

Review Article

Subclinical Hypothyroidism during Pregnancy: Controversies

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Hypothyroidism is associated with increased risk of adverse maternal and fetal outcomes, including infertility, miscarriages, preterm deliveries, perinatal death, gestational hypertension, gestational diabetes and impaired neurocognitive development in the offspring. While it is clear that overt hypothyroidism is associated with increased risk and must be treated optimally, the diagnostic thresholds and the significance of subclinical hypothyroidism during pregnancy are debated. The diagnosis of SCH should be based on assay-specific, population-specific and trimester-specific reference ranges. In the absence of such reference ranges, the upper limit of TSH of the non-pregnant population can be reduced by 0.5mIU/l. Treatment with levothyroxine is associated with reduced rates of miscarriage, gestational hypertension, gestational diabetes, preterm deliveries and perinatal death. However, the effect on neurocognitive outcomes has not been demonstrated. Consistent benefits have been demonstrated in women with SCH who are TPO-Ab positive and therefore, assessment of thyroid autoimmunity must be done for clinical decision-making. Levothyroxine is indicated in women with TSH > 10mIU/l or in women with TSH above the upper limit of reference range with TPO-Ab positivity. In others, the decision should be individualized based on assessment of risk.

[J Indian Med Assoc 2018; 116: 45-51]

Key words : Hypothyroidism, subclinical hypothyroidism, isolated hypothyroxinemia, pregnancy.

Pregnancy is associated with significant alterations in thyroid physiology, resulting from the effect of placental human chorionic gonadotropin (hCG), increased concentration of thyroid binding globulin (TBG), increased iodine requirement and transplacental transfer of thyroid hormones to the developing fetus¹. These are highlighted in Table 1. Maternal thyroid hormones are critical for skeletal growth and neurological development of the fetus, especially prior to 12-14 weeks, before thyroid ontogenesis. The fetal thyroid gland activity begins at 10-12 weeks gestation but the gland becomes functionally mature at 18-20 weeks.

Thyroid hypofunction during pregnancy can be classified into overt hypothyroidism, subclinical hypothyroidism and isolated hypothyroxinemia, as detailed in table 2. Overt hypothyroidism (OH) affects approximately 0.3-0.5% pregnancies, while subclinical hypothyroidism (SCH) has been reported in 3.5-18% pregnancies². It is clear that OH increases the risk of adverse pregnancy outcomes including infertility, spontaneous abortion, gestational hypertension, placental abruption, fetal distress, preterm birth, low birth weight, perinatal death and impaired neurodevelopment and adequate levothyroxine replacement has demonstrated significant benefits. On the other hand, SCH forms a grey zone between normal physiological changes of pregnancy and thyroid hypofunction. The diagnosis is based on an elevated TSH with normal thy-

- The diagnostic thresholds and the significance of SCH in pregnancy are debated.
- Consistent benefits have been demonstrated in women with SCH who are TPO-Ab positive.
- Levothyroxine is indicated in women with TSH > 10 mIU/L or in women with TSH above the upper limit of reference range with TPO-Ab positive.
- In others, the decision should be individualized based on assessment of risk.

roid hormone levels, but the diagnostic cut-offs of TSH are highly debated. Additionally, it is not determined clearly if SCH is associated with adverse pregnancy outcomes and whether management leads to significant benefits.

Universal Screening or Targeted Case

Finding :

There is significant debate on whether screening for thyroid dysfunction during pregnancy should be universal or targeted at women with high risk³. Thyroid dysfunction during pregnancy is common, can result in adverse pregnancy outcomes, can be easily detected with a reliable blood test during routine antenatal evaluation and is relatively simple to treat. Therefore, it meets several criteria to justify screening. Several groups have reported that targeted case finding may overlook almost one-third to half of pregnant women with thyroid dysfunction, who are detected by universal screening⁴⁻⁸. However, most of these women had SCH. In addition, there seems to be little evidence that screening and treatment of SCH improves preg-

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Table 1 — *Physiological Changes in Pregnancy and Effect on Maternal Thyroid Functions*

Physiological Changes in the Mother	Changes in Maternal Thyroid Functions
<ul style="list-style-type: none"> Thyrotropic effect of placental hCG: Placental hCG increases with a peak at the end of the first trimester and then declines to plateau in second and third trimesters. Increased TBG levels: TBG increases, beginning at 6-8 weeks with 2-3 fold rise by 20th week of gestation. This results from increased production due to effect of estradiol and decreased renal clearance of more sialylated forms. Increased iodine demand: Increased renal filtration of iodine, trans-placental transfer of iodine to developing fetus and increased demand for thyroid hormone production. Transplacental transfer of thyroid hormones: Approximately 50% increase in thyroid hormone demand and transfer to fetus for skeletal growth and neurological development. Placental deiodinases: Intraplacental breakdown of T4 and T3 by placental deiodinases (D3). 	<ul style="list-style-type: none"> TSH is lower in the first trimester due to a transient increase in thyroid hormone production (thyrotropic effect of hCG). It reaches a trough around 11-14 weeks and slightly rises later. Transient increase in thyroid hormone production due to hCG, with rise in fT4 towards the end of first trimester. Free T4 slightly decreases during latter half of pregnancy. Total T3 and total T4 increase from 6-8 weeks due to increased TBG levels, starting from early pregnancy to approximately 1.5 times at 16th week of gestation and then plateau. Free T4 assays may be unreliable due to high TBG levels. Significant reduction in free T4 in third trimester may be seen in automated immunoassays. More accurate methods such as equilibrium dialysis or ultrafiltration are more expensive.
hCG – human chorionic gonadotropin, TBG – thyroid binding globulin	

