Original Article

Association between factor I fibrinogen (rs6050) and factor XI plasma thromboplastin (rs4253417) genetic polymorphisms and recurrent spontaneous miscarriage in Saudi women

Aaishah M. Kaabi, BSc, MSc, *Afrah F. Alkhuriji,* MD, PhD, *Zeneb A. Babay,* MD, *Ibrahim A. Barakat,* MSc, PhD, *Abdullah M. Kaabi,* BMLSc, *Reem M. Kaabi,* BMLSc.

ABSTRACT

الأهداف: تم تحديد تعدد الأشكال الجينية في العامل الأول الفيبرينوجين (rs6050)، والعامل الحادي عشر بلازما ثرومبوبلاستين (rs4253417) في الإناث السعوديات المصابات بالإجهاض التلقائي المتكرر. بالإضافة إلى قياس النسبة المئوية لعوامل التخثر (العامل الأول، والعامل الحادي عشر) في دم المرضى والمجموعة الضابطة.

المنهجية: أجريت الدراسة الحالية في مستشفى الملك خالد الجامعي بالرياض بالمملكة العربية السعودية، خلال الفترة من سبتمبر 2022م حتى يونيو 2023م. تضمنت الدراسة 100 مريضة سعودية (50 حامل و50 غير حامل) تعاني من الإصابة بالإجهاض التلقائي المتكرر و100 سيدة سعودية سليمة (50 حامل و50 غير حامل). تم تحديد التغيرات النيوكليوتيدية الفردية بمنطقة المحفز للعامل الأول والحادي عشر باستخدام تقنية التنميط الجيني TaqMan لقياس تعدد الأشكال الجينية.

النتائج: وجد أن هناك ارتباط معنوي بين تعدد النمط الجيني C/T للعامل الأول فيبرينوجين والاجهاض المتكرر في النساء السعوديات غير الحوامل. بينما لم يتم ملاحظة أي ارتباط معنوي بين تعدد الأشكال الجينية في العامل الحادي عشر (rs4253417 C/T) factor XI وخطر الإصابة بالإجهاض التلقائي المتكرر.

الخلاصة: أظهرت النتائج ارتباطًا مهمًا بين التعددات الجينية في جين عامل التخثر الأول «فيبرينوجين» في بعض الجينات المدروسة والإجهاض المتكرر. وقد يُعزى هذا الارتباط إلى تغيرات في مستويات الفيبرينوجين، مما يؤثر على مسار التخثر ويؤدي إلى زيادة احتمالية حدوث الجلطات، وهي عوامل خطر معروفة للإجهاض. مع ذلك، لم يرتبط التعدد الجيني في الجين الآخر الذي تم دراسته بخطر الإجهاض المتكرر.

Objectives: To identify genetic polymorphisms in factor I fibrinogen (rs6050) and factor XI plasma thromboplastin (rs4253417) in Saudi women with recurrent spontaneous miscarriage (RSM). Furthermore, to compare the levels of clotting factors in the blood of patients and healthy controls.

Methods: The current study was conducted at the King Khalid University Hospital in Riyadh, Saudi Arabia, from September 2022 to June 2023. The study involved 100 Saudi women, 50 pregnant and 50 non-pregnant individuals, who experienced RSM. Furthermore, 100 healthy Saudi women, including 50 pregnant and 50 non-pregnant individuals, were also included as controls. TaqMan genotyping assays were used to determine single nucleotide polymorphisms in the promoter regions of the factor I and XI genes.

Results: A significant correlation was found between the Factor I fibrinogen genotype (rs6050 C/T) and RSM in non-pregnant Saudi women. However, no significant correlation was observed between the Factor XI polymorphism (rs4253417 C/T) and RSM.

Conclusion: We demonstrated a significant correlation between genetic polymorphisms in factor I fibrinogen in certain genes studied and RSM. This association could be attributed to changes in fibrinogen levels, which impact the coagulation process and lead to an increase in thrombotic events, which are recognized as risk factors for miscarriage. Notably, variations in the other genes examined did not exhibit any association with the risk of RSM.

