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Hypothyroidism in pregnancy: prevalence, clinical presentation, management outcomes, and best practice

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Background: Hypothyroidism in pregnancy, both overt and subclinical, is most frequent thyroid disorders. Physiological changes in pregnancy could result in a large and various changes in thyroid function. An adequate treatment is important to prevent adverse maternal and fetal outcomes the aim of this study was to estimate the prevalence of thyroid disorders in pregnant women and their impact on maternal and fetal outcomes.

Methods: This prospective observational study in which 3400 pregnant women attending antenatal care clinic were investigated and screened for overt and subclinical hypothyroidism. A part from a thorough history, careful clinical exam, and routine antenatal investigations, high sensitive third generation, thyroid stimulating hormone (TSH) levels (before conception and during gestation) and anti-thyroid peroxidase (anti-TPO) and thyroglobulin antibodies were measured. In case of abnormal high TSH values, free T4 levels were assessed. Hypothyroid pregnant women were monitored during pregnancy using trimester-specific TSH levels as a standard and guide for proper control. Patients were followed till 12 weeks post-delivery for any obstetrical and perinatal adverse outcomes.

Results: Overall prevalence of maternal hypothyroidism in pregnancy was 10.5 (3.3% overt and 7.2% subclinical hypothyroidism). The mean age of the hypothyroid pregnant patients was 34.6 ± 4 years. Anti-TPO and anti-thymoglobulin antibodies positive rate in overt hypothyroidism were 19.0% and 11.5%, respectively, and in subclinical hypothyroidism, the prevalence of these antibodies were 12.4% and 6.5%, respectively. We further found that anti-TPO and anti-thyroglobulin were positive mainly in women with high TSH levels (≥5 MIU). The main adverse maternal effects observed postpartum hemorrhage was the most common (54, 15.2%), gestational hypertension (38, 10.6%), abortion (36, 10.1%), preeclampsia (42, 11.7%), and gestational diabetes (19, 5.3%). Adverse fetal outcomes were preterm labor (61, 17.1%) and low birth weight (62, 20.1%). Emergency cesarean delivery rate was significantly higher in overt hypothyroid patient compared with subclinical cases (16.8% vs 12.6%) ($P < 0.01$).

Conclusion: Both overt and subclinical hypothyroidism can result in adverse maternal and fetal effects. Strict control and maintaining a serum TSH within trimester-specific reference limits is the goal to avoid these adverse events. However, universal screening of pregnant women is not recommended, since benefits of identification of subclinical hypothyroid cases have not been proved and cost-ineffective.

Keywords: fetal outcomes, overt and subclinical hypothyroidism, pregnancy, prevalence, TPO antibody

Introduction

Thyroid disorders are not uncommon during pregnancy. Early diagnosis and prompt treatment are important to prevent adverse maternal and fetal outcomes. The fetus depends in early pregnancy on the maternal T4 hormone that passes through the placenta to promote development in particularly brain

HIGHLIGHTS

- Hypothyroidism in pregnancy, both overt and subclinical is most frequent thyroid disorders.
- Women with overt hypothyroidism or with subclinical hypothyroidism who are anti-TPO antibody positive are at a higher risk for adverse maternal and fetal outcomes.
- Serum TSH should be included in the investigations of high risk pregnant patients for early diagnosis and better control of their thyroid insufficiency.
- Hypothyroid pregnant should be treated by a full levothyroxine replacement dose which should be adjusted regularly every 4–6 weeks to target a TSH levels not higher than 2.5 mIU/L in the first trimester and not higher than 3 mIU/L in subsequent trimesters.
- The dose of levothyroxine may be needed to increase by 20–30% during pregnancy to avoid inadvertent outcomes.

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growth.[1,2]. The demands for iodine increases during pregnancy due to increase in the maternal–fetal metabolism and to meet this increased demand of the mother and the fetus during pregnancy, several physiological changes occur in thyroid such as mild to moderate enlargement of the gland with increased vascularity owing to thyrotropic activity of beta-human chorionic gonadotropin (B-HCG) which has a structural similar to thyroid stimulating hormone (TSH)[2,3]. Thus, the total thyroxin (T4), triiodothyronine (T3), thyrogobulin, and thyroid binding globulin increase remarkably during pregnancy secondary to enhanced activity of thyroid, increased hepatic synthesis and estrogen stimulation[2,4]. Maternal thyroid hormone synthesis is also increased secondary to high renal clearance of iodide resulting from the increased maternal glomerular filtration rate[1,3,5]. Besides, metabolism of T4 in the second and third trimesters is increased, due to a rise in placental type II and type III deiodinases, which convert T4 to T3 and T4 to reverse T3 and T2, respectively, act as further urge to T4 synthesis[5].The free T4 and T3 levels, during pregnancy is either increased or not changed[3,6].

