

**THE EFFECT OF THYROID DYSFUNCTION ON PREGNANCY OUTCOME:
SYSTEMATIC REVIEW AND META-ANALYSIS****Heni Elmiani Sari**

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heni@poltekborneomedistra.ac.id**ABSTRACT**

Thyroid dysfunction during pregnancy certain impact on pregnancy outcomes, and neonatal growth. The incidence of pregnancy with hyperthyroidism ranges from 0.5% to 1%, leading to adverse pregnancy outcomes such as abortion, premature delivery, stillbirth, gestational hypertension, placental abruption, and premature rupture of membranes. This study aimed to analyzed the effect thyroid dysfunction on pregnancy outcomes. This was a systematic review and meta-analysis. The PICO research question as follows. Population: Pregnancy; Intervention: Dysfunction Thyroid; Comparison: Thyroid Normal; Outcome: Effect of Pregnancy. The articles were obtained from four databases: PubMed, Web of Science, Springer, and Science Direct. The Keywords were “Thyroid Dysfunction” OR “Pregnancy” OR “Outcomes” AND “Prospective Cohort” AND “Retrospective comparative”. Full text article in English with study design Cohort and retrospective comparative from 2012 to 2022, were included in this study. The steps of meta-analysis followed PRISMA flow diagram. The Articles were analyzed by the Review Manager 5.4 application A total 11 cohort and retrospective comparative from India, Israel, Denmark, Pakistan, America, Finland, and China were selected for a systematic review and meta-analysis. the data collected showed that effect of thyroid disfunction on pregnancy outcome among preterm birth by 0.87 times and was statistically significant (SMD=0.87, 95% CI=0.87 to 0.93; P<0.00001); Pre-Eclampsia by 0.70 times (SMD=0.70, 95% CI=0.50 to 0.96; P=0.03); Placenta abruption by 0.27 times (SMD=0.27, 95% CI=0.19 to 0.38; P<0.00001); Fetal Distress by 0.77 times (SMD=0.77, 95% CI=0.68 to 0.86; P<0.00001); Post-partum Hemorrhage by 0.57 times (SMD=0.57, 95% CI= 0.37 to 0.87; P<0.009).

Keywords: effect thyroid; thyroid dysfunction; pregnancy outcome; meta-analysis

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INTRODUCTION

Thyroid disease is a common clinical endocrine disease, with a high incidence in women of childbearing age (Krysiak et al., 2019). Thyroid disorders constitute one of the most common endocrine disorders in pregnancy (De Groot et al., 2012). Pregnancy is associated with profound modification in the regulation of thyroid function. These changes are the result of various factors like an increase of thyroxine-binding globulin (TBG) due to elevated estrogen and human chorionic gonadotropin (HCG), increased renal losses of iodine due to increased glomerular filtration rate, modifications in the peripheral metabolism of maternal thyroid hormones, and modification in iodine transfer to the placenta (Negro et al., 2006). Thyroid hormones have two main forms Triiodothyronine (T3) and tetraiodothyronine (T4). Changes in physiological conditions in pregnant women can cause changes in thyroid function within normal limits during pregnancy. This is change is mainly manifested in that with the increase of gestational weeks, serum free T3(FT3) and free T4 (FT4) levels gradually decrease, while

thyroid stimulating hormone (TSH) level gradually increase (Gauthier et al., 2020). In the second and third trimesters of pregnancy, the mother's basal metabolic rate increases, thyroid hormone consumption increases, glomerular extraction rate increases, urinary iodine excretion increases, and fetal growth requires increased iodine requirements, which can lead to relative thyroid hormone insufficiency. In addition, negative feedback of the hypothalamic-pituitary-thyroid axis increases serum TSH (Yuan et al., 2023).

Thyroid dysfunction during pregnancy mainly includes hypothyroidism, hyperthyroidism, thyroid adenoma, thyroid nodule, and goiter (Alexander et al., 2017). Hypothyroidism occurs in up to 2.5% of pregnancies, and pregnancy with hypothyroidism is associated with abortion, premature delivery, stillbirth, placental abruption, gestational hypertension, and other adverse pregnancy outcomes (Bekkering et al., 2019). In addition, hypothyroidism in the first trimester of pregnancy has a certain impact on the intelligence and cognitive ability of newborns (Angell & Alexander, 2019). Subclinical hypothyroidism can lead to impaired cardiovascular function and abnormal lipid levels. Research conducted by Moleti et al. (2019) also showed that the prevalence of subclinical hypothyroidism in pregnant women is as high as 11.3%. The incidence of pregnancy with hyperthyroidism ranges from 0.5% to 1% leading to adverse pregnancy outcomes such as abortion, premature delivery, stillbirth, gestational hypertension, placental abruption, and premature rupture of membranes (Moleti et al., 2019).

