

Comparative Study Between the Explained and Unexplained Patient Women with Recurrent Miscarriage

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Abstract

Recurrent miscarriage can be defined as two or more consequence unsuccessful clinical pregnancies and confirmed by ultrasonography or histopathological examination and consider the most common clinical complications reproduction, and it affects (2%–5%) of reproduction couple. The present study included 140 women who were already diagnosed with recurrent miscarriage. Following complete clinical workup, including history, examination and investigations, enrolled women were classified into two main subgroups, explained group ($n = 85$) and unexplained group ($n = 55$). In this study, the result showed no significant difference found between the two subgroups explained and unexplained regarding age and the body mass index. In the obstetric history characteristics of women enrolled in the current study, there is no significant difference between the explained and unexplained group according to gravity, parity, and the number of abortions. Additionally, no significant difference according to gestational age and types of abortion but found significant in the type of complete abortion between the explained and unexplained group. Results showed that recurrent miscarriage rates increased in women with positive anti-phospholipids, in addition, a significant difference in the type of complete abortion between the explained and unexplained group of recurrent miscarriage women.

Keywords: Recurrent miscarriage, Abortion

1. Introduction

Miscarriage can be defined as the loss of prevailed pregnancy. Pre viability means the fetus weighing less than (500 grams) or gestational age less than (20 weeks) (McNamara, et al. ^[1]). Moreover, the gestational threshold for the definition differs between the places. In the United States, it was usually twenty weeks and may differ depending on the different states, whereas in the United Kingdom, the “Royal College of Obstetricians and Gynecologists” defined the gestational threshold as twenty-four weeks (de Bernis, et al. ^[2]). Anyway, two or more repeated pregnancy loss previous to twenty-two weeks of gestation is defined as “recurrent miscarriage” (Chetty, et al. ^[3]). Generally miscarriage rate was reported as the (15-20%) and that for recurrent miscarriage was (1–3%) age of reproductive women (Agenor, et al. ^[4]). Symptoms and signs of pregnancy loss may include abdomen cramp, vaginal bleeding, pain (in the lower back), tissues or fluids passing from the vagina (Costantino, et al. ^[5]). Pregnancy

loss can be caused by several factors such as genetic factors, anatomic factors, infectious and endocrine factors such as diabetes mellitus and hyperprolactinemia and by environmental factors such as smoking or alcohol, in addition, exposure to toxic substances can cause pregnancy loss (Jurkovic, et al. ^[6]), miscarriage was also associated with many autoimmune diseases, most notably, antiphospholipid syndrome (APS), systemic lupus erythematosus and also inherited thrombophilias (antithrombin deficiency, deficiency of protein (C) and protein (S), factor (V) Leiden mutation, and mild hyperhomocysteinemia) such as poorly controlled diabetes mellitus (DM); hyperprolactinemia and also thyroid diseases and pelvic anatomic abnormality (Jurkovic, et al. ^[7]).

2. Materials and Methods

This prospective case-control study was done in the Obstetrics and Gynecology Al-Muthanna teaching hospital in Samawa city, Iraq. During the period October 2018 to April 2019. The study included patients

attending Obstetrics and Gynecology Al-Muthanna teaching hospital with recurrent miscarriages. This Study included 140 women who were already diagnosed with recurrent miscarriage in the age range 19-45 years old. Following complete clinical workup, including history, examination and investigations, enrolled women were classified into two main subgroups, explained group ($n = 85$) that including women patients with (anti-phospholipids, bicornuate uterus, Cervical incompetence, Thyroid disease, cytomegalovirus (CMV) and toxoplasma virus) whereas the other group are unexplained group ($n = 55$) that including recurrent miscarriage women with no identified causes.

3. Sample Collection

About five ml of venous blood samples were collected from patients attending Obstetrics and Gynecology Al-Muthanna Teaching Hospital. venous blood samples up to 5ml were taken by using a 5ml syringe from the vein. The samples were left for thirty minutes at room temperature

then the tube was centrifuged at 1800 rpm for fifteen minutes at room temperature. The serum was transported to the plane tube and stored at -36°C until the time of the assay.

