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ORIGINAL ARTICLE

Recurrent Pregnancy Loss and Associated Risk Factors

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ABSTRACT

Background: As documented by the histopathology the recurrent pregnancy loss (RPL) is characterized as two or more miscarriages. The true prevalence of RPL is unknown, but is reported that two percent of women are affected by RPL per annum. A well-known risk factor for recurrent pregnancy losses is the high maternal age.

Objective: This study was carried out to determine the risk factors and consequences of recurrent pregnancy loss.

Study design: It is a prospective study

Place and Duration: Conducted for the duration of one year from August 2021 to July 2022. The patients attended the obstetrician and gynecology department of Khawaja Muhammad Safdar Medical College, Allama Iqbal Memorial Teaching Hospital Sialkot.

Material and Methods: This study was performed on 130 patients, admitted to tertiary care unit within the duration of one year. The written consent was taken from all the patients included in the study. The ethical and review board committee of the hospital approved the study. The women that had less than 2 miscarriages were excluded from the study.

Results: The mean age of the mother at the time of admittance to hospital was 34 years and the mean of the miscarriages reported earlier in these patients were 2.9±1.3. The risk factors were found to be linked in most of the patients. The abnormality of the uterus and the thyroid dysfunction were some of the major risk factor in most of the patients with recurrent pregnancy loss. In case of thyroid dysfunction, the hyperthyroidism and hypothyroidism were studied and the results showed that the hyperthyroidism was present in case of 17% of the patients while hypothyroidism was found in 83% of the cases. Parental karyotype abnormality was also found in 4% of the cases.

Conclusion: It was concluded that the patients suffering from recurrent pregnancy loss should underwent through the process of appropriate examination to clarify and conclude the risk factors involved in causing RPL. The protein S and factor XII deficiency may be playing a role in causing RPL, therefore LDA therapy can improve the rate of live birth in these patients.

Keywords: recurrent pregnancy loss and protein S deficiency.

INTRODUCTION

International societies have different definitions of recurrent pregnancy loss. As documented by the histopathology the recurrent pregnancy loss (RPL) is characterized as two or more miscarriages[1-2]. The true prevalence of RPL is unknown, but is reported that two percent of women are affected by RPL per annum. A well-known risk factor for recurrent pregnancy losses is the high maternal age. Early pregnancy loss is also known as miscarriage or spontaneous abortion[3-4].

Women in different countries are currently getting married later, which has raises the risk of miscarriage. In addition to infertility, RPL is also a significant issue in obstetrics and reproduction field. To lower the chance of miscarriage, it is crucial to screen the RPL risk factors and provide enough treatment for the next pregnancy[5-6]. Approximately 2.5% of women trying to conceive have the pregnancy illness known as recurrent pregnancy loss. It includes embryonic and fetal losses. It is defined as the failure of two or more clinically diagnosed pregnancies before 20–24 weeks of gestation. Because of the varying pathophysiology and the clinical presentation it is difficult to predict and prevent repeated pregnancy loss[7-8]. Chromosomal errors, defective uterus, autoimmune diseases, and dys-functioning of endometrial can all lead to recurrent pregnancy loss. RPL is a significant concern for reproductive health. It is reported that RPL affect affects 2-5% of the marriages[9]. Because of the various definitions and criteria applied, as well as the characteristics of the populations, the incidence of RPL differs significantly in the reports. The 19% of the women with RPL have the uterine anatomical defects. Women with RPL are more likely to have chronic endometritis. It is characterized as a chronic inflammation of the uterine lining. Disturbed couple's personal and professional lives, and a range of emotions, including loss and depression, hopelessness, anxiety, and resentment against a partner are reported because of RPL. Using the data collected, the study examined the frequency of risk factors and their association with RPL[10]

MATERIAL AND METHODS

This prospective study was conducted for duration of one year from August 2021 to July 2022. The patients attended the obstetrician and gynecology department of Khawaja Muhammad Safdar Medical College, Allama Iqbal Memorial Teaching Hospital Sialkot were selected for the study. A total of 130 patients were included in the study to evaluate the risk factors and their association with recurrent pregnancy loss, all patients were fully aware of the study and written consent was taken from them. The ethical and review board committee of the hospital approved the study. The selected patients were advised parental karyotype abnormality, and all the patients were subjected to examination related to recurrent pregnancy loss. Biochemical or chemical pregnancies were not included in the miscarriage number in this study. The step was taken to prevent the misinterpretation of the data collected. All women with RPL were interviewed and underwent a complete evaluation that included maternal age, history (pregnancy associated complications and medical complications), hysterosalpingogram, hysteroscopy or vaginal ultrasonography for detecting malformation of the uterus, thyroid dysfunction. The convenience sampling technique was used[11].

Features like dysfunctional thyroid, malfunctioned uterus and other abnormalities were tested and studied. Patients were checked for protein S deficiency. Serum T3, T4 and serum TSH levels were compared for diagnosing dysfunctional thyroid. Ultrasound provided the information about the working of uterus. A blood test was performed that provided the data about the protein S deficiency. All the patients showed up for examination and follow-up throughout the year. According to the inclusion criteria woman who had experienced more than two miscarriages were included in the study. The statistical analysis was performed on the

data collected from the selected patients. The SPSS software version V22.0 was used for the analysis.

RESULTS

This study was carried out to find the risk factors and consequences of recurrent pregnancy loss. The mean age of the mother at the time of admittance to hospital was 34 years and the mean of miscarriages reported earlier in these patients were 2.9±1.3 as shown in table 1. The risk factors were found to be linked in most of the patients.