Table 2 — *Hypothyroidism during Pregnancy: Classification*

Category	Definition
Overt Hypothyroidism	Serum FT3 and/ or FT4 below the reference range with TSH above the reference range.*
Subclinical Hypothyroidism	Serum fT3 and fT4 levels within the reference ranges with TSH above the reference range.*
Isolated Hypothyroxinemia	Serum fT4 below the reference range with normal TSH.*
*Reference ranges for FT3, FT4 and TSH should be population-specific and trimester-specific.	

nancy outcomes. Negro et al reported no difference in pregnancy outcomes with universal versus selective screening and treatment⁹. Ongoing large prospective trials assessing the role of universal screening and treatment of SCH may result greater clarity¹⁰.

Most international guidelines recommend targeted case-finding approach in women at high risk, as depicted in Table 3^{11-15,26}. Considering that a significant number of pregnant women would qualify for screening, it would be easier and more practical to screen everyone. The prevalence of SCH in a recent multicentre study from India was 13.3%, using a liberal TSH cut-off of 4.5 mIU/l¹⁷. Similar high prevalence has been reported in earlier studies, for both OH (3.7-4.5%) and SCH (6.5-9.2%)¹⁸⁻²⁰. While the significance of SCH during pregnancy remains debated, universal screening may still be justified due to detection of OH²¹. Moreover, universal screening has been reported to be cost-effective^{22,23}. Therefore, universal screening

appears to be more desirable and this is reflected in the Indian Thyroid Society guidelines which recommend screening of all pregnant women with TSH²⁴.

TSH Cut-offs for Diagnosis of Subclinical Hypothyroidism :

During pregnancy, TSH levels are lower than the reference values used for non-pregnant individuals. Earlier guidelines offered a somewhat simplistic approach to diagnosis of SCH, using a cut-off of 2.5mIU/l in the first trimester, as this was near the 97.5th percentile in several studies^{13,14}. While there is a downward shift in TSH during pregnancy, this seems to be small, by 0.5-1.0mIU/l, and occurs after 7 weeks of gestation²⁵. Moreover, there seems to be considerable heterogeneity between

reference ranges for TSH reported in different studies and these changes may result from differences in ethnicity, body mass index, nutritional iodine status and differences in assay methods. A study that compared 7 different TSH assay systems in first trimester reported a more than 40% variation between assay results from the same sera²⁶. Indeed, wide variations in TSH reference ranges have been reported from different populations²⁷⁻³⁰. Table 4 highlights the TSH reference ranges reported in various studies from India. Using a low cut-off of 2.5mIU/l, a very high percentage of women may be classified as SCH^{31,32}. In a study from Delhi, almost 50% pregnant women would have qualified for a diagnosis of SCH using a cut-off of 2.5mIU/l¹⁷.

Table 3 — *High Risk Screening for Thyroid Dysfunction during Pregnancy*

Who to Screen	
History of thyroid disorder	Hyperthyroidism, hypothyroidism, goitre, thyroid antibodies, postpartum thyroiditis, thyroid nodule or surgery
At risk for thyroid Disease	Clinical signs and symptoms of thyroid disorder Presence of goitre Family history of thyroid disease Age > 30 years Morbid obesity Type 1 diabetes or other autoimmune diseases Previous miscarriage or preterm delivery Infertility Previous head or neck irradiation Living in an iodine deficient region Medications such as lithium, amiodarone or recent use of iodinated contrast

Table 4 — Population-Based Trimester-Specific TSH Reference Ranges in Studies from India

Population-specific reference ranges in various studies from India			
	TSH (mU/l) in 1st trimester	TSH (mU/l) in 2nd trimester	TSH (mU/l) 3rd trimester
Marwaha, Delhi 2008 (27) (5th-95th percentile)	0.6–5.0	0.44–5.78	0.74–5.7
Rajput, Haryana 2016 (28) (2.5th-97.5th percentile)	0.37-3.69	0.54-4.47	0.70-4.64
Jebasingh, Manipur 2016 (29) (5th-95th percentile)	0.21-1.82	0.72-1.71	0.69-1.93
Sekhri, Delhi 2016 (30) (2.5th-97.5th percentile)	0.09-6.65	0.51-6.61	0.91-4.86

Hence, there is a need to determine assay-specific, population-specific and trimester-specific reference ranges of TSH and thyroid hormones, using data from healthy pregnant women who do not have thyroid dysfunction or related risk factors, are negative for thyroid auto-antibodies, are iodine sufficient, are not on any drugs affecting thyroid functions and have singleton pregnancies². Veltri et al reported that an institutional cut-off for TSH of 4mIU/l was as specific as ethnicity-specific cut-offs for the diagnosis of SCH³³. This approach is supported by the recent American Thyroid Association guidelines that recommend the use of population-specific and trimester-specific reference ranges. In the absence of these, the upper limit of TSH reference range for non-pregnant population can be reduced by 0.5mIU/l or a cut-off of 4mIU/l can be used between 7-12 weeks of gestation with a gradual return to non-pregnant ranges in second and third trimesters. Prior to 7 weeks, non-pregnant reference ranges are considered¹⁶.