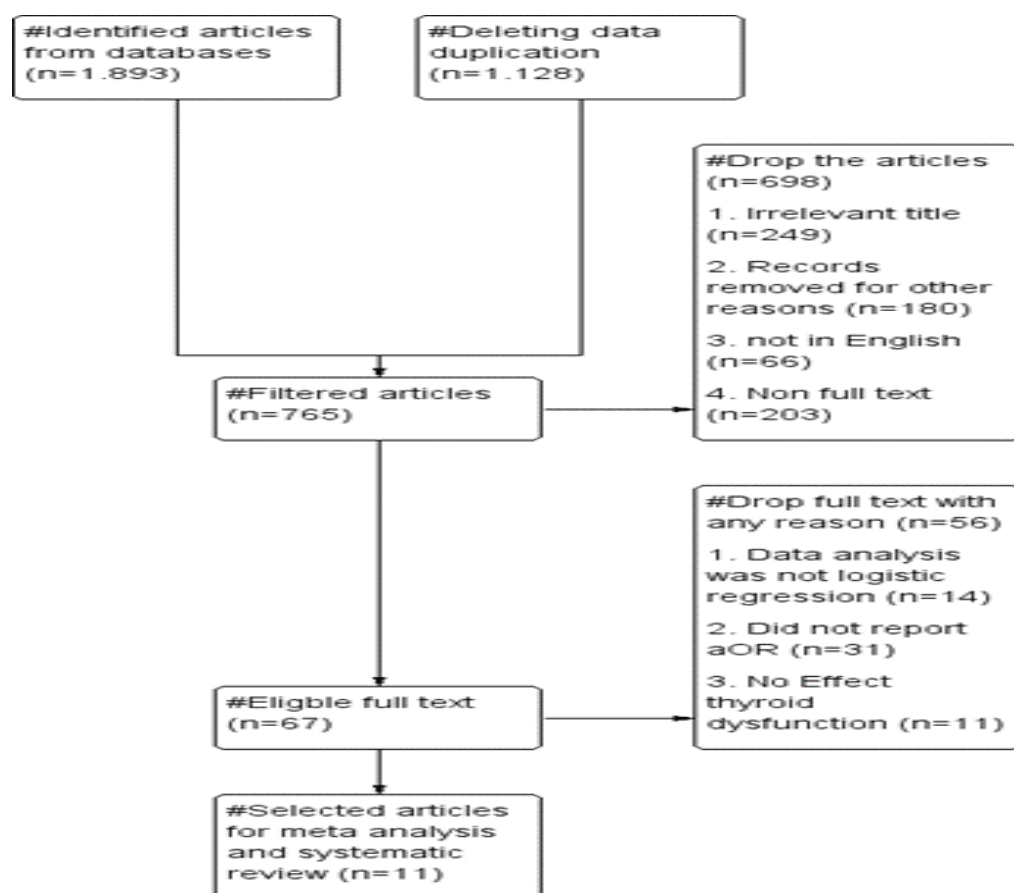
To systematically evaluate the influence of thyroid dysfunction on early pregnancy outcomes, meta-analysis was used to evaluate differences in pregnancy outcomes between patients with normal and abnormal thyroid function in early pregnancy. It aims to provide medical evidence for clinical evaluation of the influence of thyroid dysfunction in early pregnancy on pregnancy outcomes.

METHOD

This was a systematic review and meta-analysis. The articles used in this study were obtained from several database PubMed, Web of Science, Springer, and Science Direct published from 2012-2022. The keywords used in the search were "Thyroid Dysfunction" OR "Pregnancy" OR "Outcomes" AND "Prospective Cohort" AND "Retrospective comparative". The inclusion criteria in this study were: Full text articles using a Retrospective comparative study and Prospective Cohort research design, the research subjects were the results of thyroid effects. The magnitude of the relationship used is Mean and SD, the intervention is routine. The exclusion criteria in this research article are: statistical results reported in the form of bivariate analysis. Articles published in languages other than Indonesian and English. Articles published before 2012. Article searches were carried out based on eligibility criteria using the PICO Model. Population: Pregnancy, intervention: Thyroid dysfunction, Comparison: Thyroid Normal; Outcome: Effect of Pregnancy Thyroid Dysfunction: Thyroid disorders constitute one of the most common endocrine disorders in pregnancy. Data processing was carried out using the Review Manager application (RevMan 5.3) by calculating effect size and heterogeneity to determine which research models were combined and formed the final meta-analysis results.

RESULTS

The process of searching for articles using databases and journals can be seen in Figure 1. Figure 2 shows the areas for selecting articles according to the inclusion criteria. A total of 12 articles that met the quality assessment were included in the quantitative synthesis using meta-analysis. Research articles are sourced from India, Israel, Denmark, Greece, Pakistan, Turkey, Thailand, America, Finland, and China.



it can be seen in figure that the research article come from India, Israel, Denmark, Greece, Pakistan, Turkey, Thailand, America, Finland, and China. Table 1. Research conducted an assessment of the quality of the study. Table 2 shows that 12 articles from a Retrospective comparative study and Prospective cohort study provide Effect of Thyroid Dysfunction on Pregnancy Outcome.

