y, Chen H, Jing C, Li F (2017) The association between maternal subclinical hypothyroidism and growth, development, and childhood intelligence: a meta-analysis, J Clin Res Pediatr Endocrinol 10: 153-161.

80. De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, et al. (2012) Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 97: 254-265.

81. Lee RH, Spencer CA, Montoro MN, Aghajanian P, Goodwin TM (2009) Effect of thyroid peroxidase antibodies on thyroid-stimulating hormone reference limits in a primarily Latina population. Obstetric Medicine 2: 154-156.

82. Li C, Shan Z, Mao J, Wang W, Xie X, et al. (2014) Assessment of thyroid function during first-trimester pregnancy: what is the rational upper limit of serum TSH during the first trimester in Chinese pregnant women? J Clin Endocrinol Metab 99: 73-79.

83. Toft AD, Beckett GJ (2005) Measuring serum thyrotropin and thyroid hormone and assessing thyroid hormone transport. pp 329-344.

84. Yue B, Rockwood AL, Sandrock T, La'ulu SL, Kushnir MM, et al. (2008) Free thyroid hormones in serum by direct equilibrium dialysis and online solid-phase extraction–liquid chromatography/tandem mass spectrometry. Clin Chem 54: 642-651.

85. Kahric-Janicic N, Soldin SJ, Soldin OP, West T, et al. (2007) Tandem mass spectrometry improves the accuracy of free thyroxine measurements during pregnancy. Thyroid 17: 303-311.

86. Thienpont LM, VanUytfanghe K, Beastall G, Faix JD, Ieiri T, et al. (2010) Report of the IFCC Working Group for Standardization of Thyroid Function Tests; part 2: free thyroxine and free triiodothyronine. Clin Chem 56: 912-920.

87. Dosiou C, Sanders GD, Araki SS, Crapo LM (2008) Screening pregnant women for autoimmune thyroid disease: a cost-effectiveness analysis. Eur J Endocrinol 158: 841–851.

88. Thung SF, Funai EF, Grobman WA (2009) The cost-effectiveness of universal screening in pregnancy for subclinical hypothyroidism. Am J Obstet Gynecol 200: 267.e1-7.

89. Jouyandeh Z, Hasani-Ranjbar S, Mostafa Q, Bagher L (2015) Universal screening versus selective case based screening for thyroid disorders in pregnancy. Endocrine 48: 116-123.

90. Vaidya B, Anthony S, Bilous M, Shields B, Drury J, et al. (2007) Detection of thyroid dysfunction in early pregnancy: universal screening or targeted high risk case finding? J Clin Endocrinol Metab 92: 203-207.

91. Horacek J, Spitalnikova S, Dlabalova B, Malirova E, Vizda J, et al. (2010) Universal screening detects two-times more thyroid disorders in early pregnancy than targeted high-risk case finding. Eur J Endocrinol 163: 645-650.

92. Matuszek B, Zakościelna K, Baszak-Radomańska E, Pyzik A, Nowakowski A (2011) Universal screening as a recommendation for thyroid tests in pregnant women. Ann. Agric. Environ. Med. 18: 375-379.

93. Goel P, Kaur J, Saha PK, Tandon R, Devi L (2012) Prevalence, Associated Risk Factors and Effects of Hypothyroidism in Pregnancy: A Study from North India. Gynecol Obstet Invest 74: 89-94.

94. Jiskra J, Bartáková J, Holinka Š, Límanová Z, Springer D (2011) Low prevalence of clinically high-risk women and pathological thyroid ultrasound

among pregnant women positive in universal screening for thyroid disorders. Exp Clin Endocrinol Diabetes 119: 530-535.

95. Chang DLF, Leung AM, Braverman LE, Pearce EN (2011) Thyroid Testing during Pregnancy at an Academic Boston Area Medical Center. J Clin Endocrinol Metab 96: E1452-E1456.

96. Gudala K, Bansal D, Kandikatla LR, Krishna PSR (2013) PRM12 Thyroid Dysfunction Detection in Pregnancy: Universal Screening or Targeted High-Risk Case Finding? A Meta-Analysis. Value in Health 16: A701.