Keywords: Single-nucleotide polymorphisms (SNPs), TaqMan assay, clotting factors, genomic DNA, factor I fibrinogen, factor XI plasma thromboplastin, Recurrent spontaneous miscarriage.

Saudi Med J 2025; Vol. 46 (2): 150-156
doi: 10.15537/smj.2025.46.2.20240692

From the Department of Zoology (Aaishah Kaabi, Al-Khuriji), College of Science; from the Department of Obstetrics and Gynecology (Babay) King Saud University; from the Central Military Laboratory & Blood Bank (Abdullah Kaabi), Prince Sultan Military Medical City, Riyadh; and from the Department of Laboratory and Blood Bank (Reem Kaabi), Al-Bukayriyah General Hospital, Qassim, Kingdom Saudi Arabia; and from the Cell Biology Department (Barakat), National Research Center, Giza, Egypt.

Received 19th November 2024. Accepted 24th January 2025.

Address correspondence and reprint request to: Dr. Aaishah M. Kaabi, Department of Zoology, College of Science, King Saud University, Riyadh, Kingdom of Saudi Arabia. E-mail: kaby@qu.edu.sa
ORCID ID: https://orcid.org/0000-0002-9630-1718

According to the European Society of Human Reproduction and Embryology, a miscarriage occurs when a pregnancy is lost before 22 weeks of gestation.[1] The World Health Organization defines recurrent spontaneous miscarriage (RSM) as experiencing 3 or more consecutive miscarriages before the Twenty weeks of pregnancy.[2] In contrast, the American Society for Reproductive Medicine considers 2 or more clinical miscarriages as recurrent pregnancy loss (RPL).[3] This condition impacts one to three percent of women or couples of reproductive age and is the subject of extensive discussion.[4]

Several factors may prevent a normal and viable embryo from resulting in successful delivery. These factors include advanced maternal age, uterine abnormalities, placental abruption, cervical insufficiency, chromosomal abnormalities in either parent, chromosomal rearrangements in the embryo, lifestyle habits, alloimmune dysfunctions, maternal infections, autoimmune diseases, endocrine imbalances, and thrombophilia.[5-8] Approximately 50% of RSM cases have identifiable causes, while the underlying causes of the remaining 50% remain unknown.[9] Genetic factors, especially thrombophilia, have garnered considerable attention, as they are treatable and influence pregnancy outcomes. Thrombophilia, whether inherited or acquired, raises the risk of thrombosis and is associated with negative pregnancy outcomes, including recurrent miscarriage.[10,11] Specifically, this medical disorder causes abnormal blood clotting, increasing the risk of thrombosis or blood clot formation in blood vessels. Also referred to as hypercoagulability or a prothrombotic disorder, thrombophilia typically results from an imbalance in the coagulation cascade of the body or in the anticoagulation/fibrinolytic system.[12,13] Notably, individuals with thrombophilia face a higher risk of miscarriage.[11,14,15]

Fibrinogen, a complex molecule, consists of two distinct parts, each containing 3 polypeptides: alpha, beta, and gamma chains.[16] This protein is produced in the liver and is present in the plasma of human blood, with normal levels ranging from 1.5 to 4.0 g/L and a half-life ranging from 3 to 5 days. Fibrinogen works together with fibrin, which is generated through thrombin-mediated cleavage, to perform crucial functions in various physiological processes.[17] The polymorphisms Thr331Ala and Thr312Ala are similar, but their names differ due to variations in the number of codons.[18]

Coagulation defects associated with bleeding and miscarriage have been less frequently reported compared to inherited and acquired thrombophilic risk factors.[19] Certain physiological abnormalities can result in miscarriage in pregnant women, leading to bleeding and placental detachment, ultimately resulting in pregnancy termination. These irregularities also affect the successful implantation of the embryo during the early stages of pregnancy. Among them, protein fibrinogen-related deficiencies play a significant role. These deficiencies include afibrinogenemia, hypofibrinogenemia, and abnormalities in fibrinogen structure, particularly dysfibrinogenemia, which can cause pregnancy complications.[20] A correlation between fibrinogen levels and recurrent miscarriages has been demonstrated, with evidence highlighting a relationship between altered fibrinogen levels and women experiencing RSM.[18,21]

