# Transaminase elevation during the first trimester and early pregnancy loss in patients with recurrent spontaneous abortion: a cross-sectional study

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**Abstract**

Objective: To investigate the association between transaminase elevation during the first trimester and early pregnancy loss (EPL) in patients with recurrent spontaneous abortion (RSA). Further, the contributing risk factors for transaminase elevation in early pregnancy in RSA patients were analyzed Design: Cross-sectional study Setting: China Population: RSA patients during the first trimester Methods: Patients were divided into EPL group and N-EPL group as well as transaminase-elevated group (TE group) and transaminase-normal group (TN group). The relationship between transaminase level and EPL and the risk factors of elevated transaminase were investigated via student's t test, Pearson chi-square test and logistic regression analyses. Main outcome measure: The association between transaminase elevation and EPL and the risk factors for elevated transaminase. Results: Higher serum transaminase levels were observed in EPL group than in the N-EPL group ($p < 0.05$). Comparing with TN group, EPL is more common in TE group ($p = 0.018$). There is still a correlation between elevated transaminases and EPL in RSA patients after adjusting for covariates (AST: OR, 1.018; 95% CI, 1.007-1.029; p, 0.001; ALT: OR, 1.006; 95%CI, 1.001-1.011; p, 0.018). The higher the transaminases, the greater the likelihood of EPL ($p < 0.05$). Multivariate regression analysis found that the use of IVIG was an independent risk factor for elevated transaminase in RSA patients (OR, 0.374; 95% CI, 0.162-0.864; $p = 0.021$). Conclusion: Serum transaminase levels are significantly correlated with RSA early pregnancy loss. Moreover, medication use is significantly correlated with transaminase elevation in the first trimester in RSA patients, especially IVIG.

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**Abstract:**

**Objective:** To investigate the association between transaminase elevation during the first trimester and early pregnancy loss (EPL) in patients with recurrent spontaneous abortion (RSA). Further, the contributing risk factors for transaminase elevation in early pregnancy in RSA patients were analyzed.

**Design:** Cross-sectional study.

**Setting:** China.

**Population:** RSA patients during the first trimester

**Methods:** According to the outcome of early pregnancy, all patients were divided into early pregnancy loss group (EPL group, n=69 cases) and non-early pregnancy loss group (N-EPL group, n=178 cases). Then, according to the highest level of transaminase during the first trimester, all the patients were also divided into the transaminase-elevated group (TE group, n=73 cases) and the transaminase-normal group (TN group, n=174 cases). The relationship between transaminase level and EPL as well as the risk factors of elevated transaminase were investigated via student's test, Pearson chi-square test and logistic regression analyses.

**Main outcome measure:** The association between transaminase elevation and EPL as well as the risk factors for elevated transaminase.

**Results:** Higher serum transaminase levels were observed in EPL group than in the N-EPL group (AST, 47.9±39.15 vs 33.9±25.04 (U/L),$p$ =0.007; ALT, 86.38±84.16 vs 64.0±54.31 (U/L), $p$ =0.043). There was no difference in serum transaminase levels between the patients with abnormal chromosomal karyotyping and normal chromosomal karyotyping in EPL group ($p$ >0.05). Comparing with TN group, EPL is more common in TE group ($p$ =0.018). There is still a correlation between elevated serum transaminase levels and EPL in RSA patients after adjusting for covariates (serum AST level: odds ratio (OR), 1.018; 95% confidence interval (CI), 1.007-1.029; $p$,0.001; serum ALT level: OR, 1.006; 95%CI, 1.001-1.011; $p$ , 0.018). The higher the transaminases, the greater the likelihood of EPL ($p$ <0.05). Univariate analysis showed that oral glucocorticoids, hydroxychloroquine and intravenous gamma globulin (IVIG) were associated with elevated transaminase levels during the first trimester in RSA patients ($p$ <0.10). However, multivariate regression analysis found that only the use of IVIG was an independent risk factor for elevated transaminase in RSA patients (OR, 0.374; 95% CI, 0.162-0.864; $p$ =0.021).

**Conclusion:** Serum transaminase levels are significantly correlated with RSA early pregnancy loss. Moreover, medication use is significantly correlated with transaminase elevation in the first trimester in RSA patients, especially IVIG. In clinical practice, clinicians should control the indication of IVIG strictly and prescribe for short durations.