During pregnancy both hyperthyroidism and hypothyroidism can occur. Hypothyroidism however is more common than hyperthyroidism.[6,7]. Hypothyroidism reported in about 2–3% of pregnant women, whereas hyperthyroidism occurs in 0.1–0.4% of pregnant women.[5,7,8] The prevalence of overt and subclinical hypothyroidism in pregnancy is 0.3–0.5% and 2–3%, respectively. Overt hypothyroidism (high TSH level with decreased T4 and/or T3) may present in the classical pattern or more commonly subtle and mimic the symptoms of pregnancy[4,7]. Subclincal hypothyroidism (high TSH with normal T4) accounts for the majority of cases[5,6,8]. Therefore, high clinical awareness is required to detect these cases early in pregnancy to avoid adverse maternal and fetal sequlae in particularly in women with personal or family history of thyroid diseases, presence of goiter or other autoimmune diseases such as type 1 diabetes. Autoimmune thyroiditis like Hashimoto's thyroiditis with positive anti-thyroid peroxidase (anti-TPO) antibodies is the predominant cause of hypothyroidism during pregnancy.[6,7,9]. Other less frequent causes include iodine deficiency, prior thyroidectomy, and radioiodine ablation of thyroid. The rate of autoimmunity during pregnancy is 5–10%.[10,11]

Women with hypothyroidism have decreased fertility and even if they conceive, the risks of abortion, anemia, gestational hypertension and preeclampsia, abruption placenta, preterm delivery, rate of emergency cesarean section, and postpartum hemorrhage are increased.[8,10-13] The risk of these complications can occur in both overt and subclinical hypothyroidism, but greater in women with overt uncontrolled hypothyroidism. With TSH level >3 mIU/L. Further, inadequate treated maternal hypothyroidism can cause low birth weight, neonatal respiratory distress, impaired mental, cognitive and motor development, and increased fetal mortality[8,13]. On the other hand, since hypothyroidism is easily treated, timely diagnosis and prompt treatment of hypothyroidism before conception or early in pregnancy could prevent or reduce the maternal and fetal adverse outcomes[12,14,15] Several comprehensive researches by Haddow *et al*[14], Pop *et al*[15], and Mannisto *et al*[16] have shown that children born to hypothyroid mother had a significantly increased risk of mental impairment and learning difficulties with an IQ score that was 7 points below the mean IQ of children born to healthy mothers and those given adequate thyroxin supplements. These studies emphasize and recommend the need to follow-up mothers adequately and regularly after initiating treatment. Treatment of hypothyroid pregnant women with positive anti-TPO antibodies with thyroxin (T4) early in pregnancy resulted in lower abortion rates and preterm labor than those who were not treated. Thus, treatment of overt and subclinical hypothyroidism must be started as early as possible to avoid adverse maternal and fetal outcomes.

The aims of this study were to assess the prevalence, clinical presentations, management outcomes and best practice of hypothyroid pregnant women.

Methods

This is a prospective controlled study in which 3400 pregnant women attending to antenatal care clinic for the period between August 2014 and September 2023 to study the prevalence, clinical presentations, and assess maternal and fetal outcomes of hypothyroid pregnant women. A detailed history and thorough clinical exam were done. Maternal characteristics included age, weight (BMI), height, parity and twin pregnancy, abortion/miscarriages, preterm or prolonged delivery, cesarean section, preeclampsia, low birth weight or macrosomia, and history of chronic illnesses like diabetes, arterial hypertension including drugs history, and week(s) of pregnancy at first visit. Previous history of hypothyroidism, etiology, and medication taken were also recorded from their preconception throughout complete gestational periods. A universal screening of thyroid function by estimating the serum TSH and T4 levels was carried out during the first antenatal visit and results were compared to trimester specific standard reference values with the aim of evaluating the prevalence of hypothyroidism during pregnancy, maternal and fetal outcomes, and best treatment practice.

History of previous hypothyroidism was detailed as either overt or subclinical. Underlying cause of hypothyroidism, family history of hypothyroidism and drug history were noted wherever stated. Routine blood tests of antenatal care including complete blood count, blood sugar, blood urea and serum creatinine, lipid profile, and viral study were done for all pregnant women.

