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Evaluation and Treatment of Subclinical Hypothyroidism and Adverse Pregnancy Outcomes

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ABSTRACT

Background: Subclinical hypothyroidism (SCH) is a common biochemical entity identified in women during pregnancy. SCH is diagnosed when the thyroid stimulating hormone (TSH) is elevated with a normal free thyroxine (FT4) level. Although most women with SCH are asymptomatic, previous studies have shown that SCH may be associated with adverse outcomes during pregnancy. The thyroid hormone, FT4, is necessary for fetal growth and development. Insufficient thyroid hormone has been shown to impair fetal growth and brain development and it may have negative effects on neonatal survival. Women with overt hypothyroidism during pregnancy require levothyroxine treatment.

Methods and materials: The study was retrospective cross-sectional study which conducted in Tripoli university hospital at obstetrics and gynecology department during 1st May 2021 to 30th June 2022. The study data was carried out from medical record among pregnant women who's diagnosed by subclinical hypothyroidism which selected and filled by predesigned structural questionnaire.

Results: Among 136 pregnant women who diagnosed by subclinical hypothyroidism in Tripoli university hospital whose aged between 23 to 45 years with mean age 37.08 ± 5.799 SD.

Distribution of obstetrical data frequency for mean and SD: gestational age (mean was 3.01 ± 0.471 SD), gravidity (mean was 2.89 ± 0.883 SD), parity (mean was 3.09 ± 0.977 SD) and abortion (mean was 1.74 ± 1.047 SD and on evaluating the type of abortion 73% were missed, 18% were complete and only 9% were incomplete abortion).

Regarding smoking status, 66.8% were non smoker while 32.3% were passive smoker and just 1% was active smoker.

On determine the co morbidity with subclinical hypothyroidism, 45.6% had diabetes mellitus followed by 17.5% had hypertension. Majority of pregnant women had delivered by cesarean section which scored 76.3% while 23.7% had delivered vaginally.

On evaluating the maternal complications, 40% had abruption placenta followed by 37.2% had diabetic ketoacidosis while only 1% had maxedema coma.

On evaluating the neonatal complications, 23.4% had preterm delivery followed by 21.4% were macrosomic newborn while just 3.6% had developed Cretinism.

Conclusion: In this study the subclinical hypothyroidism among pregnant women show to have various adverse health outcomes to the mothers and their newborn with adjacent additional risk factors such as diabetes mellitus and hypertension the health hazard become high.

Keyword: TSH, SCH, levothyroxine, fetal complication and maternal complications.

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INTRODUCTION

Subclinical hypothyroidism (SCH) (defined as a TSH level greater than the pregnancy specific range) is a common biochemical entity identified in women during pregnancy. SCH is diagnosed when the thyroid stimulating hormone (TSH) is elevated with a normal free thyroxine (FT4) level. Although most women with SCH are asymptomatic, previous studies have shown that SCH may be associated with adverse outcomes during pregnancy [1-3], [20,26].

The thyroid hormone, FT4, is necessary for fetal growth and development. Insufficient thyroid hormone has been shown to impair fetal growth and brain development and it may have negative effects on neonatal survival [4,5,8].

Women with overt SCH during pregnancy require levothyroxine treatment. However, there is uncertainty as to whether women with SCH during pregnancy should be treated as the benefits of treating SCH during pregnancy have not been consistently demonstrated [6–9].

Several studies have examined the association of SCH and adverse outcomes during pregnancy and long-term outcomes in mothers and children including pregnancy loss, pre-term delivery, gestational diabetes, gestational hypertension, eclampsia, placental abruption, low birth weight, and childhood cognitive outcomes [10–14].

Association (ATA) guidelines recommended levothyroxine therapy for women with SCH and thyroid autoimmune disease (postive anti-thyroid peroxidase antibodies [TPOAb)]). For women with negative TPOAb levels, the guidelines recommended treatment with levothyroxine therapy for TSH levels greater than 10 mlU/L. However, levothyroxine therapy was not recommended for women with no antibodies and a TSH within the pregnancy-specific reference range [24,9,28]. Previous meta-analyses have been performed on this topic.

