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Review

Potential role of Factor V Leiden mutation in adverse pregnancy outcomes: An updated systematic review

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Abstract

Background: Thrombophilia is an inherited or acquired predisposition for development of thrombosis. One of the common thrombophilia polymorphisms is Factor V Leiden (FVL) mutation, which may contribute to negative pregnancy outcomes. This systematic review study seeks to describe the potential effects of factor V Leiden mutation on adverse pregnancy outcomes. **Methods:** Pubmed, Embase, ISI Web of Sciences, Scopus, ScienceDirect, Proquest and Google Scholar, for articles published during 1996-2017. Articles were evaluated by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for standard reporting. As well, the quality of studies was assessed by the Newcastle-Ottawa Scale (NOS). **Results:** A total of 14 studies were eligible based on the inclusion criteria. The papers were scored by the STROBE checklist. The range of STROBE score was 15-20. Only 37.5% of the studies confirmed the relationship between fetal loss and FVL. The effect of FVL mutation on spontaneous abortions and In Vitro Fertilization (IVF) failures was demonstrated in all the studies. In the reviewed studies, there was no observed relationship between FVL mutation with intrauterine growth restriction (IUGR), preeclampsia, placental abruption or small for gestational age (SGA).

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Conclusion: The reviewed studies showed an unclear association between FVL mutation and stillbirth, IUGR, preeclampsia, or placental abruption. The exact effects of hereditary thrombophilia on pregnancy outcome is also still controversial. However, FVL mutation appeared to have an effect on spontaneous abortions and IVF failures. Therefore, screening patients for thrombophilic polymorphisms might be helpful.

Keywords

Factor V Leiden, Mutation, Pregnancy outcomes

Introduction

Factor V Leiden (FVL) is a variant, mutated form of human factor V (one of several substances that helps blood clot), which causes an increase in blood clotting. With this mutation, the secreted anticoagulant protein, which normally inhibits the pro-clotting activity of factor V, is not able to bind normally to factor V. This leads to a hypercoagulable state, i.e., an increased tendency for the patient to form abnormal and potentially harmful blood clots (De Stefano and Leone, 1995). FVL mutation is the most common known genetic factor that predisposes an individual to thrombosis (Dizon-Townson et al., 2005).

Thrombosis is a common cause of death in the U.S. Thrombophilia is an inherited or acquired predisposition to develop either venous or arterial thrombosis (Rodger, 2013). The combined prevalence of different types of thrombophilia in the general population exceeds one in ten. The most commonly reported type of acquired thrombophilia is the antiphospholipid syndrome (APS). The diagnostic criteria for this condition are presence of antiphospholipid antibodies, e.g. anticardiolipin antibodies (aCL), and/or lupus anticoagulant (LA) and anti-$_{\beta}$-2-glycoprotein I (a_{β}2-GPI) antibodies, for two or more separate occasions and for at least 9-12 weeks apart (Simcox et al., 2015). Inherited risk factors of thrombophilia include protein C, protein S, and antithrombin (AT III) deficiency and FVL gene mutation (Carrington et al., 2005; Doyle and Monga, 2004). FVL gene mutation may cause miscarriage, preeclampsia, IUGR, placental abruption, and stillbirth in pregnant women (Gawish, 2011; Rai and Regan, 2006).

Thrombophilic disorders are in fact believed to exacerbate the state of hypercoagulability in pregnancy and lead to the formation of microthrombin and placental insufficiency (Kupferminc et al., 2011). Thrombophilia is a complex

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disorder with various risk factors. The most commonly reported form of acquired thrombophilia is the APS. FVL is the underlying cause of activated protein C resistance (APCR), and prothrombin time (PT) are considered to be two major genetic risk factors for the condition. Despite their significance, these two factors generally remain under-diagnosed due to the absence of symptoms and low risk of thrombosis in their carriers. Nevertheless, the presence of the mentioned factors may become clinically evident following exposure to other predisposing factors, including pregnancy, oral contraceptives, hormone replacement therapy (HRT) and vessel wall disorders, which encourage stasis and boost the risk of life-threatening thrombotic events (Gawish, 2011).

