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Characteristics of Recurrent Spontaneous Abortion in Al-Jumhouria Hospital Benghazi 2020

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ABSTRACT

Background: Recurrent spontaneous abortion defined as three or more consecutive pregnancy loss before 24 weeks is a challenge for gynecologists because of the complex and variable etiologies behind. Exploring characteristics of patients with this condition may help researchers and clinicians. Therefore, the aim of the present work was to outline the demographic and patient history wise factors related to RSA and to analyze the association of those factors with occurrence of RSA.

Methods: Case control study included cases collected from Benghazi medical center from records of deliveries January 2020 to December 2020. Statistical analysis was executed using SPSS 23.0.

Results: A total of 250 cases were investigated. Among those 30 cases met the definition of RSA. The rate of explained abortion among subset with spontaneous abortion was only 10.0%. The rate of advanced maternal age among the study population was 29.2%. The rate of RSA was higher among mothers with advanced maternal age (15.1% for 10.7%). This difference was statistically insignificant (P=0.338). The history of abortion among the study population showed a rate of first trimester abortion was 36.8% and second trimester abortion as 4.8%. RSA rate was much higher among mothers with history of 1st trimester abortion (20.7% for 7.0%) with statistically significant association (P<0.001) and OR of 3.5 (95% CI; 1.6–7.7). In multivariate analysis the history of 1st trimester abortion was an independent predictor for RSA. Also, in multivariate analysis, secondary infertility was independent negative predictor for RSA, (P=0.034 and OR=0.18; 95% CI: 0.04–0.88). The rates of bad obstetric history, HDP, GDM, any medical condition and history of low vitamin D3 were 15.2%, 17.2%, 8.8%, 16.8% and 19.2%; respectively among the study population. Mothers with bad obstetric history have a higher rate of RSA (18.4% for 10.8%), but the difference is not statistically significant (P=0.183) No significant association between HDP, GDM, history for medical conditions or history of low serum vitamin D with RSA (P=0.934, 0.735, 0.308 and 0.109 respectively).

Conclusion: Recurrent spontaneous abortion is under-investigated and seems to be more likely with first trimester abortion and it is may be associated with several factors like infertility and maternal age. Anyhow, those associations need to be verified. Considering early investigations for couples with spontaneous abortion within the first trimester and further well designed prospective study are recommended.

Keywords: Infertility; Recurrent spontaneous abortion; Predicator factors; Medical history; Pregnancy loss; First trimester abortion; Obstetric history; Risk factors; Pregnancy outcome; Secondary infertility.

1. Introduction

One of the major issues associated with infertility is recurrent spontaneous abortion (RSA), which is one of the two difficult problems in the field of obstetrics and gynecology [1,2]. Two or more consecutive pregnancy losses are referred to as RSA [3]. The American Society for Reproductive Medicine Practice Committee states that clinical abortion determined by histology or ultrasound is included in RSA [4]. Thrombophilia, infections, autoimmune endocrine disorders, genetic or uterine issues, and a number of environmental factors can all contribute to RSA [5]. One of the most frustrating and challenging areas of reproductive medicine, RSA affects roughly 0–14% of couples attempting to conceive. The etiology of RSA remains unknown in over half of affected cases due to the complex causes of pregnancy loss and the lack of evidence-based diagnostic strategies [6]. After ruling out other possible causes including infections, immunological issues, genetic abnormalities, hormonal disorders, and aberrant anatomic structures, the unexplained RSA was identified [7]. Moreover, it has been suggested that oxidative stress-induced damage contributes to hydatidiform moles, drug-induced teratogenicity, spontaneous abortion, and

unexplained recurrent pregnancy loss [8]. The impact of male factors on RSA has received increased attention recently [9]. Mothers with RSA may have a pathological background that includes derangements that could potentially impact a subsequent conception that ends in miscarriage. According to certain earlier research, women who have experienced RSA in the past are more likely to experience unfavorable maternal and fetal outcomes in their subsequent pregnancies [10-12].