Factor XI (FXI) is the precursor to the coagulation protease factor XIa (FXIa). Although FXIa contributes minimally to hemostasis, it plays a significant role in thrombus growth and stabilization.[22] Acquired FXI deficiency can result from autoimmune diseases, malignant tumors, and pregnancy.[23] In contrast, higher levels of FXI are linked to a greater risk of venous thrombosis.[24] Additionally, plasma thromboplastin levels are linked to RSM in women.[25] However, limited research has been conducted on genetic variations, specifically polymorphisms, associated with miscarriage, highlighting the need for further investigation.[26] Thus, the purpose of this study was to explore the association between factor I fibrinogen (rs6050) and FXI plasma thromboplastin (rs4253417) genetic polymorphisms and RSM in Saudi women.

Methods. The study was performed from September 2022 to June 2023. All women in the study were aged between 18 and 45 years and were part of the Saudi population. The study followed the guidelines established in the Helsinki Declaration. Informed consent was obtained from all participants, and the study protocol was approved by King Saud University's local ethics committees. Relevant publications were searched using the Google Scholar and PubMed platforms.

This study included 100 women (50 pregnant and 50 non-pregnant) who had experienced 2 or more spontaneous miscarriages before 12 weeks of gestation and were evaluated in the Department of Obstetrics and Gynecology at King Khalid University Hospital in Riyadh. Furthermore, a control group of 100 healthy

Disclosure. This study was funded by the Researchers Supporting Project (RSP2025R97), King Saud University in Riyadh, Kingdom of Saudi Arabia.

women (50 pregnant and 50 non-pregnant) was also included, all aged between 18–45 years, with at least one live birth and no history of miscarriage. Women with known causes of miscarriage were excluded through anatomical, hormonal, and chromosomal tests to identify those experiencing recurrent miscarriages.

Blood samples (5 mL) were obtained via venipuncture from each participant and stored in EDTA-coated purple tubes to prevent clotting for deoxyribonucleic acid (DNA) extraction. Genomic DNA was extracted using the Puregene Purification Kit (Qiagen, Hilden, Germany), As per the manufacturer's guidelines. The Nanodrop spectrophotometer (ND-2000c; Thermo Fisher Scientific, Waltham, MA, USA) was used to assess the quality and quantity of the DNA samples, which were maintained at –20°C for future analysis. Additionally, 2 mL of blood was collected from the participants using tubes containing sodium citrate to isolate plasma. Fibrinogen and plasma thromboplastin levels were measured using the STA Compact Max coagulation analyzer (Diagnostica Stago, Hauts-de-Seine, France).

Assays-on-Demand TaqMan® SNP genotyping assays (Thermo Fisher Scientific, Applied Biosystems, Foster City, CA, USA) were utilized following the manufacturer's instructions to perform genotyping assays for factor I (rs6050) and FXI (rs4253417).

The TaqMan genotyping assay mix included two primers and two TaqMan® Minor Groove Binder (MGB) probes, each designed to identify specific sequences and different alleles. TaqMan® MGB probes, which contain the reporter allele-specific dyes VIC® in Allele 1 and 6FAM™ in Allele 2 at the 5′ termini, allowed simultaneous detection of both potential variants within the SNP site in the target DNA sequence. This assay relies on the distinct fluorescence emitted by these reporter dyes when the probes are cleaved during target amplification, allowing for the determination of the specific SNP present.