Extensive research over the past 50 years has confirmed significant relationships between thrombophilia (both inherited and acquired) and elevated risk of serious obstetric complications such as miscarriage, stillbirth, severe preeclampsia, placental abruption, IUGR, and other adverse obstetric outcomes. Although the exact mechanisms involved are unknown, inadequate maternal-fetal circulation and decreased placental perfusion caused by abnormal placental vasculature and disturbances in hemostasis might be responsible for the aforementioned complications (Pavlova et al., 2008) since higher frequency of FVL mutation has been documented in women with such complications (Kupferminc et al., 1999). Based on the results of previous studies, the rates of preterm births have increased over time. Furthermore, thrombophilia may have negative impacts on pregnancy outcomes, especially preterm birth and the consequent neonatal and childhood injuries and deaths, and can exert a heavy economic burden on society and families.

According to searches in various databases no systematic review has assessed the effect of FVL mutation on pregnancy outcomes in recent years. A systematic review article provides an outline of research study results and is the best method for summarizing the overall evidence (Abdi and Roozbeh, 2016; Roozbeh et al., 2017b). Hence, our study aimed to estimate the prevalence of FVL mutation in women with pregnancy outcomes such as preterm birth, recurrent pregnancy loss (RPL), and other pregnancy complications. This will lead to a better understanding of the pathogenesis of those conditions.

Methods

In order to review the relevant literature, a comprehensive search was performed on several international databases, including Pubmed, EMBASE, ISI Web of Science, Scopus, ScienceDirect, Proquest and Google Scholar, along with Iranian databases. Boolean operators (OR, AND) were applied to produce combinations of appropriate keywords "factor V Leiden" OR "FVL mutation" AND "pregnancy outcomes", "preterm labor", "abortion", or "IVF". Using advanced search

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options of each search engine, articles were retrieved if they were published during 1996-2017 and had one of the first four keywords in either their title or abstract. The search was performed until August 2017. The inclusion criterion was any observational study that demonstrated adverse pregnancy outcomes in pregnant women with FVL mutations. We also inspected the reference list of the retrieved papers and searched other search engines. Papers in all languages were surveyed. Letters to the editor, case reports, case series articles, and studies without quantitative outcome data were excluded. The standard reporting of papers was demonstrated by using the 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) checklist (Roozbeh et al., 2017a). Data extraction was performed by authors individually; the data form included year of study, type of study, study method, participant, sample size, study result and outcomes. Newcastle-Ottawa Scale (NOS) was used for quality assessment of articles; tis tool was used in observational studies with the range of scale between 0-9 for the checklist (Roozbeh et al., 2016) (**Fig. 1**).