Map of study areas

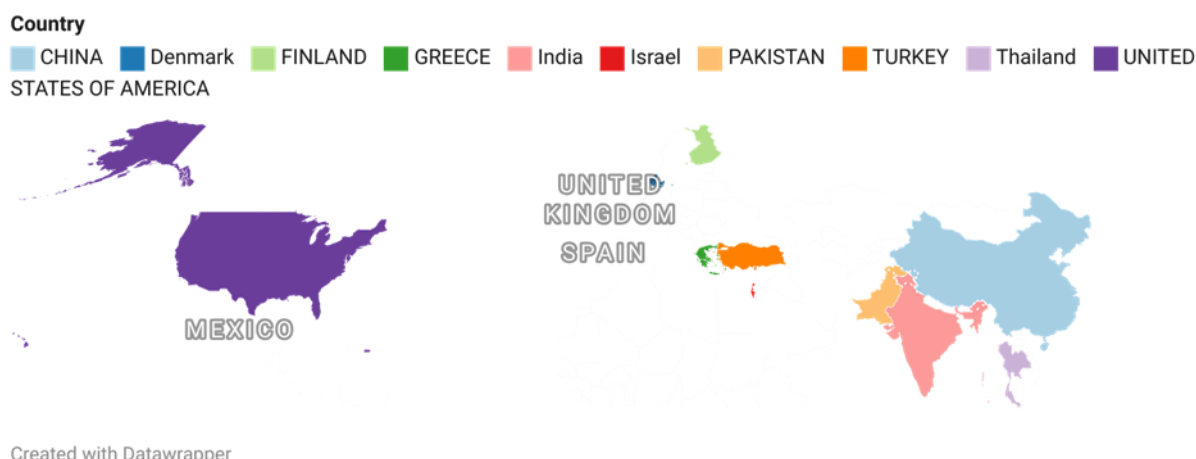


Figure 2. Maps of Study Area Effect of Thyroid Dysfunction on Pregnancy Outcome

Effect of thyroid dysfunction on Pregnancy outcomes

Table 1.
Descriptions of Primary Studies included in the meta-analysis

Author (year)	Title	Country	Study Design	Sample	P Population	I Intervention	C Comparison	O Outcome
Ajmani SN, et al (2014) (Ajmani et al., 2014)	Prevalence of Overt and Subclinical Thyroid Dysfunction Among Pregnant women and Its Effect on Maternal and Fetal Outcome	India	Retrospective comparative study	400	Pregnancy Women between 13 and 26 weeks of Gestation	Dysfunction thyroid Hypothyroidism	Thyroid Normal Hyperthyroidism	Effect of Pregnancy
Arbib N, et al (2017) (Arbib et al., 2017)	First trimester Thyroid stimulating hormone as an independent Risk Factor for Adverse Pregnancy Outcome	Israel	Retrospective comparative study	4.504	women with an available first trimester thyroid function testing	Hypothyroidism	Hyperthyroidism	Effect of Pregnancy
Feldthuse n AD, et al (2014) (Feldthus en et al., 2014)	Pregnancy-induced alterations in mitochondrial function in euthyroid pregnant women and pregnant women with subclinical hypothyroidism: relation to adverse outcome	Denmark	Retrospective comparative study	113	pregnant women	Hypothyroidism	Eutiroid	Effect of Pregnancy
Hirsch D, et al (2013) (Hirsch et al., 2013)	Pregnancy outcomes in women with severe hypothyroidism	Israel	Retrospective comparative study	306	pregnant women	Hypothyroidism	Eutiroid	Effect of Pregnancy
Karakosta P, et al (2012) (Karakosta et al., 2012)	Thyroid Dysfunction and Autoantibodies in Early Pregnancy are associated with Increased Risk of Gestational Diabetes and Adverse Birth Outcomes	Greece	Prospective cohort study	1.141	Pregnant women	Hypothyroidism	Eutiroid	Effect of Pregnancy
Kiran Z, et al (2021) (Kiran et al., 2021)	Association of thyroid antibodies status on the outcomes of	Pakistan	Retrospective comparative study	292	maternal outcomes of pregnancies affected by hypothyroidism,	Hypothyroidism	Eutiroid	Effect of Pregnancy

Author (year)	Title	Country	Study Design	Sample	P Population	I Intervention	C Comparison	O Outcome
	pregnant women with hypothyroidism (maternal hypothyroidism on pregnancy outcomes, MHPO-4)							
Konar H, et al (2018) (Konar et al., 2018)	Association of Thyroid Dysfunction and Autoimmunity in Pregnant Women with Diabetes Mellitus	India	Retrospective comparative study	64	pregnant women with diabetes, both PGDM and GDM	Thyroid Dysfunction	Thyroid Normal	Effect of Pregnancy
Kumru P, et al (2014) (Kumru et al., 2015)	Effect of thyroid dysfunction and autoimmunity on pregnancy outcomes in low risk population	Turkey	Prospective cohort study	395	pregnant women between 10 and 12 gestational age	thyroid function	anti-TPO results	pregnancy outcomes
Luewan S, et al (2011) (Luewan et al., 2011)	Outcomes of Pregnancy complicated with hyperthyroidism: a cohort study	Thailand	Prospective cohort study	540	pregnant women	hyperthyroidism	Thyroid Normal	pregnancy outcomes
Mannistö T, et al (2013) (Mannistö et al., 2013)	Neonatal Outcomes and Birth Weight in Pregnancies Complicated by maternal Thyroid Disease	America	Retrospective comparative study	223.512				
Turunen S, et al (2020) (Turunen et al., 2020)	Maternal hyperthyroidism and pregnancy outcomes: a Population-based cohort study	Finland	Retrospective comparative study	553.004	Pregnant women	Hyperthyroid	Without thyroid	pregnancy outcomes
Zhang Y, et al (2019) (Zhang et al., 2019)	Association of Overt and Subclinical Hyperthyroidism During Weeks 4-8 with Adverse Pregnancy Outcomes	China	Prospective cohort study	3.783	4th-8th week of pregnancy	Hyperthyroid	Thyroid Normal	pregnancy outcomes

