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ORIGINAL ARTICLE

Recent Approach of Endocrine Function of Thyroid Gland and its Impact on Pregnancy

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ABSTRACT

Introductions: Pregnancy is a period in which there are physical and hormonal changes for the development of the fetus and essentials nutrients supply and the preparation of the maternal organism for birth and lactation. There is a paucity of data on the endocrine function of the thyroid gland in pregnancy in Saudi Arabia. The purpose of this study was to assess the impact of the endocrine function of thyroid gland in pregnancy and current techniques for its management.

Methods: In this systematic review and meta-analysis, PRISMA (preferred reporting items for systematic review and meta-analysis) was used. Cochrane handbook guidelines were used for all aspects of this study. It includes published and unpublished studies with different study designs. Such studies were found from databases which include Google Scholar, Embase Medline, PsycINFO, Google, and Cochrane library up to the last week of January 2022 without any language restriction and identified all RCTs related to the endocrine function of the thyroid gland and its impact on pregnancy.

Results: All RCTs connected to the endocrine function of the thyroid gland and its impact on pregnancy were found using a total of 304 articles from the electronic database Google Scholar, PubMed, Embase, PsycINFO, and the Cochrane Library, which were searched without any language restrictions. "Endocrine", "Endocrine function", "Thyroid", "TSH'', ‘‘T3'', ‘‘T4'', ‘‘hormones'' and ‘‘pregnancy'' and ‘‘randomized controlled trial'' were some of the search terms we utilized. In addition, we searched references in a few journals to find more potentially relevant studies. Due to redundancy, 92 articles were excluded from the total of 304. A total of 107 articles were reviewed, with 77 rejected following a preliminary review. There were 30 full-text papers reviewed for eligibility, and 10 of them met the inclusion requirements, with all of the selected articles being of high quality. The parameters of the trials differed greatly in terms of treatment length and population investigated. All of the studies were nonrandomized and compared groups based on retrospective chart reviews. Out of 10 studies, three were from Iran, two from Saudi Arabia, one from the United States, one from Denmark, one from Ireland, one from Netherland, and one from Australia.

Conclusion: Thyroid diseases are the most significant endocrine dysfunction related to pregnancy; however, treatments for subclinical thyroid dysfunction are still controversial; the purpose of therapy should be to maintain euthyroidism during pregnancy. Adequate circulation of thyroid hormone levels is important for appropriate reproductive function. A greater understanding of these problems will allow practitioners to enhance the maternal and perinatal outcomes in such pregnancies. This study concludes that there is a requirement for additional research on TSH during pregnancy without instances of autoimmune thyroid dysfunction for the development of trimester-specific TSH normal range in the population of Saudi Arabia, whereas it also supports the use of TSH as a marker of pregnancy-induced hypothyroidism.

Keywords: Endocrine System, Pregnancy, Thyroid hormone, TSH, Thyroid Gland.

INTRODUCTION

Pregnancy is a period in which there are physical and hormonal changes for the development of the fetus and essentials nutrients supply and the preparation of the maternal organism for birth and lactation. However, this biological phenomenon is taken as a window into maternal and fetal health in the future.[1]

Endocrine disorders have their own impact on pregnancy and fetal development; hence, endocrinologists, clinicians, obstetricians, gynecologists, and other medical disciplines consider endocrine disorders and their management during pregnancy as an important topic. Pregnancy causes several changes and disorders in normal physiological phenomena, while others are increased by it.[2]

During pregnancy, there is a constant change in the maternal and fetal endocrine physiology, as well as several endocrine events take place. Both the mother and the fetus adjust via distinct mechanisms during pregnancy, including modifications in the endocrine system in both the mother and the fetus and related alterations of feedback.[3] Because most endocrine glands begin producing the hormone in the second trimester of pregnancy, the fetus's endocrine function initially completely relies on the mother. Following that, the fetus does not rely much on the endocrine function of the mother, whereas the fetal glands continue to develop in function and appearance until birth.[3,4] There is a high risk of developing difficulties in the mother and the fetus in women with pregnancy complications by endocrine problems, which can be reduced with proper management and clinical surveillance.[5]

Irritability, tiredness, weakness, nausea, vomiting, poor health, and depression are symptoms of hyperemesis gravidarum during pregnancy. It is induced by an increase in the human chronic gonadotropin (hCG) in a pregnant woman's body. During the first trimester of pregnancy, hCG increases the production of hormones required for development and management in pregnancy, including progesterone and the estrogen estradiol and free estriol.[5] Steroid hormones such as progesterone and estradiol and gonadotropins like human chronic gonadotropin (hCG), are crucial to regulating the menstrual cycle as well as the creation and maintenance of the pregnancy.[6,7] These hormones, as well as human placental lactogen (hPL), are released by the placenta during pregnancy. The placental lactogen hormone actively influences metabolism, increasing the intake of the amino acids to construct tissue of the baby while causing headache, nausea, and fatigue in the mother.[5] The placenta's inner cytotrophoblast layer generates hypothalamic-like peptides such as GnRH, TRH, CRH, GHRH, and somatostatin. In addition, these hormones may influence the production of pituitary-like peptides such as TSH, ACTH, and GH, which are produced by the outer syncytiotrophoblast layer in a paracrine way.