4. Clinical Investigation

Anti-phospholipid (APO) and thyroid hormones were measured depending on the ELISA instrument (Elisys Uno human-Germany).

5. Results

Women with only Anti-APS antibody, positive results accounted for 72 (51.4 %). Women with bicornuate uterus in addition to Anti-phospholipid positivity accounted for 2 (1.4 %); women with cervical incompetence in addition to Anti-APS positivity accounted for 2 (1.4 %); women with cytomegalovirus (CMV) and toxoplasma virus in addition to Anti-APS positivity accounted for 2 (1.4 %) and women with thyroid disease in addition to Anti-APS positivity accounted for 2 (1.4 %). Women with anti-phospholipid negatively who had only bicornuate uterus

accounted for 4 (2.9 %) and there was a single woman with only thyroid abnormality (0.7 %), as shown in Table (1). Those women were regarded as an explained group and they included 85 members, whereas, women with no identifiable cause, even after thorough clinical workup, were considered unexplained group and they had been represented by 55 members, as shown in Table (1).

5.1 Demographic Characteristics of Women Enrolled in the Study

Mean age of all women was 28.97 ± 6.40 years, that of the explained group was 29.04 ± 6.83 years and that of unexplained group was 28.87 ± 5.74 years; there was no significant difference in the mean age of explained and unexplained group ($P = 0.884$), as shown in Table (2) and

Table (1): Frequency distributions of women with recurrent miscarriage according to the cause of miscarriage

Group	Cause	n	%
Explained <i>n</i> = 85	APS +ve	72	51.4
	APS +ve + Bicornuate Uterus	2	1.4
	APS +ve + Cervical Incompetence	2	1.4
	APS +ve + CMV+ Toxoplasma	2	1.4
	APS +ve + Thyroid Disease	2	1.4
	APS -ve + Bicornuate Uterus	4	2.9
	APS -ve + Thyroid Disease	1	0.7
Unexplained <i>n</i> = 55	No identifiable cause	55	39.3
Total <i>n</i> = 140	Total <i>n</i> = 140	140	100.0

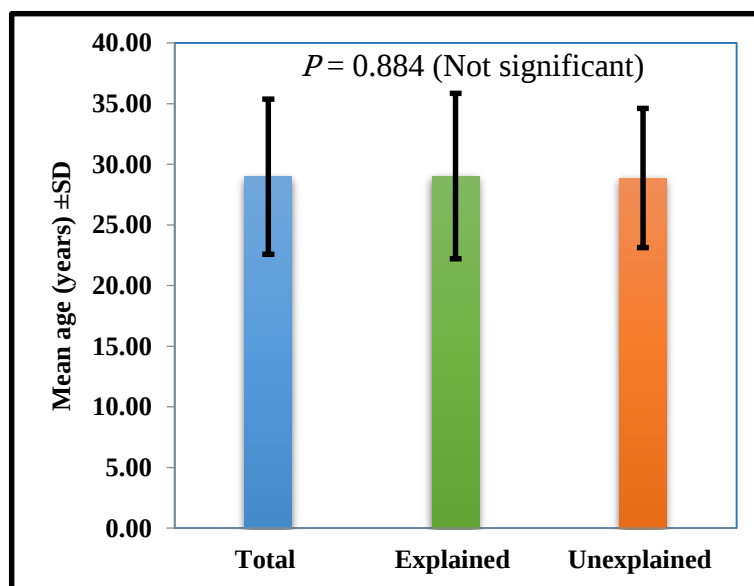


Figure (1): Bar chart showing a comparison of the mean age between explained and unexplained groups