Effect of thyroid dysfunction on pregnancy outcome among preterm birth

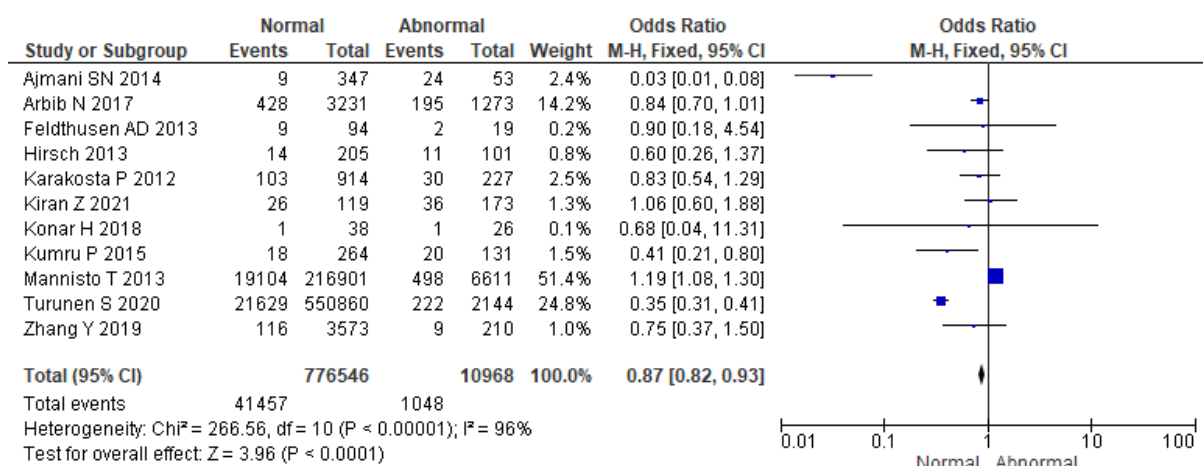


Figure 3. Forest Plot effect of thyroid dysfunction on pregnancy outcome among preterm birth

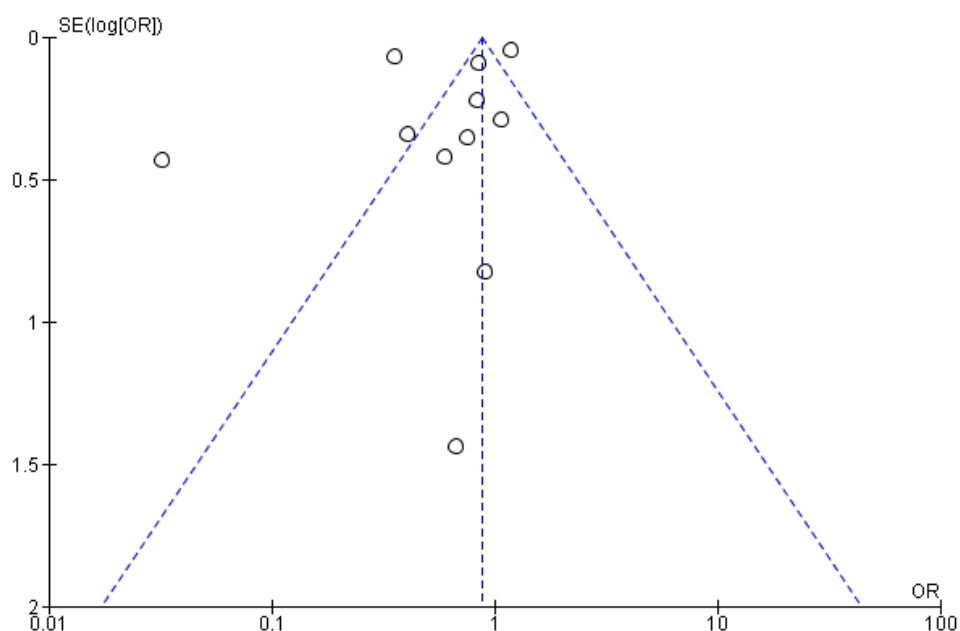


Figure 4. Forest Plot effect of thyroid dysfunction on pregnancy outcome among preterm birth