**Keywords:** RSA; transaminase elevation; early pregnancy loss; medication use; IVIG

## INTRODUCTION

Recurrent spontaneous abortion (RSA) refers to 2 or more pregnancy failures that exclude biochemical pregnancy, accounting for 5% of all pregnancies[1]. Early pregnancy loss (EPL) is defined as an intrauterine, non-viable pregnancy, within the first 12 weeks[2], commonly occurring in about 15–20% of all pregnancies[3]. The incidence of abnormal liver function during pregnancy is approximately 3%[4]. Found in clinical practice that, even healthy pregnant women may have transaminase elevation in early pregnancy, which is often related to pregnancy hyperthyroidism syndrome, hyperemesis gravidarum, and early pregnancy reactions caused by elevated human chorionic gonadotropin (HCG)[5, 6]. Recent prospective study has found that nonalcoholic fatty liver was a major risk factor for EPL[7]. According to our knowledge, none of the cross-sectional studies are available globally about the association between transaminase level and EPL in RSA patients.

Due to the complex etiology of RSA, long-term combined medication is often required during pregnancy, especially in the first trimester[8]. As the main human organ of drug metabolism, the liver is also the main

target organ of drug damage. However, the relationship between elevated transaminases in early pregnancy and medication use in RSA patients is unclear.

With this background, we aim to illustrate the transaminase level during the first trimester of RSA patients and the correlation between elevated transaminase and early pregnancy loss. Further, we analyzed the risks factor for elevated transaminase, especially the correlation with medication use.

## METHODS

### 2.1 Study Population

A total of 247 RSA patients were included in this cross-sectional study, consisting of 69 patients with EPL and 178 without EPL in the RSA special clinic, Department of Obstetrics & Gynecology in Shengjing Hospital of China Medical University, from January 2018 to December 2019. We used the American Society for Reproductive Medicine (ASRM) and Practice bulletin No. 200 criteria for RSA and EPL diagnosis.

All the enrolled RSA patients were treated with medication after preconception systematic screening the cause of RSA, including oral aspirin (ASP), glucocorticoids, calcium carbonate, dydrogesterone, levothyroxine, hydroxychloroquine, multivitamins, subcutaneous injection of low molecular weight heparin (LMWH), intravenous gamma globulin (IVIG), etc.

Subjects were eligible if they met the following inclusion criteria: 1) Meet the diagnostic criteria for RSA of the American Society for Reproductive Medicine; 2) Intrauterine pregnancy and the gestational age less than 13 $^{+6}$ weeks confirmed by Doppler ultrasound; 3) Normal liver function before pregnancy;4) Complete preconception systematic etiology examination for RSA. Patients were excluded if they had any of the following conditions: 1) Complicated with primary thyroid disease, diabetes, cardiovascular disease, and blood system disease during pregnancy; 2) The current pregnancy is biochemical pregnancy, multiple pregnancy and ectopic pregnancy; 3) Previous or current pregnancy with viral, fatty, toxic, alcoholic, autoimmune liver disease, hepatolenticular degeneration, liver cirrhosis and other liver diseases; 4) This pregnancy is diagnosed as hyperemesis gravidarum; 5) Any chromosomal abnormality in either spouse; 6) This pregnancy with infectious factors such as Toxoplasma gondii, cytomegalovirus, herpes virus, rubella virus, etc.) Anatomical abnormalities of reproductive system: bicornuate uterus, unicornuate uterus, bicornuate uterus, arcuate uterus, endometrial polyps, submucosal fibroids without surgical treatment.

### 2.2 Data Collection

Data on maternal demographic characteristics were collected from questionnaires completed by women at the first antenatal visit. The liver function test was completed before pregnancy and during early pregnancy, with 1–2week intervals. The first post-pregnancy liver function test was performed after the pregnancy was confirmed. For patients with abnormal liver function screening, re-examination within 1 week is required. Patients with abnormal liver function must complete liver ultrasonography and liver disease consultation to exclude non-alcoholic fatty liver and other liver diseases.