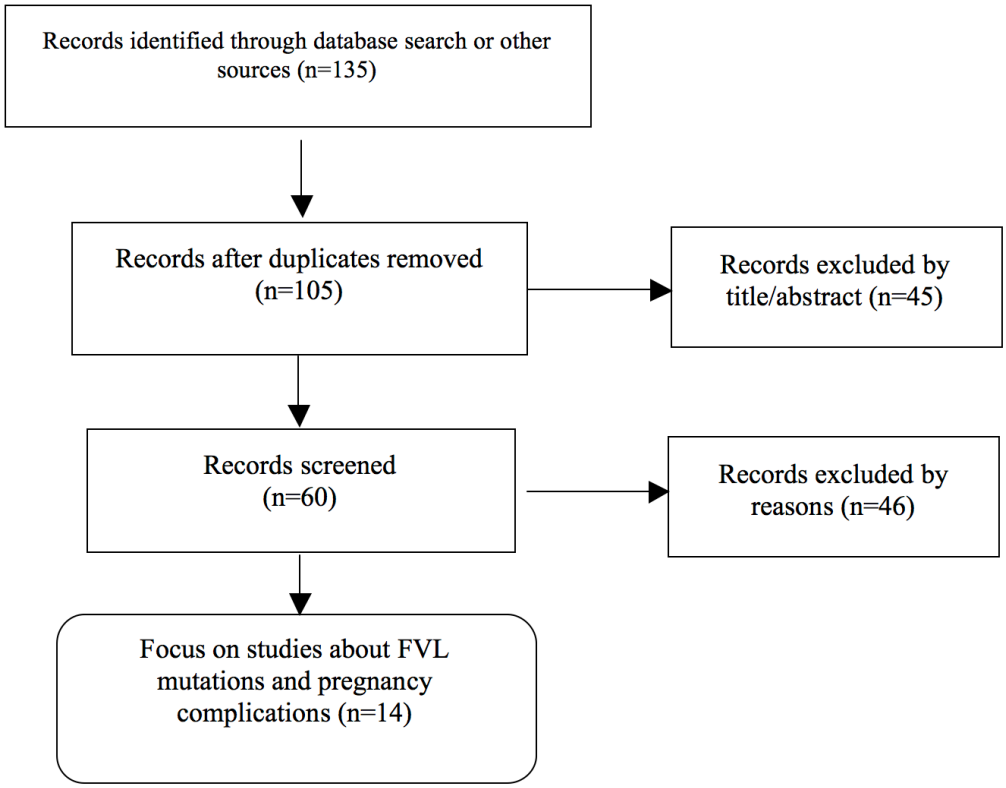

Figure 1. Flow chart for selection of articles for the review study.

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Results

A total of 14 studies were eligible based on the inclusion criteria. Table 1 presents a brief description of the selected studies and their findings. Most studies (n = 9) used a case-control design. One study had a nested case-control design. Two cohort studies and two cross-sectional studies were also included. After that, the key findings of the selected documents were summarized; the papers were scored by STROBE checklist (Table 1). The range of the STROBE score was between 5 and 20. The sample size of the selected studies ranged from 10-4167 individuals. A total of 356,129 women were examined in the 14 reviewed studies. Most of studies evaluated the relationship between fetal loss and FVL (n=8); only one study evaluated spontaneous abortion and IUGR. Three studies looked at IVF failure and FVL, and one study assessed other pregnancy complications. Among those 8 studies, only 3 of them (37.5%) confirmed the relationship between fetal loss and FVL. The effect of FVL on spontaneous abortion and IVF failure was demonstrated in all the studies. Moreover, in the studies reviewed, there was no relationship shown between FVL and IUGR, preeclampsia, abruption, or small for gestational age (SGA).

Table 1. Reviewed articles about effects of FVL mutation on pregnancy outcomes

Author (year)	Study type	Sample size	Pregnancy outcomes	Participant	Statistical analysis	Results	STROBE score
Foka (2000), (Foka et al., 2000)	case-control	80 cases, 100 controls	fetal loss	Women with RPL	The odds ratio (OR) and 95% confidence interval (CI) for each was calculated. Note: OR was used as a measure of the strength of the association. All p-values were two tailed; p-value < 0.05 was considered as statistically significant.	The report documented a clear association between FVL mutation and fetal loss (OR=5.5).	18
Lissaldelavigne (2005), (Lissalde–Lavigne et al., 2005)	nested case-control	3496 pairs of Caucasian women	spontaneous abortion	Women with spontaneous abortion	Conditional logistic regression and OR were used	There was an association between FVL and unexplained pregnancy loss during the first intended pregnancy (p<0.001).	20

