Journal of Pharmaceutical Research International

34(52A): 15-25, 2022; Article no.JPRI.92863
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Prevalence and Risk Factors of Recurrent Pregnancy Loss in Saudi Women: Systematic Review

Maha Fouad Messawa [a*], Salma Yousef Omar [b], Reem Ahmed Babagi [c], Basim Mohammad Alradadi [b] and Dalia abdullah Qalai [c]

[a] Heraa General Hospital (HGH), Makkah, KSA.
[b] Maternity and Children Hospital (MCH), Makkah, KSA.
[c] King Abdullah Medical Complex (KAMC), Jeddah, KSA.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2022/v34i52A7213

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/92863

Systematic Review Article

Received 09 August 2022
Accepted 16 October 2022
Published 25 October 2022

ABSTRACT

Background: About 15% of all clinically confirmed pregnancies around the world, result in spontaneous loss. More than 80% of miscarriages occur in the first trimester, or before 12 weeks of gestation, and almost half of them are caused by chromosomal abnormalities. The loss of three or more pregnancies in a row constitutes recurrent miscarriage; there are several potential reasons. According to the WHO, the phases of spontaneous miscarriage are: Threatened miscarriage, inevitable miscarriage, incomplete miscarriage, and full miscarriage. This article will be looking at different RPL causes, its prevalence and psychological effects on Saudi women.
Objectives: The study aims to summarize current evidences regarding recurrent pregnancy lost risk factors, and its prevalence among Saudi women in different demographics and regions.
Methods: For article selection, the PubMed database and EBSCO Information Services were used. All relevant articles relevant with our topic and other articles were used in our review. Other articles that were not related to this field were excluded. The data was extracted in a specific format that was reviewed by the group members.
Conclusion: Our study included 9 studies in total, 3 of these studies focused on the prevalence of RPL in different Saudi regions, 5 others focused on different risk factors correlated

**Corresponding author;*

with miscarriage among Saudi women such as genetic reasons, long working hours and consanguinity. One study included discussed the psychological effects of RPL on Saudi women.

Keywords: Miscarriage; phospholipid; antibody syndrome; pregnancy loss; breast cancer; obesity.

1. INTRODUCTION

Around 15% of all clinically confirmed pregnancies result in spontaneous loss, which makes spontaneous pregnancy loss shockingly widespread around the world. For couples, unexpected pregnancy loss can be emotionally and physically difficult, especially if it happens often. Three successive pregnancy losses before 20 weeks from the last menstrual cycle are considered a habitual pregnancy loss, also known as a recurrent pregnancy loss [1,2]. Out of this group, 12% had repeated pregnancy losses that occurred more than twice in a row [3]. According to Lok *et al.,* over 50% of women who lose a pregnancy develop psychological morbidity in the weeks or months that follow the loss. Following pregnancy loss, heightened anxiety, depression symptoms, and even severe depressive disorder were often recorded in 10–50% of cases [4].

More than 80% of miscarriages occur in the first trimester, or before 12 weeks of gestation, and almost half of them are caused by chromosomal abnormalities. Less than 20% of pregnancies end in miscarriage between weeks 12 and 20 (the second trimester), and these miscarriages are more frequently brought on by uterine structural malformations than by chromosomal abnormalities [5]. Vaginal bleeding and crampy pelvic aches are symptoms of an unavoidable miscarriage; although the pregnancy has not yet been discharged, it will ultimately do so. If the cervix is still open and there is still some foetal tissue in the uterus, the miscarriage is considered incomplete. If the cervix has closed and an ultrasound examination reveals an empty uterus, the miscarriage is said to be over. When a miscarriage occurs after 20 to 24 weeks and the foetus has not showed any signs of life after delivery, it is considered late. The loss of three or more pregnancies in a row constitutes recurrent miscarriage; there are several potential reasons, including antiIJSER phospholipid antibody syndrome. Threatened miscarriage, inevitable miscarriage, incomplete miscarriage, and full miscarriage are the phases of spontaneous miscarriage according to the WHO [6].

