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Maternal Anemia and Pregnancy outcomes: a Systematic Review and Meta-Analysis

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Abstract

Background

The aim of this study was to determine the relationship between maternal anemia during pregnancy and pregnancy outcomes.

Materials and Methods

This systematic review was conducted in domestic (Sid, Iran.doc, Iran medex and Magiran) and international (PubMed, Science Direct, Cochrane, Medline, Web of Science, Scopus, Springer, Embase, Google scholar) databases from January 1, 1990 to April 10, 2016 with using standard key words "Pregnancy", "Pregnant women", "Hemoglobin/ haemoglobin", "Anemia/ anaemia", and "Pregnancy outcome". Relative risks (RR) and confidence intervals were extracted from each study.

Results

Overall 30 studies with a total sample size of 1,194,746 were entered into the final meta-analysis. Maternal anemia in the first trimester showed a significant relationship with low birth weight (RR: 1.28, 95% CI, 1.10 - 1.50, P<0.01), pre-term birth (RR: 1.26, 95% CI, 1.11- 1.44, P<0.01) and small for gestational age (RR: 1.12, 95% CI, 1.05 - 1.19, P<0.01`), that means maternal anemia in the first trimester raises the risk of these outcomes.

Even though, maternal anemia in the second trimester has no significant relationship with low birth weight (RR, 1.19, 95% CI, 0.65- 2.17, P>0.05) and pre-term birth (RR: 1.35, 95% CI, 0.54 - 3.24, P>0.05). Similarly, maternal anemia in the third trimester has also, no significant relationship with low birth weight (RR: 1.23, 95% CI, 0.97 - 1.55, P>0.05) and pre-term birth (RR: 1.55, 95% CI, 0.83 - 2.88, P>0.05).

Conclusion

Maternal anemia during pregnancy in the first trimester in particular can be considered as a risk factor for pregnancy outcomes and must be treated as an advance.

Key Words: Anemia, Hemoglobin, Pregnancy, Meta-Analysis, Systematic review, Women.

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1-INTRODUCTION

Iron is one of the most essential elements during pregnancy and iron deficiency anemia is the most common nutritional deficiency worldwide. So, maternal anemia is a common health problem during pregnancy (1). Parasitic diseases such as malaria, hookworm infection, schistosomiasis, micronutrient deficiencies including folic acid, vitamin A, vitamin B12, genetic hemoglobin apathies such as thalassemia and Helicobacter pylori has been shown in the etiology of anemia in pregnant women (2-4). The prevalence of anemia among pregnant women is 52 percent in developing countries and 22.5 percent in developed countries (5).The high prevalence of the disease burden has been reported in Asia (60%) and Africa (52%) and 80 percent of anemic pregnant women live in South Asia (6-8).

Prevalence is different during all trimesters of pregnancy. According to meta-analysis that had been conducted in Iran in 2015, the prevalence of anemia was estimated to 19.6 percent in the first trimester, 10.1 percent in the second trimester and 16.1 percent in the third trimester, respectively (9). According to the US Center for Disease Control (CDC), if hemoglobin levels in the first and the second trimester of pregnancy is less than 11 grams per deciliter, and in the third trimester is less than 10.5 grams per deciliter is considered anemia (10, 11). Anemia during pregnancy is a risk factor for mother and the fetus. Many studies have shown pregnancy outcomes, including low birth weight, neonatal deaths, perinatal deaths, premature birth, low gestational age, fetal death as a result of maternal anemia (12-19). A U-shaped distribution has been shown between hemoglobin concentration and pregnancy complications (20, 21). This means that the increase of hemoglobin (more than g / dL13 / 2) As reductions, lead to complications such as preterm delivery, intrauterine growth restriction and increased blood pressure Intrauterine growth retardation (IUGR) (21); while others study not have been achieved no association between Hemoglobin concentration and adverse pregnancy outcomes(27). So far, various studies which measured the link between hemoglobin concentrations with pregnancy outcomes have been conducted in the world. Previous research has demonstrated a strong association between severe anemia and maternal mortality (29); also, other meta-analysis with the same title was conducted in 2011. Since then, there have been many studies in this regard. To put all the findings together and provide a more accurate picture of the problem, performing another meta-analysis, seems to be necessary. The aim of this study was to evaluate the relationship between maternal anemia in all trimesters separately with pregnancy outcomes from Jan 1990 to Apr 2016 and to investigate its overall trend in the world by performing a systematic review and meta-analysis study.

2- MATERIALS AND METHODS

2-1. Search strategy

This systematic review study was conducted from Jan 1990 to Apr 2016. Articles extracted by using related key words in domestic (Sid, Iran.doc, Iran medex and Magiran) and international (PubMed, Science Direct, Cochrane, Medline, Web of Science, Scopus, Springer, Embase, Google scholar) databases. To maximize the comprehensiveness of the search results, Persian key words and all possible combinations of words were searched in domestic database. MESH key words including "Pregnancy", "Pregnant women", "Hemoglobin/haemoglobin", "Anemia/anaemia", "Hematologic", "Haematologic parameter", "Mortality", "Preterm birth delivery", "Low birth weight" and "Small for gestational age",

were searched in the international electronic database. Boolean searches using "AND" or "OR" applied for searching combination words to get comprehensive results. The list of evaluated article references was used to find more studies. The study was performed based on the PRISMA check list for meta-analysis studies (38) (**Figure.1**).

2-2. Inclusion and exclusion criteria

Inclusion criteria in the present study, including:

- Studies in which the relationship between maternal anemia during pregnancy and pregnancy outcomes was identified,
- Availability of full text articles,
- The studies with population of infants and pregnancy outcomes,
- The studies science 1990 to next.

Exclusion criteria include studies:

- With non-random sample sizes,
- **2**-Unrelated to the topic,
- with inadequate data,
- Unidentified the month of pregnancy,
- With a different definition of maternal anemia,
- Inaccessible to needed data,
- 7-the studies before 1990.

To prevent the bias, search process, study selection, quality assessment and extracting data conducted by two researchers independently.

2-3. Study Selection

Firstly, the researchers obtained some articles from throughout the search. Every study about hemoglobin concentration and pregnancy outcomes was selected. Then, by reviewing abstract and full text, all the studies that had a real connection to the topic entered into the study. In this study, all cohort, case-control and cross-sectional studies that measured the relationship between maternal anemia and pregnancy outcomes were analyzed. Pregnancy outcomes including: low birth weight (LBW), pre-term birth (PTB), Small for gestational age (SGA), stillbirth (SB), neonatal deaths (ND) and perinatal deaths (PD). Only LBW, PTB and SGA were analyzed during analysis, because few studies were conducted to evaluate other outcomes. To assess the significance, the relative risk with 95% confidence intervals (CI) and P-value less than 0.05 was considered.

2-4. Data Extraction

Data extraction was performed by two researchers independently and an extraction form (the author's name, year of publication, country, Continent, the number of participants, trimester and pregnancy outcome, relative risk and confidence interval and P-value of pregnancy outcomes) was used to minimize bias and error in collecting data. If some information in the articles, was not clear and need to ask specific questions, needed questions were asked from the author by e-mail. Each of the researchers compared the extracted data and discussed together if they had any conflict about extracted data. They discussed with a third researcher, until they came to an agreement by re-evaluating and comparing the results.

2-5. Outcomes of interests

The outcomes of interests were LBW, PTB and SGA. Low birth weight was defined as a newborn with weight at birth of less than 2,500 grams. Pre-term birth was defined as a neonate born before 37 weeks of gestational age (the 259^{th} day). Small for gestational age was a newborn whose birth weight was below the 10^{th} percentile for gestational age (47).

2-6. Statistical Analysis

Extracted data in the present study, including the study code, type of the study,

the author's name, year of publication, continent, the number of participants, trimester, pregnancy outcomes, relative risk, confidence interval and P-value. A hemoglobin classification was conducted as follows: <14, 11-13, 11> g/dl (10, 11). In this study, a mother with hemoglobin less than 11 has been considered as anemic and also, pregnancy outcomes were analyzed based on their definition. The effect of hemoglobin in pregnant women in the first, the second and third trimester of pregnancy was investigated about all types of pregnancy outcomes using the relative risk index and the heterogeneities were assessed using I^2 index statistic. I^2 is an index that shows heterogeneities among studies, I^2 less than 25% show low heterogeneities, $\%25 < I^2 < 75\%$ moderate heterogeneity, and $I^2 > 75\%$ high heterogeneity. When Q statistics was significance we used random effect models. For the heterogeneity of studies, the random effect model was used to combine the study's results. In every study, Relative risks (RR) or Odds ratio (OR) extracted the lower and higher limit. In studies that this index was not extracted, it was calculated through OR=ad/bc (Articles that had not the OR to use the formula) and the logarithm of OR or RR was used to polarize the effect size. Error standard was calculated by SE= 1n (upper 95% CI / lower 95% CI) / (2× 1.96). If only upper and lower limit had been reported in studies, OR= ad/bc was used. Meta-regression was used for evaluating the relation between year of study and effect size and evaluating the cause of heterogeneity of studies. Begg's funnel plot, was used to investigate publication bias and sensitivity analysis was performed to evaluate the effect of each study on the overall results. STATA software version 3.2 was used to analyze in this study and P<0.05 has been considered significance level for all analyzes.