Third generation TSH levels available before conception and during each trimester of pregnancy women as a highly sensitive screening and diagnostic test for hypothyroidism, with the generally accepted references value for normal serum TSH ranges of less than 2.5 mIU/L in the first trimester and ≤3.0 mIU/L in the second and third trimesters according to American thyroid association (ATA) guidelines together with free T4 levels and thyroid peroxidase and thyroglobulin antibodies were assayed. Assays were done for all pregnant Women taking Pregnancy supplements containing biotin were asked to stop these supplements at least 2 days prior to TSH testing since biotin may interfere with immunoassays of TSH hormone, resulting in values that are falsely suppressed or elevated. According to the results of TSH, free T4 levels, previously diagnosed and newly discovered hypothyroid pregnant women were classified as overt hypothyroidism defined as elevated TSH and low free T4 and subclinical hypothyroidism defined as elevated TSH and normal free T4 level.

Hypothyroid pregnant patients were managed with thyroid hormone replacement using levothyroxin with doses adjusted to

normalize maternal serum TSH values within the trimester-specific pregnancy reference range (first trimester: 0.1–2.5 mIU/L, second trimester:0.2–0.3 mIU/L, third trimester: 0.3–3 mIU/L). A full replacement dosage of 1.6 – 2.0 mcg/kg/day was given at the time of diagnosis. The dosage of levothyroxine was regularly (every 4–6 weeks) titrated and adjusted according to TSH level to be maintained within trimester-specific reference range due to anticipated increase in thyroid hormone requirements throughout the first half of pregnancy. Previously hypothyroid women who became pregnant; thyroxin replacement dose was increased by 30%. This increase was achieved by doubling the daily dose on 2 separate days each week to maintain the serum TSH below 3.0 mIU/L. Third generation serum TSH and free T4 were regularly checked every 4–6 weeks throughout whole pregnancy since even mild hypothyroidism can results in adverse maternal and fetal outcomes. Besides, hypothyroid pregnant women received three ultrasound scan during pregnancy. The first was in the first trimester to confirm the due date, the second was at 20–22 weeks looking for normal growth and gender of the baby and the third ultrasound was at the 36–38 weeks of gestation to confirm the well being and presentation of the baby.

At the end of pregnancy, modes of labor whether normal vaginal delivery or emergency or elective cesarean sections, gestational age at delivery and pregnancy outcomes including full term or preterm and whether single or twin babies were recorded. Lastly, we noticed maternal outcomes according to international criteria such as pregnancy loss due to spontaneous abortion, intrauterine death, stillbirth, ectopic pregnancy and medical termination of pregnancy. Gestational hypertension, pre-eclampsia, postpartum hemorrhage, and placental abruption were recorded as well.

All newborn of hypothyroid women were screened for congenital hypothyroidism when a baby is 3 days old and more using initial TSH assay of blood sample obtained after heel prick to avoid a false-positive result because of a brief rise in TSH levels before a baby is 3 days old. Third-generation TSH assays and anti-TPO antibody test were done for all hypothyroid patients 4–6 weeks after delivery for evaluation and follow-up and to adjust the dose of levothyroxine to preconception dose within the normal reference value due to decrease thyroxin demand after delivery. This study was approved by the Ethics and Clinical Research Committee at College of Medicine, University of Basrah, and carried out in accordance with the principle of Helsinki. Results are presented as mean with standard deviation for normal distributed data and as median for skewed distribution of quantitative variables. We used percentage for qualitative variables. Statistical significance was taken as $P \leq 0.05$. Data analysis was performed on SPSS (Statistical Package for the Social Sciences) version 20.0. Subgroup analysis of maternal outcomes of pregnancies affected by uncontrolled hypothyroidism during preconception and trimester-wise gestational periods was assessed using the Chi-square and Fischer Exact test. The work has been reported in line with the STROCSS criteria.[17] The study was registered at Researcregistry: http://www.researchregistry.com.

Results

Out of 3400 pregnant women attending the antenatal care clinic, 356 cases were discovered after screening and investigation using trimester specific TSH reference ranges as suggested by the American Thyroid Association (ATA) which recommends TSH levels >2.5 and >3.0 mIU/L as cutoff range for diagnosis of hypothyroidism during the first and later part of pregnancy, respectively, recording a prevalence of 10.5% of which 182 (51.1%), 98 (27.5%), and 76 (21.4%) were diagnosed in the 1st, 2nd, and 3rd trimesters, respectively. Subclinical hypothyroid cases were 244 (68.5%) cases while overt hypothyroid cases were 112 (31.5%). The prevalence of hypothyroidism was 12.4%, 10.1%, and 9.6% in the first, second, and third trimesters, respectively.