Table (2): Demographic characteristics of women enrolled in the current study

Characteristic	Total <i>n</i> = 140	Explained <i>n</i> = 85	Unexplained <i>n</i> = 55	<i>P</i>
Age (years)				
Mean ±SD	28.97±6.40	29.04 ±6.83	28.87 ±5.74	0.884 † NS
Range	19 -45	19 -45	20 -42	
< 20, <i>n</i> (%)	4 (2.9 %)	4 (4.7 %)	0 (0.0 %)	0.077 ¥ NS
20-34, <i>n</i> (%)	110 (78.6 %)	62 (72.9 %)	48 (87.3 %)	
≥ 35, <i>n</i> (%)	26 (18.6 %)	19 (22.4 %)	7 (12.7 %)	
BMI				
Mean ±SD	27.99 ±6.05	27.82 ±5.16	28.25 ±7.25	0.686 † NS
Range	17.75 -52.73	17.75 -41.55	19.82 -52.73	
Underweight, <i>n</i> (%)	2 (1.4 %)	2 (2.4 %)	0 (0.0 %)	0.419 ¥ NS
Normal, <i>n</i> (%)	46 (32.9 %)	26 (30.6 %)	20 (36.4 %)	
Overweight, <i>n</i> (%)	54 (38.6 %)	31 (36.5 %)	23 (41.8 %)	
Obese, <i>n</i> (%)	38 (27.1 %)	26 (30.6 %)	12 (21.8 %)	

n: number of cases; SD: standard deviation; BMI: body mass index; †: independent samples t-test; ¥: Chi-square test; NS: not-significant at *P* > 0.05

Figure (1). Besides, there were no significant- different in the frequency-distributions of women according to age intervals, < 20 versus 20-34 versus $\geq$ 35, between explained and unexplained groups (*P* = 0.077), as shown in Table (2).

The mean body mass index of all enrolled women was 27.99 $\pm$ 6.05 kg/m², that of explained group was 27.82 $\pm$ 5.16 kg/m² and that of unexplained group was 28.25 $\pm$ 7.25 kg/m²; there were no significant-different in mean

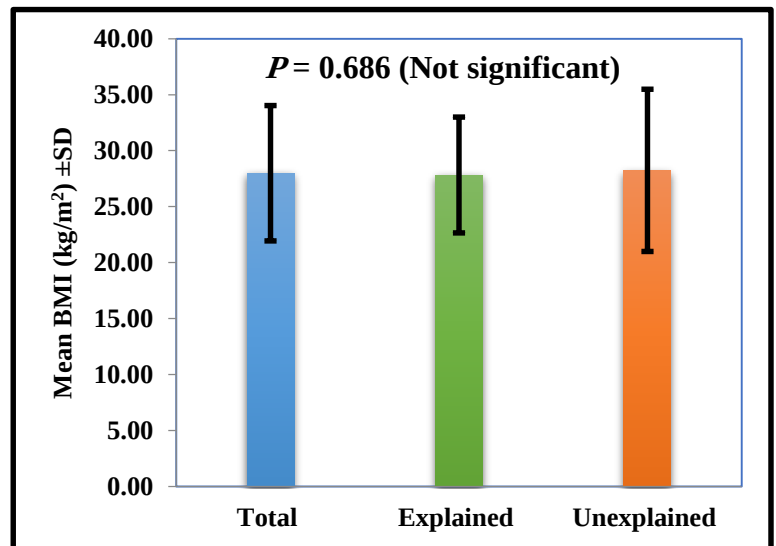


Figure (2): Bar chart showing a comparison of the mean age between explained and unexplained groups

of body mass index (BMI) between explained and unexplained group (*P* = 0.686), as shown in Table (2) and Figure

(2). Moreover, there was no significant difference in the frequency distribution of women according to BMI, underweight versus normal versus overweight versus obese, between explained and unexplained groups ($P = 0.419$), as shown in Table (2).

5.2 Obstetric History

Characteristics of Women Enrolled in the Study

Information regarding past obstetric history was obtained from each participant and included gravidity, parity, and the number of previous abortions. From a statistical perspective, these variables, namely gravidity, parity and number of previous abortions, were non-parametric (not normally- distributed variable) according to “Kolmogorov Smirnov” normality tests; therefore, they were expressed in the form of median (inter-quartile range) instead of (mean) and (standard deviation). Moreover, for the purpose of comparison, the Mann Whitney U test was used instead of independent-samples (t-test). The results were outlined in Table (3) and Figure 3.