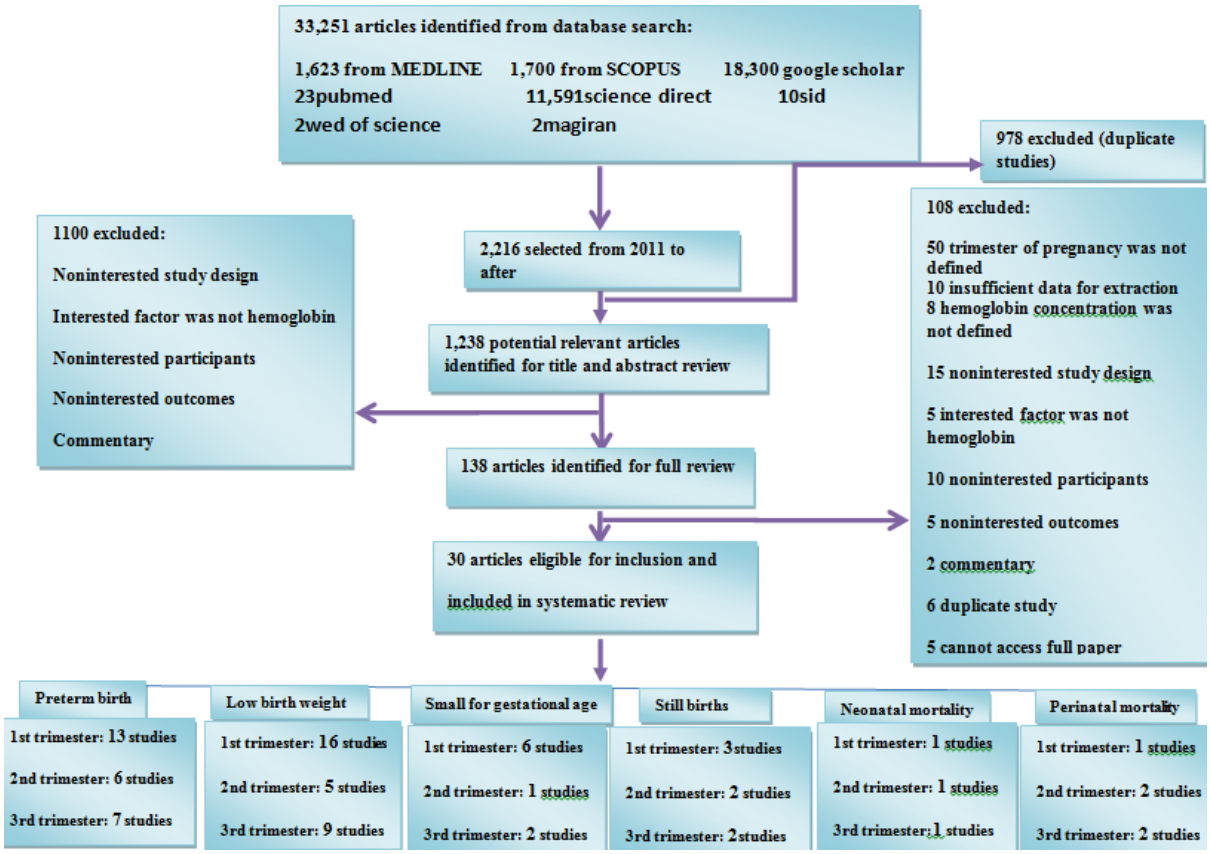

Fig.1: Entry procedures of studies to meta-analysis

3- RESULTS

Overall 30 studies with a total sample size of 1,194,746 were entered into the final meta-analysis. In the present meta-analysis about 80 percent of the studies were cohort, 13.3 percent cross-sectional and 6.6 percent case-control. The mean age of the studies was under 30± SD years old. Therefore, the age item was excluded during analysis and the majority of studies had been conducted in Asian countries.

3-1. The relationship between maternal anemia in the first trimester of pregnancy and low birth weight

3-1-1. By type of study

There were 12 cohort studies that evaluated maternal anemia in the first trimester and chronic low birth weight. When these studies were combined using a random effects model, it showed that there is a significant relationship between maternal anemia in the first trimester of pregnancy and LBW (relative risk, 1.28 [95% CI: 1.10 to 1.50]). Also, it showed that the Levy study (ref) had the highest weight among these studies. As shown in the following (**Figure.2)**, Chi-square tests show that the results of 12 cohort studies were heterogeneous and significant (I^2 Index= 76%, P = 0.000). When there is heterogeneity among results of studies that means the results of studies are differents.

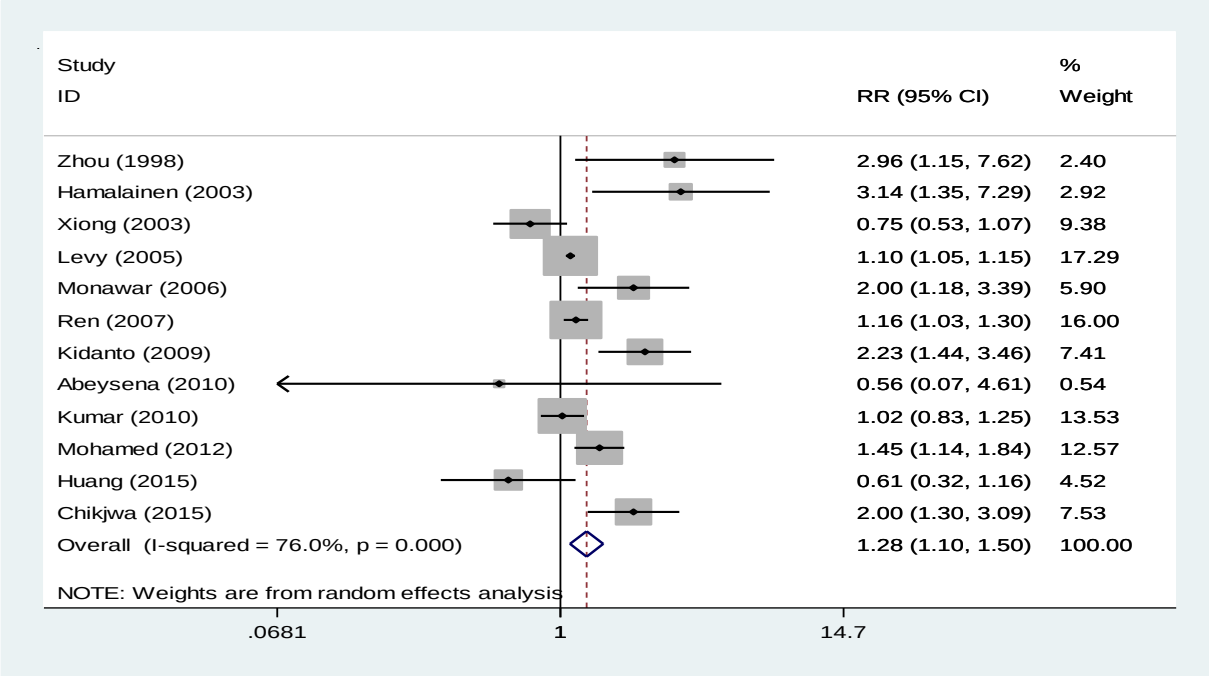

Fig.2: The relationship between maternal anemia in the first trimester of pregnancy and low birth weight by type of study

3-2. The relationship between maternal anemia in the first trimester of pregnancy and low birth weight

3-2-1. By continent

This relationship has been evaluated by 11 studies in Asia and one in Europe. By combining Asian studies using a random effects model, this relationship was significant (relative risk, 1.24 [95% CI: 1.07 to 1.45]). That means: study that was conducted in Asia have been significancy relationship. So in developing countries maternal anemia in the first trimester increases the risk of low birth weight. Chi-square tests show that heterogeneity was 75.1 percent and it was significant (P=0.000)**(Figure3).**