The mean age of the hypothyroid pregnant patients was 34.6 ± 4 years (range 18–42 years) and mean BMI 26.8 ± 2 (range 18.5–28.9). Previous diagnosis of hypothyroidism (preconceptional hypothyroidism) was recorded in 154 (4.5%) patients while newly discovered maternal hypothyroidism (gestational hypothyroidism) was noticed in 202 (5.9%) pregnant women. Overt hypothyroidism defined as an increased TSH and a decreased free T4 level was recorded in 112 (3.3%) patients whereas subclinical hypothyroidism defined as low TSH level and normal free T4 was recorded in 244 (7.2%) pregnant women. There were more subclinical cases compared to overt hypothyroidism both in those diagnosed in preconception and during pregnancy. TSH levels were determined in 42 (11.8%), 189 (53.1%), 92 (25.8%), and (9.3%) of pregnant women in preconception, 1st, 2nd, and 3rd trimester periods, respectively. Median TSH before conception was 3.1 (1.2–5.5), whereas during first, second and third trimesters, was 3.3 (1.1–5.8), 2.6 (1.0–4.1) and 2.4 (0.9–3.2), respectively. Our findings did not show any significant association between baseline characteristics and trimester-specific TSH levels.

Most of these women were presented in the first and second trimesters (281, 78.9%) with a majority present in the 8–18 weeks of gestation. Positive family history of hypothyroidism was reported in 73 (20.5%) cases. There was a higher prevalence of hypothyroidism (both subclinical and overt) in the primigravida young women between 20 and 30 years compared with mutigravida women (225, 63.2% vs 131, 36.8%). This association was statistically significant on chi-square test ($P \leq 0.05$). Baseline maternal characteristics and the etiology of hypothyroidism are illustrated in Table 1.

Anti-TPO antibodies were positive in 566 (16.6%) of all pregnant women whereas anti-TPO antibodies were positive in 112 (31.4%) hypothyroid cases. Hashimoto's thyroiditis was noticed in 69 (19.4%) pregnant patients in whom 72 (20.2%) cases had a goiter also. Postpartum thyroiditis was reported in 37 (10.4%) cases. Anti-thyroglobulin antibodies were positive in 64 (18%) of hypothyroid pregnant women, mainly in those patients with Hashimoto's thyroiditis. Family history of hypothyroidism was positive in 12.6%.

Regarding maternal adverse effects and complications, we found that postpartum hemorrhage was the most common maternal adverse outcomes recorded in 54 (15.2%) cases followed by preeclampsia in 42 (11.7%) and gestational hypertension in 38 (10.6%) cases to be the next most common maternal outcomes. We found that postpartum hemorrhage is significantly associated with a TSH levels ≥3 mIU/L in the third trimester ($P \leq 0.05$). Our results also shown that abortions were recorded in 36 (10.1%) cases, antepartum hemorrhage in 31 (8.7%) cases, gestational diabetes in 19 (5.3%) cases, and placental abruption in 19 (5.3%) cases. Termination of pregnancy was reported in 11 (3.1%) cases

Table 1

Maternal characteristics of hypothyroid pregnant women.

	Subclinical hypothyroidism		Overt hypothyroidism		Total	
Patients characteristics	**No.**	**%**	**No.**	**%**	**No.**	**%**
Overall prevalence of hypothyroidism in population study (3400 pregnant women)	244	7.2	112	3.3	356	10.5
Previous diagnosis of Hypothyroidism	89	2.6	65	1.9	154	4.5
Hypothyroidism diagnosed in pregnancy	155	4.5	47	1.4	202	5.9
Hypothyroid pregnant women (total)	244	68.5%	112	31.5%	356	100
Prevalence of hypothyroidism in trimester						
1st trimester	275	8.1	145	4.3	420	12.4
2nd trimester	209	6.1	135	4.0	344	10.1
3rd trimester	193	5.7	132	3.9	325	9.6
Age (mean)	34.8 ± 4		35.8 ± 3		34.6 ± 4	
BMI (mean)	23.6 ± 2		27.4 ± 4		26.8 ± 2	
Parity						
Primipara	92	25.8	76	21.3	168	47.1
Multipara	102	28.7	86	24.2	188	52.9
Time of 1st estimation of TSH levels						
1st trimester	134	37.6	48	13.5	182	51.1
2nd trimester	63	17.7	35	9.8	98	27.5
3rd trimester	52	14.6	24	6.8	76	21.4
Co-morbidities	33	9.3	35	9.8	68	19.1
Diabetes	10	2.8	14	3.9	24	6.7
Hypertension	8	2.3	11	3.0	19	5.3
Autoimmune disorders	4	1.2	14	3.9	18	5.1
Others	2	0.6	5	1.4	7	2.0
Gestational age at first antenatal care visit (weeks of pregnancy)	8 (6–20)		12 (10–18)		9 (8–18)	
Gravidity						
Primigravida	136	38.2	89	25	225	63.2
Multigravida	73	20.5	58	16.3	131	36.8
Positive anti-TPO antibody	44	12.4	68	19.0	112	31.4
Antithyroglobulin antibody	23	6.5	41	11.5	64	18
Causes of hypothyroidism						
Autoimmune (Hashimoto) thyroiditis	22	6.2	47	13.2	69	19.4
Post-treatment (thyroidectomy)	11	3.1	21	5.9	32	9.0
Secondary hypothyroidism	18	5.1	12	3.3	30	8.4
Postpartum thyroiditis	11	3.1	12	3.4	23	6.5
Congenital	9	2.5	7	2.0	16	4.5
Undetermined	79	22.2	107	30.0	186	52.2
Family history of hypothyroidism	21	5.9	24	6.7	45	12.6