97. Yang H, Shao M, Chen L, Chen Q, Yu L, Cai L, et al. (2014) Screening strategies for thyroid disorders in the first and second trimester of pregnancy in China. PLoS ONE 9: e99611.

98. Blumenthal NJ, Byth K, Eastman CJ (2016) Prevalence of thyroid dysfunction and thyroid antibodies in a private obstetrical practice in Sydney. Aust N Z J Obstet Gynaecol 56: 307-311.

99. Foster WG (2005) Subclinical hypothyroidism increased the risk of placental abruption and poor neonatal outcomes Evidence Based Medicine 10: 153.

100. Chen LM, Du WJ, Dai J, Zhang Q, Si GX, et al. (2014) Effects of Subclinical Hypothyroidism on Maternal and Perinatal Outcomes during Pregnancy: A Single-Center Cohort Study of a Chinese Population PLoS One 9: e109364.

101. Zhang Y, Wang H, Pan X, Teng W, Shan Z (2017) Patients with subclinical hypothyroidism before 20 weeks of pregnancy have a higher risk of miscarriage: A systematic review and meta-analysis PLoS ONE 12: e0175708.

102. Ajmani AN, Aggarwal D, Bhatia P, Sharma M, Sarabhai V, et al. (2014) Prevalence of Overt and Subclinical Thyroid Dysfunction Among Pregnant Women and Its Effect on Maternal and Fetal Outcome. J Obstet Gynaecol India 64: 105-110.

103. Lazarus JH, Bestwick JP, Channon S, Paradice R, Maina A, et al. (2012) Antenatal thyroid screening and childhood Cognitive function. N Engl J Med 366: 493-501.

104. Päkkilä F, Männistö T, Pouta A, Hartikainen AL, Ruokonen A, et al. (2014) The Impact of Gestational Thyroid Hormone Concentrations on ADHD Symptoms of the Child. J Clin Endocrinol Metab 99: E1-E8.

105. Henrichs J, Bongers-Schokking JJ, Schenk JJ, Ghassabian A, Schmidt HG, et al. (2010) Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the generation R study. J Clin Endocrinol Metab 95: 4227-4234.

106. Julvez J, Alvarez-Pedrerol M, Rebagliato M, Murcia M, Forns J, et al. (2013) Thyroxine levels during pregnancy in healthy women and early child neurodevelopment. Epidemiology 24: 150-157.

107. Männistö T, Mendola P, Grewal J, Xie Y, Chen Z, et al. (2013)Thyroid diseases and adverse pregnancy outcomes in a contemporary US cohort. J Clin Endocrinol Metab 98:2725-33.

108. Furukawa S, Miyakawa K, Shibata J, Iwashita M (2017) Women with Subclinical Hypothyroidism Are at Low Risk of Poor Pregnancy Outcome in Japan. Tohoku J Exp Med 242: 167-172.

109. Casey BM, Dashe JS, Mcintire DD, Wells EC, Byrd W, et al. (2003) Pregnancy outcomes in women with subclinical hypothyroidism. Am J Obstet Gynecol 189: S145.

110. Wilson KL, Casey BM, McIntire DD, Halvorson LM, Cunningham FG (2011) 854: Is hypertension related to subclinical thyroid disease identified during pregnancy? Am J Obstet Gynecol 204: S331.

111. Wang S, Teng WP, Li JX, Wang WW, Shan ZY (2012) Effects of maternal subclinical hypothyroidism on obstetrical outcomes during early pregnancy. J Endocrinol Invest 35: 322-325.

112. Breathnach FM, Donnelly J, Cooley SM, Geary M, Malone FD (2013) Subclinical hypothyroidism as a risk factor for placental abruption: Evidence from a low□risk primigravid population. Aust N Z J Obstet Gynaecol 53: 553-560.

113. Chittamuri S, Bongi V, Ayyagari M, Kandregula DK, Kandregula SAV (2016) Pregnancy outcomes in subclinical hypothyroidism and thyroid autoimmunity. Thyroid Res Pract 13: 1-4.