Laboratory testing was performed at the Department of Clinical Laboratory, Shengjing Hospital of China Medical University. Venous blood samples of the upper extremities were collected in the morning after subjects fasted for 8 hours. Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) levels were detected by ultraviolet continuous detection method on an AU5400 automatic biochemical analyzer (Olympus, USA) with commercial kits (Desay); total protein (TP) was detected by biuret method, albumin(ALB) was detected by bromocresol green method, glutamyltransferase(GGT) was detected by diazo colorimetry, alkaline phosphatase(ALP) was detected by continuous detection method, prealbumin(PA) was detected by immunoturbidimetry, cholinesterase(CHE) was detected by semi-quantitative method, total bile acids(TBA) was detected by enzymatic cycling assay; total bilirubin (TBIL), conjugated bilirubin (CB), unconjugated bilirubin(UCB) levels were detected by Vanadate oxidation method; monoamine oxidase(MAO) was detected by UV spectrophotometry on an AU5400 automatic biochemical analyzer (Olympus, USA); FT3, FT4 and TSH were detected by enzyme-linked immunosorbent assay (Abbott Laboratories, USA). Chemiluminescence assay was used to detect thyroid peroxidase antibody (TPOAb), thyroglobulin antibody

(TgAb; Abbott Laboratories USA), anticardiolipin antibody (ACA), anti-β2 glycoprotein 1 (β2GP1) antibody (Werfen Group , Spain); coagulation method to detect lupus anticoagulant (lupus anticoagulant, LAC; Werfen Group, Spain), indirect immunofluorescence method to detect antinuclear antibody (ANA; CaptiaTM, China), Anti-α-fodrin antibody (Kexin Biotech) was detected by enzyme-linked immunosorbent assay method, and ANA spectrum was detected by western blotting (Oumeng, China). The positive diagnosis of the antibodies above must be continuously positive for at least 12 weeks. Arachidonic acid (arachidonic acid)-induced platelet aggregation test, using optical turbidimetry (Helena AggRAM, USA), according to the reference value of our hospital, platelet aggregation rate $> 0.90$ is abnormal platelet aggregation function; immunoturbidimetric method detects blood isotype Cysteine (BECKMAN AU5800, USA), the reference range of normal values in our hospital is 0-15 μmol/L; fasting blood glucose detected by hexokinase method (BECKMAN AU5800, USA), according to WHO diagnostic criteria, 6.1-7.0 mmol/L is diagnosed with impaired fasting glucose(IFG)[9]. Conception methods are divided into natural conception and conception with assisted reproductive technology (ART, including artificial insemination, in vitro fertilization, embryo transfer, etc.).

Impaired indicators of transaminase detection set by the laboratory department of our hospital is: AST >34 U/L or ALT >40 U/L. Since there is no reference range for impaired transaminases in pregnancy, according to American Association for the Study of Liver Disease(AASLD), elevated transaminase is defined as: ALT or AST $> 2\times$upper limit of normal(ULN) in the study[10]. 73 RSA patients with elevated transaminase and 174 controls are included. The highest value of transaminases measured before $13^{+6}$ weeks of gestation were selected for the study.

### 2.3 Statistical analysis

Data analyses were performed using SPSS version 25.0, and the normality of the continuous variables was assessed by Kolmogorov-Smirnov test. Normally distributed continuous variables were reported as mean ± standard deviation and compared with Student's t-test. Pearson chi-square test or Fisher test was utilized to select the covariates affecting EPL and elevated transaminase, and variables found significant by the Pearson chi-square test or Fisher test ($p < 0.1$) were included in the multivariate logistic regression analysis. Multivariate logistic regression analysis was used to estimate the odds ratio (OR) and 95% confidence interval (CI) for the presence of EPL and elevated transaminases. All the statistical tests were 2-sided, and$p < 0.05$ was considered significant.

## RESULTS

### 3.1 Study population

During the study period, a total of 247 RSA patients were eligible for this study. Table 1 compares the baseline characteristics over the study period. Among all these characteristics, only maternal age was significantly higher in the patients with EPL than N-EPL.

### 3.2 Patients with EPL presented with higher serum transaminase levels.

We compared the EPL group and N-EPL group patients with the highest values of liver function indexes before $13^{+6}$ weeks of pregnancy. As shown in Table 2, among all liver function indexes, only AST and ALT were correlated with EPL. Serum transaminase levels were higher in the patients with EPL than N-EPL (Figure 1a).