mainly due to severe eclampsia and abruption of placenta. These adverse outcomes were significantly associated in overt hypothyroidism. There were no maternal deaths in both overt and subclinical hypothyroidism and no still birth was reported.

Further, women with overt hypothyroidism depicted a higher incidence of preterm labor compared to subclinical hypothyroidism (44, 12.4% vs 17, and 4.7%). The difference was significant ($P \leq 0.05$)

The overall pregnancy loss occurred in 47 cases. Thus, by excluding the abortion and pregnancy termination cases, out of 309 remaining pregnant patients, 136 (44%) delivered by the vaginal route and 173 (56%) patients presented for cesarean sections. Out of those who underwent cesarean section, 82 (26.5%) did so electively mainly because of previous cesarean section and due to obstetric indications like abnormal fetal presentation, twin pregnancy, cephalopelvic disproportion, failure to progress, and maternal request. Emergency lower segment cesarean section were done for 91 (29.4%) due to fetal distress, antepartum hemorrhage, preeclampsia, and non-reassuring fetal status such as abnormal fetal heart tracing. There was a significantly higher incidence of emergency lower segment cesarean section in hypothyroid women with preconception and third trimester TSL levels ≥3 mIU/L ($P \leq 0.05$). Emergency cesarean sections were also higher in those women with positive anti-TPO and thyroglobulin antibodies but the association was not significant, $P \geq 0.05$.

The incidence of preterm birth and low birth weight neonates in hypothyroid women were 61 (17.1%) and 62 (20.1%), respectively. Overt hypothyroid patients with third-trimester TSH levels >3 mIU/L. and those with positive antithyroid antibodies were particularly at increased risk for maternal complications in particularly postpartum hemorrhage and preterm labor whereas Subclinical controlled hypothyroidism with TSH levels <2.5 mIU/L was associated with minimum or no adverse maternal outcomes. Lastly, we noticed that there is no significant impact of TSH levels during each trimester on other maternal outcomes, when the TSH levels remained below 2.5 uIU/mL in all trimesters. Postpartum thyroiditis was reported in 17 (5.5%) cases.

Table 2

Maternal and fetal outcomes of hypothyroid pregnant women.

Maternal and fetal outcomes	Subclinical hypothyroidism		Overt hypothyroidism		Total	
	No.	%	No.	%	No.	%
Uneventful normal pregnancy (live birth)	229	64.3	80	22.5	309	86.8
Mode of delivery for live births						
Normal vaginal delivery	89	28.8	47	15.2	136	44
Elective cesarean section	42	13.6	40	12.9	82	26.5
Emergency cesarean section	39	12.6	52	16.8	91	29.4
Abortion	11	3.1	25	7.0	36	10.1
Termination of pregnancy (still birth and intrauterine death)	4	1.1	7	2.0	11	3.1
Preterm labor	17	4.7	44	12.4	61	17.1
Low birth weight baby	21	6.8	41	13.3	62	20.1
Overall pregnancy loss	17	4.8	30	8.4	47	13.2
Gestational hypertension	13	3.6	25	7.0	38	10.6
Gestational diabetes	11	3.1	8	2.2	19	5.3
Preeclampsia	11	3.0	31	8.7	42	11.7
Placental abruption	6	1.6	13	3.7	19	5.3
Antepartum hemorrhage	9	2.5	22	6.2	31	8.7
Postpartum hemorrhage	17	4.8	37	10.4	54	15.2
Postpartum thyroiditis	4	1.3	13	4.2	17	5.5
Maternal mortality	0	0	0	0	0	0

Details of maternal outcomes in the hypothyroid pregnant patients are described for these patients in Table 2.