Several studies have been done to look into the causes of RSA. For example, a study by Franssen M.T., and colleagues found that chromosomal anomalies were linked to RSA [13] and a study by Homer H.A., et al. [14] concluded that genital malformations of the reproductive tract were the cause of RSA. Moreover, Rey and colleagues [15] have demonstrated that thrombophilic disorders constitute an additional factor. The development of RSA has been linked to immune system and neuroendocrine system dysfunction [16,17]. In accordance with research by Kaur & Gupta [18], obesity, hyperinsulinemia, insulin resistance (IR), and polycystic ovarian syndrome (PCOS) were the main endocrine factors contributing to recurrent abortions. Li J., et al. [19] discovered recently that sperm density, viability, progressive motility rate, normal morphology rate, deformity rate, and other factors were associated with RSA [19,20]. Zhang K., et al. [21] investigated mechanisms supporting the inflammatory and immune-mediated pathways that result in the thromboembolic process. Strong immunomodulatory effects of vitamin D may influence the course of pregnancy. Li N., et al. [22] looked at the expression of the vitamin D receptor (VDR) and the concentration of 25-hydroxyvitamin D [25(OH) D] in the decidual tissues of RSA patients. The study came to the conclusion that vitamin D levels in the decidua are linked to the production of inflammatory cytokines, indicating a potential role for both vitamin D and VDR in the pathophysiology and etiology of RSA [22]. Here aren't many publications on the perinatal outcomes of mothers with RSA currently available. There are no data that are pertinent to the local or regional communities.

The main aim of this study is to list the demographic and patient history-related factors associated with RSA and examine the relationship between those factors and the incidence of RSA.

1.1. Study Objectives

The following are the objectives of this study: (i) to study the relationships between history of miscarriage and RSA particular in the first and second trimester, (ii) to determine the relationships between infertility and RSA, (iii) to determine the association between advanced maternal age and RSA, and (iv) to study obstetric history and medical conditions such as hypertension disorder of pregnancy, gestational diabetes mellitus and any medical condition and history of low vitamin D3.

2. Patients and Methods

Design of study and settings: Case control study in patient admitted to Jumhouria hospital/Benghazi medical center BMC.

Study period: The number of patients included in the study was selected from patients admitted to the hospital in the period from January the 1st, 2020 to December the 31st, 2020.

Data synthesis: Review of records for randomly selected patients with history met criteria of RSA.

Participant criteria and Recruitment

Study groups: GROUP 1; Controls: A number of delivered mothers randomly selected without history of RSA. GROUP 2; Cases: Thirty delivered pregnant mothers without history of RSA.

Inclusion criteria for the participants: All pregnant women included in the study were pregnant.

Exclusion criteria for cases: Cases with files with incomplete data.

Ethical considerations: All participants were consented for study performance. Confidentiality of data was assured using anonymous questionnaire.

Statistical analysis: Data were analyzed using statistical package for social science (SPSS) version 23. Inferential statistics were used when needed Chi-square (X^2), t test and Mann-Whitney U test to find the difference in the distribution of the variables between the two groups, P-value were considered significant when ≤ 0.05. Data were presented in form of tables and figures, were the figures done by Microsoft Excel 2010. Multivariate analysis with binary logistic regression was applied for analysis of independent associations of factors with P <0.25 with the event of RSA.

3. Results

3.1. Distribution of RSA

Figures 1 and 2 show rates of RSA among the study population and explained abortion among subset with spontaneous abortion. In the figure 1, approximately 88% of the patients have no RSA. The majorities of patients have been reported No SA (90%) (Figure 2).

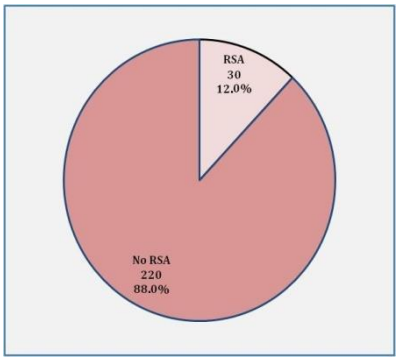

Figure 1. Rate of RSA among the study population

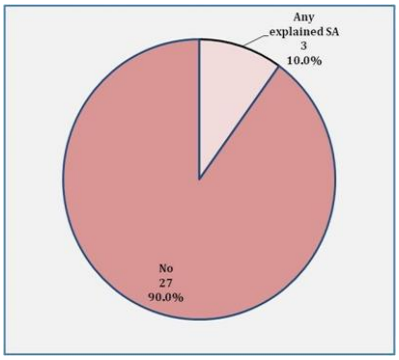

Figure 2. Rate of explained SA among the patients with RSA

3.2. Demographic characteristics

The demographic characteristics of patients shown that optimal maternal age present by about 70.8% and the remaining 29.2% was advanced maternal ages (Figure 3). In the table 1 shown the association between advanced maternal age and RSA in which RSA was found low in both advanced maternal ages and optimal maternal age 15.1% and 10.7% respectively (*P*=0.33). The figure 4 shown that the rate of primiparous among the studied population represent about 19.2% while multiparous 80.8%.The association between primiparity and RSA presented in table 4. There was no statistical significant between RSA and primiparity (*P*=0.26).