### 3.3 Abnormal chromosomal karyotyping has no correlation with elevated transaminase

In EPL group, fetal karyotyping was performed in 55 pregnancies, with chromosomal aberrations detected in 23 (41.8%) cases. There was no difference in serum transaminase levels between the embryo chromosome-normal patients and chromosome-abnormal patients in EPL group. The results are shown in Figure 1b.

### 3.4 Early pregnancy loss was more common in the transaminase-elevated group

To further study the correlation between elevated transaminases and EPL, we went on to investigate whether EPL was more common in patients with elevated transaminases. When the participants were split by transaminase concentration, EPL was more common in TE-group (28/73, 38.36%) compared with TN-group (41/174, 23.56%, $\chi 2$=5.590, $p$ =0.018).

We then set out to explore deeper relationship between the serum transaminase levels and EPL. Serum transaminase levels, several etiologies of RSA, conception methods, autoimmunity and coagulation-related clinical indicators were included in Pearson correlation analyses[11]. The results showed that age[?]35, serum transaminase levels, ANA15 (+), LAC (+), and anti-β2GP1 antibody (+) were risk factors for EPL in RSA patients ($p<$ 0.10, Table 3).

Pearson correlation analysis found that age, multiple antibodies, and serum transaminase levels were risk factors for EPL in RSA patients. To verify the independence of the above factors, the collinearity analysis of each factor was carried out using the collinearity diagnosis in linear regression. When the tolerance in the model¡0.1, the variance inflation factor (VIF) [?]3, the eigenvalue is close to 0, and the maximum value of the condition index > 10, the model is considered to have a collinear relationship. The tolerances of anti-β2GP1 antibody (+), ANA 15 (+), LAC (+), age [?]35 years, serum AST level, serum ALT level were 0.925, 0.960, 0.944, 0.940, 0.267, 0.271, VIF were 1.081, 1.041, 1.060, 1.064, 3.752, 3.687, the minimum value of the eigenvalue of the model is 0.062, and the maximum value of the condition index is 7.249. It suggested that there was a collinear relationship between serum AST levels and serum ALT levels.

Because of the collinearity of serum AST and ALT levels, these two factors are included in multivariate analysis respectively. After adjusting for the covariates affecting EPL identified in the Pearson correlation analyses as above, there was still a significant correlation between the AST, ALT levels and EPL (serum AST level: OR, 1.018; 95% CI, 1.007-1.029; $p$ , 0.001; serum ALT level: OR, 1.006; 95%CI, 1.001-1.011; $p$ , 0.018).

We also grouped the patients based on different serum transaminase ULN multiples and evaluated the relationship between each transaminase ULN multiple and EPL using logistic regression analysis (Table 4). After adjusting for the covariates affecting EPL identified in the Pearson correlation analyses as above, this evaluation revealed that the incidence of EPL in the group of patients with AST > 4×ULN(102U/L)was significantly higher(OR,6.033;95% CI,1.625˜22.40; $p$ = 0.007) as compared to the group of patients with AST< 1xULN (34 U/L). Meanwhile, the incidence of EPL in the group of patients with ALT > 4xULN (120U/L)was significantly higher (OR,5.373;95% CI,1.999˜14.445; $p$ = 0.001) as compared to the group of patients with ALT < 1xULN (40 U/L). Taken together, higher circulating transaminase concentrations were associated with EPL in RSA patients.

### 3.5 Medication correlated with transaminase elevation in the first trimester in RSA patients

Finally, we aimed to explore the related risk factors for elevated transaminase levels during the first trimester in RSA patients. This study excluded patients with abnormal liver function tests and liver disease diagnosed before pregnancy. All of the enrolled RSA patients have no history of alcoholism. The type of medication used when the patients with the highest transaminase value in the first trimester were included in the study, including oral ASP, glucocorticoids, calcium carbonate, dydrogesterone, levothyroxine, hydroxychloroquine, multivitamins, subcutaneous injection of LMWH and intravenous gamma globulin (IVIG). The characteristics of TE group and TN group are summarized in Table 1($P$ all > 0.05).

