META-ANALYSIS

# Meta Analysis of the Effects of Thalassemia Minor on the Incidence of Amniotic Fluid Abnormalities and the Amount of Bleeding During Delivery

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## ABSTRACT

**Objective** • To analyze the effects of thalassemia minor on the incidence of amniotic fluid abnormalities and the blood loss of pregnant women during delivery based on the database.

**Methods** • PubMed, EMBASE, EBSCO, Web of Knowledge and Ovid databases were searched for articles on the incidence of amniotic fluid abnormalities and the amount of bleeding during delivery in pregnant women with mild thalassemia; it can also be combined with manual retrieval for literature review. The data retrieval period was from the establishment of the database to June 2022. According to the Newcastle Ottawa scale score, the quality of the six included literature was evaluated, and the Revman processing software was used for meta-analysis.

**Results** • The 6 included articles are all high-quality literature, including 364 cases in the case group and 689 cases in the control group. The publication years of the literature are mainly from 2013 to 2021, and they are all high-quality literature. All literature was blinded, and a total of 4 pregnancy outcomes were extracted from the 6 included literature, including oligohydramnios/oligohydramnios, postpartum hemorrhage, preterm delivery, and cesarean section. Compared to normal pregnant women, the level of postpartum bleeding in thalassemia pregnant women was significantly increased [RR = 2.40, 95% CI (1.63-3.54), $P < .05$], and the difference was statistically significant. Compared to normal pregnant women, thalassemia pregnant women have a significantly higher risk of developing excessive/insufficient amniotic fluid [RR = 2.71, 95% CI (2.52-2.81), $P < .01$], and the difference is statistically significant. Compared to normal pregnant women, pregnant women with thalassemia have a significantly higher risk of premature birth [RR = 3.02, 95% CI (1.84~4.96), $P < .05$], and the difference is statistically significant. Compared to normal pregnant women, the risk of cesarean section in thalassemia pregnant women is significantly increased [RR = 1.68, 95% CI (1.39-2.02), $P < .05$], and the difference is statistically significant.

**Conclusion** • Thalassemia minor can increase the incidence of amniotic fluid abnormalities and the amount of bleeding during labor. In the future, we should strengthen the health education of pregnant women, improve the understanding of the disease, avoid or reduce the impact of thalassemia on newborns, improve the pregnancy outcome, and provide a more reliable basis for clinical decision-making.However, there are still certain limitations: (1) the literature selected in the study for the past 5 years is relatively small, and they are all single center, retrospective studies, and have a small sample size, resulting in insufficient accuracy of the results of the meta-analysis; (2) Some literature lacks blind methods, which may lead to language bias and implementation bias in the results; (3) The research time is still short, and it has not been clear how different types of thalassemia affect abnormal amniotic fluid volume and postpartum bleeding. (*Altern Ther Health Med.* 2024;30(1):192-197).


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## INTRODUCTION

Thalassemia is a blood disease with a genetic nature, and its main clinical feature is the obvious reduction of hemoglobin globin chain synthesis. It will not only cause anemia in patients but also affect the growth and development of infants and skeletal abnormalities, and even affect the life of patients.[1-2] For pregnant women during pregnancy, with the increase of gestational time, the iron requirement of fetal development increases, and the incidence of anemia in pregnant women