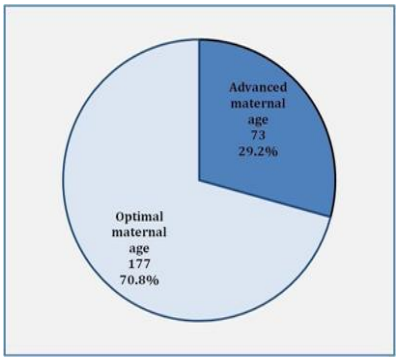

Figure 3. Distribution of the study population according to maternal age

Table 1. Advanced maternal age and Recurrent spontaneous abortion

Advanced maternal age	**Recurrent spontaneous abortion**		
	Yes	**No**	**Total**
Advanced maternal age	11	62	73
	15.1%	84.9%	100.0%
Optimal maternal age	19	158	177
	10.7%	89.3%	100.0%
Total	30	220	250
	12.0%	88.0%	100.0%

Pearson Chi-Square 0.919 P=0.338

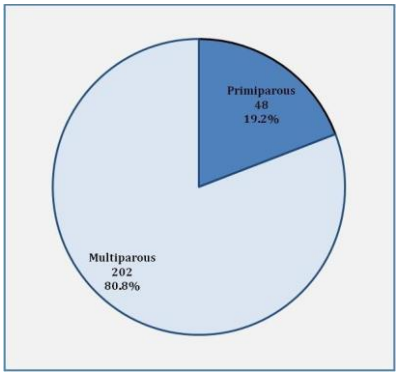

Figure 4. Distribution of the study population according to parity

Table 2. Primi and Recurrent spontaneous abortion

Primi	Recurrent spontaneous abortion		Total
	Yes	No	
Primiparous	8	40	48
	16.7%	83.3%	100.0%
Multiparous	22	180	202
	10.9%	89.1%	100.0%
Total	30	220	250
	12.0%	88.0%	100.0%

Pearson Chi-Square 1.225 P=0.268

3.3. Analysis the history of previous abortions

The distribution of the study population according to history of abortion shown in the figure 5, no history of miscarriage was twice than history of miscarriage in first trimester (61.2% vs 34%) while the miscarriage in the second trimester being the least 2%. Tables 3 and 4 shows the association between miscarriage in the first and second trimester and history of RSA. There was relationship between history of miscarriage and RSA particular in the first trimester (*P*=0.001) (Table 3).

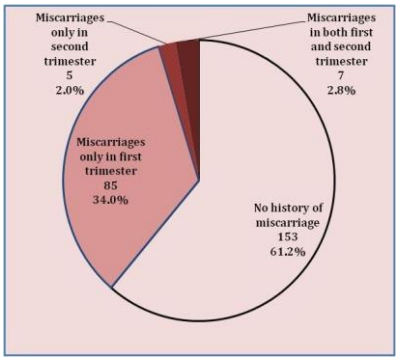

Figure 5. Distribution of the study population according to history of miscarriage

Table 3. History of first trimester abortion and Recurrent spontaneous abortion

History of first trimester abortion	Recurrent spontaneous abortion		Total
	Yes	No	
Yes	19	73	92
	20.7%	79.3%	100.0%
No	11	147	158
	7.0%	93.0%	100.0%
Total	30	220	250
	12.0%	88.0%	100.0%

Pearson Chi-Square=10.319 P = 0.001 (Odds Ratio 3.48 95% CI: 1.57 - 7.69)

Table 4. History of second trimester abortion and Recurrent spontaneous abortion

History of second trimester abortion	Recurrent spontaneous Abortion		Total
	Yes	No	
Yes	1	11	12
	8.3%	91.7%	100.0%
No	29	209	238
	12.2%	87.8%	100.0%
Total	30	220	250
	12.0%	88.0%	100.0%

Fisher's Exact Test P=1.000

3.4. History of infertility

The history of infertility has been investigated and found that 13.2% and 12.4 % have history of primary and secondary infertility respectively (Figure 6). Furthermore, the relationship between infertility and RSA has been studied. In the tables 5 and 6 the association of primary and secondary infertility revealed no significant relationship between RSA and infertility *P*= 0.47 and 0.10 for primary and secondary infertility respectively.