Three or more consecutive pregnancy losses that happen before 20 weeks post-menstruation are referred to as recurrent miscarriage (RM) or recurrent pregnancy loss (RPL). One percent of fertile couples are thought to experience the occurrence. But if there are two or more losses, the frequency rises to 5%. Preclinical, embryonic, and foetal loss have been further divided by clinicians into three categories: death occurs before 6 weeks of pregnancy; death occurs after 6 weeks but before 10 weeks of pregnancy; and death occurs after 10 weeks but before 20 weeks of pregnancy. Some medical professionals classify the stage of pregnancy loss as either embryonic or foetal based on the presence or absence of foetal heart activity (loss after the foetal cardiac activity has been identified) [7-13]. Aged women, uterine anomalies, placental abruption, incompetent cervix, parents' chromosomal and genetic background, immunological problems, and/or endocrine imbalances are a few of the stated explanations underpinning this inability to deliver a normal and viable embryo. Three of these reasons, specifically: I structural and numerical chromosomal abnormalities, (ii) inflammatory and autoimmune illnesses, and (iii) allelic polymorphisms of several pro-thrombophilic genes, were identified as the main contributors to RM. In fact, there have been reports of positive connections between increased RM and chromosomal defects in the embryos. This embryonic/abortus mosaicism and chromosomal aneuploidies were linked to the foetal genome's incompatible with life [14-26].

2. MATERIALS AND METHODS

2.1 Study Design

A systematic review of the current evidence on recurrent pregnancy lost risk factors, and its prevalence among Saudi women in different demographics and regions. is considered a robust way of identifying and synthesizing the peer reviewed articles for evidence in this area to define a cohesive empirical research agenda that builds on prior knowledge. This review will include qualitative evidence only to produce an interpretation. Further, a synthesis of qualitative

data aims to generate findings that are meaningful, relevant and appropriate to individuals, to inform a research agenda and ultimately to more effectively practices on association between obesity and breast cancer. The review will use methods of qualitative synthesis to combine, integrate and interpret, where possible, the evidence from the included papers.

The review aims to move beyond the aggregation of available data to provide further interpretive insights into association between obesity and breast cancer and define where future research can add to what is known.

2.2 Study Eligibility Criteria

The review will include qualitative peer-appraised studies. Qualitative data from mixed methods-studies will be screened for inclusion and included if the qualitative element is pertinent. We will include those studies that have been conducted in twenty years. All peer-reviewed articles published in English, reporting association between obesity and breast cancer will be included.

To be included for the review, the studies should have been published from January 2002 up to August 2022 to ensure the currency of the work while enabling a broad view of the emerging issues to be identified.

2.3 Study Inclusion and Exclusion Criteria

The articles will be selected based on the relevance to the project, English and time restriction on twenty years will be considered. All other articles which do not have one of these topics as their primary end, or repeated studies, and reviews studies were excluded. The reviewers will exclude any studies not available in English, conference abstracts, books or grey literature and editorial comments. Studies reporting only qualitative data will be excluded.

2.4 Search Strategy

A systematic search strategy will be developed using a combination of Medical Subject Headings (MeSH) and controlled vocabulary to identify peer-reviewed articles on primary dysmenorrhea in Saudi Arabia. The databases will be PubMed/MEDLINE, Scopus/Embase (Elsevier), EbscoHost, and Google Scholar. We will limit our search from January 2002 to August 2022.

2.5 Selection of Study

The ENTREQ guidelines for reporting qualitative systematic reviews will be used to demonstrate the selection processes and results. All retrieved studies will initially be imported into Endnote library to assist removing duplicates. After removing the duplicates, the Endnote library will be shared between the two reviewers to independently screen the articles by title and abstract, guided by the eligibility criteria. The studies which the two reviewers would have agreed on will be subjected to the full-text review. A third reviewer will adjudicate any discrepancies between the two reviewers. The two reviewers will independently review the full text of all eligible studies. In the case where there are differences between the two reviewers, consensus will be sought through discussion on the differences with the third reviewer. Finally, the full texts of all relevant studies found to meet the inclusion criteria will be retained for the final framework synthesis.