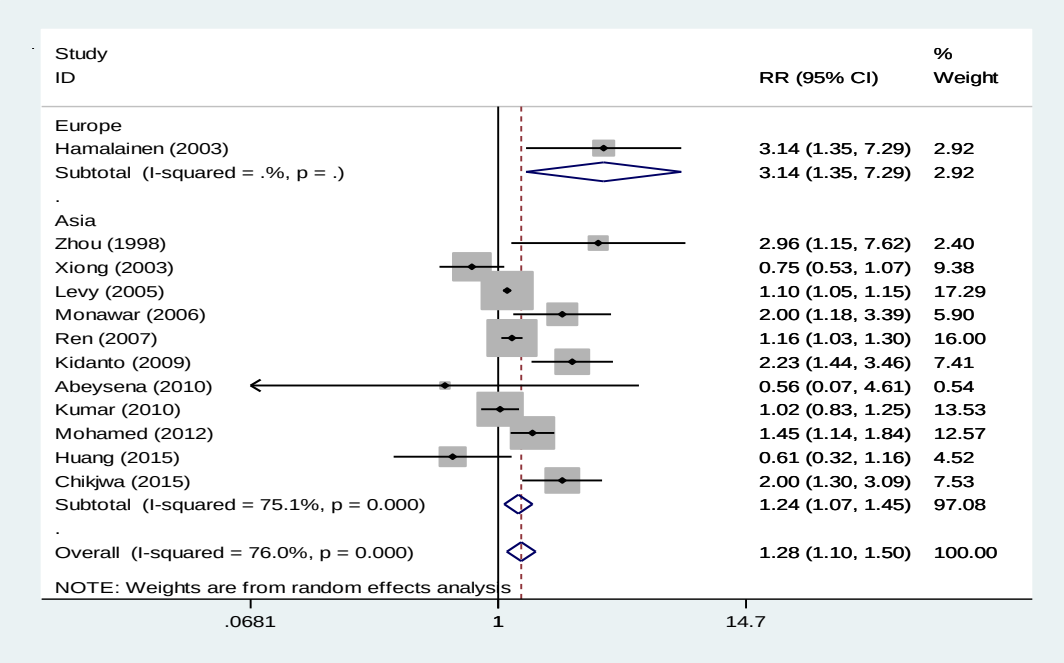

Fig.3: The relationship between maternal anemia in the first trimester of pregnancy and low birth weight by continent

3-2-2. By sensitivity analysis

Sensitivity analysis showed that the elimination of a study can change the results or not. It shows influence studies in meta-analysis, sometimes, elimination a study can change overall effect of meta-analysis significantly. In this study as shown in the following **Figure.4**, eliminating a study had no effect on the overall results.

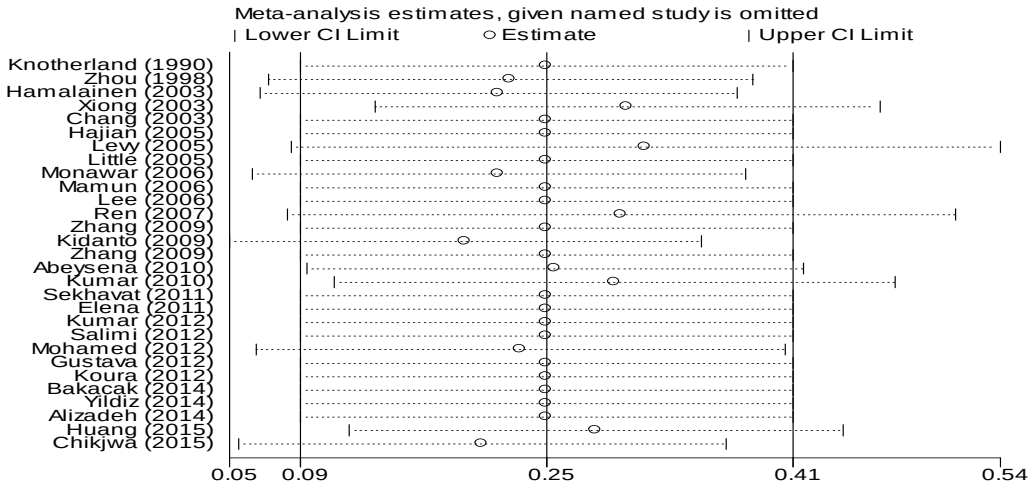

Fig.4: The relationship between maternal anemia in the first trimester of pregnancy and low birth weight by sensitivity analysis

3-3. Begg's funnel plot for the first trimester maternal anemia relationship with low birth weight

Egger test has greater power to detect publication bias. The Kendall correlation coefficient is 0.69 at Begg's test and is not significant statistically (P=0. 493). Egger's test also, showed that there hasn't been publication bias (P = 0.152) (**Figure.5**).

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Note: default data input format (theta, se_theta) assumed.

Tests for Publication Bias

Begg's Test

  adj. Kendall's Score (P-Q) =      10
         Std. Dev. of Score =   14.58
          Number of Studies =      12
                          z =    0.69
                    Pr > |z| =   0.493
                          z =    0.62 (continuity corrected)
                    Pr > |z| =   0.537 (continuity corrected)