Polymerase chain reaction (PCR) was conducted as multiplex reactions with a total volume of 15 µL. The mixture consisted of 8.25 µL of TaqMan® Genotyping Master Mix (Thermo Fisher Scientific, Applied Biosystems), 0.39 µL of the TaqMan® SNP Genotyping Assay specific for the target SNP, and 20 ng/µL of DNA template. The target sequence was amplified using the ViiA™7 real-time PCR system (Applied Biosystems). The cycling conditions included an initial enzyme activation at 95 degrees Celsius for 10 minutes, followed by 40 cycles of denaturation at 95 degrees Celsius for 15 seconds, and annealing at 60 degrees Celsius for 60 seconds.[27] Subsequent analysis of amplified products was performed using ViiA™7, v.1.1. (Applied Biosystems).

Statistical analysis. Data were collected from 50 women in each of the different study groups. Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA), with a significance level set as $p \leq 0.05$. The correlation between allele and genotype frequencies and RSM was evaluated in control and patient groups using the MedCalc® online statistical platform (Belgium). For small expected values, the Chi-square (X^2), 95% confidence interval (CI), *p*-value, and odds ratio (OR) were calculated using the 2-tailed Fisher's exact test. A comparison of the percentage levels of fibrinogen and plasma thromboplastin between the control and patient groups was made using an independent sample t-test. The Shapiro–Wilk test confirmed the normal distribution of the data, and the Hardy–Weinberg equilibrium was evaluated as well. Allele and genotype frequencies were presented as numbers and percentages, while the percentage levels of fibrinogen and plasma thromboplastin were presented as mean ± SEM.

Results. *Factor I fibrinogen (rs6050 C/T) polymorphism in Saudi pregnant women.* **Table 1** presents the analysis of the factor I fibrinogen (rs6050 C/T) polymorphism in its promoter region. We observed no statistically significant association between the CC genotype and RSM in the Saudi pregnant women cohort ($p=0.14$). Similarly, there were no significant differences in allele frequencies (C and T) between the groups. However, we observed a significant correlation between the CT and TT genotypes and susceptibility to RSM. Our results suggest that the CT exhibited an odds ratio (OR) of 4.18 ($p=0.001$) and TT genotype exhibited and OR of 0.38 ($p=0.002$) for RSM. Therefore, there was a significant correlation between these 2 genotypes and RSM.

Factor I fibrinogen (rs6050 C/T) polymorphism in Saudi non-pregnant women. We observed no statistically significant correlation between the CC genotype and the risk of RSM risk ($p=0.75$) (**Table 2**). In contrast, the CT and TT genotypes of the factor I fibrinogen polymorphism (rs6050 C/T) polymorphism exhibited a significant correlation with RSM susceptibility ($p \leq 0.05$). Importantly, allele frequencies (C and T) demonstrated a significant correlation with RSM risk ($p=0.001$). The adjusted OR for RSM in CT was 5.46 and that in TT genotype was 0.15. Therefore, the CT genotype was the most strongly associated with RSM, followed by the TT genotypes; both alleles (C and T) were significantly associated with RSM.

Factor XI plasma thromboplastin (rs4253417 C/T) polymorphism in pregnant Saudi women. We observed no significant correlation between allele frequencies, genotype distribution of FXI plasma thromboplastin (rs4253417 C/T), and RSM risk. The statistical analysis is presented in Table 3. Therefore, for pregnant Saudi women, there was no association between the genetic polymorphism of FXI plasma thromboplastin and RSM.

Factor XI plasma thromboplastin (rs4253417 C/T) polymorphism in non-pregnant Saudi women. As depicted in Table 4, the genotype and allele distribution did not indicate any statistically significant correlation with RSM risk in non-pregnant Saudi women, as the statistical analysis revealed $p>0.05$ for all genotypes and alleles.

Evaluation of fibrinogen and plasma thromboplastin levels in the blood of Saudi women. We observed no statistically significant differences in the percentage of fibrinogen in the blood and RSM between the control group and patients (Table 5). However, we noted significant differences in plasma thromboplastin percentage between the non-pregnant control group (92.900 ± 4.519) and the non-pregnant patient group

Table 1 - Association of Factor I fibrinogen rs6050 C/T polymorphism with recurrent spontaneous miscarriage (RSM) in pregnant Saudi women.