Median gravidity of total sample explained group and the unexplained group were 4.00 (3.00), 4.00 (3.00) and 4.00 (3.00), respectively with lack of significant difference between explained and unexplained groups ($P = 0.497$), as shown in Table (3) and Figure 3 (a).

Median parity of total sample explained group and the unexplained group were 1.00 (2.00), 2.00 (2.00) and 1.00 (3.00), respectively with lack of significant difference between explained and unexplained groups ($P = 0.277$), as shown in Table (3) and Figure 3 (b).

The median number of previous abortions of total sample explained group and the unexplained group were 3.00 (2.00), 2.00 (2.00) and 3.00 (2.00), respectively with lack of significant difference between explained and unexplained groups ($P = 0.277$), as shown in Table (3) and Figure 3 (c).

Table (3): Obstetric history characteristics of women enrolled in the current study

Characteristic	Total <i>n</i> = 140	Explained <i>n</i> = 85	Unexplained <i>n</i> = 55	<i>P</i>
Gravity				
Median (IQR)	4.00 (3.00)	4.00 (3.00)	4.00 (3.00)	0.497 †
Range	1.00 -13.00	2.00 -11.00	1.00 -13.00	NS
Parity				
Median (IQR)	1.00 (2.00)	2.00 (2.00)	1.00 (3.00)	0.277 †
Range	0.00 -6.00	0.00 -6.00	0.00 -5.00	NS
Number of abortions				
Median (IQR)	3.00 (2.00)	2.00 (2.00)	3.00 (2.00)	0.364 †
Range	1.00 -8.00	2.00 -8.00	1.00 -8.00	NS

n: numbers of cases; IQR: inter-quartile range; †: Mann Whitney U t-test; NS: not significant at $P > 0.05$