2.6 Data Extraction

Data will be independently extracted by two reviewers from eligible studies onto a customised data extraction form and populated with variables pertaining to the study population and phenomena of interest. Double checking and verification of extracted articles will be done by the third review author. Study characteristics that will be extracted will include name of the first author and year of publication, data collection period and region in which the study was conducted. Specific study details including the study design, study population, sample size, sampling procedures and data collection procedures will then be captured. Association between obesity and breast cancer will be systematically identified.

2.7 Data Synthesis and Analysis

No software will be utilized to analyze the data. The reviewers will sort the data by theme and present the themes in the form of an analysis table (chart). The columns and rows of the table will reflect the studies, and related themes and will enable us to compare findings of the studies across different themes and subthemes.

2.8 Mapping and Interpretation

The reviewers will use charts to define the identified concepts and map the range and nature of the phenomena. Our review will explore associations between the themes to help clarify the findings. Our review will map and interpret findings in line with the review objectives and emerging themes.

3. RESULTS

Fig. 1 shows the selection and identification of studies. The search of the mentioned databases returned a total of 286 studies that were included for title screening. 198 of them were included for abstract screening, which lead to the exclusion of 52 articles. The remaining 146 publications full-texts were reviewed. The full-text revision led to the exclusion of 137 studies due to difference in study objectives, and 9 were enrolled for final data extraction (Table 1).

The first three studies discussed prevalence of miscarriage in different Saudi demographics, it ranged from 5% to 18% per total live birth [1,5,6].

The other five studies indicated that congenital uterine abnormalities, APS, and Protein S deficiency were the three most frequent causes of RPL [7]. Different genetic abnormalities are lined to RPL [27,14,28,29]. Such as Thrombophilic mutations in the FVL and FII genes, [27] chromosomal abnormalities, hereditary thrombophilia, [14] autosomal recessive genes may be involved in the pathophysiology of PTD and RPL which is contributed by consanguinity that increases homozygosity of autosomal recessive diseases [28]. Moreover ASIC5 Saudi mutations are linked to RPL [29].

The last study included psychological impact of RPL on Saudi women who miscarried. Following a miscarriage, 35%, 14%, and 22% of women reported feeling guilty, ashamed, or alone, whereas 10% reported feeling all three of these emotions and 47% reported feeling none of them [30].

4. DISCUSSION

According to studies, about 50% of women who lose a pregnancy endure psychological morbidity in the weeks or months that follow the loss. Following pregnancy loss, heightened anxiety, depressed symptoms, and even severe depressive disorder were often recorded in 10–50% of cases. After a miscarriage, these psychological symptoms may last for up to 6 months or one year. Additionally, losing a pregnancy may be physically and emotionally taxing for couples, particularly when it happens repeatedly. Uterine abnormalities and paternal balanced chromosomal rearrangements are established as etiological causes for pregnancy loss. Many more elements have been put out as potential risk factors. Among these potential contributing variables, it has been suggested that stress from daily life and a lack of social support during pregnancy are linked to spontaneous pregnancy loss [1]. According to statistical analysis of the surveys, 10% of miscarriage cases presented to Baljurashi hospital. Most of the responders were housewives, older than 25, and in their first trimester of pregnancy. Half of the respondents had Secondary education. All of the interviewees were from socioeconomic backgrounds that were good or moderate [5].

For every 1,000 live births, 54.87% abortions occurred (either spontaneous or recurring), with spontaneous abortions accounting for 86.1% and recurrent abortions for 13.9% of all abortions (7.64 per 1000 live birth). These findings are related to the 29 and 28 abortions per 1000 women between the ages of 15 and 44 that occur globally. Additionally, in the US, there were 6.401,000 pregnancies between 1990 and 2000 with an estimated 1,030,000 spontaneous foetal losses (16%). In healthy women, recurrent miscarriages occur in 0.5% to 2% of cases. Recurrent pregnancy loss (RPL), which is characterised as 3 consecutive miscarriages, affects an estimated 2-5% of women [6].