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Ardestani (2013), (Ardestani et al., 2013)	case-control	80 cases, 80 controls	RPL	Women with RPL	Results were compared by chi-square (x2) test; p-value < 0.05 was set as statistically significant. ORs and 95% CIs were calculated.	The results showed FVL mutations were not frequently found in women with RPL.	16
Mierla (2012), (Mierla et al., 2012)	case-control	283 cases, 100 controls	fetal loss	Women with RPL	The results of the two groups were compared using two-tailed Fisher's exact test; data were calculated using GraphPad software.	The study did not find a strong association between FVL gene polymorphism and recurrent miscarriages.	15
Cardona (2012), (Cardona et al., 2012)	case-control	93 cases, 206 controls	RPL	Women with RPL	The allele and genotype frequencies were compared between patients and controls using Mantel-Haenszel chi-square test and one-tail analysis. ORs were calculated along with Cornfield's 95% CI using Epi 6 Stat Calc.	FVL was not associated with RPL.	17
Kazerooni (2013), (Kazerooni et al., 2013)	case-control	-60 cases with RPL -60 cases with PCOS and without RPL -60 cases with RPL and without PCOS -60 controls	Combination of RPL and polycystic ovary syndrome (PCOS)	Women with RPL and PCOS	Differences among groups were compared using one-way analysis of variance (ANOVA). A two-sided p-value <0.05 was considered statistically significant.	FVL was associated with PCOS and RPL.	20
Ivanov (2009), (Ivanov et al., 2009)	case-control	-94 women with embryonic loss before 10 wk -59 women with postembryonic loss occurring between 10-14 wk -100 healthy women with at least one uncomplicated full-term pregnancy	RPL	Women with RPL	Statistical analysis was performed using Statgraphics statistics program (version 2.1). Statistical significance and differences in genotype distribution were calculated using chi-square test. ORs and 95% CIs were calculated.	FVL was not associated with RPL.	16

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Serrano (2011), (Serrano et al., 2011)	case-control	100 cases, 100 controls	RPL	Women with RPL	Data were expressed in the form of mean±SD and % (as appropriate). To compare the groups in terms of categorical variables, chi-square test (v2) was used. The magnitude of association via ORs and their 95% CIs were calculated by logistic regression.	No difference was found in the prevalence of these two polymorphisms in women with RM or in a control group of healthy, parous women.	18
Proite (2016), (Proite et al., 2016)	cross-sectional	247 cases, 247 controls	RPL	Women with a history of miscarriages	The Hardy-Weinberg and allelic/genotypic frequencies were compared using either chi-square test or Fisher's exact test. The ORs were derived from logistic regression models. For analysis of quantitative variables, ANOVA was used for normal data distribution but Mann-Whitney test was used when the assumption of normal distribution of data was rejected.	FVL showed probable importance in the genesis of abortions due to its association with greater frequency of normal karyotype miscarriages.	17
ALHusseini (2011) (Al Husseini et al., 2011)	cross-sectional	20 cases, 40 controls	IVF	Women with IVF	The results were presented as mean+SD; comparisons of categorical variables were made between case and control groups using chi square test, student "t" test, and F test. The Spearman's rank correlation coefficient was used to measure the closeness of a linear relationship between the results of mutation in thrombophilic genes and the frequency of repeated IVF-embryo transfer cycle.	There were significant increases of allelic frequency of FVL in women with repeated IVF-embryo transfer failure.	16

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Safdarian (2014), (Safdarian et al., 2014)	case-control	96 cases, 95 controls	IVF failure	Women, with a history of recurrent IVF failure	Numerical variables were reported as mean±SD. Independent sample t-tests and chi-square tests were used to compare quantitative and qualitative variables, respectively, and logistic regression analysis was also used. Univariable analysis was performed, in which ORs and 95% CIs were calculated. P-value ≤0.05 was considered to be statistically significant.	Thrombophilia, mutation of FVL, and/or homozygote form of methylenetetra hydrofolate reductase (MTHFR) mutation were risk factors for recurrent IVF failure.	17
Ricci (2011), (Ricci et al., 2011)	cohort	510 cases, 490 controls	IVF failure	Women requiring IVF	Mann–Whitney U-test was used for continuous variables, and Fisher's exact test or chi-square test (as appropriate) was used for categorical variables, along with Bonferroni correction for multiple tests and multiple logistic regression analysis. P-value <0.05 was considered as significant.	FVL in asymptomatic women and in the absence of other risk factors did not influence IVF outcome.	18
Silver (2010), (Silver et al., 2010)	cohort	4157 cases	Pregnancy loss, preeclampsia, abruption, and SGA	Uncomplicated singleton pregnancies at 14 weeks of gestation or less	Multivariable logistic regression analysis was performed, controlling for age, race, prior pregnancy loss, prior SGA neonates, and family history of thromboembolism. Proportions were compared using the Fisher exact or $\chi 2$ test; continuous variables were compared using the Wilcoxon rank-sum test. Exact binomial confidence limits were calculated when indicated owing to small sample size.	FVL was not associated with pregnancy outcome.	16
Infante-Rivard (2002), (Infante-Rivard et al., 2002)	case-control	493 cases, 472 controls	IUGR	Newborns with IUGR	The OR for one copy of the variant was calculated with the use of single-integer variables.	FVL was not associated with IUGR.	20