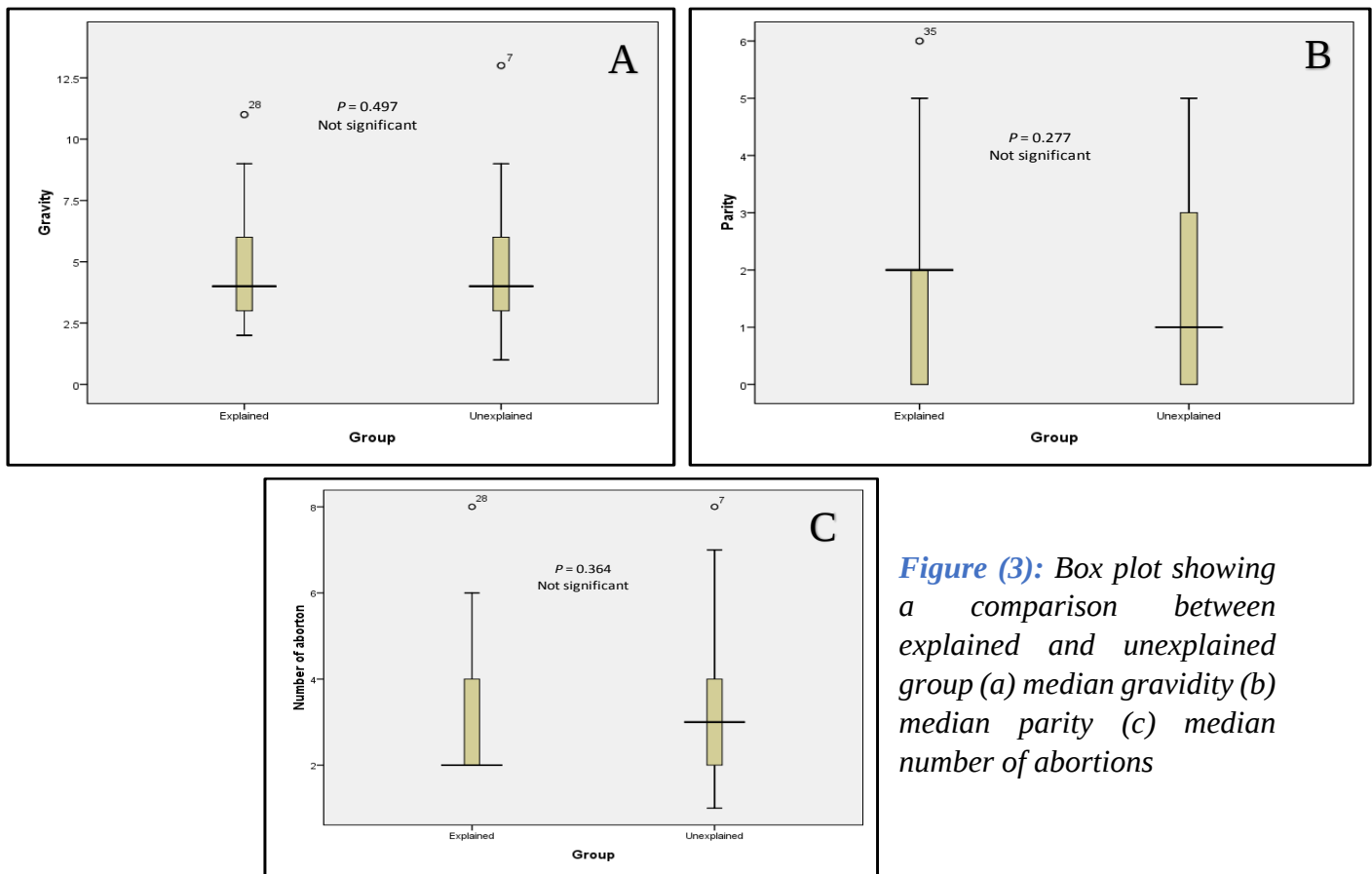


Figure (3): Box plot showing a comparison between explained and unexplained group (a) median gravity (b) median parity (c) median number of abortions

5.2 Characteristics of Abortion in Women with Recurrent Miscarriage Enrolled in the Study

Characteristics of abortion in women with recurrent miscarriage enrolled in the current study were demonstrated in Table (4) and Figures (4) and (5). The first trimester was the dominant time at which abortion happens in women with recurrent miscarriage accounting for 106 (75.7 %); whereas, second trimester (late) abortion was seen in a small proportion of women and accounted for 34 (24.3 %). Besides, there was no significant variation in the frequency distribution of women according to time of abortion, first trimester versus second trimester, between explained and unexplained group, 64 (75.3 %) and 21 (24.7 %) versus 42 (76.4 %) and 13 (23.6 %), respectively ($P = 0.885$), as shown in Table (4) and Figure (4).

The dominant type of abortion was the missed one which has been encountered in 124 (88.6 %) women followed by incomplete abortion in 12 (8.6 %) women

and complete abortion in 4 (2.9 %) women among the entire sample, as shown in Table 4 and Figure 4. missed abortion was seen in 78 (91.8 %) and 46 (83.6 %) women in explained and unexplained groups, respectively; whereas, incomplete abortion was recorded in 7 (8.2 %) and 5 (9.1 %) women in explained and unexplained groups, respectively. Complete abortion was not seen in the explained group; however, it was observed in 4 (7.3 %) women in the unexplained group, as shown in Table (4) and Figure (7). When missed abortion type was fixed as a reference subgroup, there was no significant difference in the frequency of incomplete abortion between explained and unexplained groups ($P = 1.000$); However, there was significant difference in the frequency of complete abortion between explained and unexplained groups ($P = 0.022$); being limited to unexplained group, as shown in Table (4) and Figure (5).