114. van Dijk MM, Vissenberg R, Bisschop PH, Dawood F, van Wely M (2016) Is subclinical hypothyroidism associated with lower live birth rates in women who have experienced unexplained recurrent miscarriage? Reprod Biomed Online 33: 745-751.

115. Plowden TC, Schisterman EF, Sjaarda LA, Perkins NJ, Silver R (2017) Thyroid-stimulating hormone, anti–thyroid antibodies, and pregnancy outcomes. Am J Obstet Gynecol 217: 697.e1-697.e7.

116. Li J, Shen J, Qin L (2017). Effects of Levothyroxine on Pregnancy Outcomes in Women with Thyroid Dysfunction: A Meta-analysis of Randomized Controlled Trials. Altern Ther Health Med 23: 49-58.

117. Allan WC, Haddow JE, Palomaki GE, Williams JR, Mitchell ML, et al. (2000) .Maternal thyroid deficiency and pregnancy complications: implications for population screening. J Med Screen 7: 127-130.

118. Sahu MT, Das V, Mittal S, Agarwal A, Sahu M (2010) Overt and subclinical thyroid dysfunction among Indian pregnant women and its effect on maternal and fetal outcome. Arch Gynecol Obstet 281: 215-220.

119. Männistö T, Vääräsmäki M, Pouta A, Hartikainen AL, Ruokonen A, et al. (2010) Thyroid dysfunction and autoantibodies during pregnancy as predictive factors of pregnancy complications and maternal morbidity in later life. J Clin Endocrinol Metab 95: 1084-1094.

120. Su PY, Huang K, Hao JH, Xu YQ, Yan SQ, et al. (2011) Maternal thyroid function in the first twenty weeks of pregnancy and subsequent fetal and infant development: A prospective population- based cohort study in China. J Clin Endocrinol Metab 96: 3234-3241.

121. Wilson KL, Casey BM, McIntire DD, Halvorson LM, Cunningham FG (2012) Subclinical thyroid disease and the incidence of hypertension in pregnancy. Obstet Gynecol 119: 315-320.

122. Tudela CM, Casey BM, McIntire DD, Cunningham FG (2012) Relationship of subclinical thyroid disease to the incidence of gestational diabetes. Obstet Gynecol 119: 983-988.

123. Schneuer FJ, Nassar N, Tasevski V, Morris JM, Roberts CL (2012) Association and predictive accuracy of high TSH serum levels in first trimester and adverse pregnancy outcomes. J Clin Endocrinol Metab 97: 3115-3122.

124. De Escobar GM, Obregón MJ, del Rey FE (2004) Maternal thyroid hormones early in pregnancy and fetal brain development. Best Pracl Res Clin Endocrinol Metab 18: 225-248

125. Maraka S, Mwangi R, McCoy RG, Yao X, Sangaralingham LR, et al. (2017) Thyroid hormone treatment among pregnant women with subclinical hypothyroidism: US national assessment. BMJ 356: i6865.

126. Negro R, Schwartz A, Gismondi R, et al. (2010b). Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. J Clin Endocrinol Metab 95: 1699-1707.

127. Lazarus JH, Parkes AB, Taylor IL, Smyth PPA, John R, et al. (2004) Controlled anti-natal thyroid screening study (CATS)-early results. Endocrine Abstracts.7: P243.

128. Abdel Rahman AH, Aly Abbassy H, Abbassy AA (2010) Improved in vitro fertilization outcomes after treatment of subclinical hypothyroidism in infertile women. Endocr Pract 16: 792-797.

129. Kim CH, Ahn JW, Kang SP, Kim SH, Chae HD, et al. (2011) Effect of levothyroxine treatment on in vitro fertilization and pregnancy outcome in infertile women with subclinical hypothyroidism undergoing in vitro fertilization/intracytoplasmic sperm injection. Fertil Steril 95: 1650-1654.

130. Negro R, Mangieri T, Coppola L, Presicce G, Casavola EC, et al. (2005) Levothyroxine treatment in thyroid peroxidase antibody-positive women undergoing assisted reproduction technologies: a prospective study. Hum Reprod 20: 1529-1533.

131. Committee on Patient Safety and Quality Improvement; Committee on Professional Liability (2007) ACOG Committee Opinion No. 381: Subclinical hypothyroidism in pregnancy Obstet Gynecol 110: 959-960.

132. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, et al. (2017) Guidelines of the American Thyroid Association for the Diagnosis and Management of thyroid disease during pregnancy and the postpartum. Thyroid 27: 315-389.

133. Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Alavi Majd H, et al. (2017) Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease. Eur J Endocrinol 176: 253-265.

134. Blumenthal NJ, Eastman CJ (2017) Beneficial Effects on Pregnancy Outcomes of Thyroid Hormone Replacement for Subclinical Hypothyroidism. J Thyroid Res 2017: 4601365.

135. Casey BM, Thom EA, Peaceman AM, Varner MW, Sorokin Y, et al.(2017)

Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. N Engl J Med 376: 815-825.

136. Yu X, Chen Y, Shan Z, Teng W, Li C, et al. (2013) The pattern of thyroid function of subclinical hypothyroid women with levothyroxine treatment during pregnancy. Endocrine 44: 710-715.

137. Abalovich M, Vázquez A, Alcaraz G, Kitaigrodsky A, Szuman G, et al. (2013) Adequate Levothyroxine Doses for the Treatment of Hypothyroidism Newly Discovered During Pregnancy. Thyroid 23: 1479-1483.

138. Yu X, Chen Y, Shan Z, Teng W, Li C, et al. (2013) The pattern of thyroid function of subclinical hypothyroid women with levothyroxine treatment during pregnancy. Endocrine 44: 710-715.

139. Abalovich M, Vázquez A, Alcaraz G, Kitaigrodsky A, Szuman G, et al. (2013) Adequate Levothyroxine Doses for the Treatment of Hypothyroidism Newly Discovered During Pregnancy. Thyroid 23: 1479-1483.

140. Penin M, Trigo C, López Y, Barragáns M (2014) Treatment of subclinical hypothyroidism in pregnancy using fixed thyroxine daily doses of 75 µg. Endocrinol Nutr 61: 347-350.

141. Chakraborty S, Chakraborty J, Bandopadhay A (2016) Study for optimal dose determination of levothyroxine in subclinical hypothyroidism in pregnancy. Thyroid Res Pract 13: 126-130.

142. Caldwell KL, Miller GA, Wang RY, Jain RB, Jones RL (2008) Iodine status of the U.S. population, National Health and Nutrition Examination Survey 2003-2004. Thyroid 18:1207-l 214.

143. Berghout A, W Wiersinga (1998) Thyroid size and thyroid function during pregnancy: an analysis. Eur J Endocrinol 138:536–542.

144. Shi X, Han C, Li C, Mao J, Wang W, et al. (2015) Optimal and safe upper limits of iodine intake for early pregnancy in iodine-sufficient regions: a cross-sectional study of 7,190 pregnant women in China. J Clin Endocrinol Metab 100: 1630-1638.

145. Roti E, Gardini E, Minelli R, Bianconi L, Flisi M (1991) Thyroid function evaluation by different commercially available free thyroid hormone measurement kits in term pregnant women and their newborns. J Endocrinol Invest 14: 1-9.

146. Blumenthal NJ, Byth K, Eastman CJ (2016) Prevalence of thyroid dysfunction and thyroid antibodies in a private obstetrical practice in Sydney. Aust N Z J Obstet Gynaecol 56: 307-311.

147. Klein RZ, Haddow JE, Faix JD, Brown RS, Hermos RJ, et al. (1991) Prevalence of thyroid deficiency in pregnant women. Clin Endocrinol (Oxf) 35: 41-46.

148. Dhanwal DK, Prasad S, Agarwal, AK, Dixit V, Banerjee AK (2013) High prevalence of subclinical hypothyroidism during first trimester of pregnancy in North India . Indian J Endocr Metab 17: 281-284.

149. Wang W, Teng W, Shan Z, Wang S, Li J, et al. (2011) .The prevalence of thyroid disorders during early pregnancy in China: the benefits of universal screening in the first trimester of pregnancy. Eur J Endocrinol 164: 263-268.