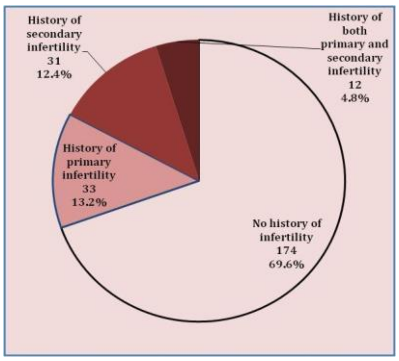

Figure 6. Distribution of the study population according to history of infertility

Table 5. Primary infertility and Recurrent spontaneous abortion

Primary infertility	Recurrent spontaneous Abortion		Total
	Yes	No	
Yes	4	41	45
	8.9%	91.1%	100.0%
No	26	179	205
	12.7%	87.3%	100.0%
Total	30	220	250
	12.0%	88.0%	100.0%

Pearson Chi-Square 0.503 P = 0.478

Table 6. Secondary infertility and Recurrent spontaneous abortion

Secondary infertility	**Recurrent spontaneous Abortion**		**Total**
	Yes	**No**	
Yes	2	41	43
	4.7%	95.3%	100.0%
No	28	179	207
	13.5%	86.5%	100.0%
Total	30	220	250
	12.0%	88.0%	100.0%

Pearson Chi-Square 2.656 P = 0.103

3.5. Study the Obstetric and Medical conditions

In the figures 7, 8, 9, 10 and 11 shows the rates of bad obstetric history, hypertension disorder of pregnancy, gestational diabetes mellitus and any medical condition and history of low vitamin D3 respectively. All of the aforementioned variables were reported at low levels by which about 20% among studied participants. There were no statistical significant between the previous variables and RSA as found in the tables 7, 8, 9, 10 and 11 ($P > 0.05$).

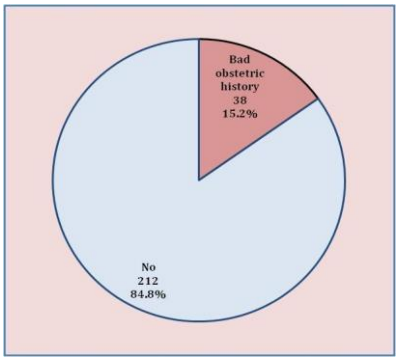

Figure 7. Distribution of the study population according to obstetric history

Table 7. Bad obstetric history and Recurrent spontaneous abortion

Bad obstetric history	**Recurrent spontaneous Abortion**		**Total**
	Yes	**No**	
Yes	7	31	38
	18.4%	81.6%	100.0%
No	23	189	212
	10.8%	89.2%	100.0%
Total	30	220	250
	12.0%	88.0%	100.0%

Fisher's Exact Test P = 0.183

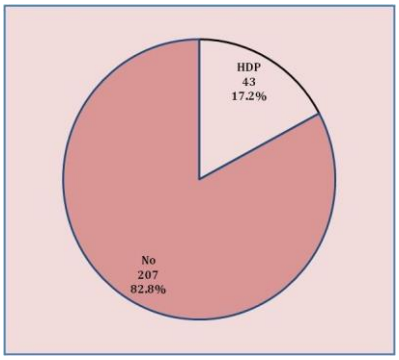

Figure 8. Distribution of the study population according to history of HDP

Table 8. Hypertensive disorders of pregnancy and Recurrent spontaneous abortion

Hypertensive disorders of pregnancy	**Recurrent spontaneous abortion**		**Total**
	Yes	**No**	
Yes	5	38	43
	11.6%	88.4%	100.0%
No	25	182	207
	12.1%	87.9%	100.0%
Total	30	220	250
	12.0%	88.0%	100.0%

Pearson Chi-Square 0.007 P=0.934

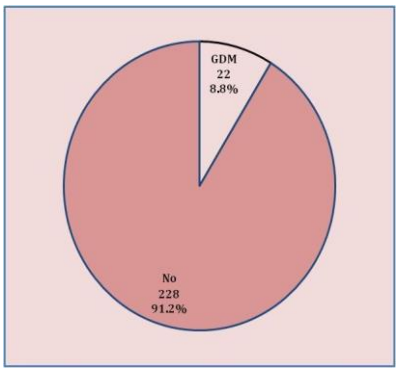

Figure 9. Distribution of the study population according to history of GDM

Table 9. Gestational diabetes and Recurrent spontaneous abortion

Gestational diabetes	**Recurrent spontaneous abortion**		**Total**
	Yes	**No**	
Yes	3	19	22
	13.6%	86.4%	100.0%
No	27	201	228