Table (4): Characteristics of abortion in women with recurrent miscarriage enrolled in the current study

Characteristic	Total <i>n</i> = 140	Explained <i>n</i> = 85	Unexplained <i>n</i> = 55	<i>P</i>
Gestational age				
First trimester, <i>n</i> (%)	106 (75.7 %)	64 (75.3 %)	42 (76.4 %)	0.885 ¥ NS
Second trimester, <i>n</i> (%)	34 (24.3 %)	21 (24.7 %)	13 (23.6 %)	
Type of abortion				
Missed, <i>n</i> (%)	124 (88.6 %)	78 (91.8 %)	46 (83.6 %)	Reference
Incomplete, <i>n</i> (%)	12 (8.6 %)	7 (8.2 %)	5 (9.1 %)	1.000 € NS
Complete, <i>n</i> (%)	4 (2.9 %)	0 (0.0 %)	4 (7.3 %)	0.022 £ S

n: numbers of cases; ¥: Chi-square test; €: Yates correction for continuity; £: Fischer exact test; NS: not significant at ($P > 0.05$); S: significant (at $P \leq 0.05$)

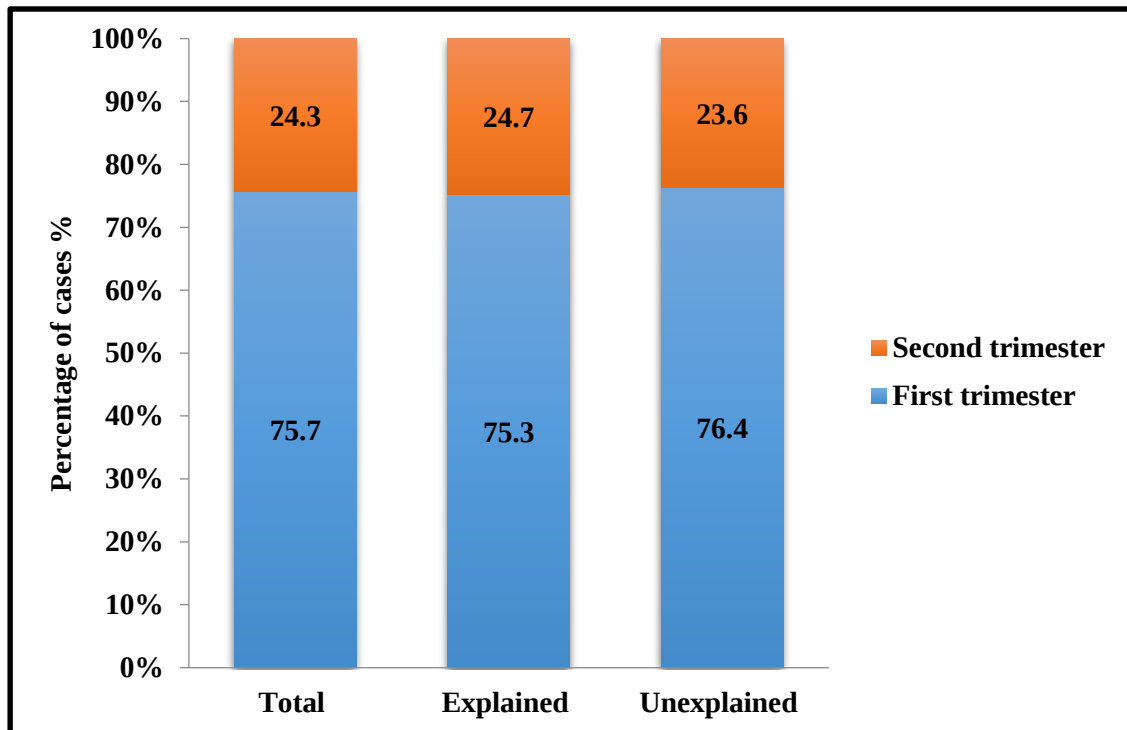


Figure (4): 100% stacked column showing the frequency distribution of women according to time of abortion in explained and unexplained groups