Pearson correlation analysis was performed to analyze the effect of medication on the elevation of transaminases, as shown in Table 5. The results showed that the use of cortisol, IVIG and hydroxychloroquine were risk factors for elevated transaminases during the first trimester in RSA patients ($p$ < 0.10). Next, multivariate analysis was performed with the factors that were statistically significant in univariate analysis as independent variables. The results showed that only IVIG had a significant correlation with elevated transaminases (IVIG: OR, 0.352; 95%CI, 0.154-0.807; $P$ , 0.014).

## Discussion

This study demonstrated that circulating transaminase levels were significantly higher in RSA patients with EPL. Moreover, we reported for the first time that medication use is significantly correlated with elevated transaminase during first trimester in RSA patients, especially IVIG.

Although there is much evidence that elevated transaminases during pregnancy can affect pregnancy outcomes, few studies focused on the transaminase level in the first trimester or its relationship with EPL. A previous study has revealed that abnormal AST was an independent risk factor for preterm birth[12]. Elad Mei-Dan et al has revealed that AST and ALT levels during the first 20 weeks of pregnancy are associated with higher risk for the development of preeclampsia during the second half of pregnancy[13]. Yarrington et al. have suggested that unexplained elevated alanine transaminase was associated with large gestational age birth weight[14]. Lots of studies have all shown that elevated transaminases lead to adverse pregnancy outcomes, but none of them conducted a study on RSA patients. This study is the first to conduct a cross-sectional study focuses on the relationship between transaminase elevation with EPL during the first trimester in RSA patients. Our results clearly indicate that the serum transaminase levels of RSA patients with EPL were higher than those without EPL(AST: 47.9+-39.15 vs 33.9+-25.04; ALT: 86.38+-84.16 vs 64.0+-54.31, $P$ all $< 0.05$).Meanwhile, EPL was more common in patients with elevated transaminase(28/73,38.36% vs 41/174,23.56%, $p < 0.05$). Collectively, transaminase elevation may be involved in the occurrence of EPL.

As we all know, abnormal chromosomal karyotyping is one of the independent risk factors for EPL[15]. This study found that abnormal chromosomal karyotyping was not associated with transaminase elevation in RSA patients with EPL. The pathophysiology of transaminases elevation in EPL is still unclear. Liver plays an essential role in synthesis, metabolism, detoxification and regulating both local and systemic inflammation[1617]. Pregnancy causes changes in physiology and laboratory of liver [18]. According to previous studies, inflammatory microenvironment was associated with RSA[19, 20]. It may implicate that local and systemic inflammation may be independent etiological factors of EPL.

The causes of transaminase elevation are various[21]. This study has excluded hepatic related causes, other related factors including excessive alcohol intake, age, BMI, and medications, etc.[22, 23]. This study founded that only IVIG use had a significant correlation with elevated transaminases. Medication use during pregnancy is common, especially in RSA patients[24, 25]. Some RSA patients blindly use multiple drugs without indication to prevent miscarriage. In recent years, IVIG has been mainly used in patients with alloimmune, unexplained recurrent pregnancy loss (URPL) and ART[26]. Hepatocellular injury caused by high-dose IVIG has been reported[27]. A previous review recommended that patients with recurrent pregnancy loss should have liver function tests before using IVIG[28]. Our results clearly indicate that IVIG using in early pregnancy increased the risk of liver injury. The fundamental cause of liver injury in response to IVIG is still unclear. The activation of release of proinflammatory cytokines or complement cascades may be involved[29]. Our previous study found that the use of IVIG in early pregnancy significantly reduced the biochemical pregnancy rate of URPL patients but had no effect on the incidence of early pregnancy loss[30]. Therefore, we believe that the indications for IVIG should be more strictly controlled and the abuse of IVIG should be avoided.

The major strength of this study is that this is the first study to assess the serum transaminases levels in RSA women in the first trimester, and to evaluate the relationships between serum transaminases and EPL. Moreover, our findings also have a clinical implication that elevated transaminase levels in RSA patients in the first trimester may correlated with medication use. Our results highlight the need to raise awareness about the possibility of liver dysfunction during medication treatment in pregnancy.

Our study has several limitations. Firstly, this study was a single-center study and only IVIG was found correlated with transaminase elevation, which may be related to our sample size. Multicenter studies should be conducted in the future and explore the effects of other medications on transaminase elevation. Although it is difficult to conduct a large sample study, this study is currently the largest cross-sectional study on the relationship between elevated transaminases and EPL during the first trimester in RSA patients. Secondly, because of the variable and complex medication regimens of RSA patients, we only included different medication types. Further cohort studies on medication dosage and duration are warranted. Thirdly, this study found the relation between transaminase elevation and EPL, but its pathogenesis is still unclear and further

research is needed.