According to reports, the prevalence of uterine abnormalities in the RPL population ranges from 1.8% to 37.6%, which is consistent with our data. According to research, correcting a septate uterus reduced miscarriage rates from 88% to 14%. RPL has also been linked to either parent's chromosomal abnormalities. Additionally, because of an uneven chromosomal arrangement, their pregnancies may result in live births with several congenital abnormalities and/or mental retardation. About 3.5% of both parents have severe chromosomal abnormalities, which is 5–6 times more than the general population and most frequently a balanced reciprocal or Robertsonian translocation [7].

Table 1. Author, country, year of publication, methodology and outcome

Author, publishing year	Region	Methodology and subjects	Results	Outcomes
Weam Bashier I, et al. 2018 [1].	Jeddah	All of the female doctors employed by King Abdul-Aziz University Hospital in Jeddah participated in a cross-sectional study by completing a self-administered online questionnaire.	A total of 25 pregnancies were lost by 17 female doctors (18.5%), with the majority occurring in the first trimester (80%), particularly when they were residents (40%), with the first pregnancy loss occurring on average once per month.	When residents had to some extent greater monthly working hours, they had more pregnancy loss with the first trimester being when most pregnancies for female doctors ended.
Mohammed Abobakr Hassan Balkheir, et al. 2018 [5]	Albaha	Women who have miscarried are the patients at Baljurashi General Hospital who were given a self-administered survey. more than "25 - 30" (27.2%) and " more than 35 years" (33.8%). 90% of the population were housewives.	10% of pregnancies ended in miscarriage. The questionnaire received 92 responses from women. The majority of the responders were in their first trimester, older than 25 years old, and unemployed. Secondary education was obtained by half of the respondents. One tenth or so experienced recurrent miscarriages. The total number of pregnancies that were diagnosed in this research's study period at Baljurashi hospital was 2935. Three hundred patients experienced miscarriages; 92 of them completed the survey. Miscarriage rates were 300/2935 or 10%. The most prevalent age ranges were	Patients visiting the Baljurashi hospital experienced miscarriages at rates similar to those seen in other areas. But the rate of subsequent abortions is high, and these instances weren't properly looked into.
Ibrahim Mohammed AlEidan, et al. 2017 [6]	Almajmaah	It was a retrospective cross-sectional survey carried out between February 2012 and March 2015. The information was gathered from Saudi women hospitalised to King Khalid General Hospital, Almajmah, who were aged 15 to 45 and had a history of spontaneous or recurrent abortion.	There were 54.87 spontaneous or recurrent abortions per 1000 live births. 86.1% of abortions were spontaneous (47.22 per 1,000 live births), while 13.9% were recurrent abortions (7.64 per 1000 live birth). Obese women made up the majority of spontaneous abortion cases (34.32%). The second and third decades were the most prevalent ages for both recurring and spontaneous abortions.	Almajmaah City has a high rate of spontaneous or recurring abortions. The second and third decades were the most prevalent ages for both recurring and spontaneous abortions. Additionally, obese women had an increased likelihood of getting pregnant.