Egger's test
```

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.0713501	.0475634	1.50	0.164	-.0346279	.1773281
bias	1.081983	.6971966	1.55	0.152	-.4714681	2.635433

Fig.5: Begg's funnel plot for the first trimester maternal anemia relationship with low birth weight

3-4. The relationship between maternal anemia in the second trimester of pregnancy with low birth weight

3-4-1. By type of study

Among all the studies, two cohort studies and a case-control study were investigated in this relationship. There was no significant relationship in these studies. When the results were combined together by using a random effects model, no significant relationship was found (relative risk, 1.19 [95% CI: 0.65 to 2.17]).

3-4-2. By continent

This relationship was investigated by a study in Asia, Europe and U.S.A, but no significant relationship was found in any of the continents.

3-4-3. By sensitivity analysis

Sensitivity analysis showed that the elimination of a study can change the results or not. In this study as shown in the following **(Figer.6**), eliminating a study had no effect on the overall results and anyway relationship between maternal anemia and low birth weight is significant.

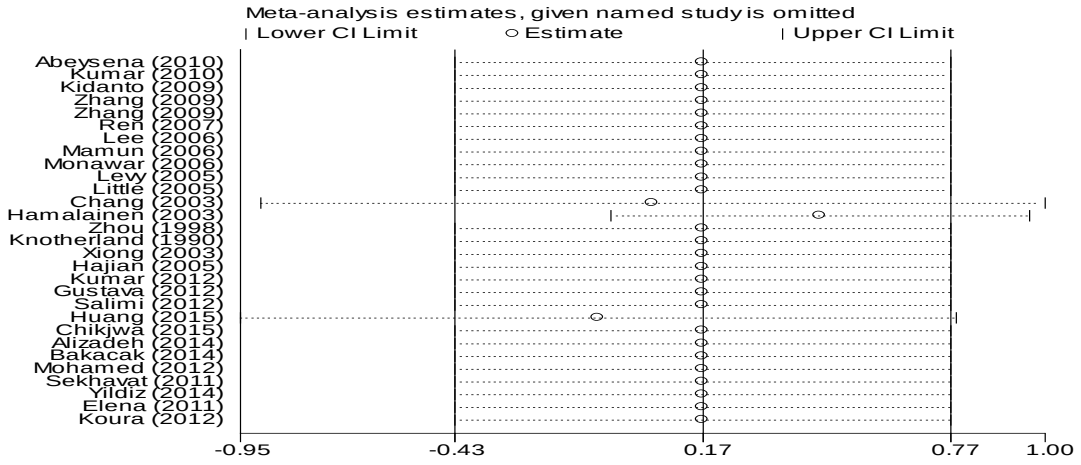

Fig.6: The relationship between maternal anemia in the second trimester of pregnancy and low birth weight by sensitivity analysis

3-5. The relationship between maternal anemia in the third trimester of pregnancy with low birth weight

3-5-1. By type of the study

Among 8 studies that have been examined this relationship, 6 cohorts (relative risk, 1.23 [95% CI: 0.94 to 1.60]), a case-control (relative risk, 1.28 [95% CI: 0.63 to 2.61]), and a cross-sectional (relative risk, 1.65 [95% CI: 0.17 to 15.90]) studies didn't show significant relationship. A random effects model was used to combine the studies and showed no significant relationship between maternal anemia in the third trimester and low birth weight (relative risk, 1.23 [95% CI: 0.97 to 1.55]). Chi-square tests showed that the results of 8 studies have been heterogeneous and significant (I-squared= 70.5%, P = 0.001) **(Figue.7).**

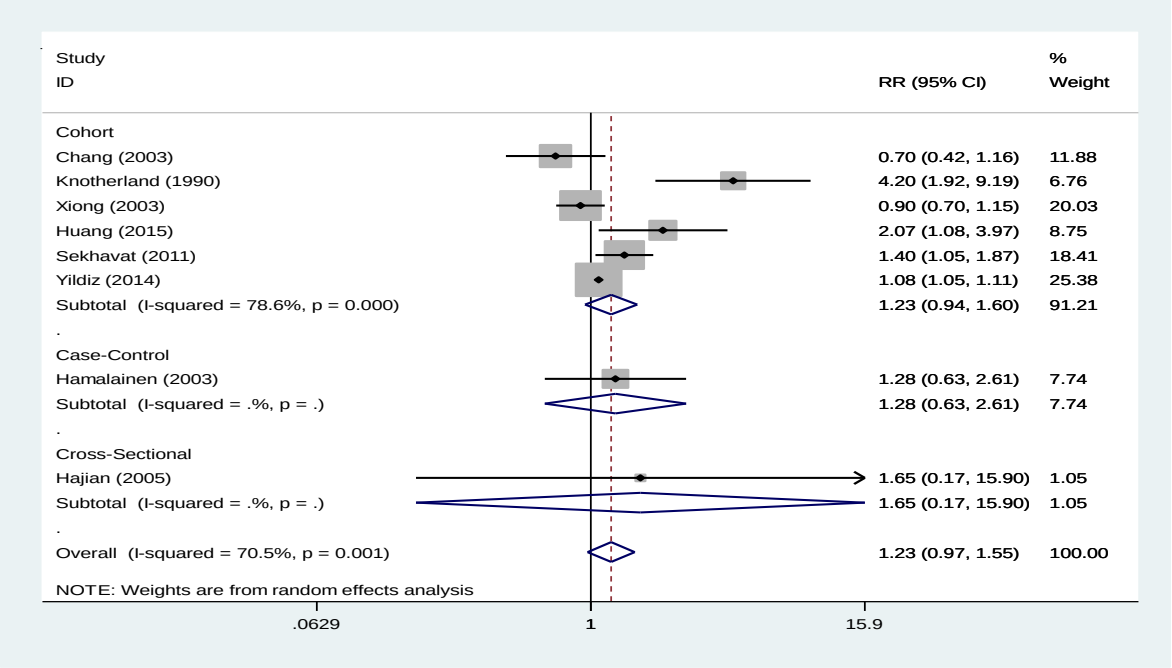

Fig.7: The relationship between maternal anemia in the third trimester of pregnancy with low birth weight by type of the study

3-5-2. By continent

In total, there were 4 studies in Asia (relative risk, 1.28 [95% CI: 0.86 to 1.90]), 3 studies in Europe (relative risk, 1.67 [95% CI: 0.79 to 3.54]), and a study in the U.S.A (relative risk, 0.70 [95% CI: 0.42 to 1.16]) that investigated this relationship and were found no significant relationship between any of the Continents. Chi-square tests showed that there is heterogeneity between studies conducted in Asia and Europe (I-squared=70. 5%, P=0. 001). The effect of heterogeneity was significant (P= 0.032, P = 0.003) **(Figer.8**).