constantly increases. According to the severity of the disease, thalassemia can be divided into stationary (loss of globin gene in hemoglobin, mild condition, mild physical fatigue and fatigue), mild (no obvious symptoms, examination can cause modern compensatory bone marrow cell proliferation and volume expansion), intermediate (deficiency or insufficiency of one or more globin chains synthesis in hemoglobin, manifested as enlarged head, widened eye distance, saddle nose, protruding forehead, etc.), and severe thalassemia (mainly manifested as pale complexion, enlarged liver and spleen, and severe underdevelopment). Compared with stationary and mild thalassemia, with the increase of the disease, the occurrence risk of adverse pregnancy outcomes such as premature delivery, maternal mortality, cesarean section rate, fetal edema syndrome of intermediate and severe thalassemia pregnant women is significantly increased, and the fertility is significantly reduced.[3-5] According to statistics,[6] around 9 million carriers become pregnant every year worldwide, and about 1.33 million people are at risk of thalassemia. Among them, more than 55000 pregnant women suffer from thalassemia major, and more than 3500 people die of fetal edema syndrome during the perinatal period, which greatly impacts patients. As the social and economic progress and the improvement of people's quality of living, the emphasis on eugenics and prepotency has increased significantly. Healthy pregnancy outcomes have successfully become expectations of people, and pregnancy outcomes are directly related to the quality of the population.[7] In recent years, with the rapid development of medical science and technology, early diagnosis, blood transfusion and the continuous progress of anemia treatment methods, the quality of life of patients with thalassemia has been greatly improved, and the desire of patients to have offspring has been significantly increased.[8] Relevant researchers have evaluated the marital status, fertility rate, and adverse pregnancy outcomes of patients with thalassemia intermedia major and found that the serum ferritin level of patients with thalassemia intermedia major is significantly increased, and the infant survival rate and health rate are greatly increased.[9-11] Close monitoring and multidisciplinary methods are believed to be important in improving the pregnancy outcome of patients with thalassemia major. Despite advancements in thalassemia treatment, there is limited consensus on how mild thalassemia may affect specific pregnancy outcomes. Based on this, This study systematically evaluates the published original literature on the impact of mild thalassemia on pregnancy outcomes in pregnant women, in order to provide new evidence for reducing the risk of adverse pregnancy outcomes such as postpartum hemorrhage, abnormal amniotic fluid, premature delivery, and cesarean section in pregnant women with mild thalassemia, and to provide new ideas for improving patient prognosis.

## DATA AND METHODS

### Literature inclusion criteria

(1) All the included literature types were case-control studies and cohort studies. (2) Case group: (a) All pregnant women were diagnosed as mild thalassemia through prenatal testing or genetic analysis; (b) All pregnant women who participated in the research gave informed consent and signed their names on the informed consent form; (c) The pregnant women who were suffered from thalassemia for the first time; (d) Those without anemia and behavior such as iron supplementation before participating in the research; (e) Those who had basic listening, reading and writing skills, had a high degree of cooperation in research, and can cooperate with the research work; (f) Approved by the Institutional Review Board (IRB) and agreed by the patient. (3) Control group: healthy pregnant women who were examined and delivered at the same time as the case group were selected as the control group.

### Literature exclusion criteria

(1)The literatures that is contrary to the literature inclusion criteria; (2) The literatures that is unable to be obtained completely; (3) The literatures that has been published many times; (4) Animal experiments, reviews, or conferences and other documents that do not conform to the type of research; (5) The research objects in the literature were complicated with other diseases; (6) The literatures without a control group or with relatively poor quality; (7) The literatures whose extraction of the available data can be affected.

### Literature search strategy

The subject words were combined with free words, and PubMed, EMBASE, EBSCO, web of Knowledge, Ovid databases were searched by computer. The data retrieval period was from the establishment of the database to June 2022, and it can be combined with a manual search for literature review to reduce or avoid the omission of literatures. Chinese search terms include: mild thalassemia, delivery, pregnancy outcomes, randomized controlled trials, case-control studies, oligohydramnios, postpartum hemorrhage, cesarean section, preterm delivery, and cohort studies. The English search terms include: Mid thalassemia, delivery, priority outputs, randomized controlled trials, case control studies, oligohydramnios, postpartum hemorrage, cesarean section, term delivery, cohort studies

### Literature data extraction

At least two researchers performed the screening based on literature entry criteria and literature exit criteria, and the data were entered and checked. When there is the difference between the two opinions, a third person shall intervene in the discussion and make relevant judgments on whether the literature is included. Researchers needed to understand the title and abstract of the research articles, analyze and judge the literatures, exclude those that do not meet the standards, and finally include the required literatures. The main contents of data extraction were: (1) the title and first author of the included literatures; (2) Sample size, clinical data (age, number of pregnancies, number of births, mode of delivery, etc.) and quality control of observation objects; (3) Matching factors, pregnancy outcomes, etc; (4) Pregnancy outcomes include oligohydramnios/oligohydramnios, delivery bleeding volume, premature delivery, and cesarean section.