Author, publishing year	Region	Methodology and subjects	Results	Outcomes
Al-Ghamdi AA, et al. 2016 [7].	Al Khobar	59 couples who attended the RPL clinic between January 2010 and December 2013 and who had finished their workup and investigations for RPL were included in a retrospective analysis of all Saudi couples with RPL. At the King Fahd University Hospital in Al Khobar, Saudi Arabia, information was gathered through patient records and computer-based laboratory findings	It was determined that all patients had experienced three or more spontaneous miscarriages. The mean age of women was 32.83 plus or minus 6.64. The range of prior miscarriages was three to twenty-three. In contrast to late losses, which ranged from none to seven losses, the number of early losses varied from 2 to 16. Out of 59 females, 19 (32%) were nulliparous and had no live births, whereas the other 40 (68%) had one. 47% of patients had Protein S deficit, 6.7% had chromosomal abnormalities, 12% had uterine abnormalities, 12% had antiphospholipid syndrome (APS), and 1.7% had antithrombin III and Protein C deficiencies. But no patient possessed the Factor V Leiden mutation. Unexplained RPL was the diagnosis given to 39% of the patients since there was no known reason.	Congenital uterine abnormalities, APS, and Protein S deficiency were the three most frequent causes of RPL. Nearly 40% of RPL couples still have unidentified etiological factors.
Alashora, et al. 2018 [27].	Jeddah	In the 142 female participants in the research, 72 had a history of two or more foetal losses in any of the three trimesters of pregnancy. The remaining 70 were taken as a control group and were clinically healthy women with positive obstetric histories. Multiplex allele-specific PCR amplification was used to detect the FV Leiden (G1691A) and FII (Prothrombin G20210A) mutations.	The findings showed that the frequency of overall mutation carrying (AA and AG) among FII patients was greater than that of FVL. Both were a lot higher than the controls. According to the frequencies of FVL & FII mutations associated to the phases of pregnancy loss, early pregnancy loss cases had a high FVL mutation ratio (26%) followed by late pregnancy loss patients (25%) and controls (1.4%), which was statistically significant. On the other hand, the statistically significant high FII mutation ratio was found in instances of late pregnancy loss (50%) followed by early pregnancy loss (38%) and controls (1.4%).	Saudi women are much more likely to have thrombophilic mutations in the FVL and FII genes. Finding women with hereditary thrombophilia may help to avoid miscarriages as well as severe maternal and neonatal problems.

Author, publishing year	Region	Methodology and subjects	Results	Outcomes
Rola F. Turki, et al 2016 [14].	Jeddah	At King Abdulaziz University Hospital in the Western part of Saudi Arabia, a cohort of patients having a history of two or more miscarriages up to 20 weeks was studied between 2008 and 2013. This research included couples who repeatedly lost pregnancies and who sought additional examination during this time. Human chorionic gonadotropin (HCG) testing utilising serum or urine in conjunction with ultrasounds was used to determine if a woman was pregnant.	In this cohort, 492 reported pregnancies occurred. The individuals' ages varied from 18 to 48, and there were 2 to 14 miscarriages overall. 32 of the 98 women were able to carry their pregnancies to term successfully, resulting in a viable baby, while the remaining 67.35% failed to do so despite making many efforts. Overall, clinical pregnancies were terminated in the first trimester in 79.59% of cases, whereas only 12.24% and 8.16% of cases reached the second and third trimesters, respectively.	This study showed a significant correlation between RPL and chromosomal abnormalities and hereditary thrombophilia prevalence. These findings highlight the significance of systematic cytogenetic investigation and genetic counselling, preferably at the premarital stage or at the very least during the early stages of pregnancy through preimplantation genetic diagnosis, given the high rate of consanguineous marriages in the Saudi population (PGD)
Arjumand S Warsy, et al. 2020. [28]	Riyadh	This study sought to determine if cousin marriages contributed to Saudi women's frequent pregnancy losses (RPL) and premature births (PTD). 300 Saudi women were enrolled in the research (150 controls, 100 RPL, and 50 PTD). On forms created especially for the research, demographic and clinical information was recorded, and the women were questioned about their relationships with their husbands. In both consanguineous and nonconsanguineous marriages, the degree of consanguinity between first and second cousins was noted, and the frequency of PTD and RPL was computed.	Consanguinity is more common in RPL and PTD (RPL = 55%; PTD = 52%) than in the control group (36%), according to the data, and the difference between the two groups is statistically significant for both PTD and RPL.	Women who give birth prematurely (PTB) and those who have RPL have considerably greater consanguinity rates.
Nourah H. Al Qahtani. 2021 [29]	Dammam	To determine the genetic cause of unexplained recurrent pregnancy loss in a family trio, a variant analysis based on next-generation sequencing was	The existence of heterozygous in one person and the lack of homozygous novel mutation among randomly chosen healthy Saudis are both confirmed by newly designed ARMS	In a high-consanguinity community, early prenatal detection of a harmful variant like ASIC5Saudi may provide the parent the option to