Interpretation of the results of the meta-analysis process can be seen in Figure 3 forest plot. Shows that the results of subgroup analysis on effect of thyroid dysfunction on pregnancy outcome among preterm birth had a 0.87 times risk of preterm birth, compared to thyroid normal and this was statistically significant (aOR= 0.87; CI 95%= 0.82 to 0.93; p<0.0001). so that the data distribution is declared heterogeneous I²=96% (random effect model). The funnel plot shows that there is no publication bias shown by the symmetrical results between the right and left plots.

effect of thyroid disfunction on pregnancy outcome among Fetal Distress

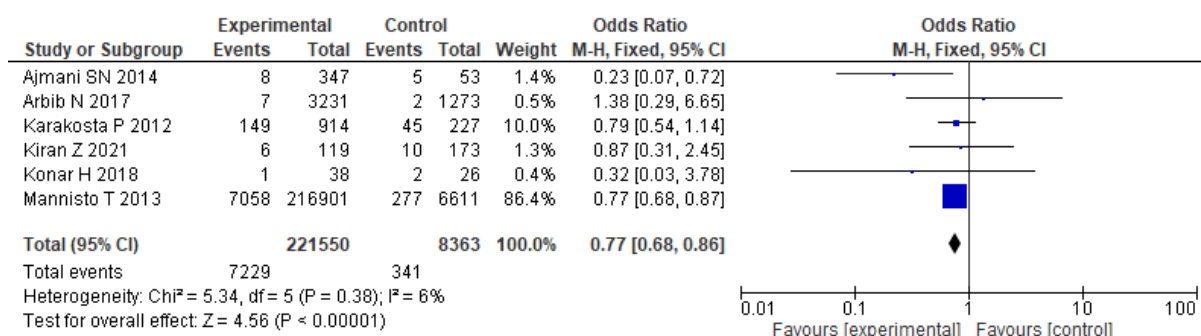


Figure 5. Forest Plot effect of thyroid disfunction on pregnancy outcome among Fetal Distress

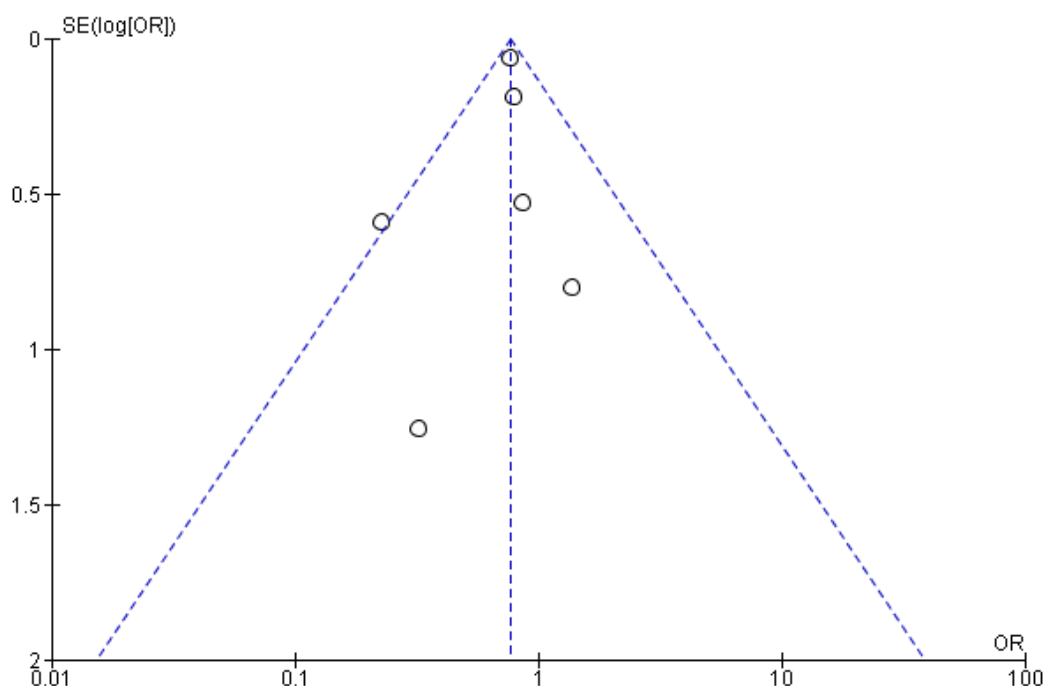


Figure 5. Forest Plot effect of thyroid disfunction on pregnancy outcome among Fetal Distress

Interpretation of the results of the meta-analysis process can be seen through the forest plots in Figures 4 and 5. Showing the results of subgroup analysis in effect of thyroid dysfunction on pregnancy outcome among Fetal Distress had a 0.77 times risk of preterm birth, compared to thyroid normal and this was statistically significant ($aOR = 0.77$; $CI\ 95\% = 0.68$ to 0.86 ; $p < 0.0001$). so that the distribution of data is declared heterogeneous $I^2 = 6\%$ (Fixed effect model). The funnel plot of shows that the distribution of effect estimates from the primary studies of this meta-analysis lies more to the left of the vertical line of mean estimates than to the right, indicating publication bias. Because the publication bias tends to be to the left of the average vertical line which is in a different direction from the location of the diamond shape in the forest plot, the publication bias tends to reduce the true effect of thyroid dysfunction of pregnancy outcome among fetal distress.