3-5-3. By sensitivity analysis

Sensitivity analysis showed that the elimination of a study can change the results or not. It shows influence studies in meta-analysis, sometimes elimination a study can change overall effect of meta-analysis significantly. In this study as shown in the following (**Figure.9)**, eliminating a study had no effect on the overall results.

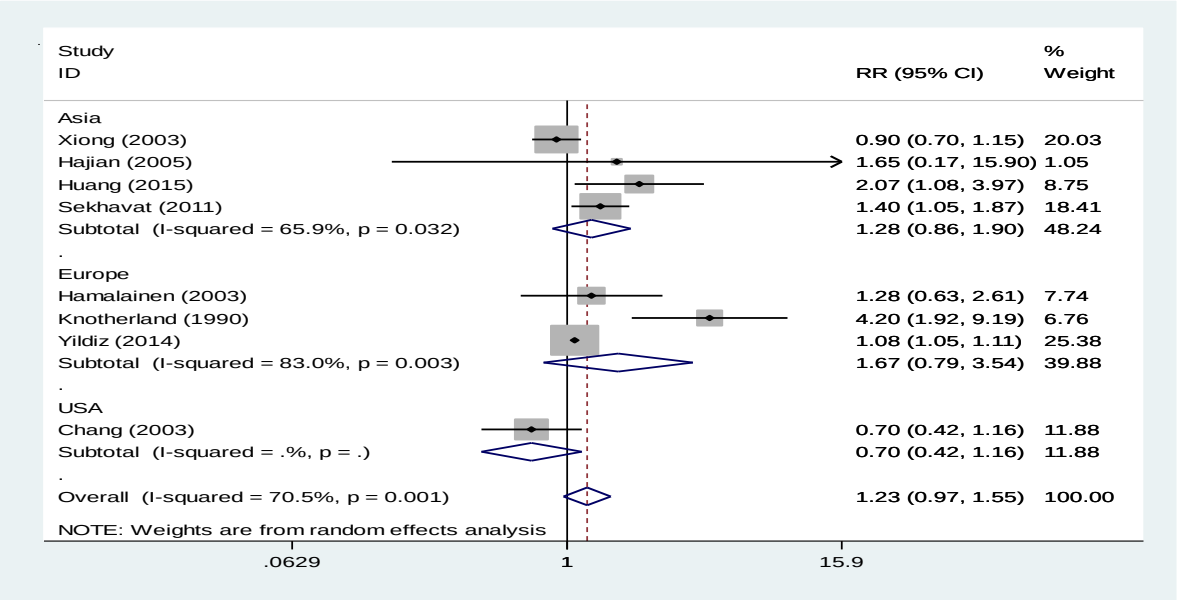

Fig.8: The relationship between maternal anemia in the third trimester of pregnancy with low birth weight by continent

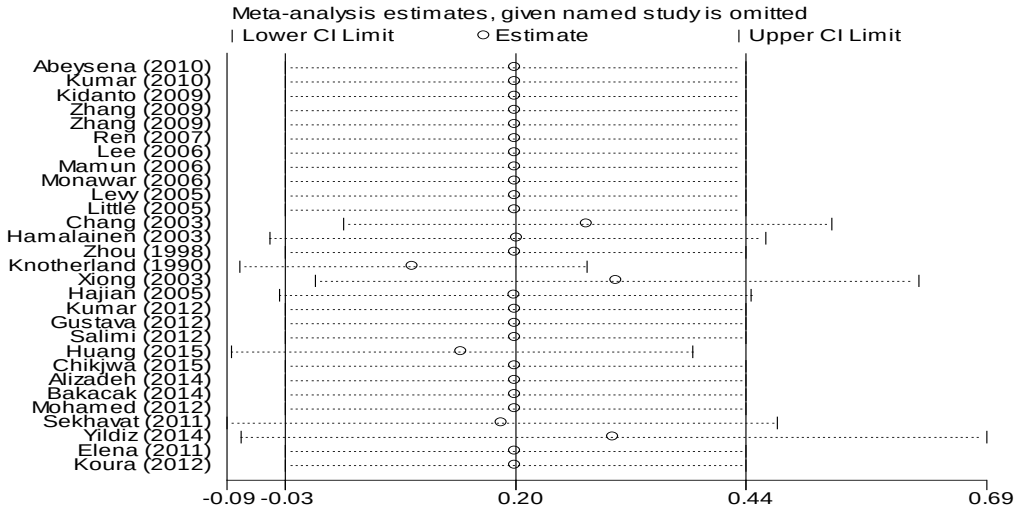

Fig.9: The relationship between maternal anemia in the third trimester of pregnancy and low birth weight by sensitivity analysis

3-6. The relationship between maternal anemia in the first trimester of pregnancy with preterm birth

In total, 9 studies were evaluated in this relationship, the studies were combined using a random effects model and showed a significant relationship (relative risk, 1.26 [95% CI: 1.11 to 1.44]). Chi-square tests showed that heterogeneity between studies is 55 percent and this moderate heterogeneity was significant (I-squared=55%, P=0.023) (**Figure.10)**

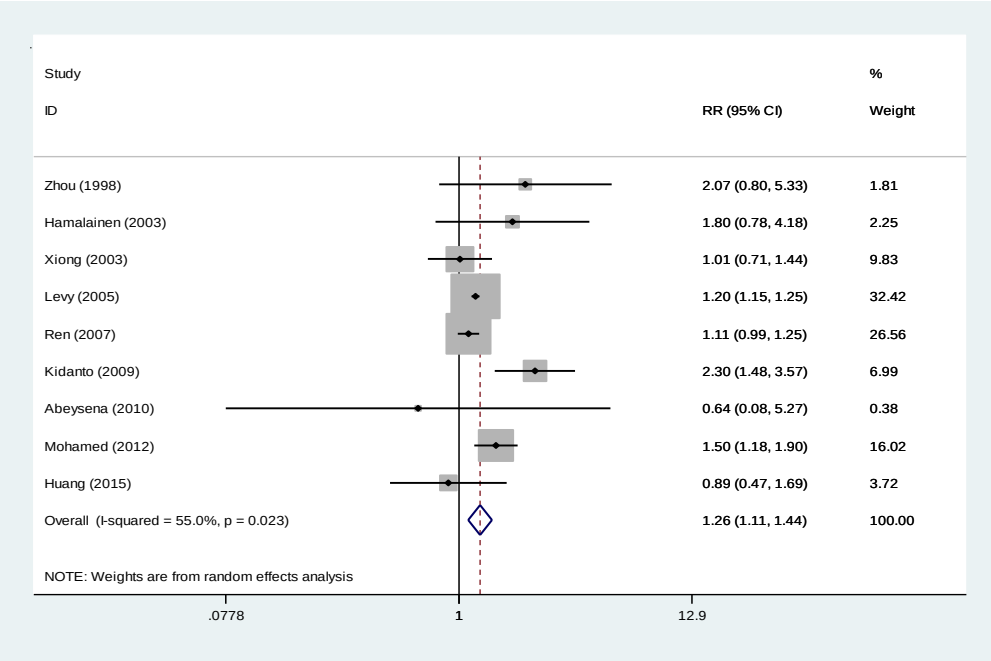

Fig.10: The relationship between maternal anemia in the first trimester of pregnancy with preterm birth

3-6-1. By type of the study

Seven cohorts (relative risk, 1.20 [95% CI: 1.05 to 1.39]) and two case-control (relative risk, 1.52 [95% CI: 1.21 to 1.91]) Studies, were investigated in this relationship, the studies were combined using a random effects model and showed a significant relationship (P=0.023) (**Figure.11).**

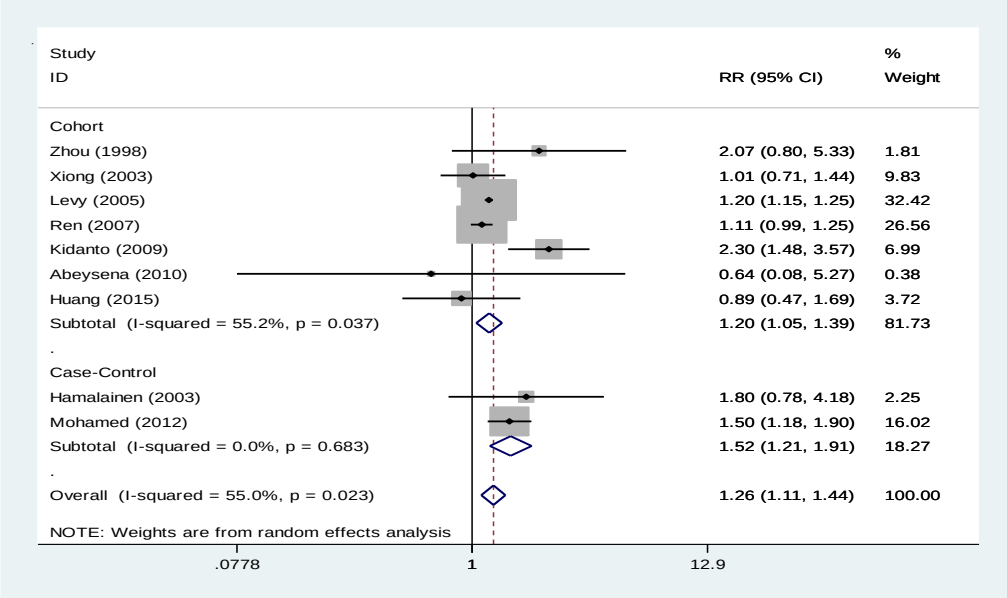

Fig.11: The relationship between maternal anemia in the first trimester of pregnancy with preterm birth by type of the study

3-6-2. By Continent

One study in Europe (relative risk, 1.80 [95% CI: 0.78 to 4.18]) and 8 studies in Asia (relative risk, 1.25 [95% CI: 1.09 to 1.43]), were conducted. The studies were combined using a random effects model and showed a significant relationship in Asian countries. Chi-square tests showed that heterogeneity between studies is 58.6 percent and this heterogeneity was significant (I-squared=55%, P=0. 018) (**Figure.12).**

3-7. Begg's funnel plot

This plot was used to check publication bias and showed the effect of publication bias was not significant with a P-value less than 0.05 (**Figure.13).**

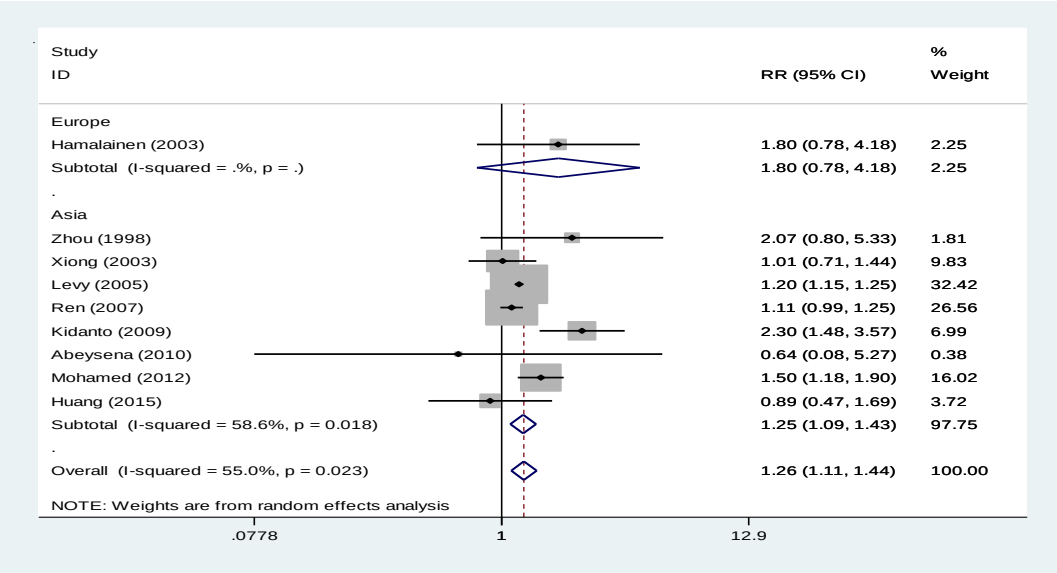

Fig.12: The relationship between maternal anemia in the first trimester of pregnancy with preterm birth by Continent

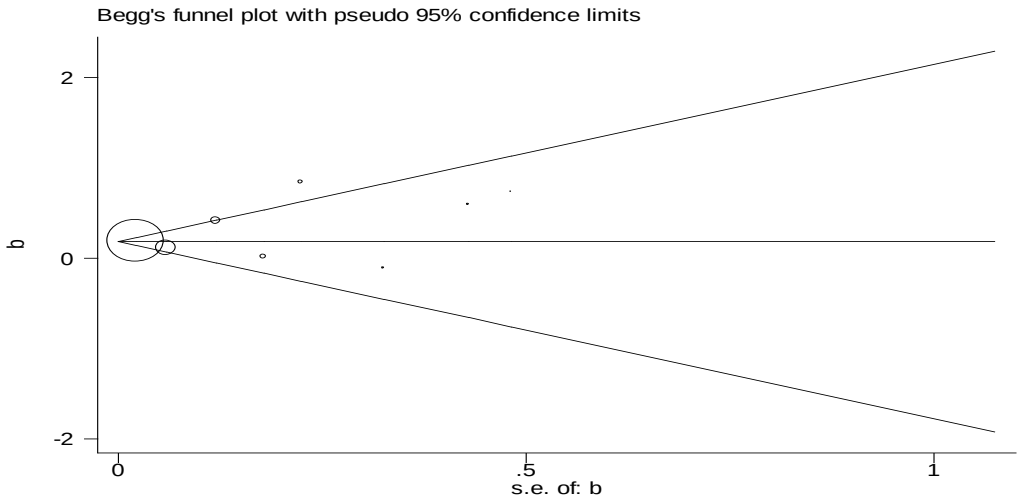

Fig13: Begg's funnel plot of relationship between maternal anemia in the first trimester of pregnancy with preterm birth