150. Fatourechi V (2009) Subclinical hypothyroidism: an update for primary care physicians. Mayo Clin Proc 84: 65-71.

151. Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, et al. (1999) Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol (Oxf) 50: 149-155.

152. Stagnaro-Green A, Chen X, Bogden JD, Davies TF, Scholl TO (2005) The thyroid and pregnancy: a novel risk factor for very preterm delivery. Thyroid 15: 351-357.

153. Tong Z, Xiaowen Z, Baomin C, Aihua L, Yingying Z, et al. (2016) The effect of subclinical maternal thyroid dysfunction and autoimmunity on intrauterine growth restriction: systematic review and meta-analysis. Medicine (Baltimore) 95: e3677.

154. Gong LL, Liu H, Liu LH (2016) Relationship between hypothyroidism and the incidence of gestational diabetes: a meta-analysis. Taiwan J Obstet Gynecol 55: 171-175.

155. Toulis KA, Stagnaro-Green A, Negro R (2014) Maternal subclinical hypothyroidism and gestational diabetes mellitus: a meta-analysis. Endocr Pract 20: 703-714.

156. Van den Boogaard E, Vissenberg R, Land JA, van Wely M, van der Post JAM, et al. (2016) Significance of subclinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. Human Reproduction Update 22: 532-533.

157. Nelson DB, Casey BM, McIntire DD, Cunningham FG (2014) Subsequent pregnancy outcomes in women previously diagnosed with subclinical hypothyroidism. Am J Perinatol 31: 77-84.

158. Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, et al. (2014) European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. Eur Thyroid J 3: 76-94.

159. Premawardhana L (2015) Universal screening for hypothyroidism in pregnancy : time for a paradigm shift? Endocrine 48: 9-11.

160. Wier FA, Farley CL (2006) Clinical controversies in screening women for thyroid disorders during pregnancy. J Midwifery Womens Health 51: 152-158.

161. Van der Zanden M, Hop-de Groot RJ, Sweep FC, Ross HA, den Heijer M, et al. (2013) Subclinical hypothyroidism after vascular complicated pregnancy. Hypertens Pregnancy 32: 1-10.

162. Gharib H, Cobin RH, Dickey RA (1999) Subclinical hypothyroidism during pregnancy: position statement from the American Association of Clinical Endocrinologists. Endocr Pract 5: 367-368.

163. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, et al. (2006) Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab 91: 2587-2591.

164. Casey BM, Thom EA, Peaceman AM, Varner MW, Sorokin Y, et al.(2017) Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. N Engl J Med 376: 815-825.

165. Behrooz HG, Tohidi M, Mehrabi Y, Behrooz EG, Tehranidoost M, et al. (2011) Subclinical hypothyroidism in pregnancy: intellectual development of offspring. Thyroid 21: 1143-1147.

166. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, FeldtRasmussen U, Henry JF, et al. (2003) Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid 13: 3-126.

167. Velkeniers B, Van Meerhaeghe A, Poppe K, Unuane D, Tournaye H, et al. (2013) Levothyroxine treatment and pregnancy outcome in women with subclinical hypothyroidism undergoing assisted reproduction technologies: systematic review and meta-analysis of RCTs. Hum Reprod Update 19: 251-258.

168. Mintziori G, Goulis DG, Kolibianakis EM (2016) Thyroid function and IVF outcome: when to investigate and when to intervene? Curr Opin Obstet Gynecol 28: 191-197.

169. Stagnaro-Green A , Dogo-Isonaige E, Pearce EN, Spencer C, Gaba ND (2015) Marginal Iodine Status and High Rate of Subclinical Hypothyroidism in Washington DC Women Planning Conception. Thyroid 25: 1151-1154.

170. Vissenberg R, van den Boogaard E, van Wely M, van der Post JA, Fliers E, et al. (2012) Treatment of thyroid disorders before conception and in early pregnancy: a systematic review. Hum Reprod Update 18: 360-373.

171. Yan J, Sripada S, Saravelos SH, Chen ZJ, Egner W, et al. (2012) Thyroid peroxidase antibody in women with unexplained recurrent miscarriage: prevalence, prognostic value, and response to empirical thyroxine therapy. Fertil Steril 98: 378-382.