In addition, measurement of free T4 by immunoassays may result in significantly lower values due to interference by increased TBG levels. More accurate methods such as equilibrium dialysis or tandem mass spectrometry are expensive and not easily available. Therefore, total T4 is considered more reliable. However, population-specific and trimester-specific reference ranges should be determined or the non-pregnant reference values can be multiplied by 1.5¹.

Effect of Subclinical Hypothyroidism on Pregnancy Outcomes :

Several studies have reported an increased risk of infertility, gestational hypertension, pre-eclampsia, gestational diabetes, miscarriage, premature delivery, placental abruption, low birth weight, intrauterine growth retardation and prenatal death in women with SCH^{9,34-39}. The risk for infertility, miscarriage, premature delivery and prenatal death seems to be particularly increased if they have thyroid autoimmunity⁴⁰. However, the association with placental abruption, low birth weight, perinatal mortality

and impaired neurocognitive development in offspring is not consistent^{34-36,41-43}.

Treatment of SCH with levothyroxine resulted in significant reduction in miscarriage rates, in both TPO-Ab positive and TPO-Ab negative women^{44,45}. In a recent meta-analysis of 14 randomized trials, levothyroxine significantly improved fertilization, clinical pregnancy and delivery rates in infertile women with thyroid dysfunction. Significant improvements were also demonstrated in miscarriage rates, gestational hypertension, preterm deliveries and prenatal deaths⁴⁶. Levothyroxine treatment was associated with significantly reduced risk of pregnancy loss in women with TSH between 4.1-10mIU/l in another large retrospective cohort⁴⁷. Maraka *et al* reported that treatment of SCH resulted in reduced risk pregnancy loss, gestational hypertension, low birth weight and low Apgar score in newborns⁴⁸. Treatment initiation at an earlier gestational age and attainment of target TSH with 4 weeks resulted in better outcomes than if treatment was delayed or TSH targets not achieved by 4 weeks⁴⁹. More recently, Nazarpour et al demonstrated that a TSH cut-off of 4mIU/l, but not 2.5mIU/l, for treatment initiation in women TPO-Ab positive women was associated with a reduced rate of preterm deliveries⁵⁰. But other studies have not demonstrated similar benefits⁵¹⁻⁵².

The impact of SCH on neurocognitive outcomes in offspring is far from clear. Large prospective studies suggested that SCH is not associated with adverse neurocognitive outcomes. However, a recent meta-analysis of 6 studies suggested that mean intelligence score was 8.76 points lower and motor score was 9.98 points lower in children of mothers with SCH than euthyroid mothers⁵³. Another meta-analysis of 15 cohort studies reported an association of SCH with delayed motor and intellectual development, prematurity, fetal growth restriction, low birth weight and fetal distress⁵⁴. There is a lack of adequate interventional studies demonstrating beneficial effects of levothyroxine treatment on neurocognitive outcomes. Several randomized trials have assessed the impact of treatment on motor and mental development of offspring and reported no effect^{51,55,56}.

Euthyroid Women with Thyroid Autoimmunity :

10-20% of women may have elevated titers of anti-thyroid autoantibodies, including TPO-Ab¹⁸. TPO-Ab positivity is associated with a higher risk of adverse maternal and fetal outcomes in women with thyroid dysfunction and also signifies an increased risk of postpartum thyroid dysfunction^{57,58}. Levothyroxine replacement in TPO-Ab positive women with overt or subclinical hypothyroidism results in improved pregnancy outcomes and is there-

fore, indicated. However, many TPO-Ab positive women may be euthyroid. Increased rates of miscarriage and premature deliveries have been reported among them. Several mechanisms have been proposed to explain this increased risk: presence of subtle hypothyroidism, blocking of β -HCG action by anti-TSH receptor antibodies, direct effect of thyroid antibodies on the feto-placental unit, or generalized immune dysfunction. Some studies have suggested that levothyroxine supplementation in TPO-Ab positive euthyroid women may improve pregnancy rates, reduce the risk of pregnancy loss and lower rates of preterm deliveries⁵⁹⁻⁶¹. However, there is clearly not enough evidence to suggest this practice at the moment. Free T4 levels in fetal blood obtained by cordocentesis were found to be higher than normal levels in almost 60% fetuses when euthyroid TPO Ab mothers were treated with LT4 and the safety of fetal thyroxine exposure needs to be ascertained⁶². Ongoing trials, including TABLET and T4LIFE trials, of levothyroxine treatment started before conception in TPO-Ab positive women will inform whether it reduces miscarriage risk.

