Systematic review

The extent of Factor V Leiden thrombophilia in maternal and fetal health. Risk of placenta-mediated pregnancy complications - a systematic review

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Abbreviations: FVL - Factor V Leiden, PMPC - placenta-mediated pregnancy complications, IUGR - intrauterine growth restriction, RPL - recurrent pregnancy loss, PT - prothrombin, PAI-1 - Plasminogen Activator Inhibitor 1, MTHFR - Methylenetetrahydrofolate reductase, LAC - Lupus Anticoagulant, IVF - in vitro fertilization, OR - odds ratio, CI - confidence interval, HDP - hypertensive disorders in pregnancy

Abstract

Factor V Leiden represents a mutation in the gene coding the production of V factor, being the most common cause for hereditary thrombophilia, affecting up to 50% of the patients with familial thrombophilia. Pregnant women are generally considered a population at risk for developing different associated pathologies potentially leading to premature parturition, or other complications. Existing literature seems to point towards a significant connection between the Factor V Leiden thrombophilia and potential complications, including thromboembolic events, preeclampsia, recurrent pregnancy loss and intrauterine growth restrictions.

Articles published in the past 9 years were sourced on PubMed, using keywords such as "factor V Leiden", "FVL", "pregnancy". We included systematic reviews, meta-analyses, case-control and retrospective studies. Placenta-mediated pregnancy complications (PMPC), such as recurrent pregnancy loss (RPL), preeclampsia (PE), and intrauterine growth restriction (IUGR) represented the inclusion criteria. Associated pathologies, comparative studies, screening, women with history of IVF and embryo transfer, clinical trials, paternal and fetal mutations were excluded. Bias risk was not assessed, and an abstraction method was used for data synthesis.

21 randomized control trials were selected. Obstetrical outcomes such as RPL, PE, and IUGR were analyzed in connection with the presence of FVL. Bias risk was not assessed. FVL was associated with a higher risk of RPL in Padda J et. al (2021), Hamedi et al. (2020), Jusić A et al. (2018), and Pietropolli A et al. (2014), with a prevalence of 12.6% (OR=2.4), 12.6% (OR=2.37), 7.5% (p=0.021), and 10% (p=0.05). A connection between FVL and preeclampsia was found in Ahmed NA et al. (2019) - 9.6% (OR=18.60), fortified by Li Y et al. (2019) and Fong FM et. al. (2014). FVL had a prevalence of 40% in patients with IUGR in Padda J et al. (2021), while

Coriu L et al. (2014) showed similar results, but without statistical significance (OR=1.58, p>0.05).

FVL is associated with higher risk of RPL, preeclampsia and IUGR. However, due to the multifactorial aspects of obstetrical complications, stronger research is recommended for a better understanding in the future.

Introduction

Factor V Leiden represents a mutation in the gene coding the production of V factor, an important piece in the coagulation cascade. People affected by this autosomal dominant condition will develop a coagulation factor that is more resistant to the anticoagulant effect of Protein S, thus leading to a procoalgulant status and an increased risk of developing thrombotic events.[1] Factor V Leiden currently represents the most common cause for hereditary thrombophilia, affecting up to 50% of the patients with familial thrombophilia.[2]

The most important consequence of FVL is the venous thromboembolism (VTE) However, not all patients with FVL mutation will develop VTE events during their lifetime, being reported that only 5%, respectively 20% for patients with familial type of disease, will suffer from venous thromboembolism. The most common site for VTE is deep venous thrombosis, with other possible scenarios being reported, such as pulmonary thromboembolism, cerebral, portal, or superficial veins of the legs also being involved to a lesser extent.[3] An interesting particularity of FVL patients is represented by the lower risk of isolated pulmonary embolism, without previous deep venous thrombosis, reported compared to the general population, leading to the coining of "Factor V Leiden Paradox".[3]