## Conclusion

This study emphasizes that higher circulating transaminases concentrations are positively correlated with EPL and are associated with medication use in RSA patients. In clinical practice, attention should be paid to the phenomenon of elevated transaminase in the first trimester in RSA patients, and surveillance of liver function should be strengthened. In addition, we should lay emphasis on medication use in the first trimester and controlling medication indications strictly. This study suggests that the risk-benefit ratio of IVIG should be evaluated carefully for the treatment of RSA. If IVIG are needed, it should be prescribed for short durations. Further prospective studies as well as experimental studies are needed to confirm these results and unveil the role of circulating transaminases in the occurrence of EPL in RSA.

## Author Contributions

YH, SWZ designed the study. SWZ, YH, and JPL performed data acquisition. ZSW, JPL and HZX analyzed the data. SWZ and CQ verified the data. SWZ and JPL wrote the manuscript. YH, HZX and CQ revised the manuscript. All authors read and approved the final manuscript.

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The funders of the present study (namely National Natural Science Foundation of China, Liaoning Province Livelihood Science and Technology Joint Project, Shenyang Science and Technology Project and Shengjing Hospital) only provided financial support and did not participate in the study design, data collection, data analysis, interpretation and writing of the report.

## Declaration of interests

The authors declare no conflict of interest.

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## Ethics statement

This study abides by the Declaration of Helsinki and was approved by the Ethical Review Committee of Shengjing Hospital Affiliated to China Medical University with the number 2018PS381K.

## Reference

1. Medicine PCotASfR. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertility and sterility. 2012;98(5).

2. Sonalkar S, Koelper N, Creinin M, Atrio J, Sammel M, McAllister A, et al. Management of early pregnancy loss with mifepristone and misoprostol: clinical predictors of treatment success from a randomized trial. American journal of obstetrics and gynecology. 2020;223(4):551.e1-.e7.

3. Mizrachi Y, Tamayev L, Shemer O, Kleiner I, Bar J, Sagiv R. Early versus delayed follow-up after misoprostol treatment for early pregnancy loss. Reproductive biomedicine online. 2019;39(1):155-60.

4. Lim E, Mouyis M, MacKillop L. Liver diseases in pregnancy. Clinical medicine (London, England). 2021;21(5):e441-e5.

5. ACOG Practice Bulletin No. 189: Nausea And Vomiting Of Pregnancy. Obstetrics and gynecology. 2018;131(1):e15-e30.

6. Kofinas J, Kruczek A, Sample J, Eglinton G. Thyroid storm-induced multi-organ failure in the setting of gestational trophoblastic disease. The Journal of emergency medicine. 2015;48(1):35-8.

7. Koralegedara I, Warnasekara J, Dayaratne K, De Silva F, Premadasa J, Agampodi S. Non-alcoholic fatty liver disease (NAFLD): a significant predictor of gestational diabetes mellitus (GDM) and early pregnancy miscarriages-prospective study in Rajarata Pregnancy Cohort (RaPCo). BMJ open gastroenterology. 2022;9(1).

8. El Hachem H, Crepaux V, May-Panloup P, Descamps P, Legendre G, Bouet P. Recurrent pregnancy loss: current perspectives. International journal of women's health. 2017;9:331-45.

9. Alberti K, Zimmet PZ. definition, diagnosis and classification of diabetes mellitus and its complications part 1: diagnosis and classification of diabetes mellitus provisional report of a who consultation original articles.

10. Terrault N, Lok A, McMahon B, Chang K, Hwang J, Jonas M, et al. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance. Clinical liver disease. 2018;12(1):33-4.

11. La X, Wang W, Zhang M, Liang L. Definition and Multiple Factors of Recurrent Spontaneous Abortion. Advances in experimental medicine and biology. 2021;1300:231-57.

12. Zhuang X, Cui AM, Wang Q, Cheng XY, Shen Y, Cai WH, et al. Liver Dysfunction during Pregnancy and Its Association of With Preterm Birth in China: A Prospective Cohort Study. EBioMedicine. 2017;26:152-6.