The thyroid hormone has an important role in the neurocognitive development of the fetus. The deficiency of maternal thyroid hormones might cause severe neurological disorders in the child. Hypothyroidism may not always present overtly; hence it may go undetected in several cases. There are many physiological effects of pregnancy on thyroid gland function.[8] The countries where iodine is adequate, the thyroid gland's size increases by 10% during pregnancy, whereas it may increase to a greater extent in countries where there is a deficiency of iodine.[9] during pregnancy, deficiency of thyroid hormone and requirement of iodine both exacerbates by 50% approximately as part of physiology.[10] Moreover, women who suffer iodine deficiency or have limited thyroid reserve suffer hypothyroidism; as for the thyroid gland, pregnancy is a stressful condition.

Due to the chronic gonadotrophin's role in thyroid regulation, thyroid function keeps on changing throughout pregnancy. For the normal development of the fetus, thyroid equilibrium is needed. In the first trimester, hCG functions as a potent stimulator for thyroid stimulator hormone (TSH) receptors, decreasing TSH levels and increasing thyroid activity. TSH and hCG levels mirror each other as TSH falls when hCG rises, this condition is known as gestational thyrotoxicosis.[11] After 12 weeks of pregnancy, TSH rises again when the hCG level falls. In the nonpregnant woman, total thyroxin levels rise immediately above the top limit of the reference range due to increased liver synthesis of thyroxin binding globulin promoted by high estradiol levels of the placenta, which results in a rise in total thyroxin levels.[12] in pregnancy, the estimated prevalence of hypothyroidism is 0.1-0.4%.[13] The placenta cannot be crossed by maternal TSH, whereas the thyrotropin-releasing hormone(TRH) generates and activates the fetal pituitary, which contributes to the thyroid function of the fetus.[14] There is a paucity of data on the endocrine function of the thyroid gland in pregnancy in Saudi. The purpose of this study was to assess the impact of the endocrine function of thyroid gland in pregnancy and current techniques for its management.

METHODS

PRISMA (preferred reporting items for systematic review and meta-analysis) was used in this systematic review and meta-analysis.[15] Cochrane handbook guidelines were used for all aspects of this study.[16] It includes published and unpublished studies with different study designs. Such studies were found from databases which include Google Scholar, Embase Medline, PsycINFO, Google, and Cochrane library up to the last week of January 2022 without any language restriction and identified all RCTs related to the endocrine function of the thyroid gland and its impact on pregnancy.

Following search keywords such as “Endocrine”, ‘‘Endocrine function’’, ‘‘Thyroid’’, ‘‘THS’’, ‘‘T3’’, ‘‘T4’’, ‘‘hormones’’ and ‘‘pregnancy’’ and ‘‘randomized controlled trial’’ were used In addition, the references of a few journals were manually revised to uncover more works that might be linked. A comprehensive set of search terms, as well as a methodical evaluation technique, were used. In summary, one author examined relevant titles and abstracts before receiving full-text publication if needed. The final research list was included only after the approval of all the authors. Among them, only randomized controlled trials with the endocrine function of the thyroid gland and its impact on pregnancy were examined.

Inclusion criteria: The articles that met the following criteria: published or unpublished, pregnant women's, and randomized controlled trials with different study designs were included in this systematic review and meta-analysis. The review was only limited to pregnant women.

Data extraction and Statistical analysis: Two experts independently assessed all eligible articles. The author's name, country, published year, study design, criteria, gestational age, methods, and quality score were all extracted. With the help of predesigned data extraction forms, the Cochrane review manager application and this systematic review and meta-analysis were conducted by a random effect model.

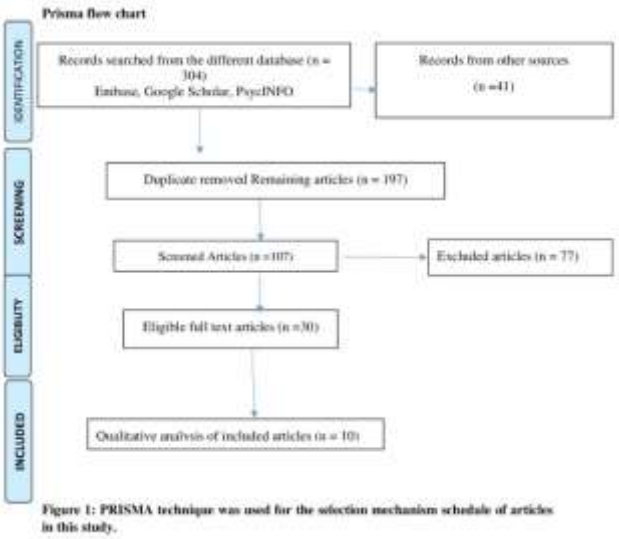

Figure 1: PRISMA technique was used for the selection mechanism schedule of articles in this study.