Pregnant women are generally considered a population at risk for developing different associated pathologies potentially leading to premature parturition, or other complications. Some of the most severe such complications include eclampsia and preeclampsia potentially resulting in higher mortality and morbidity for both the mother and the fetus. Preeclampsia is defined as a novel onset of hypertension above 140 mmHg in women past 20 weeks of gestation, proteinuria, and/or multiple organ dysfunction (kidney, liver, central nervous system etc).[4] Eclampsia is defined as the new onset of generalized tonic-clonic seizures in a woman with preeclampsia.[4]

Thromboembolism is reported in 1.2/1000 deliveries, being associated with increased risk of mortality and morbidity. Women with FVL and other inherited thrombophilia with or without a family history of VTE are at increased risk of VTE and VTE-related complications during pregnancy. However, there is still debate concerning the risk at which are exposed women with FVL mutations during pregnancy.[5] Existing literature seems to point towards a significant connection between the Factor V Leiden thrombophilia and potential complications, including thromboembolic events, preeclampsia, recurrent pregnancy loss and intrauterine growth restrictions. However, current guidelines do not consider FVL and other hereditary thrombophilias as potential risk factors for pregnancy losses.[6] Alas, further research needs to be conducted in order to establish a definitive answer to this question, especially when considering the potential severe repercussions in terms of both maternal and fetal mortality and morbidity that such a condition may generate.

Materials & Methods

This systematic review was conducted and reported according to the quality standards described in the PRISMA 2020 Checklist, and bias risk was not assessed. Two reviewers independently carried out study selection, evaluation, and data abstraction. All disagreements were resolved by consensus or settled between the other two reviewers.

Sources and criteria

Articles published between 2014 and 2023 were sourced on PubMed. We included systematic reviews, meta-analyses, case-control studies and retrospective studies. Inclusion criteria used were placenta-mediated pregnancy complications (PMPC), such as placental abruption, preeclampsia, intrauterine growth restriction (IUGR), recurrent pregnancy loss (RPL), and stillbirth in pregnant women with Factor V Leiden mutation. The following gene mutations associated with hereditary thrombophilia were included: prothrombin, PAI polymerphisms, MTHFR. Deficiency of antithrombin III, protein C or protein S also appeared in a number of studies. We excluded associated pathologies, such as venous thromboembolism, deep vein thrombosis, pulmonary embolism, ischemic encephalopathy, other ischemic arteriopathies, inflammation and sepsis, as well as comparative studies, screening, women with history of IVF and embryo transfer, clinical trials, paternal mutations and fetal mutations. Publications written in languages other than English were excluded.

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Search strategy

Our advanced search was done in three steps, as shown in Table 1:

Table 1. Search strategy

	Keywords	Search formula
Ist search	"factor V Leiden", "FVL", "pregnancy", "maternal", "fetal" and "health"	(factor V Leiden[All Fields] OR FVL[All Fields]) AND (pregnancy[All Fields] OR maternal health[All Fields] OR maternal[All Fields] OR fetal health[All Fields] OR fetal[All Fields])
IInd search	"factor V Leiden", "FVL", "miscarriage", "recurrent" and "preeclampsia"	(factor V Leiden [Title] OR FVL[Title]) AND (miscarriage, recurrent[MeSH Terms] OR miscarriages, recurrent[MeSH Terms] OR recurrent miscarriage[MeSH Terms] OR recurrent miscarriages[MeSH Terms] OR preeclampsia[MeSH Terms])
IIIrd search	"G1691A","mutation" and "pregnancy"	(G1691A[All Fields] OR G1691A mutation[All Fields]) AND pregnancy[All Fields]

Data abstraction

Research was made individually by two of the four reviewers. After removing the duplicates, studies were selected in a two-stage process. In the first stage, we identified relevant citations from titles and abstracts and created a database. In the next stage, we reviewed full texts and selected the studies with relevant conclusions. The full text of two articles could not be retrieved. For inclusion in the review, the data was abstracted from each study using a consensual abstraction method, based on the year of publication, study design, presence and frequency of FVL mutation, variety of complications (excluding stage and intensity), ethnic diversity of the targeted populations, geographic region, and risk estimates, with their corresponding OR and 95% CIs (if available). Normal, uncomplicated pregnancies, with present mutation factors were combined to form the control group. Heterogeneity within the group was not assessed.