Discussion

Thyroid dysfunction is not uncommon in women, in particularly during reproductive age. The prevalence of overt and subclinical hypothyroidism in pregnancy is estimated to be 0.5–3% and 2–10% or even more, respectively, which are consistent to our prevalence. Subclinical hypothyroid patients (high TSH with normal free T4) which accounts for most of the cases are asymptomatic[4,18]. Besides, the presentation of overt hypothyroidism during pregnancy is often vague, non-specific, and mimics the symptoms of pregnancy. Therefore, high index of suspicion and strict clinical awareness are required especially in those women with a personal or family history of thyroid disorders, autoimmune diseases. Early in pregnancy, TSH, is maintained at concentrations lower than that of non-pregnant women because TSH has a structural analogue to HCG, the levels of which rise in early pregnancy[19]. Maternal hypothyroidism is the most common thyroid dysfunction in pregnancy. Both overt and subclinical hypothyroidism can result in adverse effects on the pregnancy like miscarriage, still birth, premature birth, gestational hypertension, and preeclampsia and fetal growth especially the brain and nervous system. Therefore, a sufficient and normal level of thyroid hormone must be maintained during pregnancy and hypothyroidism should be addressed and corrected before pregnancy. Further, women with subclinical hypothyroidism are almost always asymptomatic, so detection of these cases are paramount since subclinical hypothyroidism is also associated with an adverse outcome for the mother and fetus and most up-to-date guidelines recommend thyroxin replacement in subclinical hypothyroid pregnant women as well.[7,11,20]

The overall prevalence of hypothyroidism was 10.5% in our study (3.3% overt and 7.2% subclinical hypothyroidism). Thus out of 3400 pregnant women attended antenatal care unit, 356 was discovered to have maternal hypothyroidism, of whom 112 (31.5%) were over hypothyroid and 244 (68.5%) were subclinical hypothyroid cases. Our results are consistent with results of previous similar studies[21,22], whereas Wang *et al*[18] and Kumar *et al*[23] reported a high prevalence rate of maternal hypothyroidism. The prevalence of hypothyroidism when trimester specific TSH reference ranges according to the American Thyroid Association (ATA) guidelines was 12.4%, 10.1%, and 9.6% in the first, second, and third trimesters, respectively.

Prior (preconception) diagnosis of hypothyroidism among our patients was recorded in 154 patients and 202 cases were newly discovered during their pregnancy. For all overt hypothyroid pregnant cases, the initiation of a full dose of L-thyroxin is considered necessary and routine to prevent complications related to hypothyroidism. To determine the optimum dose, the trimester-specific values for TSH and the total and free T4 hormone levels were regularly measured every 6 weeks to correctly adjust the dose of thyroxin using the pregnancy specific reference interval. The baseline characteristics of the study population are shown in Table 1. The mean age of the study population was 34.6 ± 4 years with a mean gestational age of 9 ± 2 (8–18) weeks. We did not find any significant association between baseline characteristics and preconception TSH groups (Table 1).

Although the etiology of hypothyroidism during pregnancy remained obscure in the most of cases. Our findings revealed that the most common cause of hypothyroidism in our cohort was autoimmune thyroiditis (69, 19.4%) which is consistent with a similar studies reported in the literatures[24,25]. Other causes were iodine deficiency, postsurgical hypothyroidism, postpartum thyroiditis, and radioiodine ablation with idiopathic or undetermined causes reported in the most of the patients (186, 52.2%) cases.

It has been documented that patients with both overt and subclinical hypothyroidism are more likely than euthyroid women to have anti-TPO and thyroglobulin antibodies positivity[6,15,25] Our results have shown that the overall

prevalence of positive anti-TPO and anti-thyroglobulin antibodies among hypothyroid pregnant women were 31.4% and 18%, respectively. The prevalence of these antibodies in overt hypothyroidism were 19.0% and 11.5%, respectively, while in subclinical hypothyroidism, were 12.4% and 6.5%, respectively. We further found that anti-TPO and anti-thyroglobulin were positive mainly in women with high TSH levels (≥5 MIU). Our findings are consistent with that of Sharma *et al*[26]. The prevalence of thyroid anti-TPO antibodies were variable and inconsistent in several studies; in one study, anti-TPO was positive in 57%[27], while another study recorded 40% of hypothyroid pregnant females[28], whether all women should be checked for anti-TPO antibodies once diagnosed with hypothyroidism remains an issue of debate.