Isolated Maternal Hypothyroxinemia :

Some women have low free T4 concentration (below 2.5th or 5th percentile) in the presence of normal TSH levels. While iodine deficiency may result in relative hypothyroxinemia, the etiopathogenesis of isolated hypothyroxinemia is not known. In fact, women with high urinary iodine concentrations were at a higher risk of hypothyroxinemia than women with low urinary iodine concentration⁶³.

Since free T4 assays are difficult to interpret during pregnancy and may report lower values due to increased TBG, the definition and clinical significance of isolated hypothyroxinemia is highly debated. Some studies reported an association of maternal hypothyroxinemia in first trimester with increased risk of adverse neurodevelopmental outcomes in offspring, such as decreased psychomotor test scores and IQ, language delays, worsened motor function and risk of autism^{64,65}. The risk is not increased with low FT4 during second or third trimesters^{66,67}. The risk of miscarriage, preterm delivery, low birth weight, gestational hypertension or gestational diabetes does not seem to be increased⁶⁸. Additionally, no studies have demonstrated benefits of treating isolated hypothyroxinemia during pregnancy with levothyroxine. There was no improvement in neurocognitive functions in offspring at 3 years in the CATS trial⁵¹. At present, treatment of isolated maternal hypothyroxinemia is not recommended.

Indications for Treatment :

While the earlier guidelines recommended initiation of levothyroxine in women with first trimester TSH >

2.5mIU/l, this has been clearly demonstrated to lack evidence base^{13,14}. Not only would this result in labeling and treatment of a large number of otherwise healthy women, there is no evidence of its benefits on maternal and fetal outcomes and there is a potential risk of overtreatment. Thyroid hormones have a U-shaped effect on fetal development such that both deficiency and excess may impair fetal neurological development. In fact, higher maternal FT4 has also been associated with lower IQ in children⁶⁹, lower birth weight and increased risk of SGA⁷⁰.

Women with overt hypothyroidism should be treated, regardless of TPO-Ab status. In women with SCH, TPO-Ab status should be determined and treatment decision should be based on estimation of individual risk¹⁶. In Table 5, we enlist the indications of treatment for hypothyroidism during pregnancy. Treatment is not indicated if TSH is within trimester-specific reference range and TPO-Ab is negative. In women who are already on levothyroxine, dose is recommended to be empirically increased by 25-50% on pregnancy confirmation based on results from cohort studies. Dose increments are particularly needed in athyreotic women but women with TSH < 1.2mU/l need not increase their dose as reported in few observational studies⁴⁰.

Conclusion :

There is a high prevalence of subclinical hypothyroidism and universal screening may be a better approach than targeted case-finding in India. The diagnosis of SCH should

Table 5 — Indications for Initiation of Levothyroxine Treatment during Pregnancy

TSH	Treatment
TPO Ab positive :	
TSH > 10 mIU/l	LT4 treatment strongly recommended. Reduced risk of pregnancy complications and improved neurocognitive outcomes (with early intervention).
TSH > upper limit of reference range * but < 10 mIU/l	LT4 recommended. Reduced risk of pregnancy complications. Effect on neurocognitive outcomes not known.
TSH > 2.5 mIU/l	LT4 may be considered in women with high risk of complications (infertility, recurrent pregnancy losses)
TSH < 2.5 mIU/l	LT4 not recommended. May consider in some cases at high risk such as women with infertility, recurrent pregnancy losses or those undergoing ART.
TP cx O Ab negative :	
TSH > 10 mIU/l	LT4 strongly recommended. Reduced risk of complications and improved neurocognitive outcomes (with early intervention).
TSH > upper limit of reference range* but < 10 mIU/l	LT4 recommended. Reduced risk of pregnancy complications. Effect on neurocognitive outcomes not known.
TSH > 2.5 mIU/l but < upper limit of reference range*	LT4 not recommended. May be considered in women undergoing ICSI or IVF (insufficient evidence).
TSH < 2.5 mIU/l	LT4 not recommended.
*Trimester-specific, population-specific reference range.	

be based on assay-specific, population-specific and trimester-specific reference ranges. In the absence of such reference ranges, the upper limit of TSH of the non-pregnant population can be reduced by 0.5mIU/l. While there is increased risk of adverse maternal and fetal outcomes in SCH, there is limited evidence of benefit from treatment with levothyroxine. Consistent benefits have been demonstrated in women with SCH who are TPO-Ab positive and therefore, assessment of thyroid autoimmunity must be done for clinical decision-making. Levothyroxine is indicated in women with TSH > 10mIU/l or in women with TSH above the upper limit of reference range with TPO-Ab positivity. In others, the decision should be individualized based on assessment of risk.