	11.8%	88.2%	100.0%
	30	220	250
Total	12.0%	88.0%	100.0%

Fisher's Exact Test P=0.735

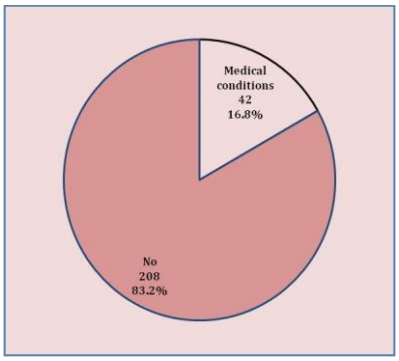

Figure 10. Distribution of the study population according to history of medicalconditions

Table 10. Medical condition and Recurrent spontaneous abortion

Medical condition	**Recurrent spontaneous abortion**		**Total**
	Yes	**No**	
Yes	7	35	42
	16.7%	83.3%	100.0%
No	23	185	208
	11.1%	88.9%	100.0%
Total	30	220	250
	12.0%	88.0%	100.0%

Pearson Chi-Square 1.041 P=0.308

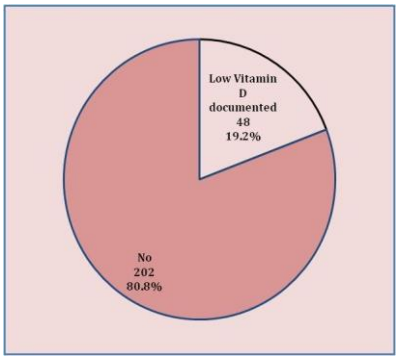

Figure 11. Distribution of the study population according to history of low vitamin D

Table 11. Low vitamin D and Recurrent spontaneous abortion

Low vitamin D	**Recurrent spontaneous abortion**		**Total**
	Yes	**No**	
Yes	9	39	48

	18.8%	81.3%	100.0%
No	21	181	202
	10.4%	89.6%	100.0%
Total	30	220	250
	12.0%	88.0%	100.0%

Pearson Chi-Square 2.563 P=0.109

3.6. Multivariate analysis of predictors factors for RSA

Table 12 shown that the results of multivariate analysis of predictors factors that have been studied. There were association found between history of Secondary infertility and RSA (*P*=0.034) and between History of first trimester Miscarriage and RSA (P=0.003) by Binary logistic regression analysis.

Table 12. Multivariate analysis for predictors of recurrent spontaneous abortion

Factors	**B**	**Chi square**	***P***	**OR**	**95% C.I. for OR**	
					Lower	**Upper**
History of Bad obstetric history	0.838	2.451	0.117	2.311	0.810	6.598
History of Secondary infertility	-1.703	4.497	0.034*	0.182	0.038	0.879
Low vitamin D	0.528	1.301	0.254	1.696	0.684	4.206
History of 1st trimester Miscarriage	1.257	9.107	0.003*	3.514	1.553	7.947

Binary logistic regression analysis.

B=Beta coefficient, OR Odds Ratio, CI Confidence Interval,

**** Independent predictor at level of confidence of 95%.***

4. Discussions

A total of 250 cases were investigated. Among those 30 cases met the definition of RSA. The rate of explained abortion among subset with spontaneous abortion was only 10.0%. This proportion may not be concordant with American College of Obstetricians and Gynecologists and Shahine & Lathi who stated that approximately 50% of the reason for RSA occurring remains unknown. The available laboratory facilities in our country are in short of diagnosing the complex etiology of SA, in addition to that those investigations are not considered in the current clinical practice in most of the cases.