**Table 1**. Basic characteristics of the included articles

| Included literature | Country | Number of cases in case group | Number of cases in the control group | Study type | Time | Pregnancy Outcome |
|---|---|---|---|---|---|---|
| Li 2014[12] | China | 50 | 50 | Case control study | 2012~2012 | Blood loss during delivery |
| Jiang 2015[13] | China | 95 | 420 | Case control study | 2013~2013 | Abnormal amniotic fluid , blood loss during delivery , premature birth, cesarean section |
| Zhang 2016[14] | China | 48 | 48 | Case control study | 2013~2015 | Amniotic fluid abnormality, premature birth, cesarean section |
| Chen 2018[15] | China | 44 | 44 | Case control study | 2016~2017 | Abnormal amniotic fluid and blood loss during delivery |
| Li 2020[16] | China | 67 | 67 | Case control study | 2017~2018 | Abnormal amniotic fluid and blood loss during delivery, premature birth, cesarean section |
| Hou 2021[17] | China | 60 | 60 | Case control study | 2019~2020 | Abnormal amniotic fluid and blood loss during delivery, premature birth, cesarean section |

**Table 2.** Quality assessment of included literatures

| Included literature | Random method | Allocation concealment | Patients and Implementation Person blindness | Outcome evaluation Person blindness | Of the outcome data Integrity | Selective reporting of findings | Other sources of bias |
|---|---|---|---|---|---|---|---|
| Li 2014[12] | unknown | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Jiang 2015[13] | Low risk | High risk | Low risk | Low risk | unknown | Low risk | Low risk |
| Zhang 2016[14] | unknown | Low risk | Low risk | Low risk | unknown | Low risk | Low risk |
| Chen 2018[15] | unknown | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Li 2020[16] | Low risk | High risk | Low risk | Low risk | unknown | Low risk | Low risk |
| Hou 2021[17] | High risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |

### Literature quality evaluation

Based on the quality evaluation of the 6 included literature using the Cochrane tool, the analysis includes: (1) the generation of random sequences; (2) Other sources of bias; (3) Whether to hide the allocation scheme; (4) The implementation of blind methods; (5) Selective reporting of research results; (6) Is there any bias caused by missing data? (7) Is the result data complete. Evaluate the included studies through 'high risk', 'low risk', and 'unclear'. The quality evaluation of all literature is independently analyzed by at least two researchers without mutual influence. When there are different opinions in the evaluation, a third person participates in the discussion until a consensus is reached.

### Statistical methods

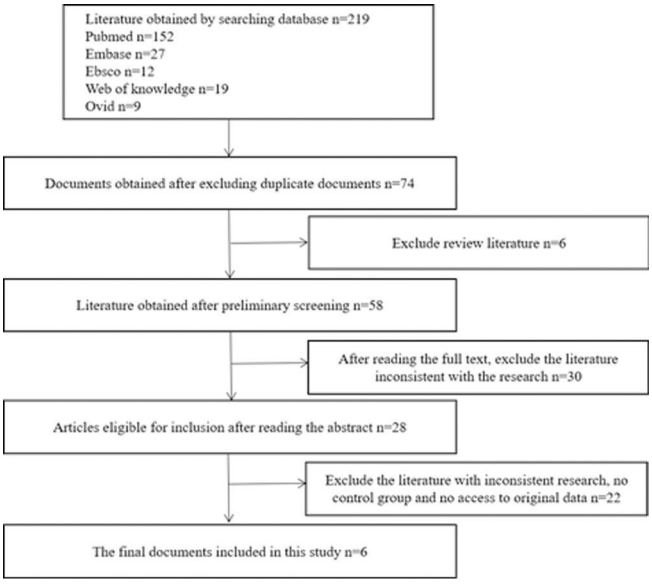
The meta-analysis was processed by Revman software. The count data were expressed by relative risk (RR), and the corresponding 95% confidence interval (CI) was calculated. It was expressed by forest plot, and the included researches' effect size and confidence interval were described by multiple lines parallel to the horizontal axis. The length of the horizontal line was negatively correlated with the sample size and the accuracy of the results. Whether there was heterogeneity between studies was determined using $I^2$. If $P > .1$, $I^2 < 50\%$ meant that the included studies had less statistical heterogeneity and a fixed effects model was opted for. If $P < .1$, $I^2 > 50\%$ meant that the enrolled studies were statistically homogeneous. Random-effects models were chosen, and subgroup analyses were performed as needed to assess publication bias via funnel plot.

## RESULTS

### Process and results of literature search

A total of 219 relevant original literatures were detected by database search, including 52 in English and 167 in Chinese. 145 cases of duplicate literatures and 6 cases of review literatures were excluded. After carefully reading the title and abstract of the articles and preliminary screening of the literatures, 58 cases were obtained. After reading the full text, 30 literatures inconsistent with the research were excluded. After excluding 22 literatures with inconsistent studies, no control group, and no access to original data, 6[12-17] literatures were finally included in this research. The retrieval process is shown in Figure 1.