The key exposure variable was the presence of Factor V Leiden (FVL) mutation in pregnant women.

Exposure and outcome

Results of other thrombophilia specific mutations found in the studies, such as PT G20210A, MTHFR C677T and A1298C, and PAI-1 4G/5G were not considered, since the FVL G1691A mutation was the element of interest in this review. The FVL mutation causes a coagulation defect of factor V, inherited as a dominant autosomal trait, with G > A substitution at nucleotide 1691 located on chromosome 1q23 (the heterozygote genotype of FVL mutation is GA and homozygote genotype is AA).[7]

The outcome of interest was PMPC, namely the extent of involvement of thrombophilia (particularly FVL mutation) in these anomalies, and how it affects maternal and fetal health. A statistically significant predominance of studies that focused on RPL was found. RPL was defined as having two or more miscarriages. Early RPL was defined as pregnancy losses before the 13th week of pregnancy, whereas late RPL was defined as pregnancy losses after the 13th week of pregnancy.[7]

Bias risk assessment

The reviewers of this article considered the risk of bias based on self-made criteria, such as 1. searching skills of reviewers, 2. match between model and question (using the PICO method for constructing a clinical question), 3. relevance of searches, 4. relevance of outcomes, and 5. the statistical power of the studies. Thus, we did not perform quantitative analyses, and therefore, we did not follow the sections in the PRISMA 2020 Checklist that relate to meta-analysis.

Results

1. Study selection

A total of 301 unique records were identified, and after the removal of duplicates and initial screening, 44 articles were selected. From these, 25 were excluded based on our abstraction criteria, and 19 were included and further analyzed.