3-8. The relationship between maternal anemia in the first trimester of pregnancy and SGA

3-8-1. By type of study

Among all the studies, 5 cohort studies and a case-control study were investigated in this relationship. By using a random-effects model cohort studies were combined together and this relationship was significant (relative risk, 1.12 [95% CI: 1.05 to 1.19]). That means maternal anemia in the first trimester increases the risk of SGA (**Figure.14).**

3-8-2. By continent

In total, 4 studies in Asia, a study in Europe and a study in the U.S.A were investigated this relationship. By using a random-effects model, the studies were combined together and this relationship was significant (relative risk, 1.12 [95% CI: 1.05 to 1.19]) (**Figure.15).**

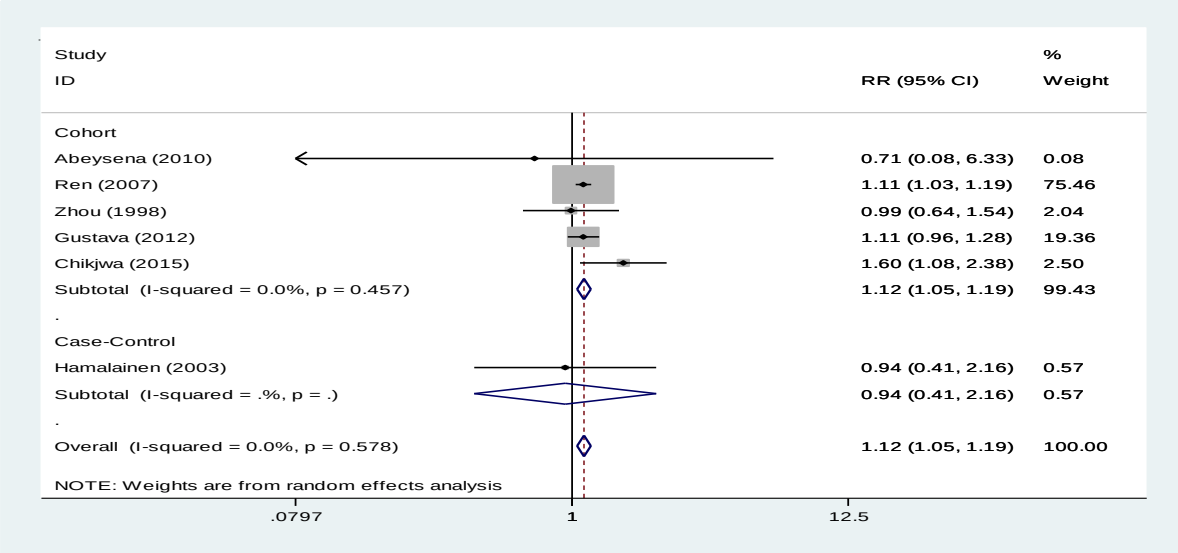

Fig.14: The relationship between maternal anemia in the first trimester of pregnancy and SGA by type of study

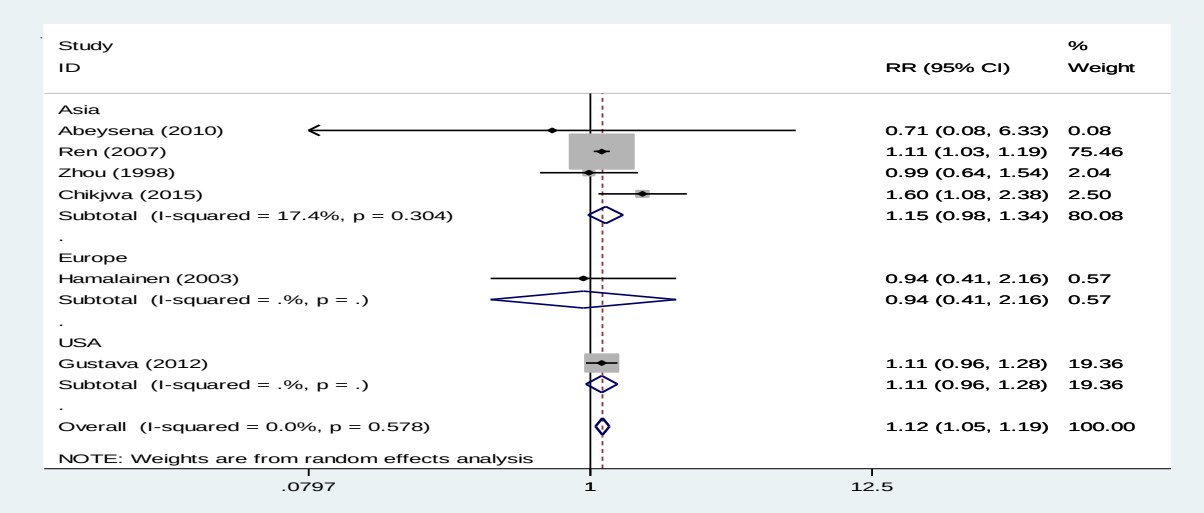

Fig.15: The relationship between maternal anemia in the first trimester of pregnancy and SGA by Continent

3-9. The relationship between maternal anemia in the second trimester of pregnancy and PTB

3-9-1. By type of study

Among all the studies, 3 cohort studies (relative risk, 1.50 [95% CI: 0.51 to 4.38]), and a case-control study (relative risk, 0.97 [95% CI: 0.53 to 1.78]) showed significant relationship. Then, by using a random-effects model studies were combined together and no significant relationship was observed between maternal anemia in the second trimester of pregnancy and PTB (relative risk, 1.35 [95% CI: 0.54 to 3.34, P=0.86]) (**Figure.16).**

3-9-2. By continent

Two studies in Asia (relative risk, 1.87 [95% CI: 0.53 to 6.65]), a study in Europe (relative risk, 0.97 [95% CI: 0.53 to 1.78]) and a study in U.S.A (relative risk, 0.85 [95% CI: 0.31 to 2.23]) had been conducted and showed no significant relationship in any of the Continents (**Figure.17).**

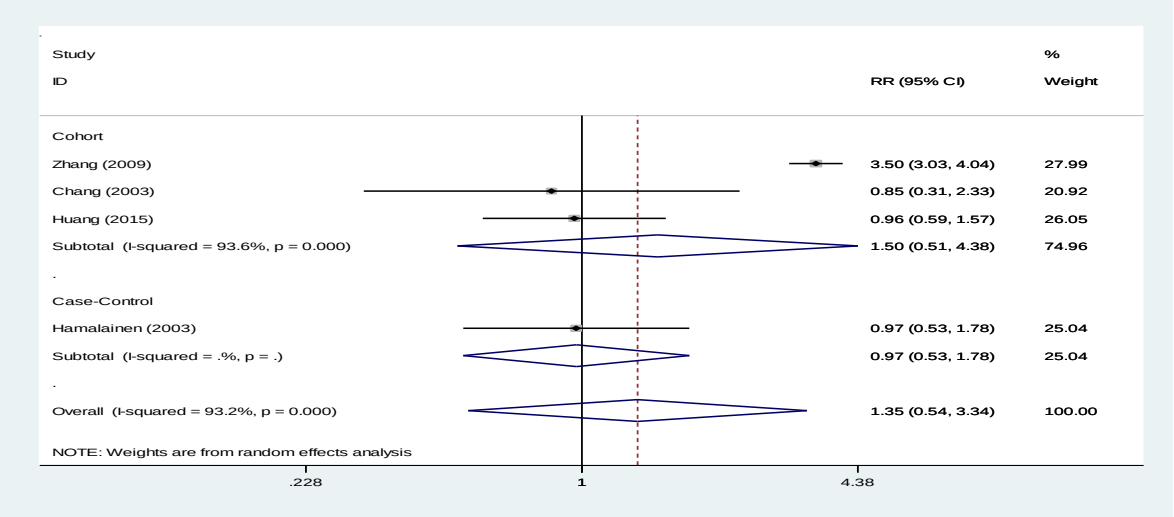

Fig.16: The relationship between maternal anemia in the second trimester of pregnancy and PTB by type of study

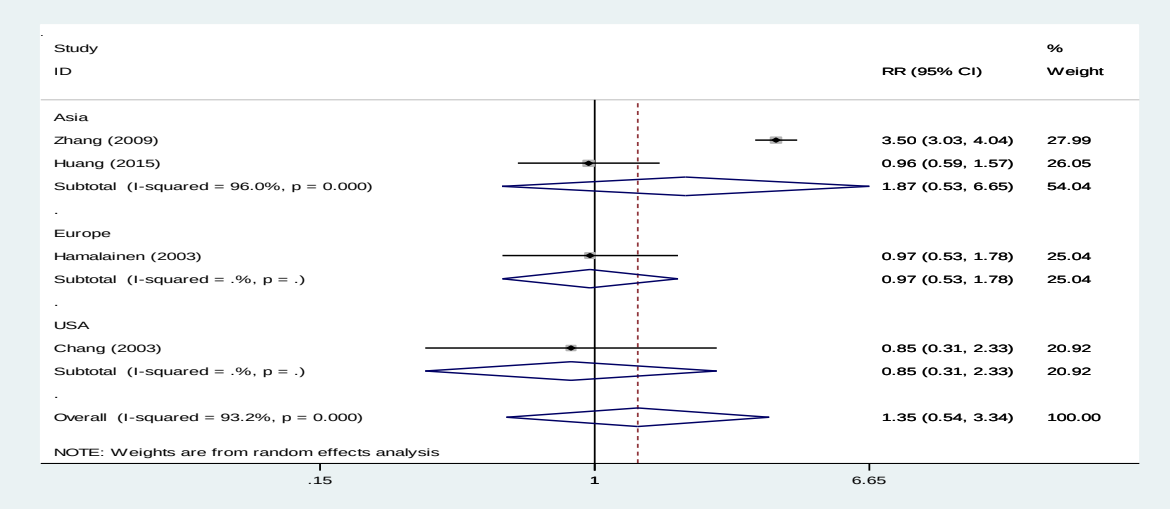

Fig.17: The relationship between maternal anemia in the second trimester of pregnancy and PTB by Continent

3-9-3. By sensitivity analysis

It showed among the studies that were measured in this relationship, removing a study has no effect to the results of other studies **(Figure.18).**

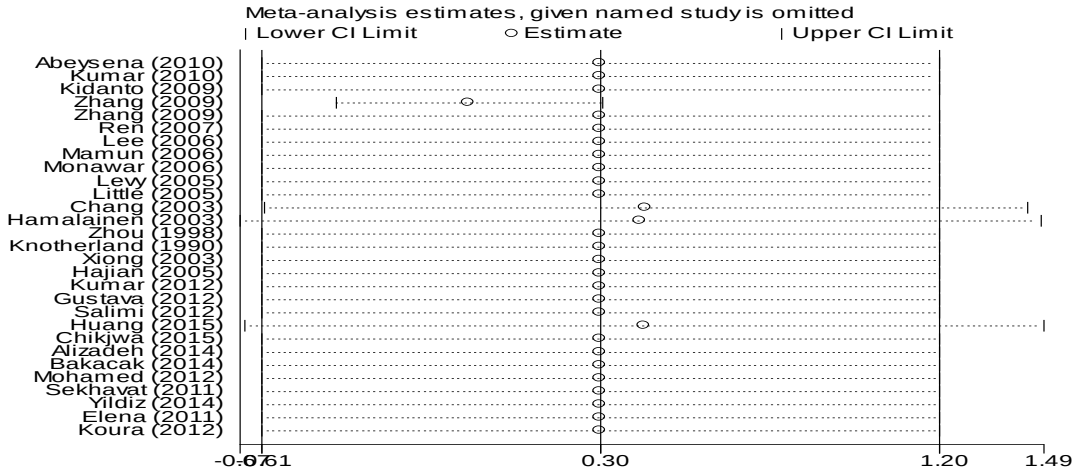

Fig.18: The relationship between maternal anemia in the second trimester of pregnancy and PTB by sensitivity analysis

3-10. The relationship between maternal anemia in the third trimester of pregnancy and PTB

3-10-1. By type of study