The meta-analysis by Nazapour et al. (2019), compared women with SCH during pregnancy treated with levothyroxine with women who were euthyroid. However, this meta-analysis performed a subgroup analysis comparing the risk of pregnancy loss associated with levothyroxine treatment versus no treatment among women with SCH and found that levothyroxine was associated with a decreased risk of pregnancy loss among SCH women treated with levothyroxine during pregnancy (odds ratio: 0.78; 95% confidence interval [CI]: 0.66–0.94) [18]. Although women with SCH treated with levothyroxine have normal TSH levels similar to euthyroid women, it is uncertain whether euthyroid women are comparable to women with treated SCH [29].

Serum TSH levels increase with age, meaning that a mild increase may be normal for older individuals, additional other factors such as pregnancy, obesity, and dwelling conditions can also impact the TSH reference level. TSH range are usually lower during pregnancy, especially in the first trimester, and gradually rise in the second and third trimesters [17,25,21]. Compared to Western countries, Asian countries, including China and Korea, show a modest reduction in the ULN of TSH during the first trimester [22,23,27]. Iodine intake, cigarette smoking, and cold environmental temperatures have been identified as other risk factors [38,39,33].

The serum TSH levels change transiently without thyroid diseases, In response to various external and internal stimuli. Iodine or food with high iodine levels, medications, or testing reagents are classic examples of external stimuli [16,31]. As well the concentrations fluctuates as a result of diurnal or seasonal variations [32,33]. In patients who are taking LT4, an inadequate dosage or consumption of substances that prevent absorption or increase the clearance of LT4 also lead to Subclinical hypothyroidism (sHypo). In these transient cases, only a re-evaluation of thyroid function without LT4-Tx could be recommended. Thus, the first step of sHypo management is to confirm the persistence of TSH elevation and exclude transient cases [34].

LT4-Tx considered in pregnant Subclinical hypothyroidism (sHypo) patients, regardless of etiologic factors. levothyroxine treatment (LT4-Tx) is strongly recommended in women who are TPO-Ab-positive with TSH levels greater than the pregnancy-specific reference range, or TPO-Ab- negative with TSH levels greater than 10.0 mlU/L. In these instances, a higher-than-usual initial LT4 dose could also be considered. Women of child-bearing age who have sHypo and TPO-Ab should also receive active LT4-Tx treatment, close follow-up, and

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education about the possible risks of sHypo for maternity [15]. the aim of the study was to evaluate the subclinical hypothyroidism and adverse pregnancy outcomes.

METHODS AND MATERIALS

This study was a Retrospective cross-sectional study, it was conducted in Tripoli medical center at the Clinic of Gynecology and Obstetrics from 1st May 2021 to 30th June 2022, the study included 136 pregnant women who had subclinical hypothyroidism (SCH). Diagnosis of SCH is According to TSH level guideline:

TSH can be considered 4.0 to 6.0 mIU/L and subclinical hypothyroidism is often classified as grade 1 (TSH level between the ULN and 9.9 mIU/L) and grade 2 (TSH levels 10 mIU/L or higher) [24]., the data collected by a doctor according to questionnaire some of the women by face to face interview and some of them by telephone, the collected answers were analyzed and the results were presented using tables and figures. patients were asked about demographic data and data related to subclinical hypothyroidism and adverse pregnancy outcomes, treatment of SCH.

Ethical clearance

The study was ethically cleared and approved by the ethical review committee of the Tripoli medical center with a supporting letter from the Medical Technology Research Team at the University of Tripoli/ Faculty of Medical Technology. Data were collected after getting approval from the hospital medical director and head of Gynecology and Obstetrics department. Written informed consent from each study participant. Data confidentiality was kept through avoiding personal identifiers and anonymity of personal data records.

Statistical analysis: the collected data was coded & analyzed by using SPSS software (Statistical Package for the Social Sciences) 21 version.