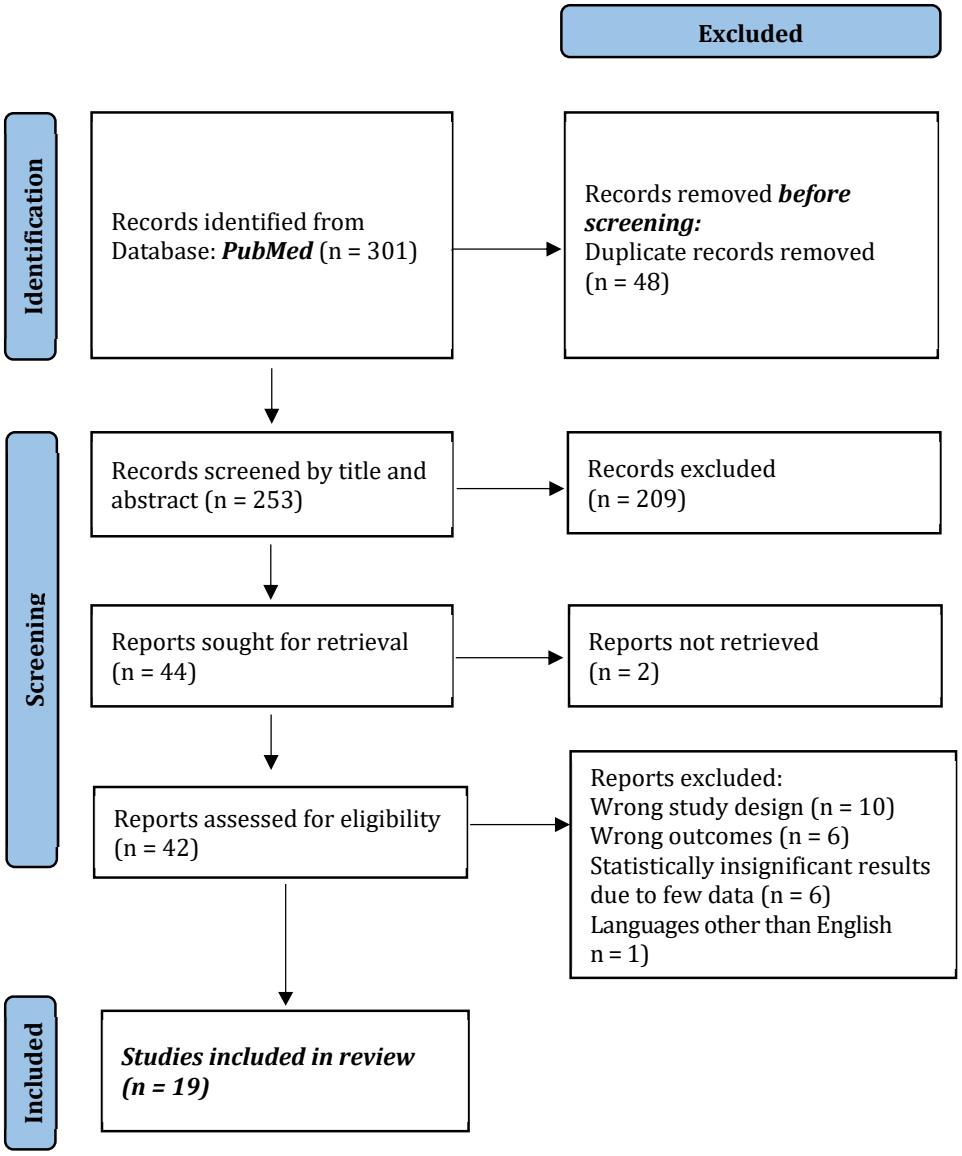

Figure 1. Flow diagram

Studies with poor or little documentation, unexpected outcomes, or low statistical power,[8] those which stratified the results based on multiple criteria, such as intensity (mild/severe) or stage (early/ late) of preeclampsia[9] etc., and studies from certain unreliable sources,[10] that appeared to meet the inclusion criteria, were excluded from our review.

1. Study characteristics

A. Methods

All 21 papers selected for the review were randomized control trials published in English. The various obstetric outcomes followed in the research process for a potential link with FVL G1619A gene mutation were not analyzed depending on their occurrence as *early* or *late* complications, nor on their intensity as *severe* or *mild,* since there was no homogeneity in the selected studies when exposing the way each complication emerged. An identical constraint was encountered in layering the outcomes of the genetic mutation of FVL depending on the homozygous and the heterozygous variant. Hence, to make our review more generalized, we included both early and late outcomes, in addition to heterozygous and homozygous mutations of FVL.

B. Participants

The included studies involve a pattern of a feminine population which can be divided into four groups based on the variety of complications:
I. patients with **recurrent pregnancy loss**
II. patients with **preeclampsia**
III. patients with **intrauterine growth restriction**
IV. patients with normal pregnancies and term-delivered healthy neonates.

Each complication that occurred in the first three groups was analyzed in connection with the presence, and respectively, with the frequency of FVL mutation, aiming to settle a conclusion whether the presence of FVL is related to the susceptibility to develop these kinds of obstetric outcomes. In addition, the fourth category of patients represents the control group used for quantifying the results.

Another characteristic of the patients involved in the cited papers is the ethnic diversity of the targeted populations, headed to validate the hypothesis that the prevalence of obstetric complications, affected or not by the presence of FVL, is strongly related to the genetic susceptibility, shaped by the ethnicity of each case. According to this, to offer a highly particular perspective, the presented studies analyze populations from Europe, the Middle East, North America, Latin America, Asia, and Australia.