Although women with anti-TPO antibodies with or without subclinical hypothyroidism are at increased risk of adverse maternal and fetal outcomes, there is no currently enough evidence to recommend TSH and TPO antibody screening in a low-risk women[8,23,29] We noticed that presence of anti-TPO and anti-thymoglobulin antibodies was significantly associated with adverse maternal and fetal outcomes such as miscarriage, antepartum hemorrhage, preterm labor, low birth weight baby, gestational DM, and postpartum hemorrhage. Postpartum thyroiditis was significantly more in these patients as well. Monika *et al*[30] reported in their similar study that anti-TPO positivity is common in overt and subclinical hypothyroid women. They concluded that the presence of these antibodies even in euthyroid patients was associated with a higher prevalence of infertility, anemia, and preterm delivery for which they advised anti-TPO screening in pregnancy for early identification of the women at risk. Etiology is similar to overt hypothyroidism, most guidelines recommend thyroxin replacement in women with subclinical hypothyroidism in particularly those women with positive anti-TPO and anti-thyroglobulin antibodies[17,27,31]. The goal of thyroxin replacement is to normalize and maintain maternal TSH level within trimester specific reference range (first trimester, 0.01–2.5 mIU/L; second trimester, 0.2–3.05 mIU/L; third trimester, 0.3–35 mIU/L). A full replacement therapy should be started at the time of diagnosis in the first antenatal visit. The dosage of thyroxin should be increased at 4–6 weeks of gestation due to increased requirement for thyroid hormone; an increase of 25%–30% may be required[32]. This can be achieved by doubling the daily dose on 2 separate days each week.

There is a little and controversial evidences on the effect of maternal comorbidities on hypothyroidism during pregnancy in the literatures. One study from Finland in which more than 5000 pregnant women participated revealed that patients with overt hypothyroidism were at a high risk of developing gestational diabetes and gestational hypertension, with hazard ratio (HR) 6.0 (95% confidence interval)[16,33]. In our study, gestational diabetes was noticed in 13.5% cases and gestational hypertension in 7.1% cases. Both diabetes and hypertension were more in overt hypothyroidism as compared with subclinical hypothyroidism. Our findings did not show any impact of comorbidities on maternal hypothyroidism.

In the present study, we observed several adverse maternal complications that varied in presentation and severity, including preeclampsia, anemia, abortions, preterm delivery, and low birth weight. Our results revealed a significant association of preeclampsia, abruption, abortion, and mode of delivery including cesarean section (emergency & elective) with a TSH value of more than 3 mIU/L before pregnancy ($P \leq 0.05$). Besides, still birth, low birth weight, and postpartum hemorrhage is also significantly associated with a TSH value of more than 3 mIU/L in the third trimester ($P \leq 0.01$). However, there is no significant effect of TSH levels during each trimester on maternal outcomes in those patients with TSH remained below 2.5 mIU/L. Abortions were recorded in 36 (10.1%) patients and termination of pregnancy in 11 (3.1%) due to still birth and intrauterine death. Abortion was significantly more in overt hypothyroid cases compared with subclinical cases (25, 7.0% vs 11, 3.1%) noted in particularly in overt hypothyroid women who have preconception and early gestational TSH levels above 2.5–5 mIU/L with a strong risk of abortion at the levels exceeding 4 mIU/L. Therefore, improving the adequacy of thyroid hormone replacement therapy before or during early pregnancy is crucial. Ajmani *et al*[32] reported in their similar study that the prevalence of abortion was significantly more in overt hypothyroid cases compared with subclinical hypothyroid pregnant women (16.6% vs 5.5%). They also found that preterm delivery, low birth weight, and intrauterine growth retardation compared to euthyroid women. They recommended routine screening of thyroid dysfunction early in pregnancy to prevent adverse maternal outcome.

In our study, among 356 hypothyroid pregnant women, 309 (86.8%) had live births. Postpartum hemorrhage was the most frequent complications of maternal hypothyroidism encountered in 54 (15.2%) cases associated with TSH level ≥3 mIU/L in preconception and in third trimester; however, the relationship was not significant ($P \geq 0.05$). Our findings were consistent with that of Wang *et al*[18] and Nazarpour *et al*[34]. Gur *et al*[35] noted in their comparative study, in which the relationship between TSH level, thyroid antibodies level, certain hematological parameters and amount of postpartum hemorrhage was investigated, they noted no difference was found in terms of hematological parameters and postpartum hemorrhage between euthyroid, subclinical hypothyroid with thyroid antibodies from healthy controls. Kiran *et al*[36] in their study on maternal outcomes affected by hypothyroidism reported a significant association between postpartum hemorrhage (which was also the most common adverse maternal outcomes) and preconception and third trimester TSH level was ≥3.0 mIU/L.