Effect of thyroid disfunction on pregnancy outcome among pre-eclampsia

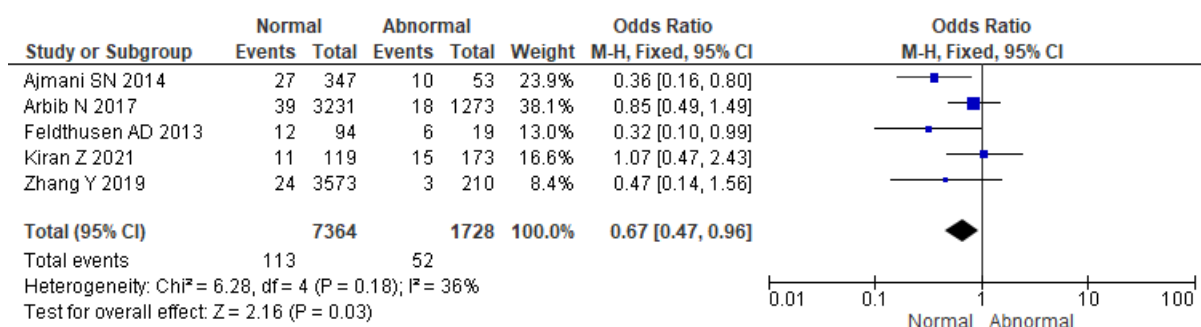


Figure 6. Forest Plot effect of thyroid disfunction on pregnancy outcome among pre-eclampsia

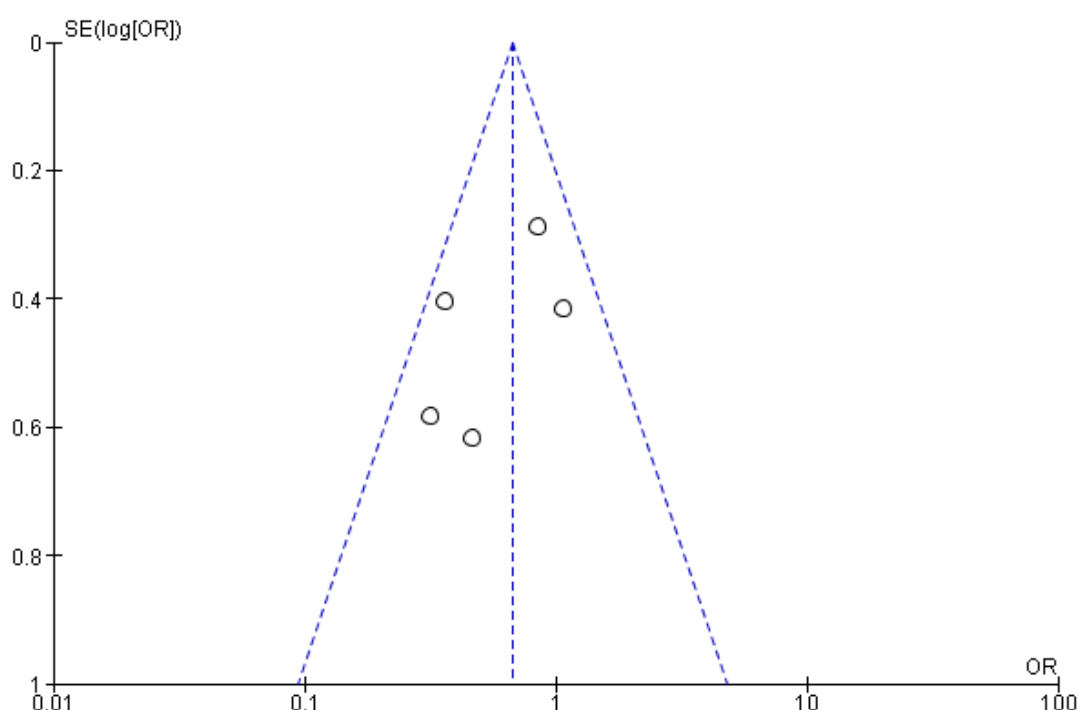


Figure 7. Funnel Plot effect of thyroid disfunction on pregnancy outcome among pre-eclampsia

Interpretation of the results from the meta-analysis process can be seen through a forest plot figure 4 and 5. Shows that the results of the subgroup analysis in effect of thyroid disfunction on pregnancy outcome among pre-eclampsia had a 0.77 times risk of preterm birth, compared to thyroid normal and this was statistically significant (aOR= 0.67; CI 95%= 0.47 to 0.96; p=0.03). so that the distribution of data is declared heterogeneous I²=36% (Fixed effect model). The funnel plot shows that the distribution of effect estimates from the main studies of this meta-analysis lies further to the left of the vertical line of mean estimates than to the right, indicating publication bias. Because the publication bias tends to the left of the mean vertical line in a different direction to the location of the diamond shape in the forest plot, the publication bias tends to understate the true effect of thyroid dysfunction on pregnancy outcomes among pre-eclampsia.