Descriptive statistics used to evaluate mean, percentage and standard deviation and the data presented on graphs and tables. Chi square test was used to assess the significant correlation between nominal and categorical data. And all variables results considered as statistically significant with P value less than 0.05.

RESULTS

Among 136 pregnant women who diagnosed by subclinical hypothyroidism in Tripoli university hospital whose aged between 23 to 45 years with mean age 37.08 ± 5.799 SD. (Table 1).

Table 1: Determination of age group range, Tripoli, Libya

Age distribution (n=136)	
Mean	**37.08**
Median	39.00
Std. Deviation	5.799
Minimum	23
Maximum	45

Distribution of obstetrical data frequency for mean and SD: gestational age (mean was 3.01 ± 0.471 SD), gravidity (mean was 2.89 ± 0.883 SD), parity (mean was 3.09 ± 0.977 SD) and abortion (mean was 1.74 ± 1.047 SD and on evaluating the type of abortion 73% were missed, 18% were complete and only 9% were incomplete abortion) (Figure 1).

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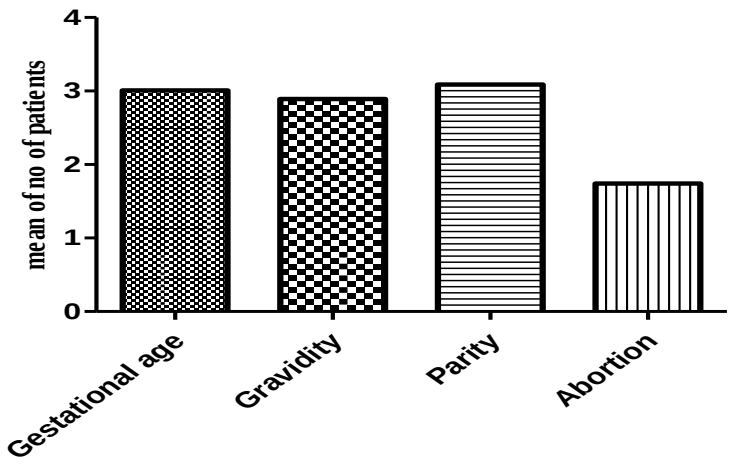

Fig.1: Distribution of obstetrical data frequency variables

Regarding smoking status, 66.8% were non smoker while 32.3% were passive smoker and just 1% was active smoker (Figure 2).

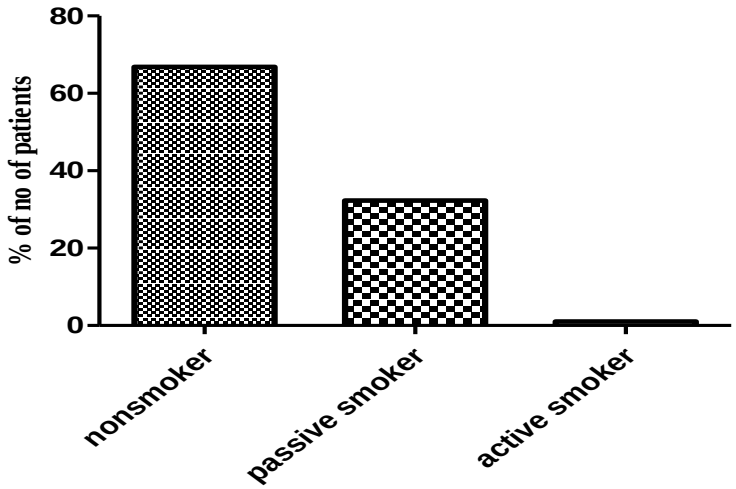

Figure 2: Distribution of smoking status frequency

On assessing the thyroid function test in controlled patients (30.20%), the mean TSH level was 5.7 ± 1.453 SD and 69.8% were uncontrolled hypothyroidism with TSH level >10.0 mIU/l (not on levothyroxine treatment) (Figure 3).