**Figure 1.** Retrieval flow chart




### Basic information and quality evaluation of the included literatures

The six included literatures were all in English and were of high quality, including 364 cases in the case group and 689 cases in the control group. The year of publication of the literature is mainly between 2013 and 2021. The NOS scores of the included literatures is ≥ 6, suggesting that the general quality of the incorporated literature was relatively good. Refer to Table 1 and Table 2.

### Mate analysis results

Among the 6 included literatures, a total of 4 pregnancy outcomes were extracted, namely, maternal blood loss during delivery; amniotic fluid abnormalities; premature delivery and cesarean section.

**Maternal blood loss during delivery.** A total of 5 literature were included in the analysis of maternal blood loss

**Figure 2.** Analysis of the occurrence risk of pregnant women's delivery bleeding volume in case group and control group

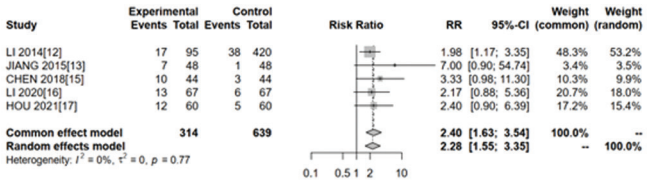



**Figure 3.** Analysis of occurrence risk of abnormal amniotic fluid in case group and control group

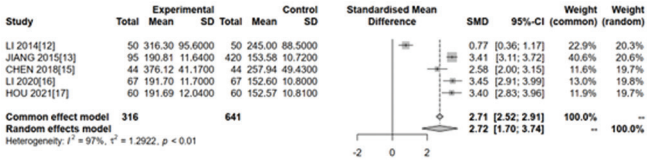



**Figure 4.** Risk analysis of premature infants in the case group and control group

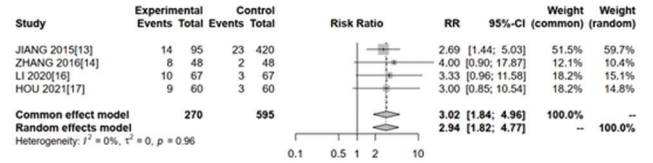
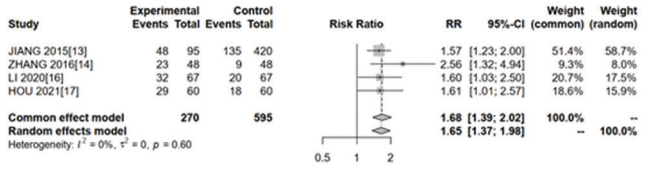



**Figure 5.** Risk analysis of cesarean section in the case group and control group




during delivery, and the changes in the level of pregnant women's delivery blood loss between the case group and the control group were analyzed. The heterogeneity test results of the included literature were $I^2$ = 20% and $P$ > .10, indicating that there was relatively little heterogeneity among the incorporated studies, so the fixed effect model should be used to analyze the changes in the level of pregnant women's delivery blood loss between the case group and the control group. The results of the forest plot revealed that the level of maternal blood loss at delivery was clearly above the controlling group in the case group, and the discrepancy between the two groups was statistically meaningful [RR = 1.35, 95% CI (0.92 to 1.93), $P$ < .05]. Refer to Figure 2.

**Amniotic fluid abnormalities.** A total of 5 literatures were included in the analysis of abnormal amniotic fluid for pregnant women. The occurrence risk of amniotic fluid abnormalities in pregnant women in the case group and the control group was analyzed. The heterogeneity test results of the included literatures were $I^2$ = 27% and $P$ > .10. It was indicated that the variance between the included studies was minor, so a fixed effects model was applied to analyze the risk of occurrence of amniotic fluid abnormalities in pregnant females in the case and control groups. The results of the forest plot showed a statistically valid discrepancy in the risk of occurrence of amniotic fluid abnormalities between the case and control groups [RR = 1.29, 95% CI (0.86-1.71), $P$ < .05]. Refer to Figure 3.