3. Risk of bias in studies

Bias risk was not assessed for any of the presented studies. An important limitation should still be taken into account when interpreting the results of this systematic review. The Middle East population is heterogeneous, mixing a wide variety of ethnicities such as Arabs, Jews, Persians, Kurdish, etc. This fact might be an impediment to stating a clear connection between the genetic susceptibility to develop the mentioned complications, influenced by ethnicity in addition to FVL mutation. Even if none of the studies deviated from the Hardy-Weinberg equilibrium, the results might not be conclusive because of the lack of uniformity in the genetic arsenal of each population. This inclusion criterion might cause a level of bias in the results.

4. Results of individual studies

Table 2. Assessment of obstetric complications in targeted populations based on the prevalence of FVL, as shown in individual studies.

Author (year)	Obstetrical complication followed in the targeted population	The prevalence of FVL in the targeted population	The prevalence of FVL in control group	Statistical power indicator
Padda J et. al (2021)[11]	Recurrent Pregnancy Loss	12.6%	4.9%	OR = 2.4
Ahmed NA et al. (2019)[12]	Preeclampsia	9.6%	0.6%	OR = 18.60
Hamedi et al. (2020)[13]	Recurrent Pregnancy Loss	12.6%	4.9%	OR = 2.37
Jusić A et al. (2018)[14]	Recurrent Pregnancy Loss	7.5%	3.75%	p=0.021
Pietropolli A et al. (2014)[15]	Recurrent Pregnancy Loss	10%	3%	p=0.05
Coriu L et al. (2014)[16]	Intrauterine Growth Restriction	13%	2.2%	OR = 6.9
Gils C et al. (2016)[17]	Placental Abruption	10.7%	7%	p=0.05

5. Results of syntheses

There is still a lot of controversy regarding the association between FVL and its effect on pregnancy loss, despite the substantial amount of data available in the literature. Study design, research bias, and racial differences among the targeted patients could stand as possible factors for the inconclusive findings.

To address this limitation, *Eslami*[18] performed the first meta-analysis to provide a consistent conclusion of the association between FVL mutation and RPL risk. The studies included in the mentioned meta-analysis were performed in Asia, Europe, South America, and Africa. The conclusion revealed a significant link between FVL mutation and the risk of RPL in the Asian, European, and African populations, apart from the South Americans.