The rate of advanced maternal age among the study population was 29.2%. The rate of RSA was higher among mothers with advanced maternal age (15.1% for 10.7%). This difference was statistically insignificant (P=0.338). This finding was congruent with that of Dai R., et al. [23] found that more women in the ≥40 and 35- to 39-year

groups had a history of three consecutive miscarriages. Their findings were statistically significant, the explanation was chromosomal anomalies. The history of abortion among the study population showed a rate of first trimester abortion was 36.8% and second trimester abortion as 4.8%. Regarding the association of 1st and 2nd trimester miscarriages with history of RSA. The RSA rate was much higher among mothers with history of 1st trimester abortion (20.7% for 7.0%) with statistically significant association (P <0.001) and OR of 3.5 (95% CI; 1.6–7.7). The finding of this study was consistent in multivariate analysis and the history of 1st trimester abortion was an independent predictor for RSA. The rate of RSA was lower among those with 2nd trimester abortion (8.3% for 12.2%) with statistically insignificant association (P=1.0). This may point to the tendency of first trimester abortion to recurrent. Which stress the importance of early investigation for the probable underlying conditions, not awaiting for recurrence of abortion.

History of primary infertility was prevalent in 18.0% of the study population while secondary infertility was reported in 17.2% of the study population. The rate of RSA was lower among those with primary infertility (8.9% for 12.7%) and also among those with secondary infertility (4.7% for 13.5%). In multivariate analysis, secondary infertility was independent negative predictor for RSA, (P = 0.034 and OR = 0.18; 95% CI: 0.04 – 0.88). This paradoxical result seems conflicting with Coulam C.B [24]. According to Coulam [24]; women experiencing RSA have a higher frequency of infertility than that expected in the general population. In a descriptive study, he investigated the obstetrical histories of 43 women with unexplained secondary infertility and evaluated them for the frequency of spontaneous abortion. Of the 88 pregnancies studied, 39 (44%) resulted in spontaneous abortion. Women with unexplained secondary infertility experienced a three-fold increase in the frequency of spontaneous abortions compared with the general population. No available published case control study verified this finding.

According to Kaur & Gupta [18] the major endocrinal causes of recurrent abortions are polycystic ovarian syndrome (PCOS), obesity, hyperinsulinemia, and insulin resistance (IR) among others. Several studies investigated such relationship in which study published by Carrington B., et al. [16], Kikkatalo K., et al. [17], and Shankarkumar et al. [20] emphasize the role of autoimmunity in both infertility as well as RSA, which is also in opposite to the finding presented by this study. The explanations may include the design of the present study, demographic factors and the possible inaccuracy of the reported data.

The rates of bad obstetric history, HDP, GDM, any medical condition and history of low vitamin D3 were 15.2%, 17.2%, 8.8%, 16.8% and 19.2%; respectively among the study population. Mothers with bad obstetric history have a higher rate of RSA (18.4% for 10.8%), but the difference is not statistically significant (P=0.183). No significant association between HDP, GDM, history for medical conditions or history of low serum vitamin D with RSA (P = 0.934, 0.735, 0.308 and 0.109 respectively). This is also was not supported by findings regarding vitamin D found by Li N., et al. [22]. The methodology used in the later study was based on placental tissue and fluid analysis. Vitamin D levels were not objectively measured in the present study.

There were some limitations encountered in the present work include data collection and case finding as record were not well informative and also temporal relationship was not well explored as prospective cohort design may be more suitable for this purpose.

5. Conclusion and Future Recommendations

Recurrent spontaneous abortion is under-investigated and seems to be more likely with first trimester abortion and it is may be associated with several factors like infertility and maternal age. Anyhow, those associations need to be verified. The present study suggested:

- **Longitudinal Studies:** Conduct longitudinal studies to track couples with a history of first trimester abortions over time. This could help identify additional risk factors and establish causal relationships with recurrent spontaneous abortion.
- **Genetic and Hormonal Assessments:** Explore genetic screening and hormonal assessments in women experiencing recurrent spontaneous abortion. This may uncover underlying genetic conditions or hormonal imbalances contributing to pregnancy loss.
- **Multicenter Research Collaboration:** Initiate multicenter studies across different regions of Libya to gather a more diverse patient population. This would enhance the generalizability of findings and provide a comprehensive understanding of RSA in the Libyan context.
- **Interventional Studies:** Design interventional studies focusing on early interventions for at-risk couples, such as counseling, nutritional support, and medical management of underlying conditions. Evaluating the impact of these interventions could improve pregnancy outcomes in future pregnancies.

Declarations

Source of Funding

This study did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing Interests Statement

The authors declare no competing financial, professional, or personal interests.

Consent for publication

The authors declare that they consented to the publication of this study.

Authors' contributions

All the authors took part in literature review, analysis and manuscript writing equally.

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