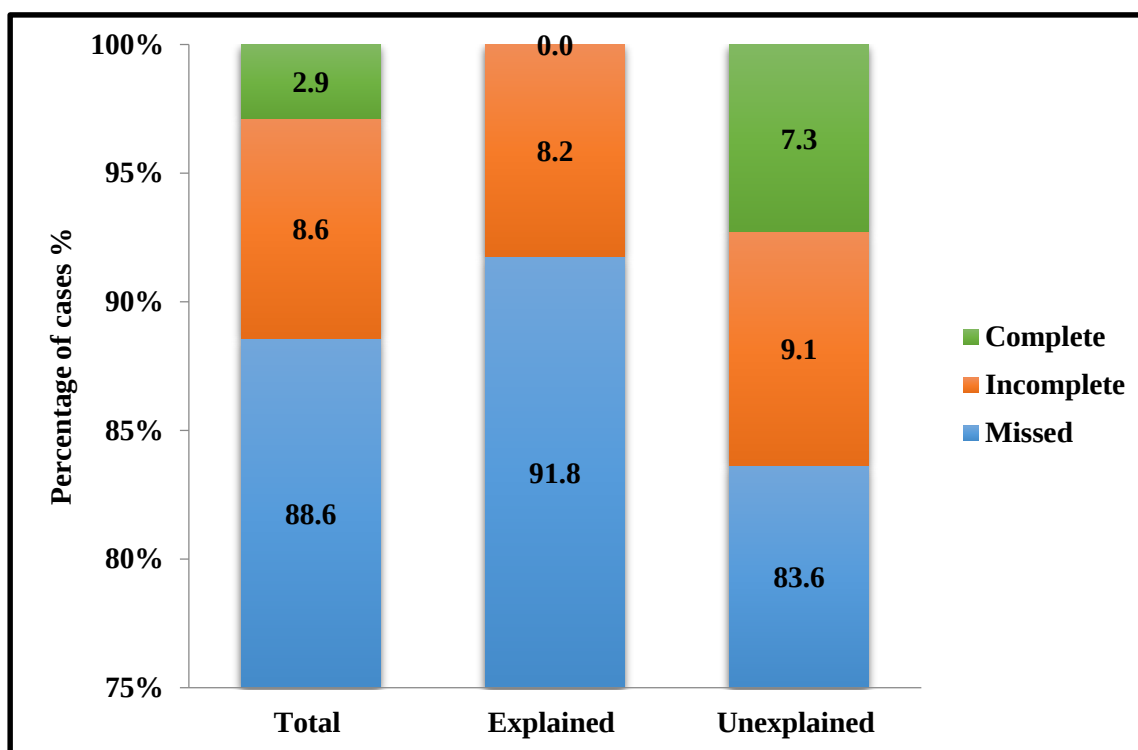


Figure (5): 100% stacked column showing the frequency distribution of women according to the type of abortion in explained and unexplained groups

6. Discussion

Pregnancy loss was considered the most common adverse outcome in early pregnancy. It was defined as the spontaneous demise of a pregnancy from the time of conception until twenty-four weeks' gestation (McNamara, et al. [8]). It can be clinically classified as first-trimester miscarriage within thirteen weeks' gestation or second-trimester miscarriage after twelve and before twenty-four of completed weeks'

conception (Morris, et al. [9]). The risk causes for miscarriages are maternal-age with a higher risk after thirty-five years old, paternal age after forty-five years old (Brandt, et al. [10]), maternal body mass index (BMI) with a higher risk for body mass index more than twenty-five, toxic consumption alcohol, tobacco and coffee and exposure to magnetic field and ionizing-radiation (Wang, et al. [11]). A previous pregnancy loss is also a risk cause such as infertility and alteration of the

ovarian reserve (Sahu, et al. ^[12]). Recurrent pregnancy loss characterizes significant health problems. Approximately (5%) of couples that trying to conceive suffer recurrent pregnancy loss. Various definitions for recurrent miscarriage had been explained. In this study, recurrent pregnancy loss had been defined as two or more not necessarily sequential miscarriages (Vissenberg, et al. ^[13]). As shown in Table (1) recurrent miscarriage women were classified to explained causes of recurrent miscarriage with the mean cause antiphospholipid antibodies which gave 60.7%. of women with recurrent miscarriage. Whereas unexplained recurrent miscarriage (RM) still characterizes as a major scientific and clinical problem in reproductive medicines, as approximately (39.3%) of recurrent miscarriage (RM) is known as unexplained at the final of (the standard diagnostic workup). these are due to the deficiency of a full understanding of the complex- mechanism that involved in the proper implantation and early pregnancy