**Premature birth.** A total of 4 articles were included in the study of premature infants, and the risk of premature infants in the case and control groups was analyzed. The heterogeneity test results of the included articles were $I^2$ = 0% and $P$ = .96, indicating that the heterogeneity between the included studies was small. Therefore, a fixed effects model was used to analyze the risk of abnormal amniotic fluid in pregnant women in the case group and control group. The forest map results showed that there was a statistically significant difference in the risk of premature birth between the case group and the control group [RR = 3.02, 95% CI (1.84~4.96), $P$ < .05]. Refer to Figure 4.

**Cesarean section.** A total of 4 articles were included in the study of cesarean section, and the risk of cesarean section in the case group and control group was analyzed. The heterogeneity test results of the included articles were $I^2$ = 0% and $P$ = .60, indicating that the heterogeneity between the included studies was small. Therefore, a fixed effects model was used to analyze the risk of cesarean section in the case and control groups. The forest map results showed that there was a statistically significant difference in the risk of cesarean section between the case group and the control group [RR = 1.68, 95% CI (1.39-2.02), $P$ < .05]. Refer to Figure 5.

### Funnel plot analysis

There is significant heterogeneity in the amount of bleeding during childbirth, premature delivery, and cesarean section among pregnant women, and a random effects model should be selected. Bias analysis needs to be conducted through a funnel plot. Due to the need for more than 9 references to draw a funnel plot, and the use of fixed effects models through heterogeneity testing for analysis is often used to understand whether there is publication bias. However, due to the inclusion of a total of 6 references in this study, funnel plot analysis cannot be conducted due to the limited number of references included.

## DISCUSSION

Thalassemia is an inherited quantitative disorder of hemoglobin synthesis, and it is also a widespread disease that causes a significant burden worldwide, ranging from the mildest asymptomatic carriers to the most severe transfusion-dependent state.[18] According to the different inhibited peptide chains, it can be divided into four types, inchuding Type α, Type β, Type γ and Type δ. Among them, Type α Type β are the most common.[19] Generally, patients with stationary or mild thalassemia have no obvious symptoms, while intermediate and severe patients may cause hemolytic anemia, fetal edema, poor growth of infants and other serious reactions; it can even result in children requiring regular blood transfusions for life, which not only increases the pain and economic burden of patients, but also has a

serious impact on their family harmony.[20-21] Due to the physiological changes of pregnancy, most studies have reported that the blood consumption of women with thalassemia major increases, and maternal anemia will significantly impact the birth weight of newborns, and even cause premature birth.[22-23] Therefore, early diagnosis and timely treatment of thalassemia are of great significance in reducing the incidence of thalassemia and improving pregnancy outcomes.

So far, it is believed that pregnancy and the health of newborns are especially affected by maternal infection, hypertensive disorder complicating pregnancy, smoking, and other factors. In addition, environmental pollution has recently been added to the list of threats to fetal health.[24-25] Due to the rapid proliferation of cells, poor detoxification or elimination ability, high absorption rate, and immature repair mechanism, the fetus has a unique sensitivity to harmful health effects caused by in-utero exposure to environmental pollution.[26] In this research, a total of 6 cases of case-control studies on mild thalassemia and normal pregnant women were collected through systematic evaluation, and all of them were high-quality literatures. The effects of mild thalassemia on the incidence of amniotic fluid abnormalities and the amount of bleeding during delivery ere systematically analyzed to provide new ideas for early intervention treatment of clinical thalassemia pregnant women to improve pregnancy outcomes. The results of this research found that compared with normal pregnant women, the level of the amount of bleeding during delivery in thalassemia pregnant women was significantly higher [RR = 2.40, 95%CI(1.63~3.54), $P > .05$], and the occurrence risk of amniotic fluid abnormalities in thalassemia pregnant women was significantly higher than that in the control group [RR = 2.71, 95%CI(2.52~2.) $P < .01$]. There was a statistically significant difference in the risk of premature birth between the case group and the control group [RR = 3.02, 95% CI (1.84~4.96), $P > .05$], as well as the risk of cesarean section [RR = 1.68, 95% CI (1.39~2.02), $P > .05$].The RR values of the two groups were greater than 1, indicating that pregnant women with mild thalassemia have a certain relationship with amniotic fluid abnormalities and the amount of bleeding during delivery, which can increase the incidence of amniotic fluid abnormalities and the amount of bleeding during delivery. The reason may be that amniotic fluid is the main "external factor" of fetal growth and development, which provides mechanical protection and immune defense against pathogens for the fetus, and the appropriate amount of amniotic fluid has beneficial effects on both fetus and mother. On the contrary, if the amniotic fluid is abnormal, it may seriously impact the fetus, including fetal malformation, fetal central nervous system disease, fetal death, etc.[27-28] In previous studies,[29] by analyzing the impact of amniotic fluid volume and perinatal outcomes, it has been found that the incidence of preterm birth, premature rupture of membranes and stillbirth in patients with abnormal initial amniotic fluid volume was significantly higher than that in patients with normal initial amniotic fluid volume. Normally, in early pregnancy, amniotic fluid is mainly composed of maternal serum entering through the fetal membrane, while with the development of the fetus, fetal urine gradually enters the composition of amniotic fluid. The exchange of amniotic fluid between mother and fetus makes amniotic fluid in a dynamic balance, and once the amniotic fluid volume is abnormal, it can cause a variety of the occurrence of adverse pregnancy outcomes.[30] When thalassemia occurs, the incidence of fetal distress increases significantly, and with the aggravation of the disease, the incidence of hypoxemia increases significantly, the placenta increases, which also can cause the occurrence of amniotic fluid abnormalities.[31] In addition, thalassemia, also known as hemoglobinopathy, is an autosomal negative genetic defect in hemoglobin production. When the patients are in pregnant, the hemoglobin level increases significantly, but the level of its increase is lower than that in plasma so the blood of pregnant women in pregnancy is at the dilution level. If the patients have thalassemia, the erythropoiesis is significantly reduced, the hemoglobin level is reduced, and the iron load is increased, further aggravating the patients' condition, increasing the possibility of excessive bleeding during delivery.[32-33]