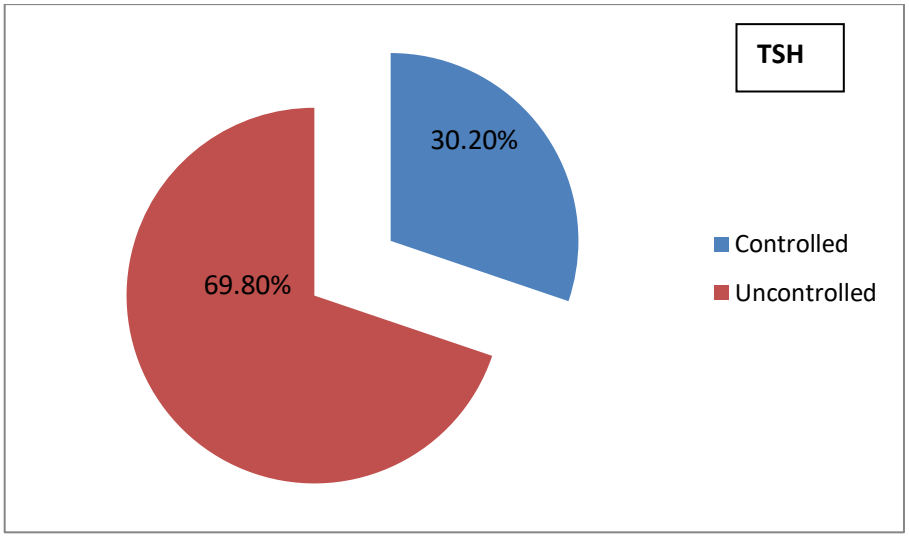

Figure 3: Distribution of TSH status frequency, Tripoli, Libya.

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On determine the Co morbidity with subclinical hypothyroidism, 45.6% had diabetes mellitus followed by 17.5% had hypertension (Figure 4).

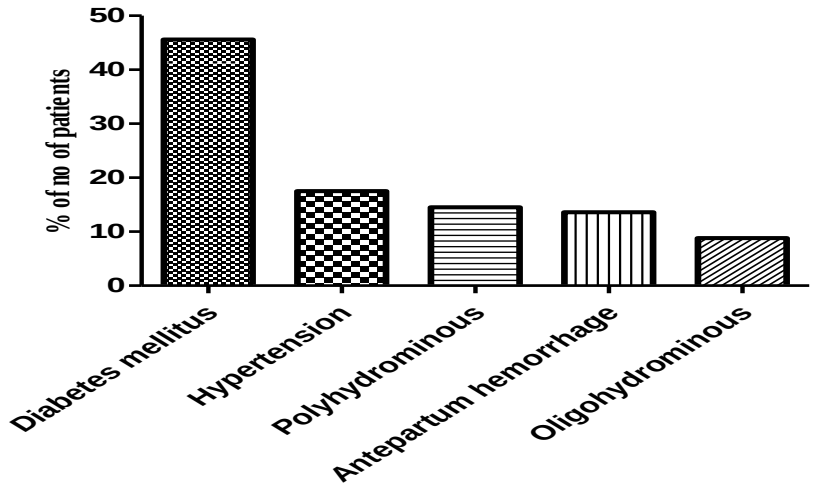

Fig.4: Distribution of co morbidity frequency variables

Majority of pregnant women had delivered by cesarean section which scored 76.3% while 23.7% had delivered vaginally (Figure 5).