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Discussion

Considering the importance of pregnancy outcomes, we reviewed studies which focused on the potential role of FVL mutation on adverse pregnancy outcomes. The reviewed studies suggested unclear associations between FVL mutation and PRL, stillbirth, IUGR, preeclampsia, or placental abruption. Our results indicated that the exact effects of hereditary thrombophilia on RPL is still a controversial issue. A Greek study found FVL in about 25% of women with a history of fetal loss and concluded that this mutation could be a risk factor for RPL (Foka et al., 2000). Another study on Caucasian women indicated FVL had a significant relationship with the risk of spontaneous abortion occurring from the 10th week of the first intended pregnancy (Lissalde-Lavigne et al., 2005).

In contrast, some researchers do not accept FVL as a risk factor for RPL. For instance, according to an Iranian study, FVL were not frequently found in women with RPL (Ardestani et al., 2013). Another study found no significant differences in the allele frequencies and genotype distribution for FVL gene polymorphisms for patients with RPL versus control subjects (Mierla et al., 2012). Goodman et al. reported significantly higher frequency of FVL mutation among American women with a history of RPL (Goodman et al., 2006). In contrast, another study on a similar population of American women did not detect any differences in the frequency of definite FVL mutations (Colman, 2006). Previous meta-analyses introduced FVL as the only thrombophilic mutation involved in RPL (Rey et al., 2003; Robertson et al., 2006).

The frequency of thrombophilic mutations varies in different ethnic groups and societies. FVL was rarely detected in Malay women with RPL (Ayadurai et al., 2009). Brazilian FVL carriers had a 4.9 fold higher risk of RPL than the non-carrier counterparts. Likewise, the risk of RPL was five times higher in Uruguayan women heterozygous for FVL than in non-carriers (Daniela et al., 2004). Two prospective cohort studies have also reported the absence of any associations between hereditary thrombophilia and RPL (Cardona et al., 2012). Kazerooni et al. detected elevated levels of thrombophilic parameters in patients with a combination of polycystic ovary syndrome (PCOS) and RPL. They also found FVL mutations to be more frequent in these individuals than in PCOS patients without RPL (Kazerooni et al., 2013). A study in Portugal negated any relationship between FVL and RPL during the first 10 weeks of gestation. It concluded that testing for these mutations in the initial screening of women with RPL and negative personal thromboembolic history was not cost-effective (Serrano et al., 2011). Similarly, in a controlled study, Dilley et al. found the frequency of FVL to be similar in 60 women with RPL and 92 controls without a history of miscarriage (Dilley et al., 2002).

Meanwhile, previous meta-analyses have suggested FVL-related losses to be more common after the 14th week than in the first trimester (Kist et al., 2008; Robertson et al., 2006). In a study of Caucasian women with unexplained RPL, Ivanov et al. found FVL to have a similar prevalence in subjects with embryonic

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losses and controls. In contrast, FVL was more prevalent (18.6%) in women who experienced pregnancy losses during the 10-14th week of gestation (Ivanov et al., 2009). Considering the controversial results of previous studies, clinicians prefer to incorporate FVL testing in RPL investigation protocols (Kist et al., 2008; Norrie et al., 2009). Due to lack of adequate evidence, recent guidelines on the assessment and management of women with RPL, published by the Royal College of Obstetricians and Gynecologist and the American College of Obstetricians and Gynecologists, do not assert the need for routine thrombophilia screening and anticoagulant therapy (Idali et al., 2012).

