Original Article

Association of structural uterine defects with repeated pregnancy loss: hysteroscopic assessment

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ABSTRACT

Background: *Recurrent pregnancy loss (RPL) is defined as the loss of two or more pregnancies. Structural uterine defects (SUD) are often associated with RPL which can be either congenital or acquired. Hysteroscopy is the gold-standard method for evaluation of SUD. The objective of this study was to evaluate the prevalence of SUD among Bangladeshi women with RPL based on hysteroscopic findings.*

Methods: *This cross-sectional study was conducted at Farida Clinic and Infertility Management Center from January 2021 to December 2023. In total of seventy-six women who underwent hysteroscopic assessment for two or more consecutive miscarriages were included in the study.*

Results: *Majority (n=36, 47.4%) of the women belonged to age group 31-35 years with mean age of 31.75 years. Sixty-two women had repeated miscarriages in first trimester (81.6%) and 14 (18.4%) in second trimester of pregnancy. On hysteroscopy, abnormal uterine cavity was found in 30 (39.5%) and normal cavity was in 46 (60.5%) patients. Congenital structural defects (n=24) were mostly septate or sub-septate uterus (n=11) followed by bicornuate uterus (n=8). Among the acquired structural anomalies (n=16), polyps were the commonest (n=8) followed equally by fibroids (n=4) and synechea (n=4). No significant association ($P=0.390^{ns}$) was found between timing and number of miscarriages with endometrial cavity abnormality.*

Conclusions: *The result of our study suggests that nearly 40% had SUD and timing and number of miscarriages in RPL did not correlate with the different types of SUD on hysteroscopy.*

Key words: *miscarriage, repeated pregnancy loss, hysteroscopy, structural uterine defects.*

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INTRODUCTION

A pregnancy loss (miscarriage) is defined as the spontaneous demise of a pregnancy before the fetus reaches viability.[1] There is no general consensus for defining recurrent pregnancy loss (RPL). Classically RPL is defined by the occurrence of three of more miscarriages, consecutive or not, occurring before 20 weeks of gestation, that is, before the age of fetal viability.[2] Royal College of Obstetricians and Gynecologists in their much-acclaimed green-top guideline (published in 2011) defined recurrent miscarriage as the loss of three or more consecutive pregnancies.[3] The guideline on RPL published by European Society of Human Reproduction and Embryology (ESHRE) in 2017 accepted 24 weeks as the defined age of viability and updated ESHRE guideline (published in 2022) states that a diagnosis of can be considered after the loss of two or more pregnancies. It includes both spontaneous pregnancies and those obtained through assisted reproductive technology (ART) but excludes molar and ectopic pregnancies, as well as implantation failures.[4] American College of Obstetrics and Gynecology (ACOG) in their

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Practice Bulletin also defined RPL as two or more miscarriages but recommended thorough physical exam and testing after three repeated miscarriages.[5] So, there is a wide variation in definition of RPL even among guidelines but it is widely accepted that investigations should be started after two consecutive pregnancy losses.

It is a general consensus that RPL occurs in 1% -3% of couples who try to conceive.[1] Causes of RPL may be varied depending on the gestational age. Chromosomal anomalies in the couples or the embryo, maternal thrombophilia, environmental factors, maternal immune dysfunctions, various endocrine disorders and structural uterine defects (SUD) – all can contribute to RPL. In around 50% of women, no cause can be found in either partner or in the embryo, these cases are then called idiopathic RPL.

SUD including congenital malformations and acquired abnormalities like fibroids, polyps and synechiae can play an important role in RPL but their exact prevalence is not known. The prevalence of uterine malformations is higher in women having a history of RPL (13.3%; 95% CI 8.9-20) than in the general/fertile population (5.5%; 95% CI 3.5-8.5).[5] Systematic reviews on anatomical abnormalities of uterus have also reported a higher prevalence of miscarriage in women with congenital uterine malformations compared to controls.[6]

As part of investigation in RPL, different imaging techniques with different potentials and limitations have been used to diagnose congenital and acquired SUDs. According to RCOG, a two-dimensional pelvic ultrasound for initial screening and three-dimensional (3D) pelvic ultrasound, hysteroscopy, sonohysterography or laparoscopy can be advised only in those with abnormal ultrasonography findings.[3] On the other hand, ESHRE recommends a 3D pelvic ultrasound in the initial screening of uterine abnormalities.[4] In contrast, ASRM guideline suggests performing sonohysterogram, a hysterosalpingogram and/or a hysteroscopy for initial assessment.[5]