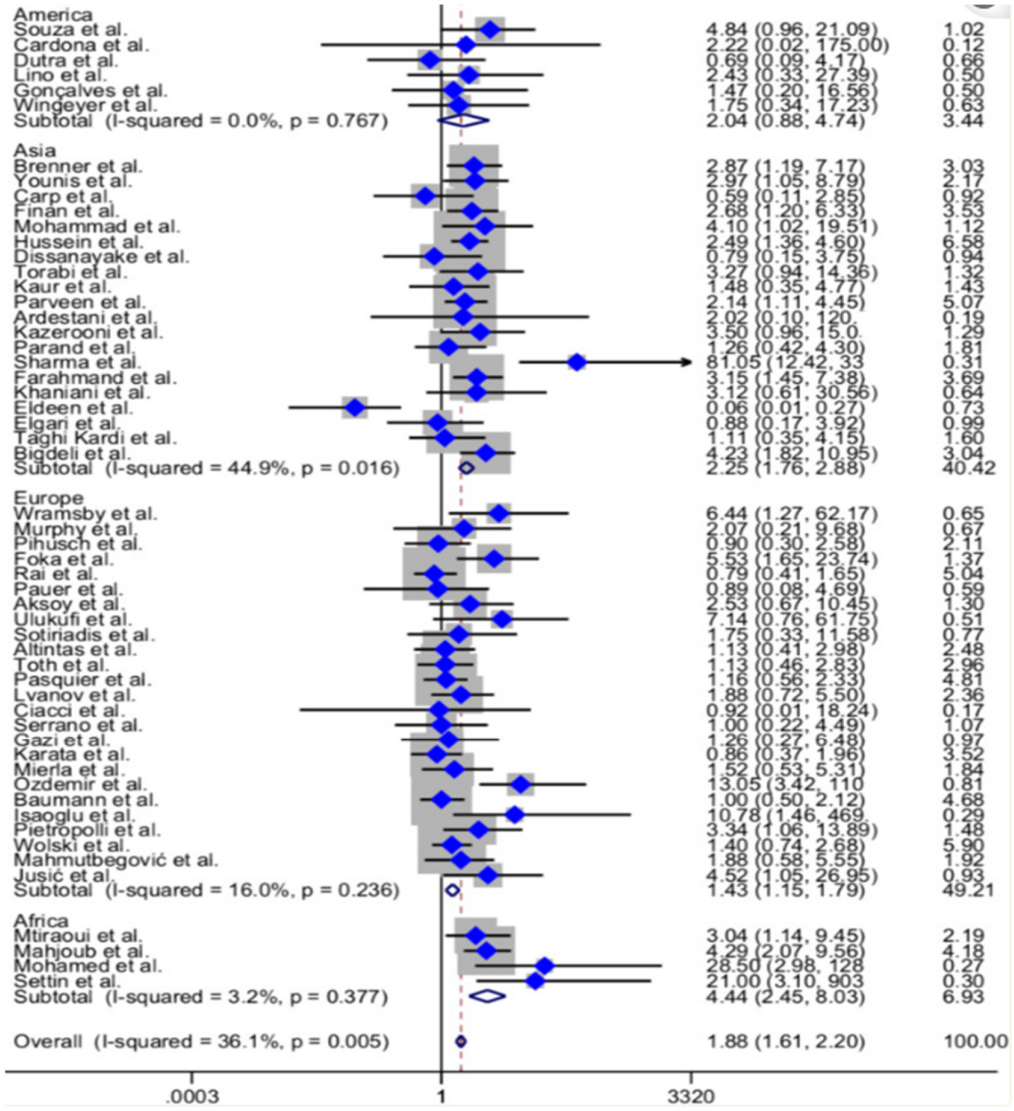

Figure 2. Pooled OR and 95% CI of individual studies and pooled data for the association between FVL 1691G>A mutation and the risk of RPL in different continents - *courtesy of Eslami MM et al. (2020)*[18]

Hamedi[13] support the identical association between FVL mutation status and RPL in women of the Middle East countries, reaching congruent results with those studies where frequencies of FVL were higher in RPL patients than in controls. The mentioned review includes 19 studies, and overall, 2561 cases and 1883 controls from four countries in the Middle East. The Forest Plot was used to evaluate the link between FVL mutation and RPL - corroborating all the countries considered, FVL mutation was associated with a higher risk of RPL (12.4% and 4.9% in patients and controls, respectively).

In the same context, *Sergi*[19] priorly conducted a systematic review involving nine studies, summing up a total of 2,147 women who were screened for the FVL mutation, from which 1,305 women experienced RPL, and 842 women had no gestational complications. When the ratio comparing the odds of FVL mutation in the RPL group and the control group were calculated with its 95% CI by Mantel–Haenszel method, women with RPL had indeed a statistically significant increase of carrier frequency of FVL mutation, the common OR being 1.68 (95% CI: 1.16-2.44).

References	FVL mutation	RPL	Normal reproductive history	OR and 95 % CI
Balash [45]	Present	1	1	0.9 (0.02–34.29)
	Absent	54	49	
Grandone [46]	Present	2	5	1.8 (0.22–11.48)
	Absent	25	113	
Dizon-Townson [47]	Present	0	1	1.1 (0–63.62)
	Absent	22	49	
Younis [49]	Present	6	8	3.16 (0.89–11.06)
	Absent	31	131	
Foka [50]	Present	15	4	5.53 (1.61–20.78)
	Absent	65	96	
Reznikoff [52]	Present	27	11	2.41 (1.11–5.31)
	Absent	233	229	
Rai [51]	Present	59	12	0.85 (0.43–1.72)
	Absent	765	133	
Summary OR; 95 % CI: 1.68 (1.16–2.44). Breslow–Day: $P = 0.11$				