RESULTS

The preferred reporting items for systematic review and meta-analysis (PRISMA) technique were used to conduct the randomized controlled trial study (fig.1). All RCTs connected to the endocrine function of the thyroid gland and its impact on pregnancy were found using a total of 304 articles from the electronic database Google Schola, PubMed, Embase, PsycINFO, and the Cochrane Library, which were searched without any language restrictions. ‘‘Endocrine’’, ‘‘Endocrine function’’, ‘‘Thyroid’’, ‘‘TSH’’, ‘‘T3’’, ‘‘T4’’, ‘‘hormones’’ and ‘‘pregnancy’’ and ‘‘randomized controlled trial’’ were some of the search terms we utilized. In addition, the references of a few journals were manually searched to find more potentially relevant studies. Due to redundancy, 92 articles were excluded from the total of 304. A total of 107 articles were reviewed, with 77 rejected following a preliminary review. There were 30 full-text papers reviewed for eligibility, and 10 of them met the inclusion requirements, with all of the selected articles being of high quality (Figure 1). The parameters of the trials differed greatly in terms of treatment length and population investigated. Table 1 summarizes these specifics.

Table 1: Summary of randomized controlled trials.

SN.	Author	Country	Year of publication	No. of patients	Study design	Gestational age	Criteria	Methods	Quality Score
1	Kianpour M et al. [17]	Iran	2019	418	Prospective, Cohort study	First trimester	Hypothyroidism: TSH<0.1 mIU/L, Anti-TPo Ab Positive>60 mIU/L	NA	8
2	Ong et al. [18]	Australia	2014	117	Prospective study	9-14 weeks	TSH >2.15 mIU/L, fT4 Normal	ECLIA	8
3	Breathnach et al. [19]	Ireland	2013	16	Prospective	Early second trimester	TSH>98th percentile (4.1 mIU/L), fT4 Normal	NA	7
4	Borzouei Sh et al. [20]	Iran	2019	852	Prospective	First trimester	Hypothyroidism: TSH >2.5 mIU/L and low FT4 or TSH ≥ 10 mIU/L, subclinical hyperthyroidism: TSH <0.1 mIU/L and normal FT3 and FT4; subclinical hyperthyroidism:	RIA for fT4, IRMA for TSH, and ELISA for anti-TPO Ab.	7

							Anti-TPO Ab positive: >40 IU/mL, TSH <0.1 mIU/L and high FT4 and FT.		
5	Cleary Goldman et al. [21]	USA	2008	240	Prospective	10-13 weeks	FT4 2.5th -97.5th percentile , TSH >97.5th percentile (TSH>4.29 mIU/L);	ECLIA	
6	Lotfalizadeh M et al. [22]	Iran	2017	1000	Prospective	First trimester	Hypothyroidism: TSH>3mIU/L	RIA for TSH and ELISA for FT4	7
7	Korevaar et al. [23]	Netherlands	2013	188	Prospective	Early pregnancy	FT4 normal, TSH >97.5th percentile (TSH>4.04 mIU/L)	ECLIA	8
8	Feldthusen et al. [24]	Denmark	2014	19	Prospective	Third trimester	FT4 Normal, TSH≠3.4 mIU/L	ECLIA	7
9	Hussein KS et.[25]	Saudi Arabia	2017	154	Prospective	Early pregnancy	Hyperthyroidism: TSH ≤0.03 mIU/L Hypothyroidism: TSH <2.5 mIU/L	ECLIA	8
10	Refaat B et al. [26]	Saudi Arabia	2021	810	Prospective	All trimester	FT4 within trimester-specific ranges. and TSH levels between 2.5 mIU/L - 10 mIU/L According to the American Thyroid Association Guidelines.	ECLIA	9

All of the studies were nonrandomized and compared groups based on retrospective chart reviews. Out of 10 studies, three were from Iran, two from Saudi Arabia, one from the United States, one from Denmark, one from Ireland, one from Netherland, and one from Australia.

DISCUSSION

Among the endocrine disorders, thyroid diseases are the commonest. Physical examination combined with laboratory and radiological tools is fundamental for thyroid endocrine dysfunction's early diagnosis and treatment. Depending on various factors in different regions, thyroid dysfunction in pregnancy and complication in the mother and fetus differs vastly. The purpose of the study was to reach the impact of the endocrine function of thyroid gland in pregnancy and current techniques for its management.