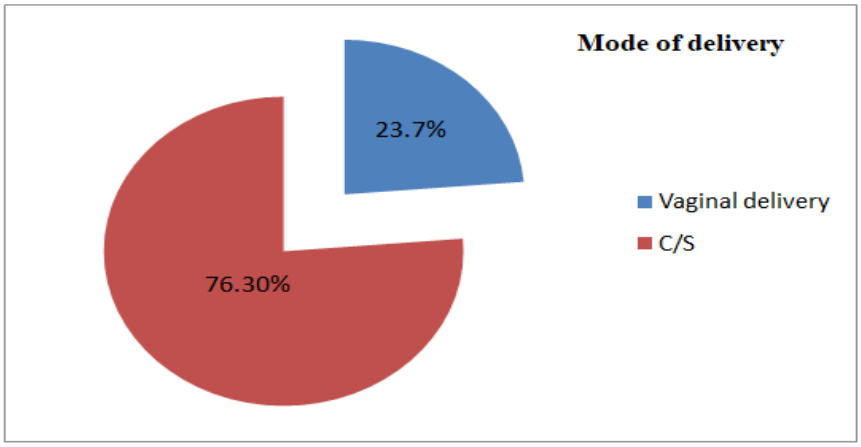

Figure 5: Distribution of mode of delivery frequency, Tripoli, Libya.

On evaluating the maternal complications, 40% had abruption placenta followed by 37.2% had diabetic ketoacidosis while only 1% had maxedemic coma. (Figure 6).

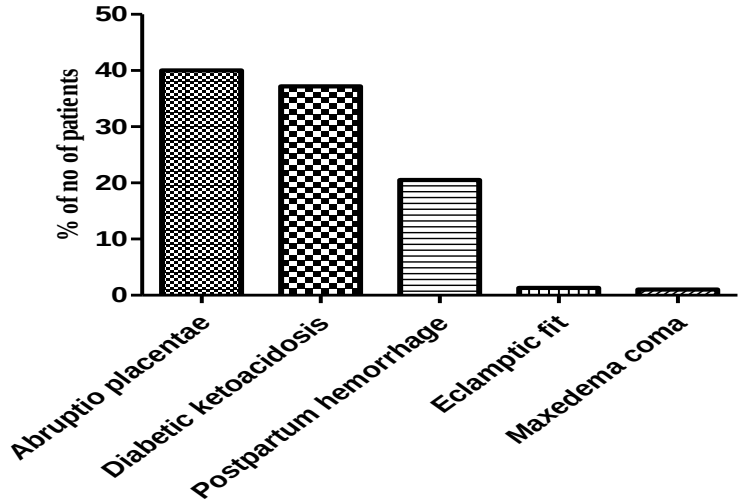

Fig.6: Distribution of maternal complications frequency variables

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On evaluating the neonatal complications, 23.4% had preterm delivery followed by 21.4% were macrosomic newborn while just 3.6% had developed cretinism (Figure 7).

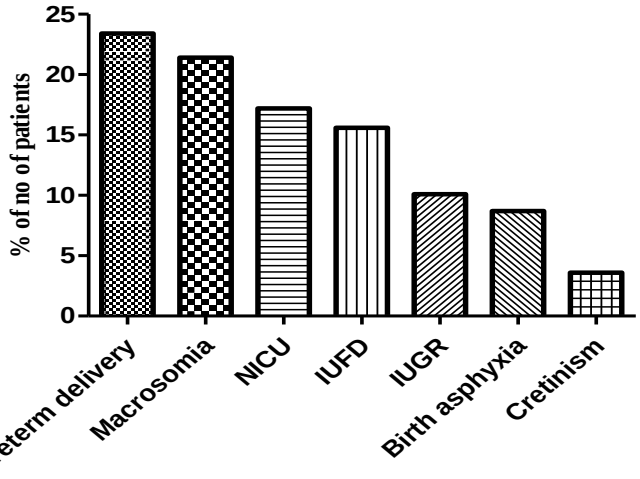

Fig. 7: Distribution of neonatal complications frequency variables

On assessing the Chi square test for TSH status and their relationship with maternal and neonatal complications show 74.3% with maternal complications in uncontrolled patients as well with 61.8% with neonatal complication compared to controlled patients statistical significant results (P – value was 0.003 and P- value was 0.021 respectively) (Table 2).