Elective cesarean delivery rate among our patient was 26.5% (82 patients), while emergency cesarean delivery rate was 29.4% (91 patients). Patients with normal TSH level (well controlled) and subclinical hypothyroid women had lower and comparable cesarean rates whereas emergency cesarean section was higher in the overt hypothyroid patients but because the sample was relatively small and the variance distribution was not homogeneous, so the statistical significance could not be estimated. Kumar *et al*[23] reported a significantly higher incidence of emergency lower segment cesarean section in hypothyroid women as compared to euthyroid women. The increased risk of cesarean delivery may be due to the associated pregnancy complications, such as gestational hypertension, preeclampsia, fetal distress, gestational diabetes, and preterm birth. Jain *et al*[37] had shown that cesarean section rate for fetal distress was significantly higher among pregnant hypothyroid women. Moreover, they also found that hypothyroid women were prone to have pregnancy-induced hypertension, intrauterine growth restriction,

and preterm delivery as compared to euthroid control group. The rates of cesarean delivery in hypothyroid pregnant women in previous similar studies were 20–25%.[27,38-40]

Correlation between TSH levels and, maternal age, anti-TPO, and birth weight were performed. Our results revealed an increase in TSH levels were correlated positively with maternal age. TSH level was found to increase with age. Although there is a positive association of increased TSH levels with anti-TPO and birth weight, the relationship, however, was not statistically significant ($P \geq 0.05$). The well-controlled subclinical and overt hypothyroid pregnant patients groups were approximately similar in terms of birth weights ($P > 0.05$).

The main limitations of our study, was relatively small sample size to universally evaluate the impact of thyroid disorders during pregnancy and to decide whether routine thyroid dysfunction screening is needed for pregnant women as the results of this study cannot be generalized to all pregnant populations. Screening for thyroid dysfunction and the autoimmune status (anti-TPO antibodies) during pregnancy are not routinely. This study, however, can be regarded as a baseline reflection of our hypothyroid pregnant population. Large prospective and multicenter studies are needed to assess the strength of associations between maternal hypothyroidism and outcome variables, which may contribute toward unifying universal screening and follow-up management in hypothyroid pregnant cases.

Conclusion

Hypothyroidism in pregnancy is not uncommon and it could be the most common maternal thyroid disorder. Subclinical hypothyroidism represents the majority of the cases. Maternal hypothyroidism could significantly impacts the maternal and fetal outcomes if adequate treatment is not initiated early in pregnancy.

Women with overt hypothyroidism or with subclinical hypothyroidism who are anti-TPO antibody positive are art a higher risk for adverse maternal and fetal outcomes. Therefore, serum TSH should be included in the investigations of high-risk pregnant patients for early diagnosis and better control of their thyroid insufficiency although still there is no general consensus on routine screening of thyroid dysfunction during pregnancy and its cost-benefit not proved yet. High-risk group for which screening of hypothyroidism is better to be done includes those with prior treatment for hyper- or hypothyroidism, a family history of thyroid disease, a personal history of autoimmune disease and those with goiter. Hypothyroid pregnant should be treated promptly by a full levothyroxine replacement dose which should be adjusted regularly every 4–6 weeks to target a TSH levels not higher than 2.5 mIU/L in the first trimester and not higher than 3 mIU/L in subsequent trimesters. The dose of levothyroxine may be needed to increase by 20–30% during pregnancy to avoid inadvertent outcomes. This can be easily achieved by increasing the dose by 2 extra daily doses per week on separate days.

Ethical approval

The study was approved by Ethical Committee of College of Medicine, Department of Surgery, University of Basrah (Ref. No. 232/2023).

Consent

Written informed consent was obtained from the patient for publication of this randomized controlled study and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

The surgical and imaging aspect of this study was done by prof. Dr. Ibrahim Falih Noori and Dr. Rafid Abduljabbar, The tables, results, and statistical analysis of this study were done by Dr. Qais Khadim and Dr Maysaa Ja'far Kadhum.

Conflicts of interest disclosure

None declared.

Research registration unique identifying number (UIN)

Research registration is at Researcregistry (http://www.researchregistry.com). UIN is researchregistry10017.

Guarantor

The study is under the authors responsibility: Prof Dr. Ibrahim Falih Noori Alsubaiee.

Data availability statement

The data used during the current study are available from the corresponding author upon request.

Provenance and peer review

Not applicable.

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