REFERENCES

- McNeil AR, Stanford PE — Reporting thyroid function tests in pregnancy. *Clin Biochem Rev* 2015; **36**: 109-26.
- Korevaar TIM, Medici M, Visser TJ, Peeters RP — Thyroid disease in pregnancy: new insights in diagnosis and clinical management. *Nat Rev Endocrinol* 2017; **13**: 610-22. doi: 10.1038/nrendo.2017.93. Epub 2017 Aug 4.
- Vila L, Velasco I, González S, Morales F, Sánchez E, Torrejón S, Soldevila B, Stagnaro-Green A, Puig-Domingo M — Controversies in endocrinology: On the need for universal thyroid screening in pregnant women. *Eur J Endocrinol* 2013; **170**: R17-30. doi: 10.1530/EJE-13-0561.
- Nazarpour S, Tehrani FR, Simbar M, Tohidi M, AlaviMajid H, Azizi F — Comparison of universal screening with targeted high-risk case finding for diagnosis of thyroid disorders. *Eur J Endocrinol* 2016; **174**: 77-83. doi: 10.1530/EJE-15-0750. Epub 2015 Oct 28.
- Vaidya B, Anthony S, Bilous M, Shields B, Drury J, Hutchinson S, et al — Detection of thyroid dysfunction in early pregnancy: universal screening or targeted high-risk case finding? *J Clin Endocrinol Metab* 2007; **92**: 203-7.
- Horacek J, Spitalnikova S, Dlabalova B, Malirova E, Vizda J, Svilius I, et al — Universal screening detects two-times more thyroid disorders in early pregnancy than targeted high-risk case finding. *Eur J Endocrinol* 2010; **163**: 645-50.
- Akram FH, Johansson B, Mollerstrom G, Landgren BM, Stavreus-Evers A, Skjoldebrand-Sparre L — Incidence of subclinical hypothyroidism and hypothyroidism in early pregnancy. *J Womens Health (Larchmt)* 2017; **26**: 1231-35. doi: 10.1089/jwh.2016.6111. Epub 2017 Oct 5.
- Ahmed IZ, Eid YM, El Orabi H, Ibrahim HR — Comparison of universal and targeted screening for thyroid dysfunction in pregnant Egyptian women. *Eur J Endocrinol* 2014; **171**: 285-91. doi: 10.1530/EJE-14-0100. Epub 2014 May 19.
- Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A — Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. *J Clin Endocrinol Metab* 2010; **95**: 1699-707. doi: 10.1210/jc.2009-2009. Epub 2010 Feb 3.
- Hales C, Channon S, Taylor PN, Draman MS, Muller I, Lazarus J, et al — The second wave of the Controlled Antenatal Thyroid Screening (CATS II) study: the cognitive assessment protocol. *BMC Endocr Disord* 2014; **14**: 95.
- Abalovich M, Amino N, Barbour LA, Cobin RH, De Groot LJ, Glinoe D, et al — Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. *Clin Endocrinol Metab* 2007; **92**: 1-47.
- American College of Obstetricians and Gynecologists. Practice bulletin no. 148: thyroid disease in pregnancy. *Obstet Gynecol* 2015; **125**: 996-1005.
- Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, et al — Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* 2011; **21**: 1081-25.
- De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, et al — Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2012; **97**: 2543-65.
- Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B — European Thyroid Association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. *Eur Thyroid J* 2014; **3**: 76-94.
- Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S — Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. *Thyroid* 2017; **27**: 315-89. doi: 10.1089/thy.2016.0457.
- Dhanwal DK, Bajaj S, Rajput R, Subramaniam KA, Chowdhury S5, Bhandari R, Dharmalingam M, Sahay R, Ganie A, Kotwal N, Shriram U — Prevalence of hypothyroidism in pregnancy: An epidemiological study from 11 cities in 9 states of India. *Indian J Endocrinol Metab* 2016; **20**: 387-90. doi: 10.4103/2230-8210.179992.
- Dhanwal DK, Prasad S, Agarwal AK, Dixit V, Banerjee AK — High prevalence of subclinical hypothyroidism during first trimester of pregnancy in North India. *Indian J Endocrinol Metab* 2013; **17**: 281-4.
- Jaiswal N, Melse-Boonstra A, Thomas T, Basavaraj C, Sharma SK, Srinivasan K, Zimmermann MB — High prevalence of maternal hypothyroidism despite adequate iodine status in Indian pregnant women in the first trimester. *Thyroid* 2014; **24**: 1419-29. doi: 10.1089/thy.2014.0071. Epub 2014 Jul 21.
- Sahu MT, Das V, Mittal S, Agarwal A, Sahu M — Overt and subclinical thyroid dysfunction among Indian pregnant women and its effect on maternal and fetal outcome. *Arch Gynecol Obstet* 2010; **281**: 215-20. doi: 10.1007/s00404-009-1105-1. Epub 2009 May 13.
- Klein RZ, Haddow JE, Faix JD, Brown RS, Hermos RJ, Pulkkinen A, et al — Prevalence of thyroid deficiency in pregnant women. *Clin Endocrinol (Oxf)* 1991; **35**: 41-6.
- Dosiou C, Barnes J, Schwartz A, Negro R, Crapo L, Stagnaro-Green A — Cost-effectiveness of universal and risk-based screening for autoimmune thyroid disease in pregnant women. *J Clin Endocrinol Metab* 2012; **97**: 1536-46.
- Thung SF, Funai EF, Grobman WA — The cost-effectiveness of universal screening in pregnancy for subclinical hypothyroidism. *Am J Obstet Gynecol* 2009; **200**: 267.e1-7. doi: 10.1016/j.ajog.2008.10.035. Epub 2008 Dec 27.
- Clinical Practice Guidelines. ed. 1. New Delhi: Elsevier; 2012. Indian Thyroid Society guidelines for management of thyroid dysfunction during pregnancy.
- Khan I, Okosieme OE, Lazarus JH — Current challenges in