Although this research conducted a systematic analysis of most of the literature on the impact of thalassemia minor on the incidence of amniotic fluid abnormalities and the amount of bleeding during delivery, which has certain clinical value, it still has certain limitations: (1) The literatures selected in the research in the past five years is relatively few, and all of them are single center, retrospective studies, with a small sample size, which makes the accuracy of the results of meta-analysis is insufficient; (2) The lack of blinding in some literatures may lead to language bias and implementation bias in the results; (3) The research time is still short, and the influence of different types of thalassemia on the abnormal amniotic fluid volume and the amount of bleeding during delivery has not been clarified.In the future, further improvements should be made based on the shortcomings of research to clarify the impact of different types of thalassemia on pregnancy outcomes and increase the reliability of research.

In conclusion, thalassemia minor can increase the incidence of amniotic fluid abnormalities and the amount of bleeding during delivery. In the future, the health education of pregnant women should be strengthened, which can improve the understanding of the disease. And the impact of thalassemia on newborns should be avoided or reduced to improve the pregnancy outcome, providing a more reliable basis for clinical decision-making.

## DATA AVAILABILITY

The experimental data used to support the findings of this study are available from the corresponding author upon request.

## CONFLICTS OF INTEREST

The authors declared that they have no conflicts of interest regarding this work.

## AUTHOR CONTRIBUTIONS

Yan Huang and Ting Zhang contributed equally to this work.

## ACKNOWLEDGMENTS

Any funding did not fund the work.