Effect of thyroid disfunction on pregnancy outcome among Placenta Abruption

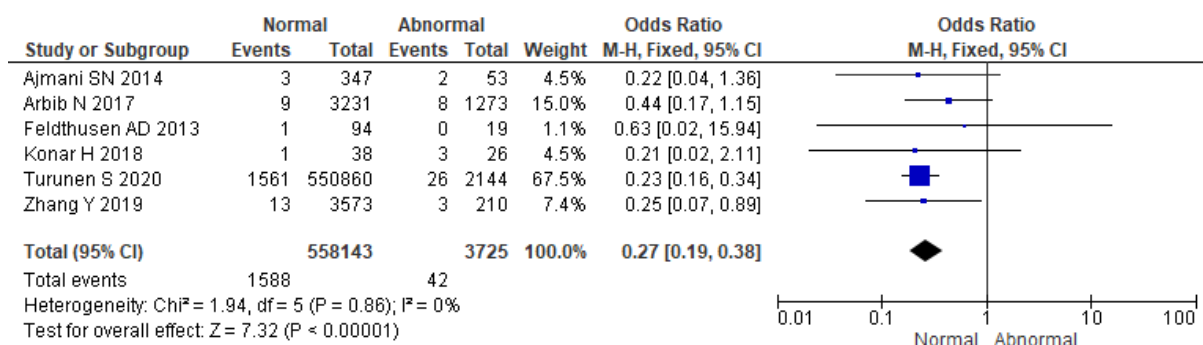


Figure 7. Forest Plot effect of thyroid disfunction on pregnancy outcome among Placenta Abruption

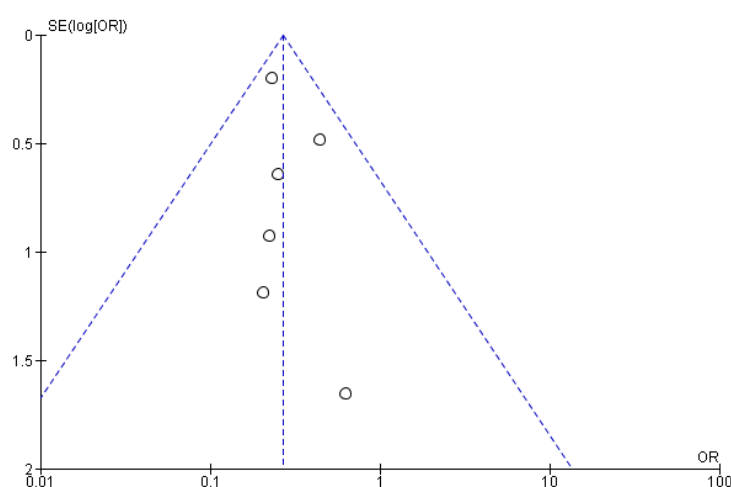


Figure 8. Funnel Plot effect of thyroid disfunction on pregnancy outcome among Placenta abruption

Interpretation of the results from the meta-analysis process can be seen through a forest plot figure 4 and 5. Shows that the results of the subgroup analysis in effect of thyroid dysfunction on pregnancy outcome among placenta abruption had a 0.27 times risk of preterm birth, compared to thyroid normal and this was statistically significant ($aOR = 0.27$; $CI\ 95\% = 0.19$ to 0.38 ; $p < 0.0001$). so that the distribution of data is declared heterogeneous $I^2 = 0\%$ (Fixed effect model). The funnel plot of shows that the distribution of effect estimates from the primary studies of this meta-analysis lies more to the left of the vertical line of mean estimates than to the right, indicating publication bias. Because the publication bias tends to be to the left of the average vertical line which is in a different direction from the location of the diamond shape in the forest plot, the publication bias tends to reduce the true effect of thyroid dysfunction of pregnancy outcome among abruption.

DISCUSSION

Changes in the physiological state of pregnant women can cause changes in thyroid function within the normal range during pregnancy (Stagnaro-Green et al., 2020). Such changes mainly manifest as gradual decreases in the serum levels of free T3 and free thyroxine with the increase of gestational age, while the level of TSH gradually increase (Maraka et al., 2017). This research is systematic review and meta-analysis. The aim of this research is to obtain conclusions from various things similar studies regarding the effects of thyroid dysfunction on

pregnancy outcomes. Number relevant research that is published and accessible still small and also has access to data problem (data duplication) (Murti, 2018). Most of the statistical results reported are in percentage or crude Odds Ratio (cOR), where the study cannot control confounders factors (confounding factors). Supporting factors influence this relationship or as a result of exposure to the event the diseases predicted by these studies are not the same equal to that relationship or effect actually occurs in the target population aka invalid learning results (Murti, 2018). Many studies have suggested that the incidence of thyroid dysfunction in pregnant women is dramatically high and is related to changes in maternal and fetal physiological hormone metabolism during pregnancy.