Table 2: Distribution of relationship between maternal and neonatal complications with TSH status frequency variables, Tripoli, Libya

Variables (N = 136)	Controlled TSH	Un controlled TSH	P - value
Maternal complications	25.7%	74.3%	0.003
Neonatal complications	38.2%	61.8%	0.021

DISCUSSION

The current research is conducted at Tripoli university hospital at obstetrics and gynecology department to evaluate the magnitude of hypothyroidism during pregnancy and the adverse pregnancy outcomes associated with hypothyroidism. The prevalence of subclinical of hypothyroidism during pregnancy ranges from 1.5% to 42.9% [52].

Our finding indicates that the risk of SCH becomes significantly with mean age 37.08 year. Deshauer and Wyne (2017)reported that the risk factor of SCH at age over 30year [53].

It has been shown that almost 69.8% of patients with SCH were uncontrolled (not on levothyroxine treatment) with level of TSH >10.0 mIU/l and 30.20% of people who were diagnosed as having SCH on levothyroxine treatment had TSH level 5.7mIU/l [25].

Recent studies have shown that untreated gestational SCH is associated with multiple adverse perinatal outcomes including spontaneous abortion, gestational hypertension, preeclampsia, preterm delivery, and decreased IQ in offspring [12, 54]. in this study 40% had abruption placenta followed by 37.2% had diabetic ketoacidosis while only 1% had maxedema coma.

This study has shown that subclinical hypothyroidism during pregnancy has a significant association with the neonatal complications, 23.4% had preterm delivery followed by 21.4% were macrosomic newborn while just

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3.6% had developed cretinism. however, previous document showed that Maternal thyroid hypofunction is not associated with a consistent pattern of adverse outcomes [55].

On compare with a recent systematic review and meta-analysis of studies comparing women with SCH and euthyroid women during pregnancy found that SCH was associated with an increased risk of multiple adverse maternal and fetal outcomes [10], including pregnancy loss (RR: 2.01; 95% CI: 1.66–2.44) [41], placental abruption (RR: 2.14; 95% CI: 1.23–3.70), premature rupture of membranes (PROM) (RR: 1.43; 95% CI: 1.04–1.95) and neonatal death (RR: 2.58; 95% CI: 1.41–4.73).

A recent systematic review of SCH patients treated with levothyroxine sodium tablets until delivery found that the incidence of adverse maternal and fetal outcomes was significantly lower in patients treated with levothyroxine sodium tablets [51]. However, the meta-analysis of RCTs assessed whether levothyroxine treatment during pregnancy among women with SCH has an impact on obstetrical and fetal outcomes [16].

Previous study included 3 trials and found no difference in obstetrical and neonatal outcomes, including childhood IQ and neurocognitive outcomes among children born to women with SCH who were treated with levothyroxine compared to those who received no treatment [11,16,37].

Finally, a meta-analysis by Rao et al., [17] showed that levothyroxine treatment among women with SCH and women with thyroid autoimmune disease was associated with a decreased risk of pregnancy loss and preterm birth compared to women who received no treatment.

In a sub-group analysis of women with SCH, levothyroxine treatment was associated with a decreased risk of pregnancy loss compared to no treatment (RR: 0.43; 95% CI: 0.26–0.72) but there was no association between levothyroxine treatment and preterm birth (RR: 0.67; 95% CI: 0.41–1.12). Although this meta-analysis included fewer studies than our meta-analysis, [17] the findings are consistent with the current study. Nazarpour et al., [18] performed a meta-analysis comparing women with SCH during pregnancy treated with levothyroxine with women who were not treated or were euthyroid. In a subgroup analysis, they compared women with SCH who were treated with levothyroxine versus no treatment, and found a decreased risk of pregnancy loss associated with levothyroxine treatment (odds ratio: 0.78; 95% CI: 0.66–0.94). Although the types of studies included in this meta-analysis differed from ours and included studies that had different TSH targets for treatment of SCH (i.e. targeted TSH to < 4.2 mIU/L [43]), the findings are consistent with our study. In addition, this previous meta-analysis did not assess neonatal and cognitive outcomes in children.