progress, which can prevent a thorough definition of the reasons and mechanism underlying recurrent miscarriage; there are still various methodological- difficulties that obstruct the reliability of different clinical diagnostic on recurrent miscarriage (Ticconi, et al. ^[14]). Antiphospholipid-antibody (APL) is known as a family of approximately (20) autoantibodies directed against phospholipids-binding plasma-proteins. Anyway, the most two clinically important anti-phospholipids are the lupus anticoagulant (LA) and the anti-cardiolipin antibody (ACL). Approximately fifteen percent of women with recurrent abortion have persistently positive tests for either (LA) or (ACL), compared to two percent of women with an uncomplicated obstetric history (Dobson and Jayaprasakan ^[15]). Maternal-age was known as the risk factor for recurrent pregnancy loss. ladies above the age of thirty-five years have an increased rate of meiotic-errors in oocyte development that leading to increasing

embryonic-aneuploidy. The reported-miscarriage rate among ladies under (35 years) of age is fourteen percentage compared with forty percentages for ladies over 40 years old (Marquard, et al. ^[16]). Given this, one would expect the recurrent pregnancy loss rate to be more than 20 times higher in women over 40 compared with ladies under 35 years old. However, in our study, 78.6% of women with recurrent mismanage were age between 20-34 years old as shown in Table (2) and Figure (1). Obesity and excess weight consider a cause for concern among specialists in (reproductive medicine) because of the higher risk of these conditions inducing complications in the pregestational-period. Such complications include abortion, fetal death, congenital malformations, fetal macrosomia, gestational diabetes, pre-eclampsia, complications during vaginal-delivery, higher cesarean section rates, thromboembolic-events, post-partum infection and trouble in breastfeeding (Cavalcante, et al. ^[17]) and in result of this

study show 54% of women with recurrent miscarriage in overweight (25-29 BMI) whereas 38% of women with recurrent miscarriage suffer from obesity (BMI $\geq$ 29) as shown in Table (2) and Figure (2). Recurrent miscarriage is a heterogeneous-condition which is still incompletely-understood, although the extensive investigation which has been carried out in the last decades in the field. Multiple known and apparent causes of (RM) had been detected, including genetic-alterations, female genital tract anatomical-malformations, endocrines, and autoimmune-alterations, in addition, coagulation-disorders (Jaslow, et al. ^[18]). More than (76%) of the (RM) occurs during early-gestation, mainly within the first-trimester and these results agree with other studies by (Allison and Schust ^[19]). The present investigation showed no significant difference in explained and unexplained recurrent miscarriage. In addition, 124 cases (88.6%) of recurrent miscarriage in missed abortion and this agreement with a previous study by Ashaat

and Hussein that conclusion, most of the abortions in the first trimester are early missed abortions (Ashaat and Hussein [20]). Moreover, no significant difference between explained and unexplained recurrent miscarriage cases depending on missed abortion. In addition, complete abortion shows no cases in explained group compared to unexplained which shows 7.3% of cases in type complete abortion as shown in Table (4) and Figure (5). Although the results show a significant difference between explained and unexplained recurrent miscarriage groups according to the type of abortion especially complete abortion, these results are not considered as main results of this study due to the limited number of case samples and limited time of collected samples.

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Author Contribution

Zahrah S. Mahdi performed the study, Mohammad O. Selman supervised the work, Shiamaa M. Mohammad examined and reviewed results and manuscript writing.

Conflict of Interest

The authors declare no conflict of interest.

Ethical Clearance

The study was approved by the Ethical Approval Committee.

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Biography



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