- the pharmacological management of thyroid dysfunction in pregnancy. *Expert Rev Clin Pharmacol* 2017; **10**: 97-109. doi: 10.1080/17512433.2017.1253471. Epub 2016 Nov 8.
- 26 Springer D, Bartos V & Zima T — Reference intervals for thyroid markers in early pregnancy determined by 7 different analytical systems. *Scandinavian Journal of Clinical and Laboratory Investigation* 2014; **74**: 95-101. doi:10.3109/00365513.2013.860617
 - 27 Marwaha R, Chopra S, Gopalakrishnan S, Sharma B, Kanwar R, Sastry A, *et al* — Establishment of reference range for thyroid hormones in normal pregnant Indian women. *BJOG* 2008; **115**: 602-6.
 - 28 Rajput R, Singh B, Goel V, Verma A, Seth S, Nanda S — Trimester-specific reference interval for thyroid hormones during pregnancy at a Tertiary Care Hospital in Haryana, India. *Indian J Endocrinol Metab* 2016; **20**: 810–815. doi: 10.4103/2230-8210.192903
 - 29 Jebasingh FK, Salam R, Meetei TL, Singh PT, Singh NN, Prasad L — Reference intervals in evaluation of maternal thyroid function of Manipuri women. *Indian J Endocrinol Metab* 2016; **20**: 167-70. doi: 10.4103/2230-8210.176354
 - 30 Sekhri T, Juhi A, Wilfred R, Kanwar RS, Sethi J, Kuntal B, Nair S, Singh S — Trimester specific reference intervals for thyroid function tests in normal Indian pregnant women. *Indian J Endocrinol Metab* 2016; **20**: 101-7. doi: 10.4103/2230-8210.172239
 - 31 Li C, Shan Z, Mao J, Wang W, Xie X, Zhou W, Li C, Xu B, Bi L, Meng T, *et al* — 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? *Journal of Clinical Endocrinology and Metabolism* 2014; **99**: 73-9. (doi:10.1210/jc.2013-1674)
 - 32 Blatt AJ, Nakamoto JM, Kaufman HW — National status of testing for hypothyroidism during pregnancy and postpartum. *J Clin Endocrinol Metab* 2012; **97**: 777-84.
 - 33 Veltri F, Belhomme J, Kleynen P, Grabczan L, Rozenberg S, Peppersack T, Poppe K — Maternal thyroid parameters in pregnant women with different ethnic backgrounds: Do ethnicity-specific reference ranges improve the diagnosis of subclinical hypothyroidism. *Clin Endocrinol (Oxf)* 2017; **86**: 830-6. doi: 10.1111/cen.13340. Epub 2017 Apr 24.
 - 34 Cleary-Goldman J, Malone FD, Lambert-Messerlian G, Sullivan L, Canick J, Porter TF, Luthy D, Gross S, Bianchi DW, D'Alton ME, *et al* — Maternal thyroid hypofunction and pregnancy outcome. *Obstetrics and Gynecology* 2008; **112**: 85-92. (doi:10.1097/AOG.0b013e3181788dd7)
 - 35 Mannisto T, Vaarasmaki M, Pouta A, Hartikainen AL, Ruokonen A, Surcel HM, Bloigu A, Jarvelin MR, Suvanto-Luukkonen E — Perinatal outcome of children born to mothers with thyroid dysfunction or antibodies: a prospective population-based cohort study. *J Clin Endocrinol Metab* 2009; **94**: 772-9
 - 36 Maraka S, Ospina NM, O'Keefe DT, Espinosa De Ycaza AE, Gionfriddo MR, Erwin PJ, *et al* — Subclinical hypothyroidism in pregnancy: a systematic review and meta-analysis. *Thyroid* 2016; **26**: 580-90.
 - 37 Gong LL, Liu H, Liu LH. Relationship between hypothyroidism and the incidence of gestational diabetes: A meta-analysis. *Taiwanese Journal of Obstetrics & Gynecology* 2016; **55**: 171e175.