Five cohort studies (relative risk, 1.44 [95% CI: 0.66 to 3.16]), a case-control study (relative risk, 1.53 [95% CI: 0.88 to 2.65]) and a cross-sectional study (relative risk, 2.37 [95% CI: 1.01 to 5.57]), were investigated this relationship and a significant relationship was observed only in cross-sectional study (P<0.05). Overall results showed no significant relationship by using a random-effects model (relative risk, 1.55 [95% CI: 0.83 to 2.88]) (**Figure.19).**

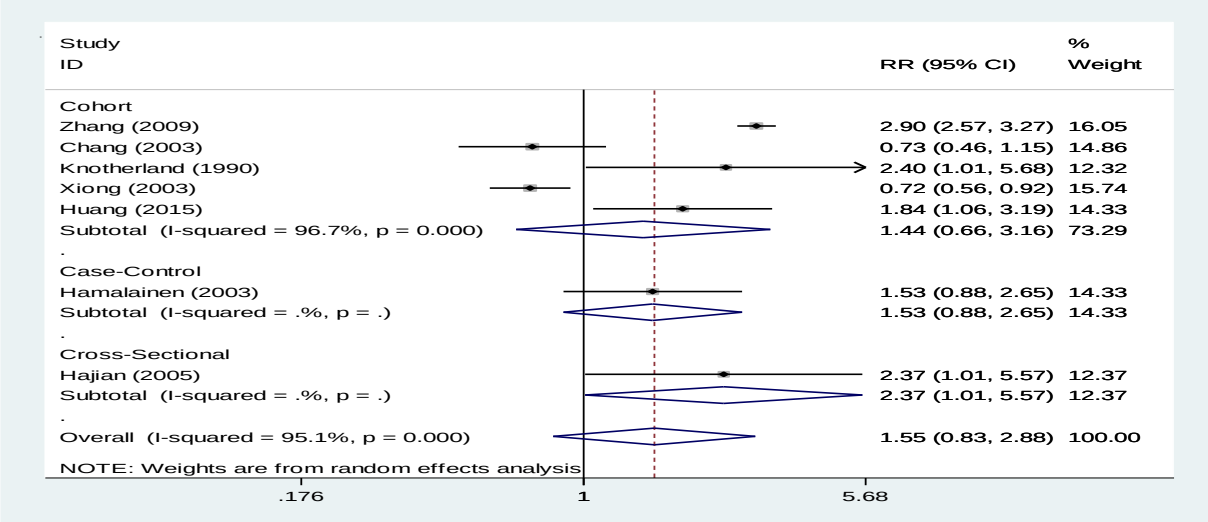

Fig.19: The relationship between maternal anemia in the third trimester of pregnancy and PTB by type of study

3-10-2. By Continent

Four studies in Asia (relative risk, 1.77 [95% CI: 0.71 to 4.11]), two studies in Europe (relative risk, 1.74 [95% CI: 1.10 to 2.77]), and a study in U.S.A (relative risk, 0.73 [95% CI: 0.46 to 1.15]) had investigated this relationship and was found a significant relationship only in Europe (P<0.05). Overall results by using random-effects model showed no significant relationship (relative risk, 1.55 [95% CI: 0.88 to 2.88]) **(Figure.20).**

3-10-3. By year of publication

The size of the circle shows the sample size. Whatever sample size is large, the size of the circle is bigger and the regression equation was estimated as: y = -18.61 + 0.0094x. Since, P=0.81 was estimated for the slope of the line. It was concluded that there was no significant relationship between article's publication year and effect size (**Figure.21**).

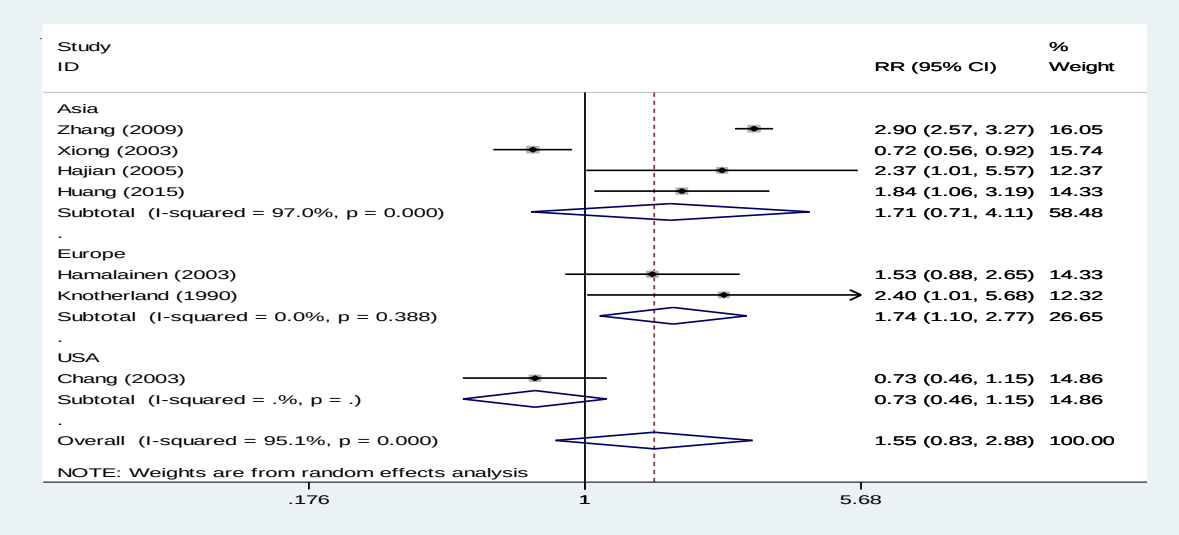

Fig.20: The relationship between maternal anemia in the third trimester of pregnancy and PTB by Continent

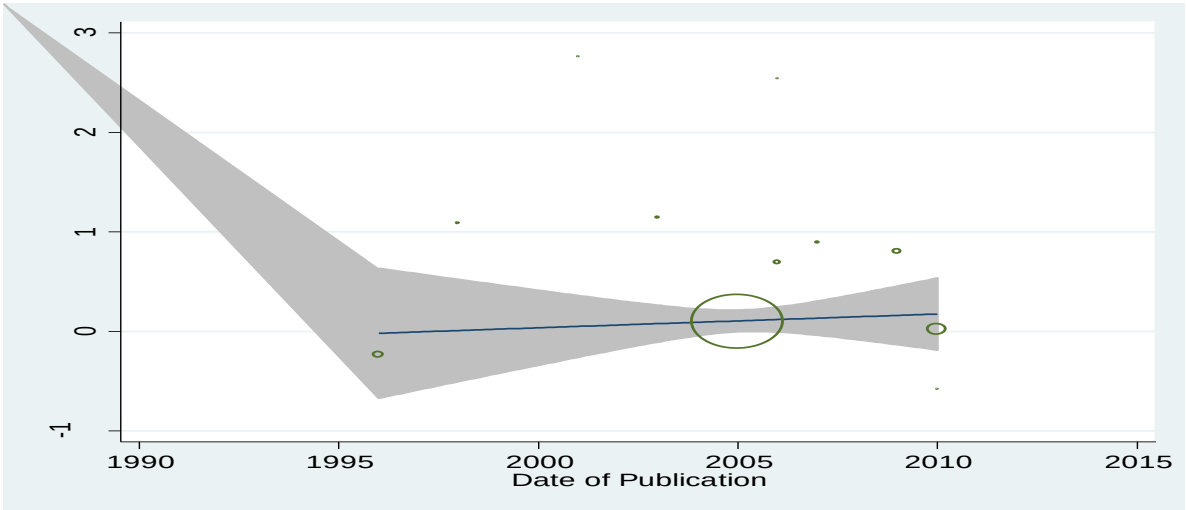

Fig.21: The relationship between maternal anemia in the third trimester of pregnancy and PTB by year of publication

3-10-4. By sensitivity analysis

Sensitivity analysis showed that the elimination of a study can change the results or not. In this study as shown in the following (**Figer.22)**, eliminating a study had no effect on the overall results.

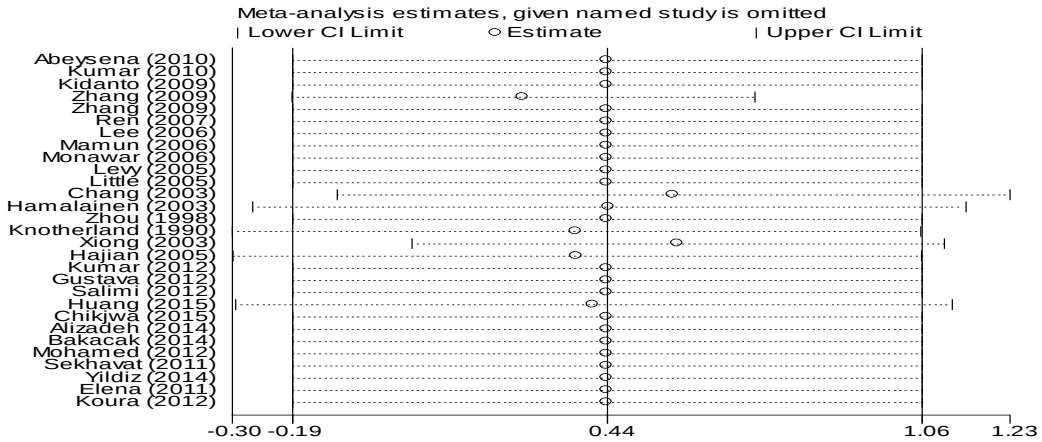

Fig.22: The relationship between maternal anemia in the third trimester of pregnancy and PTB by sensitivity analysis

4- DISCUSSION

The present study is a systematic review and meta-analysis about hemoglobin concentration and pregnancy outcomes in the world that showed how much effect maternal anemia has on pregnancy outcomes. Nowadays, maternal anemia is considered as a public health problem in the world, especially in developing countries. For example, the prevalence of anemia among pregnant women is 52 percent in developing countries and 22.5 percent in developed countries (5). In this study the relationship between hemoglobin concentrations and pregnancy outcomes was investigated by the type of study, year of publication, country, continent, sample size and by the trimesters of pregnancy. The result showed that maternal anemia in the first trimester of pregnancy has a significant