Author, publishing year	Region	Methodology and subjects	Results	Outcomes
		performed. The research involved a family from Saudi Arabia who had previously had three inexplicable RPLs during the ninth week of pregnancy. Sanger sequencing was used to validate the pathogenic mutation found by whole-genome sequencing (WGS) of the parents and a deceased foetus.	PCR followed by direct sequencing. Three unexplained RPLs were used to confirm the heterozygous status of the second family. Through molecular docking and interaction studies, the pathogenicity of the R227I amino acid change in the ASIC5 protein was determined.	choose pregnancy termination within the permitted period.
A. A. Rouzi, et al. 2020. [30]	Jeddah	Women who visited the obstetrics and gynaecology clinics at the King Abdulaziz University Hospital in Jeddah (KAUH), Saudi Arabia, were invited to take part in a cross-sectional study between 2015 and 2016. The whole cohort's demographic data, miscarriage opinions, and believed reasons were gathered. Women who have miscarried provided information on miscarriages.	Of a convenience sample of 296 women, ranging in age from 18 to 57, 247 (83.4%) had never been pregnant; 81 (32.8%) of these women had previously had miscarriage. Following a miscarriage, 35%, 14%, and 22% of women reported feeling guilty, ashamed, or alone, whereas 10% reported feeling all three of these emotions and 47% reported feeling none of them. Compared to (52%) women who did not get a medical explanation for their miscarriage, only (17%) of those women thought they had contributed to the cause of the miscarriage or could have been able to avoid it. The most often acknowledged reasons of miscarriage throughout the entire group were stressful events (72%), fate/destiny (65%), long-term stress (64%), lifting (57%), and prior abortion (57%).	Although the majority of individuals who had losses said they had received enough help, miscarriage reasons were not well understood.