Genotype	RSM pregnant		Control		Patients (RSM pregnant) vs. control			
	n (%)	OR	n (%)	OR	OR	CI	X^2	*P*-value
CC	7 (14%)	0.16	13 (26%)	0.35	0.46	0.17 to 1.28	2.23	0.14
CT	31 (62%)	1.63	14 (28%)	0.39	4.18	1.81 to 9.73	11.56	0.001
TT	12 (24%)	0.32	23 (46%)	0.85	0.38	0.16 to 0.87	5.27	0.02
Total	50		50					
Alleles frequencies								
C	45 (45%)	0.82	40 (40%)	0.67	1.22	0.70 to 2.15		
T	55 (55%)	1.22	60 (60%)	1.5	0.81	0.46 to 1.43	0.51	0.48

CI: Confidence interval, vs: versus, a *p*-value of ≤0.05 determined statistical significance, OR: odds ratio, X^2: Chi-square

Table 2 - Recurrent susceptibility to spontaneous miscarriage and Factor I fibrinogen rs6050 C/T polymorphism in non-pregnant Saudi women

Genotype	RSM non-pregnant		Control		Patients (non-pregnant RSM) vs. Control			
	n (%)	OR	n (%)	OR	OR	CI	X^2	P-value
CC	6 (12%)	0.14	5 (10%)	0.11	1.27	0.35 to 4.32	0.10	0.75
CT	34 (68%)	2.13	14 (28%)	0.39	5.46	2.32 to 12.87	15.87	0.001
TT	10 (20%)	0.25	31 (62%)	1.63	0.15	0.06 to 0.38	18.05	0.001
Total	50		50					
Alleles frequencies								
C	46 (46%)	0.85	24 (24%)	0.32	2.66	1.47 to 4.94		
T	54 (54%)	1.17	76 (76%)	3.17	0.37	0.20 to 0.78	10.58	0.001

CI: Confidence interval, vs: versus, A *p*-value of ≤0.05 determined statistical significance, OR: Odds ratio, X^2: Chi-square

Table 3 - Factor XI plasma thromboplastin rs4253417 C/T polymorphism in pregnant Saudi women experiencing recurrent spontaneous miscarriage.

Genotype	RSM pregnant		Control		Patients (RSM pregnant) vs. Control			
	n (%)	OR	n (%)	OR	OR	CI	X^2	*P*-value
CC	15 (30%)	0.43	13 (26%)	0.35	1.23	0.51 to 2.93	0.20	0.66
CT	8 (16%)	0.19	15 (30%)	0.43	0.44	0.17 to 1.17	2.74	0.10
TT	27 (54%)	1.17	22 (44%)	0.79	1.48	0.68 to 3.29	0.99	0.32
Total	50		50					
Alleles frequencies								
C	38 (38%)	0.61	41 (41%)	0.69	0.88	0.50 to 1.56		
T	62 (62%)	1.63	59 (59%)	1.44	1.13	0.64 to 2.00	0.19	0.66

CI: Confidence interval, vs: versus, A *p*-value of ≤0.05 determined statistical significance, OR: Odds ratio, X^2: Chi-square

Table 4 - Factor XI plasma thromboplastin rs4253417 C/T polymorphism in non-pregnant Saudi women with recurrent spontaneous miscarriage.