relationship with LBW, PTB and SGA that means maternal anemia in the first trimester increases the risk of these outcomes. Also, it was shown that maternal anemia in the second and the third trimester has no significant relationship with LBW and PTB. The analysis of sub-groups was shown that significant relationships have been observed more in studies with larger sample sizes, in pregnant women with anemia in the first trimester. LBW and PTB have been found in most of the studies and significant relationship was observed more in developing countries like Asian countries. Similar Meta-analysis study had been conducted by Sukrat in 2013, showed that hemoglobin less than 11 g/dl in the first trimester is a risk factor for LBW (relative risk, 1.14 [95% CI: 1.05 to 1.24]), PTB (relative risk, 1.10 [95% CI:1.02 to 1.19]) and SGA (relative risk, 1.17 [95% CI: 1.03 to 1.33]) (53).

This finding is consistent with the results of this study. This study showed that maternal anemia in the third trimester has no significant relationship with the risk of LBW (relative risk, 1.23 [95% CI: 0.97 to 1.55]). Although, it can be said that maternal anemia in the third trimester could be a borderline risk for LBW but, it wasn't consistent with Sukrat study that showed maternal anemia in the third trimester increasing the risk of LBW (relative risk, 1.30 [95% CI 1.08 to 1.58]) (53).

Another review study had been conducted by Ahankari about maternal hemoglobin and low birth weight in 2015. The finding is consistent with our results (54). In a subgroup analysis, the present study showed that this relationship is observed more in developing countries that were consistent with other study results (54-56).

4-1. Limitations of the study

1. Inability of domestic and international databases for searching the combined keywords, combination keywords cannot be used.
2. Anemia is defined differently in various studies.
3. The majority of studies have been conducted in Asian countries.
4. Some studies were excluded due to:

- Poor quality such as studies with a small sample size;
- Not identifying the months of pregnancy;
- Publication bias;
- Inadequate data;
- Failure to report particular outcome;
- Definition of outcome was not clear;
- Medical theses.

5- CONCLUSION

The study showed that hemoglobin below11g/dl increases the risk of LBW, PTB and SGA in the first trimester that this relationship observed more in developing countries. But, this relationship (maternal anemia and pregnancy outcome) in the second and third trimester of pregnancy was not significant. So, maternal anemia during pregnancy in the first trimester in particular, can be considered as a risk factor for pregnancy outcomes and should be treated as advance.

6- CONFLICT OF INTEREST: None.

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