 - 38 Chen S, Zhou X, Zhu H, Yang H, Gong F, Wang L, Zhang M, Jiang Y, Yan X, Li J, Wang Q, Zhang S, Pan H — Preconception TSH and pregnancy outcomes: a population-based cohort study in 184611 women. *Clin Endocrinol (Oxf)* 2017; **86**: 816-24. doi: 10.1111/cen.13329. Epub 2017 Apr 10.
 - 39 Tong Z, Xiaowen Z, Baomin C, Aihua L, Yingying Z, Weiping T, Zhongyan S — The effect of subclinical maternal thyroid dysfunction and autoimmunity on intrauterine growth restriction: A systematic review and meta-analysis. *Medicine* 2016; **95**: e3677. DOI: 10.1097/MD.0000000000003677
 - 40 Wiles KS, Jarv S, Nelson-Piercy C — Are we overtreating subclinical hypothyroidism in pregnancy? *BMJ* 2015; **351**: h4726 doi: 10.1136/bmj.h4726.
 - 41 Javed Z, Sathyapalan T — Levothyroxine treatment of mild subclinical hypothyroidism: a review of potential risks and benefits. *Ther Adv Endocrinol Metab* 2016; **7**: 12-23 DOI: 10.1177/2042018815616543.
 - 42 Plowden TC, Schisterman EF, Sjaarda LA, Zarek SM, Perkins NJ, Silver R, Galai N, DeCherney AH, Mumford SL — Subclinical Hypothyroidism and Thyroid Autoimmunity Are Not Associated With Fecundity, Pregnancy Loss, or Live Birth. *J Clin Endocrinol Metab* 2016; **101**: 2358-65. doi: 10.1210/jc.2016-1049. Epub 2016 Mar 29.
 - 43 Plowden TC, Schisterman EF, Sjaarda LA, Perkins NJ, Silver R, Radin R, Kim K, Galai N, DeCherney AH, Mumford SL — Thyroid-stimulating hormone, anti-thyroid antibodies, and pregnancy outcomes. *Am J Obstet Gynecol* 2017; **217**: 697.e1-697.e7. doi: 10.1016/j.ajog.2017.09.001. Epub 2017 Sep 14.
 - 44 Brabant G, Peeters RP, Chan SY, Bernal J, Boucharf P, Salvatore D, Boelaert K, Laurberg P — Management of subclinical hypothyroidism in pregnancy: are we too simplistic? *Eur J Endocrinol* 2015; **173**: P1–P11. DOI: 10.1530/EJE-14-1005
 - 45 Ma Li, Qi H, Chai X, Jiang F, Mao S, Liu J, Zhang S, Lian X, Sun X, Wang D, Ren J, Yan Q — 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* 2016; **29**:1391-4. doi: 10.3109/14767058.2015.1049150. Epub 2015 Jul 16.
 - 46 Li J, Shen J, Qin L — Effects of levothyroxine on pregnancy outcomes in women with thyroid dysfunction: A meta-analysis of randomized controlled trials. *Altern Ther Health Med* 2017; **23**: 49-58.
 - 47 Maraka S, Mwangi R, McCoy RG, Yao X, Sangaralingham LR, Singh Ospina NM, O'Keefe DT, De Ycaza AE, Rodriguez-Gutierrez R, Coddington CC 3rd, Stan MN, Brito JP, Mcntori VM — Thyroid hormone treatment among pregnant women with subclinical hypothyroidism: US national assessment. *BMJ* 2017; **356**:i6865. doi: 10.1136/bmj.i6865.
 - 48 Maraka S, Ospina NMS, O'Keefe DT, Rodriguez-Gutierrez R, De Ycaza AEE, Wi C, Juhn YJ, Coddington CC, Motori VM, Stan MN — Effects of levothyroxine therapy on pregnancy outcomes in women with subclinical hypothyroidism. *Thyroid* 2016; **26**: 980-6. DOI: 10.1089/thy.2016.0014
 - 49 Ju R, Lin L, Long Y, Zhang J, Huang J — Clinical efficacy of therapeutic intervention for subclinical hypothyroidism during pregnancy. *Genet Mol Res* 2016; **15**. doi: 10.4238/gmr15049019.
 - 50 Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Minooee S, Rahmati M, Azizi F — Effects of levothyroxine on pregnant women with subclinical hypothyroidism, negative for thyroid peroxidase antibodies. *J Clin Endocrinol Metab* 2017.