Genotype	RSM non-pregnant		Control		Patients (RSM non-pregnant) vs. Control			
	n (%)	OR	n (%)	OR	OR	CI	X^2	*P*-value
CC	22 (44%)	0.79	22 (44%)	0.79	1.00	0.45 to 2.20	0.00	0.99
CT	6 (12%)	0.14	9 (18%)	0.22	0.64	0.20 to 1.90	0.70	0.40
TT	22 (44%)	0.79	19 (38%)	0.61	1.30	0.58 to 2.85	0.37	0.54
Total	50		50					
Alleles frequencies								
C	50 (50%)	1.00	53 (53%)	1.13	0.88	0.51 to 1.54		
T	50 (50%)	1.00	47 (47%)	0.89	1.12	0.65 to 1.96	0.18	0.67

CI: Confidence interval, vs: versus, A *p*-value of ≤0.05 determined statistical significance, OR: odds ratio, X^2: Chi-square

Table 5 - Comparison of the mean levels of fibrinogen and plasma thromboplastin in Saudi women with recurrent spontaneous miscarriage and healthy controls.

Traits group*	Fibrinogen	Plasma thromboplastin
Non-pregnant		
Control	3.972 ± 0.104	92.900 ± 4.519†
Patient	3.839 ± 0.106	111.360 ± 3.174‡
Significant	0.375	0.001
Pregnant		
Control	4.813 ± 0.132	94.780 ± 2.385†
Patient	4.737 ± 0.135	104.480 ± 3.110‡
Significant	0.687	0.015

†,‡ indicate significant differences at $p \leq 0.05$. *Comparisons between control and patients with the same physiological status.

(111.360 ± 3.174), as well as between the pregnant control (94.780 ± 2.385) and patient groups (104.480 ± 3.110).

Discussion. Given the limited research on the correlation between the genes studied in the present study and RSM in Saudi women, our findings will be discussed in a general context. In this study, we identified the factor I fibrinogen polymorphism rs6050 C/T in Saudi women with RSM, both pregnant and non-pregnant, and observed a significant correlation between the CT and TT genotypes and RSM susceptibility. These results align with the findings of Okumura et al,[18] who conducted a retrospective analysis on pregnancies in individuals with Thr331Ala fibrinogen polymorphisms and reported an association between this polymorphism and adverse obstetric outcomes. However, our results are in contrast to those of Kavosh et al,[28] who investigated the association between gene polymorphisms of FGA A6534G (rs6050) and the risk of RPL in Iranian females, as they did not identify a significant correlation between fibrinogen alpha chain A6534G (rs6050) gene polymorphisms and RPL.

Our analysis of the genotype and allele distributions of the FXI plasma thromboplastin polymorphism (rs4253417 C/T) did not reveal a significant correlation with the risk of RSM in Saudi women, regardless of pregnancy. This finding is consistent with those of Isazadeh et al,[29] who also found no significant correlation between the FXI polymorphism and RPL in a study involving 640 Iranian Azeri women, 320 of whom had RPL compared to 320 of whom were healthy, age-and race-matched controls. However, our results contrast with those of Khorshidi et al,[26] who investigated thrombophilic gene polymorphisms in Iranian women experiencing RPL. Their study indicated that the T allele of the FXI polymorphism may increase the risk of RPL, whereas the C allele may exhibit a protective effect. This suggests that the wild-type FXI gene could be associated with RPL.

In the present study, we also revealed a correlation between fibrinogen and thromboplastin levels in the blood of Saudi women, both pregnant and non-pregnant, experiencing RSM. In terms of fibrinogen levels, we observed no significant differences in fibrinogen percentage between the control group and patients with RSM. These results contradicted the findings of Cimsir and Yildiz,[21] who reported significant differences in various blood parameters, including higher fibrinogen values in pregnant women with RPL. Similarly, our results also differed from the study by Mohamed et al,[30] which investigated pregnant

Sudanese women with RSM. The authors reported a notable decrease in fibrinogen levels, but no statistically significant variance in fibrinogen levels, based on factors such as age, number of miscarriages, and gestational age, among these women.

Regarding plasma thromboplastin levels, our results indicated statistically significant differences between the plasma thromboplastin rate between the non-pregnant control group and the non-pregnant patient group. We observed similar differences between the pregnant control group and the pregnant patient group. This finding is consistent with the results of the Sokol study,[25] which explored FXI activity in relation to patients with RSM and suggested that elevated FXI activity could pose a potential risk factor for miscarriage. The study also revealed that women experiencing spontaneous miscarriages exhibited significantly higher levels of FXI activity than the control group, suggesting a correlation between increased levels of FXI activity and a higher risk of spontaneous miscarriage.