The result of this review showed that heterozygosity for FVL mutation increases the risk of venous thromboembolism during pregnancy, implantation failure, and fetal loss after IVF. Significantly higher rates of pregnancy loss have been found in heterozygous and/or homozygous carriers of FVL gene mutations compared to their control counterparts. Al Husseini et al. confirmed an association between the presence of FVL and higher rates of fetal loss following IVF (Al Husseini et al., 2011). Similarly Azem et al. suggested higher frequency of thrombophilia in subjects with recurrent IVF-embryo transfer failure than in those without such an experience (Azem et al., 2004). Qublan et al. reported FVL to be more common in women with recurrent IVF failure than in subjects with successful IVF experience and healthy women (Qublan et al., 2006). Moreover, microthrombosis at the implantation site may alter the invasion of syncytiotrophoblast to the mother's vessels and lead to implantation failure or fetal loss. In fact, the existence of at least one thrombophilic factor has been proven in female patients with recurrent IVF-embryo transfer failures (Azem et al., 2004). On the other hand, following the detection of greater ICSI success in FVL carriers, Göpel et al. concluded that the thrombotic tendency in mothers with FVL mutation promoted successful fetal implantation (Göpel et al., 2001). Colman et al. compared healthy fertile women with those experiencing recurrent implantation failure and highlighted the presence of at least three gene mutations in the latter group (Colman, 2006).

In one study, Qublan et al. compared 90 women with more than two consecutive failed IVF attempts (group A) and two control groups (groups B and C). The control group was comprised of 90 women whose first IVF embryo transfer led to successful pregnancy. The control group C consisted of 100 women with spontaneous conception, at least one unsuccessful pregnancy, and no history of miscarriage. The researchers found higher frequency of FVL in group A (14.4%) than in groups B (1%) and C (2%) (Qublan et al., 2006). While Grandone et al. published similar findings (Grandone et al., 2001), other researchers have generally failed to establish such a link (Azem et al., 2004). Some studies indicated that after having at least one thrombophilia, the mutation of factor V Leiden is a risk factor for recurrent IVF failure (Ricci et al., 2011; Safdarian et al., 2014). Moreover, according to our results, there is little evidence to suggest a relationship between IUGR and thrombophilia. A study in Germany revealed that inherited risk factors, particularly that FVL, boosted the risk of Low Birth Weight (LBW) (von Kries et al., 2001). In a very large study, Infante-Rivard *et al*. refuted

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the idea that inherited thrombophilia served as a clinically significant cause of IUGR (Infante-Rivard et al., 2002).

Conclusion

In summary, the exact effects of hereditary thrombophilia on pregnancy outcomes are still unclear and controversial. Therefore, screening patients for thrombophilic polymorphisms might be helpful in identifying patients at increased risk for thrombophilic events and other related adverse pregnancy outcomes. Furthermore, such screening would determine the target group for prophylactic therapy. Nevertheless, based on Royal College of Obstetricians and Gynecologists, there is still a lack of evidence in favor of routine thrombophilia screening and anticoagulant-based interventions during pregnancy. Therefore, we recommend that the screening for thrombophilia should be encouraged. Regardless of the limitations of the current study, we believe that the results emphasize the relevance of the topic of thrombophilia in pregnancy complications and point the need for further research. Since the outbreak of all types of thrombophilic state including inherited and acquired in women with pregnancy complications, is not so infrequent, every specialist should consider these conditions and investigate them in their patients with severe pregnancy complications.

Abbreviations

aCL: anticardiolipin antibodies
APCR: activated protein C resistance
APS: Antiphospholipid Syndrome
AT III: antithrombin
a_{β}2-GPI: anti-$_{\beta}$-2-glycoprotein I
FVL: Factor V Leiden
HRT: Hormone replacement therapy
IUGR: Intrauterine Growth Restriction
IVF: In Vitro Fertilization
LA: lupus anticoagulant
LBW: Low Birth Weight
MTHFR: Methylenetetra hydrofolate reductase
NOS: Newcastle-Ottawa Scale
PCOS: polycystic ovary syndrome
PT: prothrombin time
RPL: recurrent pregnancy loss

SGA: small for gestational age
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Author Contribution

FA and NR developed main idea and were responsible of the article writing. FB was responsible for assessment of eligibility criteria of papers. All authors read and approved the final manuscript.

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