- Nov 6. doi: 10.1210/jc.2017-01850. [Epub ahead of print]
- 51 Lazarus JH, Bestwick JP, Channon S, Paradise R, Maina A, Rees R, Chiusano E, John R, Guaraldo V, George LM, Perona M, Dall'Amico D, Parkes AB, Joomun M, Wald NJ — Antenatal thyroid screening and childhood cognitive function. *N Engl J Med* 2012; **366**: 493-501.
 - 52 Blumenthal NJ, Eastman CJ — Beneficial effects on pregnancy outcomes of thyroid hormone replacement for subclinical hypothyroidism. *J Throid Res* 2017, Article ID 4601365. <http://dx.doi.org/10.1155/2017/4601365>
 - 53 Fan X, Wu L — The impact of thyroid abnormalities during pregnancy on subsequent neuropsychological development of the offspring: a meta-analysis. *J Matern Fetal Neonatal Med* 2016; **29**: 3971-6. doi: 10.3109/14767058.2016.1152248. Epub 2016 Mar 18.
 - 54 Liu Y, Chen H, Chen J, Li F — The association between maternal subclinical hypothyroidism and growth, development, and childhood intelligence: a meta-analysis. *J Clin Res Pediatr Endocrinol* 2017; **29**: doi: 10.4274/jcrpe.4931. [Epub ahead of print]
 - 55 Marchal J, Maurice-Stam H, Ikelaar N, Klouwer F, Verhorst K, Witteveen M, *et al* — Effects of early thyroxine treatment on development and growth at age 10.7 years: follow-up of a randomized placebo-controlled trial in children with Down's Syndrome. *J Clin Endocrinol Metab* 2014; **99**: E2722-9.
 - 56 Casey BM, Thom EA, Peaceman AM, Varner MW, Sorokin Y, Hirtz DG, *et al* — National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. *N Engl J Med* 2017; **376**: 815-25. doi: 10.1056/NEJMoa1606205.
 - 57 Jayaraman M, Verma A, Harikumar KV, Ugale M, Modi K — Pregnancy outcomes with thyroxine replacement for subclinical hypothyroidism: Role of thyroid autoimmunity. *Indian J Endocrinol Metab* 2013; **17**: 294-7. doi: 10.4103/2230-8210.109717.
 - 58 Chan S, Boelaert K — Optimal management of hypothyroidism, hypothyroxinaemia and euthyroid TPO antibody positivity preconception and in pregnancy. *Clinical Endocrinology* 2015; **82**: 313-26. (doi:10.1111/cen.12605)
 - 59 Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H — Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. *J Clin Endocrinol Metab* 2006; **91**:2587-91.
 - 60 Chen L, Hu R — Thyroid autoimmunity and miscarriage: a meta-analysis. *Clin Endocrinol (Oxf)* 2011; **74**: 513-9.
 - 61 Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Alavi Majid H, Azizi F — Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease. *Eur J Endocrinol* 2017; **176**:253-65. doi: 10.1530/EJE-16-0548. Epub 2016 Nov 22.
 - 62 Spremovic-Radjenovic S, Gudovic A, Lazovic G, Marinkovic J, Radunovic N, Ljubic A — Fetal free thyroxine concentrations in pregnant women with autoimmune thyroid disease. *Journal of Clinical Endocrinology and Metabolism* 2012; **97**: 4014-21. (<https://doi.org/10.1210/jc.2012-1392>)
 - 63 Xiaoguang Shi, Cheng Han, Chenyan Li, Jinyuan Mao, Weiwei Wang, Xiaochen Xie, Chenyang Li, Bin Xu, Tao Meng, Jianling Du, Shaowei Zhang, Zhengnan Gao, Xiaomei Zhang, Chenling Fan, Zhongyan Shan, Weiping Teng — Optimal and Safe Upper Limits of Iodine Intake for Early Pregnancy in Iodine-Sufficient Regions: A Cross-Sectional Study of 7190 Pregnant Women in China. *The Journal of Clinical Endocrinology & Metabolism* 2015; **100**: 1630-8. <https://doi.org/10.1210/jc.2014-3704>
 - 64 Henrichs J, Bongers-Schokking JJ, Schenk JJ, Ghassabian A, Schmidt HG, Visser TJ, Hooijkaas H, de Muinck Keizer-Schrama SM, Hofman A, Jaddoe VV, Visser W, Steegers EA, Verhulst FC, de Rijke YB, Tiemeier H — Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the generation R study. *J Clin Endocrinol Metab* 2010; **95**: 4227-34. doi: 10.1210/jc.2010-0415. Epub 2010 Jun 9.
 - 65 Julvez J, Alvarez-Pedrerol M, Rebagliato M, Murcia M, Forns J, Garcia-Esteban R, Lertxundi N, Espada M, Tardón A, Riaño Galán I, Sunyer J — Thyroxine levels during pregnancy in healthy women and early child neurodevelopment. *Epidemiology* 2013; **24**: 150-7. doi: 10.1097/EDE.0b013e318276ccd3.
 - 66 Pop VJ, Brouwers EP, Vader HL, Vulmsa T, vanBaar AL, deVijlder JJ — Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. *Clin Endocrinol (Oxf)* 2003; **59**: 282-8.
 - 67 Henrichs J, Ghassabian A, Peeters RP, Tiemeier H — Maternal hypothyroxinemia and effects on cognitive functioning in childhood: how and why? *Clin Endocrinol (Oxf)* 2013; **79**:152-162.
 - 68 Haddow JE, Craig WY, Neveux LM, Haddow HR, Palomaki GE, Lambert-Messerlian G, Malone FD, D'Alton ME — First and Second Trimester Risk of Aneuploidy (FaSTER) Research Consortium. Implications of high free thyroxine (FT4) concentrations in euthyroid pregnancies: the FaSTER trial. *J Clin Endocrinol Metab* 2014; **99**: 2038-44.
 - 69 Korevaar T, Muetzel R, Medici M, Chaker L, Jaddoe VW, de Rijke YB, Steegers EA, Visser TJ, White T, Tiemeier H, *et al* — Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. *Lancet Diabetes and Endocrinology* 2016; **4**: 35-43. ([https://doi.org/10.1016/S2213-8587\(15\)00327-7](https://doi.org/10.1016/S2213-8587(15)00327-7))
 - 70 Medici M, Timmermans S, Visser W, de Muinck Keizer-Schrama SM, Jaddoe VW, Hofman A, Hooijkaas H, de Rijke YB, Tiemeier H, Bongers-Schokking JJ, *et al* — Maternal thyroid hormone parameters during early pregnancy and birth weight: the Generation R Study. *Journal of Clinical Endocrinology and Metabolism* 2013; **98**: 59-66. (<https://doi.org/10.1210/jc.2012-2420>)

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