Study limitations. One limitation of this study was the small sample size, as the samples were collected exclusively from patients at King Khalid University Hospital, representing various regions of the Kingdom of Saudi Arabia.

In conclusion, we demonstrated a significant correlation between RSM risk and carriers of Factor I fibrinogen (rs6050 C/T) CT and TT genotypes. However, we observed no significant correlation between FXI plasma thromboplastin (rs4253417 C/T) and the risk of RSM. Therefore, further studies are required to explore the associations between rs4253417 C/T polymorphisms and RSM in the Saudi population.

Acknowledgment. *We express our gratitude to Editage (www.editage.com) for the English language editing.*

References

1. ESHRE Guideline Group on RPL, Atik RB, Christiansen OB, Elson J, Kolte AM, Lewis S, et al. ESHRE guideline: recurrent pregnancy loss: an update in 2022. *Hum Reprod Open* 2023; 1: 2023 hoad002.
2. Fainboim L, Belén S, González V, Fernández P. Evaluation of paternal lymphocyte immunotherapy and potential biomarker mixed lymphocyte reaction-blocking factor in an Argentinian cohort of women with unexplained recurrent spontaneous abortion and unexplained infertility. *Am J Reprod Immunol* 2021; 86: e13422.
3. Chester MR, Tirlapur A, Jayaprakasan K. Current management of recurrent pregnancy loss. *Obstet Gynaecol* 2022; 24: 260-271.
4. Quenby S, Gallos ID, Dhillon-Smith RK, Podesek M, Stephenson MD, Fisher J, et al. Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. *Lancet* 2021; 397: 1658-1667.
5. Guo H, Gao H, Li J, Cong Y, Chen Q, Wang Y, et al. Impacts of medroxyprogesterone acetate on oocytes and embryos: matched case-control study in women with stage III–IV ovarian endometriosis undergoing controlled ovarian hyperstimulation for in vitro fertilization. *Ann Transl Med* 2020; 8: 377.
6. Zhou WJ, Yang HL, Mei J, Chang KK, Lu H, Lai ZZ, et al. Fructose-1, 6-bisphosphate prevents pregnancy loss by inducing decidual COX-2+ macrophage differentiation. *Sci Adv* 2022; 8: eabj2488.
7. Dimakou DB, Tamblyn J, Justin C, Coomarasamy A, Richter A. Diagnosis and management of idiopathic recurrent pregnancy loss (RPL): current immune testing and immunomodulatory treatment practice in the United Kingdom. *J Reprod Immunol* 2022; 153: 103662.
8. García-Chávez J, Majluf-Cruz A. Acquired hemophilia. *Gac Med Mex* 2020; 156: 67-77.
9. Sultana S, Nallari P, Ananthapur V. Recurrent pregnancy loss (RPL): an overview. *J Womens Health Dev* 2020; 3: 302-315.
10. Voicu DI, Munteanu O, Gherghiceanu F, Arsene LV, Bohiltea RE, Gradinaru DM, et al. Maternal inherited thrombophilia and pregnancy outcomes. *Exp Ther Med* 2020; 20: 2411-2414.
11. Gobjila C, Craina ML, Toader DO, Petre I, Andor CB, Tudor A. et al. Pro-inflammatoru cytokines (IL6, IL8 and TNF-α) in the evaluation of ivarian endometriosis cyst. *Rev Chim* 2019; 70: 2944-2847
12. Ashorobi D, Ameer MA, Fernandez R. Thrombosis. In StatPearls. Treasure Island (FL): StatPearls Publishing; 2019.
13. Bauer AT, Gorzelanny C, Gebhardt C, Pantel K, Schneider SW. Interplay between coagulation and inflammation in cancer: Limitations and therapeutic opportunities. *Cancer Treat Rev* 2022; 102: 102322.
14. Branch DW. What's new in obstetric antiphospholipid syndrome. *Hematology Am Soc Hematol Educ Program* 2019; 2019: 421-425.
15. Liu X, Chen Y, Ye C, Xing D, Wu R, Li F, et al. Hereditary thrombophilia and recurrent pregnancy loss: a systematic review and meta-analysis. *Hum Reprod* 2021; 36: 1213-1229.
16. Litvinov R, Pieters M, de Lange-Loots Z, Weisel J. Fibrinogen and fibrin. *Subcell Biochem* 2021; 96: 471-501.
17. Vilar R, Fish RJ, Casini A, Neerman-Arbez M, Fibrin(ogen) in human disease: both friend and foe. *Haematologica* 202; 105: 284-296.
18. Okumura A, Tanaka H, Tanaka K, Katsuragi S, Kamimoto Y, Ikeda T. Retrospective study of pregnancies in women with Thr331Ala fibrinogen polymorphisms. *J Matern Fetal Neonatal Med* 2020; 33: 3894-3899.
19. Presky KO, Kadir RA. Women with inherited bleeding disorders–Challenges and strategies for improved care. *Thromb Res* 2020; 196: 569-578.
20. Zhang Y, Zuo X, Teng Y. Women with congenital hypofibrinogenemia/afibrinogenemia: from birth to death. *Clin Appl Thromb Hemost* 2020; 26: 1076029620912819.
21. Cimsir MT, Yildiz MS. Could fibrinogen to albumin ratio be a predictive marker for recurrent pregnancy loss. *Int J Clin Pract* 2021; 75: e14520.
22. Fredenburgh JC, Weitz JI. Factor XI as a target for new anticoagulants. *Hamostaseologie* 2021; 41: 104-110.
23. Somers EC. Pregnancy and autoimmune diseases. *Best Pract Res Clin Obstet Gynaecol* 2020; 64: 3-10.