The majority of the studies reported to date initiated levothyroxine during the first trimester with only two studies addressing the effects of initiating levothyroxine at other times during pregnancy [40]. Ju et al., [40, 42] found that initiation of levothyroxine during the first trimester decreased the risk of PROM, gestational diabetes, postpartum hemorrhage, gestational hypertension, and fetal macrosomia compared to women who received levothyroxine treatment in the second and third trimester [19,40].

Zhao et al., [42] also showed that initiation of levothyroxine during the first trimester was associated with a decreased risk of adverse pregnancy outcomes (i.e. including premature labor, pregnancy loss, post-partum hemorrhage, and low birth weight) compared to women who were initiated on treatment during the second trimester (incidence of pregnancy complications among women treated during first trimester versus second trimester: 3/31 versus 13/31; $p = 0.004$). None of the other studies in our meta-analysis addressed whether later initiation of levothyroxine had any impact on pregnancy outcomes. The presence of TPOAb has been shown to increase the risk of pregnancy loss by approximately two-fold among women with SCH [44,45]. Furthermore, studies have shown that treatment with levothyroxine among women with positive TPOAb levels during pregnancy decreased the rate of pregnancy complications regardless of thyroid function status (i.e. SCH and euthyroid women) [46–48]. In the present meta-analysis, two of the included studies found that levothyroxine treatment in women with SCH and elevated TPOAb was associated with a lower risk of a composite endpoint of gestational hypertension, preeclampsia, anemia, and gestational diabetes and preterm delivery [42,35]. In contrast, two recent RCTs found that levothyroxine treatment of TPO-Ab positive women who had normal thyroid function during pregnancy did not affect pregnancy outcomes and preterm delivery [49,50],[36].

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However, based on the current evidence, women with SCH and elevated TPO-Ab may benefit from levothyroxine treatment. Levothyroxine treatment for SCH during pregnancy may reduce the risk of pregnancy loss among women with infertility [9,31,39], although the number of studies in this area is few and the results are conflicting. In additional, One study included in our meta-analysis found no association between rates of live births and levothyroxine treatment among women with SCH and recurrent early pregnancy loss [32].

In contrast, the studies by Kim et al. and Al-Anbari [39,31] found that levothyroxine treatment of SCH among women with infertility, undergoing in vitro fertilization and intracytoplasmic sperm injection, had improved embryo quality and embryo implantation rate compared to women who were not treated. However, the studies were small and further research is needed to determine whether levothyroxine treatment of SCH improves pregnancy outcomes among women with infertility or recurrent pregnancy loss [20,30].

A high degree of validity of dosing of LT4 is relative importance in the setting of pregnancy, in order to prevent for the developing foetus [33]. This will treated with daily doses of LT4 are relatively low, compared with people with overt hypothyroidism [34,56]. The previous study suggests a starting dose of 25–75 μg/day, depending on the TSH level, with further follow up as necessary over time [57].

The present study had several potentially important limitations; the retrospective study may not produce data that is as complete or reliable as data collected by prospective. the study provided limited information on factors like ethnicity, BMI, iodine intake, and SCH etiology. The strength of our study, sample size consider adequate to assume adverse pregnancy outcomes.

CONCLUSION

The results of this study confirm that the prevalence of subclinical hypothyroidism during pregnancy at Tripoli university hospital have various adverse health outcomes to the mothers and their newborn with adjacent additional risk factors such as diabetes mellitus and hypertension the health hazard become high. Therefore, early discover of high risk pregnant women with subclinical hypothyroidism recommended to achieve good pregnancy outcomes and prevent maternal and neonatal complications.

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LIST OF ABBREVIATIONS

ATA = American Thyroid Association C/S = Cesarean section

FT4 = Free thyroxine level IUFD = Intrauterine feta death

IUGR = Intrauterine growth restrictionNVD = Normal vaginal delivery NICU = Neonatal intensive

SCH or sHypo = Subclinical hypothyroidismTPOAb = Anti-thyroid peroxidase antibodies

TSH = Thyroid stimulating hormone