The abnormality of the uterus and the thyroid dysfunction were some of the major risk factor in most of the patients with recurrent pregnancy loss. In case of thyroid dysfunction, the hyperthyroidism and hypothyroidism were studied and the results showed that the former was present in case of 17% of the patients and later was found in 83% of the cases. Parental karyotype abnormality was also found in 4% of the cases.

Table 1: Baseline features

Baseline Features	Number
Mean age	34 years
mean of miscarriages	2.9±1.3

Table 2: The prevalence of risk characteristics in case of RPL patients

Features	Prevalence
Malformation of the uterus	8% (11/130)
Thyroid dysfunction	10% (13/130)
Parental karyotype abnormality	4% (6/130)
Positive for antiphospholipid antibody	9% (11.7/130)
Protein S deficiency	5% (6.5/130)
Factor XII deficiency	8% (10/130)

Table 3: Risk factors and the outcome of RPL

Factors	Treatment	Pregnancy live birth	Miscarriage total	Miscarriage with abnormal fetal karyotype	Live birth rate with normal fetal karyotype	P value (treatment vs no treatment)	P value(LDA vs unfractionated heparin plus LDA)
Malformation of the uterus	NA	31	28	3	71%	0.05	0.001
Thyroid dysfunction	NA	7	3	7	91%	0.005	0.05
Parental karyotype abnormality	NA	11	27	11	89%	0.03	0.03
Positive for antiphospholipid antibody	None	5	15	6	88%	0.4	0.001
Protein S deficiency		16	6	0	93%	0.1	0.19
	No treatment		6	0	51%		
	LDA		2	0	92%		
	LDA +unfractionated heparin		1	0	99%		
Factor XII deficiency		38	26	4	83%	0.003	0.002
	No treatment		4	1	51%		
	LDA		10	2	99%		
	LDA +unfractionated heparin		7	1	72%		

DISCUSSION

The study was carried out to find the outcomes and the risk factors associated with recurrent pregnancy loss. There were 130 patients that participated in this study and all the patients were fully aware of the study. The risk factors such as uterus malfunctioning, the thyroid dysfunction, and parental karyotyping were majorly studied. The risk factors such as deficiency of protein S, the deficiency of factor XII were also studied to find the outcomes and consequences of the recurrent pregnancy loss[12-13]. As per our studies, the uterus malfunctioning was observed in 8% of the cases, whereas the previous studies reported that almost 13% of the recurrent pregnancy loss patients suffer from uterus malfunctioning. As per ESHRE guidelines, there is need of tests to measure the LA, ACA, IgM, and IgC, and the working of thyroid gland as well[14]. The malfunctioning of the thyroid was found to be 8%. As per other studies carried out to find the risk factors involved in recurrent pregnancy loss, the percentage of RPL cases reported because of malfunctioned uterus cases were observed to be slightly higher. The percentage ranged from 13 to 20 % in these cases. However, as per some of the other studies, similar results were observed. This suggest that there is need of surgery in case the uterus is septate, but in our study the exact surgical reason was not available in the data. If the more detailed analysis of the condition of uterus is carried out, then it can have positive impact on the RPL cases.

As per studies it was found that hyperthyroidism plays a very significant role in pregnancy complications and is known as one of the risk factors for RPL. The conditions like sporadic miscarriage, preterm birth, pre-eclampsia are frequently reported due to the hyperthyroidism. Previous studies have shown the elevated risk of RPL due to the hyperthyroidism condition. The percentage of hyperthyroidism and hypothyroidism was 17% and 83% respectively[15-16]. And the live birth rate was also low in these two groups. The live birth rate was found to be quite high in case of normal fetal karyotype as per our studies. This analysis therefore suggest that the thyroid dysfunction was the reason involved in miscarriage in most of the cases. In our study the parental karyotype abnormality was found in 4% of the cases. Our studies results match with the previously reported data where the parental karyotype abnormality was found to be 3.4%. The live birth rate in case of patients with balanced reciprocal transaction was also studied and it came out to be 28%. These findings were slightly different from the previous findings where the percentage was found to be less than 28%[17].

In our study, the parental karyotyping was performed for only 36% of the patients, as the patient's partners were needed for lab facilities and it was effecting sensitive matters therefore only some of the patients agreed for parental karyotyping. The hereditary thrombophilia testing was not suggested by ESHRE guidelines[18-19], but as the protein S deficiency is common now therefore it was also included in the study. Live birth rate of patients with protein S deficiency and factor XII deficiency was quite lower in case of group without treatment. Even though the sample size in case of un-treated group was small, still such results were observed. In case of factor XII deficiency the live birth rate was higher in LDA group as compared to the unfractionated heparin + LDA group. There are numerous studies that link RPL with factor XII deficency[20-21], however, the further studies are needed to confirm

the association between the two. In a study carried out it was found that the female mice homozygous for the deficiency of factor XII gave birth to the litters in a normal manner which suggest that may be the deficiency of congenital factor XII is not linked to loss of pregnancy. As per studies it was found that there can be a link between antibodies against factor XII and the recurrent pregnancy loss, therefore it was suggested that the autoantibodies produced against factor XII can be linked to thromboembolism and RPL[22].

CONCLUSION

To conclude, the patients suffering from recurrent pregnancy loss should underwent through the process of appropriate examination to clarify and conclude the risk factors involved in causing RPL. The factor XII deficiency and protein S deficiency may be playing a role in causing RPL, therefore LDA therapy can improve the rate of live birth in these patients.

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