24. Rietveld I, Lijfering W, le Cessie S, Bos M, Rosendaal F, Reitsma P, et al. High levels of coagulation factors and venous thrombosis risk: strongest association for factor VIII and von Willebrand factor. ***J Thromb Haemost*** 2019; 17: 99-109.
25. Sokol J, Biringer K, Skerenova M, Stasko J, Kubisz P. Activity of coagulation Factor XI in patients with spontaneous miscarriage: the presence of risk alleles. ***J Obstet Gynaecol*** 2015; 35: 621-624.
26. Khorshidi F, Hajizadeh S, Choobineh H, Alizadeh S, Sharifi M, Kavosh Z, et al. Determining the association of thrombophilic gene polymorphisms with recurrent pregnancy loss in Iranian women. ***Gynecol Endocrinol*** 2020; 36: 1082-1085.
27. Althubyani SA, Alkhuriji AF, Al Omar SY, El-Khadragy MF. A preliminary study of cytokine gene polymorphism effects on Saudi patients with colorectal cancer. ***Saudi Med J*** 2020; 41: 1292-1300.
28. Kavosh Z, Mohammadzadeh Z, Alizadeh S, Sharifi MJ, Hajizadeh S, Choobineh H, et al. Factor VII R353Q (rs6046), FGA A6534G (rs6050), and FGG C10034T (rs2066865) gene polymorphisms and risk of recurrent pregnancy loss in Iranian women. ***Indian J Hematol Blood Transfus*** 2024; 40: 297-302.
29. Isazadeh A, Hajazimian S, Rahmani SA, Mohammadoo-Khorasani M, Moghtaran N, Fathi Maroufi NF. The effect of Factor-XI (rs3756008) polymorphism on recurrent pregnancy loss in Iranian Azeri women. ***Gene Cell Tissue*** 2016; 4: e13330.
30. Mohamed EI, Merghani MM, Babiker NE. Estimation of fibrinogen level among Sudanese women with recurrent miscarriage. ***J Drug Deliv Ther*** 2021; 11; 140-144.