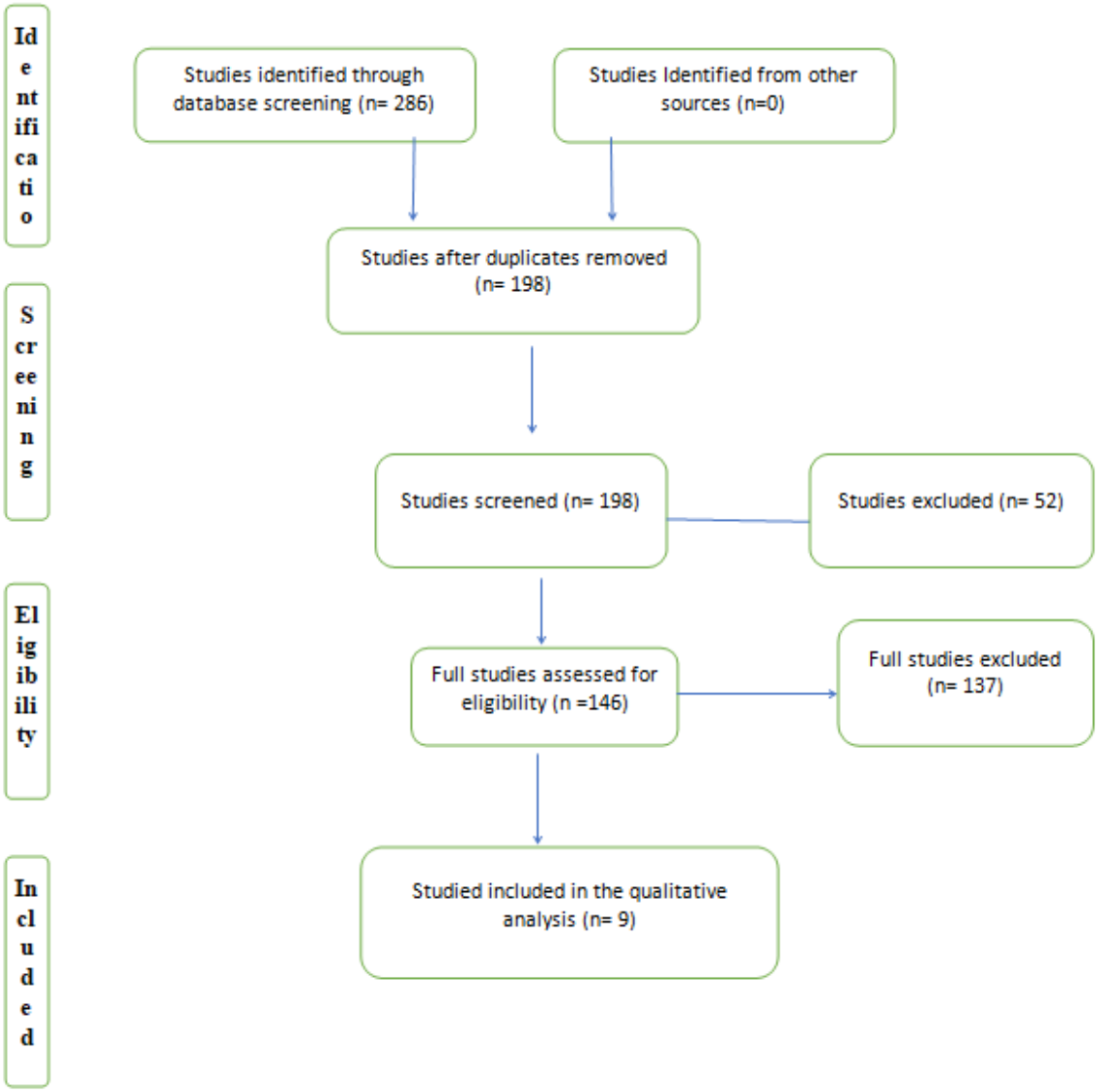

Fig. 1. The included studies had different study designs

Significant pregnancy difficulties are said to be caused by coagulation abnormalities. According to this information, pro-thrombophilic factors such FVL, Prothrombin A20210G, and MTHFR C677T are implicated in RM. These elements are known to interfere with crucial processes related to placentation, foetal growth, and the course of the pregnancy up to delivery. One research found that the rates of FVL, Prothrombin, and MTHFR mutations (including both homozygous and carriers) were, respectively, 15.5%, 6%, and 25.5 when possible SNPs in these three genes were screened. These findings support prior research that found an unusually high occurrence of thrombophilic gene polymorphisms in the Saudi population. These findings highlight the need for further preventative measures to be taken at premarital and/or before IVF operations in ART facilities, in addition to national awareness efforts [14].

Given the frequency of genetic causes of miscarriage, where over 50% of foetal losses are a result of genetic diseases, a correlation between consanguinity and miscarriage may be predicted. According to a case-control study of 452 Saudi Arabian women, considerably higher incidences of hospitalised spontaneous abortions occurred in consanguineous marriages (47.8%), compared to controls who had a normal delivery in the hospital but had no history of spontaneous abortions. High consanguinity rates are prevalent

in Saudi Arabia and other Arabic nations; a study on Saudi citizens with diabetes found a consanguinity rate of 57.7% (28.4% first cousins, 14.6% second cousins, and 15.2% distant relatives), while a study on Jordanian pregnant women receiving a second-trimester ultrasound discovered a consanguinity rate of 21% [30].

5. CONCLUSION

RPL in Saudi population is linked to genetic abnormalities which are contributed to some extent to consanguinity among Saudi populations, awareness must be spread among the populations about the risks regarding consanguinity.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/92863