## REFERENCES


1. Viprakasit V, Ekwattanakit S. ekwattanakit S. clinical classification, screening and diagnosis for thalassemia. *Hematol Oncol Clin North Am*. 2018;32(2):193-211. doi:10.1016/j.hoc.2017.11.006
2. Shafique F, Ali S, Almansouri T, et al. Thalassemia, a human blood disorder. *Braz J Biol*. 2021;83(1):e246062.
3. Hanprasertpong T, Kor-anantakul O, Leetanaporn R, et al. Pregnancy outcomes amongst thalassemia traits. *Arch Gynecol Obstet*. 2013;288(5):1051-1054. doi:10.1007/s00404-013-2886-9
4. Sorrentino F, Maffei L. caprari P, cassetta R, dell'anna D, Materazzi s, risoluti R. prognosis in thalassemia and sickle cell disease: the experience of an Italian thalassemia center. *Front Mol Biosci*. 2020;7(1):16. doi:10.3389/fmolb.2020.00016
5. Piccioni MG, Capone C, Vena F, et al. Use of deferoxamine (DFO) in transfusion-dependent β-thalassemia during pregnancy: A retrospective study. *Taiwan J Obstet Gynecol*. 2020;59(1):120-122. doi:10.1016/j.tjog.2019.11.018
6. Cao A, Kan YW. The prevention of thalassemia. *Cold Spring Harb Perspect Med*. 2013;3(2):a011775. doi:10.1101/cshperspect.a011775
7. Carlberg KT. singer st, vichinsky ep Fertility and dignity in women with transfusion dependent thalassemia. *Hematol Oncol Clin North Am*. 2018;32(2):297-315. doi:10.1016/j.hoc.2017.11.004
8. Floris F. comitini F, Leoni g, MOI P, morittu m, orecchia V, perra m, pilia MP, zappu a, casini Mr, origa R. quality of life in Sardinian patients with fusion dependent thalassemia: a cross-sectional study. *Qual Life Res*. 2018;27(10):2533-2539. doi:10.1007/s11136-018-1911-7
9. Akıncı B, Yaşar AŞ, Özdemir Karadaş N, et al. AK ı NC ı B. Ya ş Ar a Ş, Ö zdemir Karada ş N. Ö nder SIVI ş Z. Hekimci Ö zdemir h, y ı Lmaz KARAP ı NAR D, Balkan C, kavakl ı K. Ayd ı NOK y. fertility in patients with thalassemia and outcome of pregnancies: a Turkish experience. *Turk J Haematol*. 2019;36(4):274-277.
10. Cappellini MD, Motta I. new therapeutic targets in fusion dependent and -independent thalassemia Hematology. *am SOC Hematol education program* 2017 Dec 8; 2017 (1): 278-283
11. Aydınok Y, Oymak Y, Atabay B, Aydoğan G, Yeşilipek A, Ünal S, Kılınç Y, Oflaz B, Akın M, Vergin C, Sezgin Evim M, Çalışkan Ü, Ünal Ş, Bay A, Kazancı E, İleri T, Atay D, Patıroğlu T, Kahraman S, Söker M, Akcan M, Akdeniz A, Büyükavcı M, Alanoğlu G, Bör Ö, Soyer N, Özdemir Karadaş N, Uysalol E, Türker M, Akçay A, Ocak S, Güneş AM, Tokgöz H, Ünal E, Tiftik N, Karakaş Z. A National Registry of Thalassemia in Turkey: Demographic and Disease Characteristics of Patients, Achievements, and Challenges in Prevention. *Turk J Haematol*. 2018 Mar 1;35(1):12-18. doi: 10.4274/tjh.2017.0039. Epub 2017 Apr 13. PMID: 28404539; PMCID: PMC5843769.
12. Li MY, Wei JX, Wu HZ. he Li qiao HGB and SF changes during pregnancy of women with thalassemia minor pregnancy outcome. *Shandong Yiyao*. 2014;54(20):17-19.
13. Jiang L, Li M. Wu huizhen HGB SF changes and the influence on pregnancy outcome for pregnant women with light Mediterranean anemia. *Hebei Med*. 2015;21(3):369-372.
14. Zhang l. Analysis on the levels of hemoglobin and ferritin and pregnancy outcomes during pregnancy in pregnant women with thalassemia *Chinese clinical Med eng*.2016,23 (4): 493-494
15. Chen Y. Clinical value of serum ferritsn (SF) and hemoglobin (Hgb) levels in dominant women with thalassemia. *Mothers babies world*. 2018, 2018 (18): 17-18
16. Li L, Zhang H. ban zhenghe The changes of hemoglobin value and serum ferritin level of dominant women with thalassemia and their influence on matter nal and influential outcom. *Zhongguo Jihua Shengyuxue Zazhi*. 2020;28(3):446-448.
17. Min HM, Ling XJ, Zhang l. Changes and clinical significance of hemoglobin and ferritin in pregnant women with thalassemia. *Shenzhen J integr trad Chinese Western med*.2021 Nov, 31 (21): 3-6
18. Wu H, Wang H, Lan L, et al. Invasive molecular prenatal diagnosis of alpha and beta thalassemia among Hakka pregnant women. *Medicine (Baltimore)*. 2018;97(52):e13557. doi:10.1097/MD.0000000000013557