Figure 3: Table for FVL mutation in women with RPL and those with normal reproductive history *- courtesy of Sergi C et al. (2015)*[19]

On the other side of the obstetrical complications which can emerge, *Li and Ruan*[20] stated that FVL mutation is associated with an increased risk of Hypertensive Disorders in Pregnancy (HDP), particularly preeclampsia and eclampsia in European women. The authors conducted a meta-analysis based on 50 studies with 6041 cases and 8364 controls. All data were summarized from pre-existing studies, with populations from Europe, the Middle East, North America, Latin America, Asia, and Australia. The results showed that FVL mutation was strongly associated with HDP in the overall analysis (OR = 1.97, P < 0.00001). However, a certain conclusion cannot be generalized in this direction, namely the involvement of FVL mutation in the development of HDP. To support this, among all the studies in this meta-analysis, 15 of them got a negative result, proving that the FVL mutation is not an essential gene that can lead to HDP, while 35 of them had a favorable conclusion regarding the association between the two. There are many potential reasons for this inconsistency, the most relevant one for our hypothesis being the complexity of HDP as a disease, with all its influencing factors.

Thus, studies that approach preeclampsia as an individual pathogenic entity were subsequently researched, to draw a more specific conclusion in regard to our hypothesis. *Ahmed*[12] highlighted the high prevalence of FVL gene variation in the precipitation of preeclampsia in Sudanese women (9.6%), in comparison to the control group (0.6%). A similar frequency (9.1%) was quoted in 4 of 44 preeclamptic women in Tunisia, whereas the percentages advanced in Germany (20%), Israel (26%), Sweden (15%), and Hungaria (18.8%). In contrast, no association between FVL and preeclamptic women was detected in the South African population.

Similar results which confirm a link between FVL and preeclampsia were found by *Fong.*[21]

Referring to the third complication under investigation, numerous studies have been conducted to prove a connection between Intrauterine Growth Restriction (IUGR) and genetic thrombophilia, specifically FVL mutation G1691A. *Padda*[11] mentioned in the systematic review conducted in this direction a meta-analysis based on 32 cohort and case-control studies which revealed a 40% increase in the risk of IUGR in FVL mutation carriers. As mentioned above, similar findings were confirmed by *Coriu*[16], where the risk of IUGR in pregnant women with factor V Leiden was 1.58-fold higher (OR 1.58, 95% CI 0.61-4.080) than those who did not present this mutation, but the results were not statistically significant (p >0.05).

Discussion

Recurrent pregnancy loss (RPL), intrauterine growth restrictions (IUGR) and preeclampsia continue to pose a threat to both maternal and fetal health. Because of their multifactorial nature, identifying causative genomic changes without acknowledging other external factors, has proven to be difficult.

Despite the FVL G1619A mutation has been associated with increased risk of RPL[11] in many ethnic groups,[18,20] there is controversy regarding these poor pregnancy outcomes and FVL. While some authors found the higher prevalence of FVL in jewish women with RPL compared to the control group,[22] others were unable to show any associations,[23] thus highlighting the importance of individual traits, despite a similar ethnic background.

Alongside FVL, the presence of MTHFR and PAI-1 mutations, Protein C deficiency, and LAC antibodies point to high thrombophilic risk in pregnant women,[24] however, the effect of each individual marker on obstetrical outcomes, or other possible synergistic effects between multiple mutations, are still not well understood. While both FVL and MTHFR polymorphisms were significantly associated with RPL in Bosnian women, PAI-1 polymorphisms did not show a strong association.[14]

Thus being said, stronger research is recommended for better understanding on the degree to which these mutations impact obstetrical outcomes, and how this translates into clinical settings and patient care.

Conflict of interest

The authors of this article declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions

All authors equally contributed to this article and approved the submitted version.

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