13. Mei-Dan E, Wiznitzer A, Sergienko R, Hallak M, Sheiner E. Prediction of preeclampsia: liver function tests during the first 20 gestational weeks. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians. 2013;26(3):250-3.

14. Yarrington C, Cantonwine D, Seely E, Mcelrath T, Zera C. The association of early unexplained elevated alanine aminotransferase with large-for-gestational-age birthweight. American journal of obstetrics and gynecology. 2016;215(4):474.e1-5.

15. Ogasawara M, Aoki K, Okada S, Suzumori K. Embryonic karyotype of abortuses in relation to the number of previous miscarriages. 2000;73(2):300-4.

16. Fabio, Marra, Frank, Tacke. Roles for Chemokines in Liver Disease. Gastroenterology. 2014.

17. Sarkar M, Brady C, Fleckenstein J, Forde K, Khungar V, Molleston J, et al. Reproductive Health and Liver Disease: Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology (Baltimore, Md). 2021;73(1):318-65.

18. Birkness-Gartman J, Oshima K. Liver pathology in pregnancy. Pathology international. 2022;72(1):1-13.

19. Yu L, Zhang Y, Xiong J, Liu J, Zha Y, Kang Q, et al. Activated γδ T Cells With Higher CD107a Expression and Inflammatory Potential During Early Pregnancy in Patients With Recurrent Spontaneous Abortion. Frontiers in immunology. 2021;12:724662.

20. Liu M, Sun X, Zhu L, Zhu M, Deng K, Nie X, et al. Long Noncoding RNA RP11-115N4.1 Promotes Inflammatory Responses by Interacting With HNRNPH3 and Enhancing the Transcription of HSP70 in Unexplained Recurrent Spontaneous Abortion. Frontiers in immunology. 2021;12:717785.

21. Suciu A, Abenavoli L, Pellicano R, Luzza F, Dan LD. Transaminases: Oldies but goldies. A narrative review. Minerva Gastroenterologica e Dietologica. 2020;66(3).

22. Ichihara K, Yomamoto Y, Hotta T, Hosogaya S, Miyachi H, Itoh Y, et al. Collaborative derivation of reference intervals for major clinical laboratory tests in Japan. Annals of clinical biochemistry. 2016;53:347-56.

23. Sull J, Yun J, Lee S, Ohrr H, Jee S, Guallar E, et al. Body mass index and serum aminotransferase levels in Korean men and women. Journal of clinical gastroenterology. 2009;43(9):869-75.

24. Lao TT. Drug-induced Liver Injury in Pregnancy. Best practice & research Clinical obstetrics & gynaecology. 2020;68.

25. Pereira G, Surita F, Ferracini A, Madeira C, Oliveira L, Mazzola P. Self-Medication Among Pregnant Women: Prevalence and Associated Factors. Frontiers in pharmacology. 2021;12:659503.

26. Yang X, Meng T. Is there a Role of Intravenous Immunoglobulin in Immunologic Recurrent Pregnancy Loss? Journal of immunology research. 2020;2020:6672865.

27. Yuan H, Yang T, Zhang W, Wu Z. Hepatocellular injury and hematologic cytopenia after high-dose intravenous immunoglobulin administration. Clinical toxicology (Philadelphia, Pa). 2018;56(12):1208-10.

28. Saab W, Seshadri S, Huang C, Alsubki L, Sung N, Kwak-Kim J. A systemic review of intravenous immunoglobulin G treatment in women with recurrent implantation failures and recurrent pregnancy losses. American journal of reproductive immunology (New York, NY : 1989). 2021;85(4):e13395.

29. Piguet D, Tosi C, Lüthi JM, Andresen I, Juge O. Redimune NF Liquid, a ready-to-use, high-concentration intravenous immunoglobulin therapy preparation, is safe and typically well tolerated in the routine clinical management of a broad range of conditions. Clin Exp Immunol. 2008;152(1):45-9.

30. Hou Y, Li J, Liu Q, Zhang L, Chen B, Li Y, et al. The optimal timing of immunotherapy may improve pregnancy outcome in women with unexplained recurrent pregnancy loss: A perspective follow-up study in northeastern China. American journal of reproductive immunology (New York, NY : 1989). 2020;83(4):e13225.

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