19. Cannas g, Dubreuil L, fichez a, gerfaud Valentin m, DEBARD Al, hot A. delayed severe hematopoietic transfusion reaction during precision in a woman with β- Thalassemia intermediate: successful outcome after eculizumab administration. *Am J Case Rep*. 2021;22(1):e931107.
20. Sleiman J, Tarhini A, Bou-Fakhredin R, Saliba AN, Cappellini MD, Taher AT. tarhini a, bou fakhredin R, Saliba an, Cappellini MD, Taher at. non transfusion dependent thalassemia: an update on complications and management. *Int J Mol Sci*. 2018;19(1):182. doi:10.3390/ijms19010182
21. Fogel BN, Nguyen HLT, Smink G, Sekhar DL Variability in state based recommendations for management of alpha thalassaemia trait and silent carrier detected on the newborn screen. *J Pediatr*. 2018;195:283-287. doi:10.1016/j.jpeds.2017.11.048
22. Ahmad MF, Zakaria NZ, Arsad N, Chew KT, Abu MA, Shafiee MN, Omar MH. a case of post splenectomy fusion dependent homologous beta thalassemia major compounded with myocardial siderosis and osteoporosis and usage of iron chelating therapy with deferiprone in pregnancy. *Horm Mol Biol Clin Investig*. 2019;39(2):1-3.
23. Roumi JE, Moukhadder HM, Graziadei G, Pennisi M, Cappellini MD, Taher AT. pregnancy in β- Thalassemia intermedia at two tertiary care centers in Lebanon and italy: a follow-up report on fatal and material outcomes. *Am J Hematol*. 2017;92(6):e96-e99.
24. Bommer I, Juriol L, Muzzio D, et al. Characterization of murine amniotic fluid B cells in normal pregnancy and in preterm birth. *Reproduction*. 2019;158(4):369-376. doi:10.1530/REP-19-0150
25. Suliburska J, Kocyłowski R, komorowicz I, grzesiak m, Bogdański P, Barałkiewicz D. concentrations of mineral in amniotic fluid and their relations to selected material and fetal parameters. *Biol Trace Elem Res*. 2016;172(1):37-45. doi:10.1007/s12011-015-0557-3
26. Wichien P, Yamsri S, Sanchaisuriya K, Fucharoen S. direct amplification of whole blood and amniotic fluid specifications for prenatal and postnatal diagnosis of HB e- β 0-thalassemia diseases. *Lab Med*. 2021;52(5):460-468. doi:10.1093/labmed/lmaa117
27. Figueroa L, McClure EM, Swanson J, Nathan R, Garces Al, Moore JL, Krebs NF, Hammidge KM, Bauserman M, Lokangaka A, Tshefu A, Mirza W, Saleem S, Naqvi F, Carlo WA, Chomba E, Liechty EA, Esamai F, Swanson D, Bose Cl, Goldenberg rl. Oligohydramnios: a prospective study of fetal, neonatal and material outcomes in low middle income countries. *Reprod Health*. 2020;17(1):19.
28. Weiner E, Barrett J, Zaltz A, Ram M, Aviram A, Kibel M, Lipworth H, Asztalos E, Melamed N. amniotic fluid volume at presentation with early preterm prelabor breach of membranes and association with severe neonatal respiratory morbidity Ultrasonic. *Obstet Gynecol*. 2019;54(6):767-773.
29. Pylyjuk C, Majeau L. perinatal outcomes and influence of amniotic fluid volume following viable, preterm prelabor rut of membranes (ppprom): a historical cohort study. *Int j women health* 2021 Jun 28; 13: 627-637
30. Sekhon S, Rosenbloom JI, Doering M, Conner SN, Macones GA, Colditz GA, Tuuli MG, Carter EB. Diagnostic utility of maximum vertical pocket versus amniotic fluid index in assessing amniotic fluid volume for the prediction of adverse material and fatal outcomes: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med*. 2021;34(22):3730-3739. doi:10.1080/14767058.2019.1691988
31. Wax CA, Craig WY, Pinette mg. transient idiopathic polyhydramnios: material and periodic outcomes: material and periodic outcomes. *J ultrasonic med*. 2022 Nov; 41 (11): 2859-2866
32. Brenner A, Roberts I, Balogun E, Bello FA, Chaudhri R, Fleming C, Javaid K, Kayani A, Lubeya MK, Mansukhani R, Olayemi O, Prowse D, Vwalika B, Shakurstill H. postpartum hemorrhage in anaemic women: assessing outcome measures for clinical trials. *Trials*. 2022;23(1):220.
33. Virot E, Thuret I, Jardel S, Herbrecht R, Lachenal F, Lionnet F, Lucchini Mj, Machin J, Nimubona S, Ribeil JA, Galacteros F, Cannas G, Hot A. prosperity outcome in women with transfused beta thalassemia in france. *Ann Hematol*. 2022;101(2):289-296.