Before or during pregnancy, the public screening of thyroid disease is still controversial. The disease must be seen with adverse health effects as well, as it must have a cure for screening to be recommended. According to the guidelines of ATA, there is a paucity of evidence to recommend public screening for abnormal TSH concentrations in the early stages of pregnancy. Hence, a targeted TSH test is recommended with the identification of any below-mentioned risk factors in the patients intending to get pregnant or who have recently been pregnant.[28]

- Thyroid dysfunction: Hyperthyroidism/hypothyroidism
- Detection of goiter: Positive type of thyroid antibody
- History of previous thyroid surgery and radiation therapy to the head and neck
- Above 30 years of age
- Type 1 diabetes or other autoimmune disease
- Miscarriage, preterm labor, or infertility in the past
- Multiple pregnancies in the past (≥2)
- Family history of thyroid dysfunction or autoimmune disorders
- Morbid obesity (Body Mass Index(BMI)≥40kg/m^2)
- Recent administration of radiographic iodinated contrast or use of amiodarone or lithium
- Residence in a moderate to severe iodine deficiency region

In a study conducted in Saudi Arabia, a high prevalence of thyroid dysfunction was seen; the possible explanation might be due to the reasons and risk factors like poor nutrition and iodine deficiency mentioned in the study. Moreover, the different prevalence of thyroid lesions could be observed because of the sample size and variation in characteristics of the participant.

In the other studies conducted in China, Spain, India, and Belgium, the prevalence of thyroid disorders was reported to vary by (10.2–15.6%), (16.6%), (13.25%), (15.3%) respectively.[29-33] The women of reproductive age are affected by thyroid dysfunction the most among the endocrine disorders after diabetes mellitus.[34] According to the Task Force, the normal range must be as per the results of the particular population and technique of the laboratory of the institute. If the transferable or internal pregnancy-specific TSH reference range is not available, an upper range of 4.0 mU/L can be considered. This limit denotes a fall in nonpregnant TSH upper normal range limit of 0.5 mIU/L for most assays.

In different geographic and demographic regions, the limited prevalence of trimester-specific normal ranges is a significant factor in dissimilar values. In studies from India and China published in 2011 and 2014, the concept of the first-trimester value of 2.5 mU/L as a cut-off for TSH and hypothyroidism is contextual.[29,32] We follow the standard guideline of ATA 2017 in view of the paucity of reports from Saudi Arabia.

Hypothyroidism has been prevalent in various countries recently.[33,35-36] The present study results and recently reported figures from Saudi Arabia are fairly consistent. Taha et al. observed hypothyroidism in 24.2% of the women among 936 pregnant women (12-30 weeks of gestation) in their hospital-based study in the Madinah region.[37] In Makkah, a study by Refaat et al. reported hypothyroidism in 32.4% of 162 pregnant women (4-12 weeks of gestation).[26]

Management: The preferred medication for normalizing the TSH level according to gestational age is Levothyroxine which is defined as Group A by the FDA.[38-40] In case a pregnant woman is already taking L-thyroxine for hypothyroidism, the dosage is set by gestational age at the referral to an endocrinologist. In Saudi Arabia, gestational hypothyroidism is highly prevalent, which could be taken as a major public health crisis. The requirement of public screening for hypothyroidism in early pregnancy is still a debate. This study states that pregnant women in Saudi suffer hypothyroidism more commonly. In countries like Saudi, where hypothyroidism is highly prevalent, screening pregnant women for maternal thyroid disorders must be considered as early as possible.

CONCLUSION

The symptoms of endocrine abnormalities are sometimes difficult to be distinguished from those occurring biologically throughout pregnancy; care becomes more complex if endocrine dysfunctions are identified during pregnancy. The decisions about empirical treatment or the timing and appropriateness might be difficult to be made in the absence of a certain diagnosis. The factors on which decisions are made are not as substantial as in the nonpregnant woman, as there are not as many similar cases or trials of specific treatments in pregnancy. In recent times thyroid diseases are

mostly seen as endocrine complications related to pregnancy; however, treatments for subclinical thyroid illness are controversial; the therapeutic goal in these situations should be to preserve euthyroidism during pregnancy. Adequate circulation of thyroid hormone levels is important for appropriate reproductive function. A greater understanding of these problems will allow practitioners to enhance the maternal and perinatal outcomes in such pregnancies. This study concludes that there is a requirement for additional research on TSH during pregnancy without instances of autoimmune thyroid disorders for the development of trimester-specific TSH normal ranges in the population of Saudi Arabia, whereas it also supports the use of TSH as a marker of pregnancy-induced hypothyroidism.

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