172. Lepoutre T, Debiève F,Gruson D, Daumerie C (2012) Reduction of miscarriages through universal screening and treatment of thyroid autoimmune diseases. Gynecol Obstet Invest 74: 265-273.

173. Reid SM, Middleton P, Cossich MC, Crowther CA, Bain E (2013) Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy. Cochrane Database Syst Rev 5: CD007752.

174. Bernardi LA, Cohen RN, Stephenson MD (2013) Impact of subclinical hypothyroidism in women with recurrent early pregnancy loss. Fertil Steril 100: 1326-1331.

175. Bartáková J, Potluková E, Rogalewicz V, Fait T, Schöndorfová D, et al. (2013) Screening for autoimmune thyroid disorders after spontaneous abortion is cost-saving and it improves the subsequent pregnancy rate. BMC Pregnancy Childbirth 13: 217.

176. Lata K, Dutta P, Sridhar S, Rohilla M, Srinivasan A (2013) Thyroid

autoimmunity and obstetric outcomes in women with recurrent miscarriage: a case-control study. Endocr Connect 2: 118-124.

177. Jayaraman M, Verma A, Harikumar KV, Ugale M, Modi K (2013) Pregnancy outcomes with thyroxine replacement for subclinical hypothyroidism: Role of thyroid autoimmunity. Indian Journal of Endocrinology and Metabolism 17: 294-297.

178. Ma L, Qi H, Chai X, Jiang F, Mao S, et al. (2016) The effects of screening and intervention of subclinical hypothyroidism on pregnancy outcomes: a prospective multicenter single-blind, randomized, controlled study of thyroid function screening test during pregnancy. J Matern Fetal Neonatal Med 29: 1391-1394.

179. Maraka S, Singh Ospina NM, O'Keeffe DT, Rodriguez-Gutierrez R, Espinosa De Ycaza AE, et al. (2016) Effects of levothyroxine therapy on pregnancy outcomes in women with subclinical hypothyroidism. Thyroid 26: 980-986.

180. Negro R, Schwartz A, Stagnaro-Green A (2016) Impact of levothyroxine in miscarriage and preterm delivery rates in first trimester thyroid antibody-positive women with TSH less than 2.5 mIU/L. J Clin Endocrinol Metab 101: 3685-3690.

181. Casey B (2016) Effect of treatment of maternal subclinical hypothyroidism or hypothyroxinemia on IQ in offspring. American Journal of Obstetrics & Gynecology 214: S2.

182. Ju R, Lin L, Long Y, Zhang J, Huang J (2016) Clinical efficacy of therapeutic intervention for subclinical hypothyroidism during pregnancy. Genet Mol Res 15.

183. Korevaar TI, Muetzel R, Medici M, Chaker L, Jaddoe VW, et al. (2016) Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. Lancet Diabetes Endocrinol 4: 35-43.

184. Peaceman A (2016) 356: Effect of treatment of maternal subclinical hypothyroidism and hypothyroxinemia on pregnancy outcomes. Am J Obstet Gynecol 214: S200.

185. Blumenthal NJ, Eastman CJ (2017) Beneficial Effects on Pregnancy Outcomes of Thyroid Hormone Replacement for Subclinical Hypothyroidism. J Thyroid Res 2017: 4601365.

186. Li J, Shen J, Qin L (2017). Effects of Levothyroxine on Pregnancy Outcomes in Women with Thyroid Dysfunction: A Meta-analysis of Randomized Controlled Trials. Altern Ther Health Med 23: 49-58.

187. Wiles KS, Jarvis S, Nelson-Piercy C (2015) Are we over treating subclinical hypothyroidism in pregnancy? BMJ 351: h4726.

188. Rodriguez-Gutierrez R, Maraka S, Ospina NS, Montori VM, Brito JP (2017) Levothyroxine overuse: time for an about face? Lancet Diabetes Endocrinol 5: 246-248.

189. Mandal RC, Bhar D, Das A, Basunia SR, Kundu SB, et al. (2016) Subclinical Hypothyroidism in Pregnancy: An Emerging Problem in Southern West Bengal: A cross-sectional Study. J Nat Sci Biol Med 7: 80-84.