Thyroid dysfunction not only leads to pregnancy-induced hypertension, diabetes, and other diseases in pregnant women, but also affects the development of the fetal nervous system to some extent (Wildisen et al., 2021). In the 12 studies included in this meta-analysis, Preterm birth is defined as delivery between 28- and 37-week gestation. The results showed that the incidence of preterm birth in the thyroid dysfunction group had a risk of premature birth of 0.87 times dramatically higher than that in the normal. Current studies point to endocrine factors as one of the causes of preterm birth (Ollero et al., 2019), as well as chromosomal abnormalities, anatomical abnormalities, hereditary and acquired thrombocytopenia, environmental exposure, and immune factors. Hypothyroidism can be caused by inadequate or deficient thyroid hormone synthesis, secretion, or biological effects. Insufficient thyroid hormone synthesis can affect the function of trophoblast cells in the placenta and reduce the endocrine function of trophoblast cells, which can easily cause the occurrence of premature labor (Hammad et al., 2019). After 20 weeks of gestation or during delivery, the placenta in its normal position is partially or completely removed from the uterine wall before delivery (Sepasi et al., 2020). The specific mechanism of placental abruption induced by thyroid dysfunction remains unclear.

Postpartum hemorrhage is defined as blood loss with related signs or hypovolemic symptoms that occur within 24 hours of delivery, with a blood loss of 1,000 mL or more at 24 hours postpartum (Guo et al., 2020). The results in this study showed that thyroid dysfunction could increase the incidence of postpartum hemorrhage with placental abruption, the risk of experiencing it is 0.77 times. In conclusion, women with abnormal thyroid function and pregnancy, untreated or poorly controlled, have a higher risk of maternal and fetal complications. However, if the thyroid function can be basically controlled in the normal range throughout the pregnancy, the pregnancy outcome is usually good. At present, it is often treated with drugs. The goal of treatment of thyroid dysfunction is to maintain TSH and control FT4 to the upper limit of normal (Kurimoto et al., 2020). The dose of thyroxine replacement therapy needs to be increased with increasing gestational age. Therefore, in the treatment of hypothyroidism and pregnancy, the earlier the treatment is started, the better. The incidence of fetal distress in pregnancies with thyroid dysfunction also has a risk of 0.77 times experiencing fetal distress. Uncontrolled real hyperthyroidism also has a negative impact on the health of the fetus. Because the presence of thyroid autoantibodies is associated with an increased rate of obstetric complications (Luton et al., 2005). The risk of fetal hyperthyroidism is thought to be very low, with only 1% of children of GD mothers described as having hyperthyroidism. Nevertheless, fetuses of GD mothers with uncontrolled hyperthyroidism in the second half of pregnancy, and/or with high TRAb levels need to be closely monitored to allow for appropriate fetal management. Fetal thyroid ultrasound has been shown to be highly sensitive and specific for detecting intrauterine thyroid dysfunction. Ultrasonographic signs suggestive of fetal hyperthyroidism include goiter, sustained heart rate >160-170 bpm, accelerated bone maturation, growth restriction, oligo/polyhydramnios (Luton

et al., 2005) preeclamptic women was significantly different from normal pregnant. In this study, women with thyroid dysfunction had a 0.67 times risk of experiencing pre-eclampsia.

The relation between changes in thyroid function and preeclampsia may be reciprocal (Hajifoghaha et al., 2022). This means that the thyroid disorder is one of the predisposing causes for pre-eclampsia and hypothyroidism is one of the pathophysiologic causes of pre-eclampsia. Hypothyroidism can play an important role in smooth muscle contraction in the renal and systemic arteries, leading to increased peripheral vascular resistance, diastolic blood pressure, and decreased tissue perfusion. Therefore, the identification of thyroid abnormalities and their proper management can affect the incidence of preeclampsia (Hosen et al., 2014). It was suggested that evaluation of thyroid function could be useful in predicting preeclampsia (Elhaj et al., 2015). In this regard, TSH plays a central role in screening and diagnosis of many thyroid disorders. On the other hands, preeclampsia can be a key cause in the pathogenesis of hypothyroidism. Effects of preeclampsia in thyroid function is not yet elucidated, but increased levels of endothelin as a vasoconstrictor produced by vascular endothelium are involved in the pathogenesis of subclinical hypothyroidism in preeclampsia (Grammatikakis et al., 2017). This meta-analysis explored the influence of thyroid dysfunction in early pregnancy, as determined by ultrasound, on pregnancy outcomes. The results showed that the incidence of preterm birth, fetal distress syndrome, preeclampsia, placental abruption, and postpartum hemorrhage in pregnant women with thyroid dysfunction were dramatically higher than those in the normal group.

CONCLUSION

Meta-analysis conducted using 12 articles originating from India, Israel, Denmark, Greece, Pakistan, Turkey, America, Finland and China to explore the influence of thyroid dysfunction in early pregnancy on adverse pregnancy outcomes. We found that thyroid dysfunction was associated with premature delivery, fetal distress syndrome, preeclampsia, placental abruption, and postpartum haemorrhage. However, there are still some limitations in this study.

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