Despite the variation in the timing, hysteroscopy is advised by different guidelines for evaluation of structural uterine defects in women with RPL. Hysteroscopy is still considered 'gold standard' in the investigation of anatomic abnormalities of uterus as it allows direct, magnified and tridimensional visualization of the interior of the uterus and there is provision of correction of anomalies in same setting, if possible. In this study, we have done diagnostic (and therapeutic, if required) hysteroscopy in women with history of two or more consecutive pregnancy loss. Present study was designed to evaluate the prevalence of SUD in Bangladeshi women with two or more consecutive pregnancy losses in a specialized fertility clinic based on hysteroscopic findings.

METHODS

This cross- sectional study observational was conducted from January 2021 to November 2023 at Farida Clinic and Infertility Management Center, a Dhaka-based tertiary care set-up for infertility management and assisted reproduction. The study population consisted of 76 women who underwent diagnostic hysteroscopy at the center. All of them had history of two or more consecutive pregnancy loss. All the information were recorded in data collection sheet. Prior approval was obtained from the management authority of the center for ethical clearance.

Eighty women who were less of forty years of age with history of at least two consecutive miscarriages were recruited first. Four women with high risk factors like presence of anti-phospholipid syndrome or systemic co-morbidities like diabetes mellitus or hypothyroidism were excluded from the study. Demographic data and clinical history was taken before the women underwent diagnostic and if necessary therapeutic hysteroscopy. All the findings were documented in a predesigned data sheet and reviewed later on. Variables like age, menstrual history and obstetric history, past medical and surgical history and ultrasonography findings were noted.

Hysteroscopy was performed under general anesthesia. Preliminary bimanual vaginal examination was done to confirm the size, mobility and position of the uterus as well as relationship to the adjacent organs. A rigid 0^0 hysteroscope was introduced and 0.9% normal saline was used as distension media. Panoramic view of the endocervical canal, the isthmus, the whole uterine cavity (fundus, corpus, lateral, anterior and posterior walls), cornual regions, tubal ostia and endometrium were recorded and analyzed. Anatomical alterations were noted and categorized into congenital (septate uterus, arcuate and bicornuate uterus) or acquired (polyps, submucosal fibroids and adhesions). Collected data was

analyzed by the research team with the help of Statistical Package for Social Sciences (SPSS) software, version 20 (SPSS Inc, Chicago, Illinois, USA). The quantitative observations were expressed by frequency and percentage and Chi-square test was used for continuous variables. P value < 0.05 was considered statistically significant.

RESULTS

The study population was 76 in number with a mean age of 31.75 years. Majority (36, 47.4%) of women belonged to age group 31-35 years. Forty four (57.9%) patients had two miscarriages, 20 (26.3%) had three miscarriages and 12 (15.8%) had more than three miscarriages at the time of hysteroscopy (Table I). Sixty two (81.6%) patients had miscarriages at first trimester and 14 (18.4%) in second trimester (Table II). At hysteroscopy, majority (n-46, 52.2%) of the women had apparently normal endometrial cavity while 30 women (39.5%) had some structural uterine abnormality (Table I). No significant association between number of miscarriages with endometrial cavity abnormality was revealed in the result (p=0.390) (Table I). Table II also showed no significant association between timing of miscarriages with endometrial cavity (p=0.774). Figure 1 showed the distribution of congenital abnormalities among the study population. Among the congenital structural defects (n=24), septate or sub-septate uterus (n=11) was the commonest variety followed by bicornuate uterus (n=8). Likewise Figure 2 showed the distribution of acquired uterine anomalies (n=16) among which polyps were the commonest (n=8) followed equally by fibroids (n=4) and synechea (n=4).

Table I. Association between endometrial cavity with number of miscarriages (N=76)

Number of miscarriages	Total		Endometrial cavity				P Value
			Normal(n= 46)		Abnormal(n= 30)		
	N	%	n	%	n	%	
Two miscarriages	44	57.9	24	52.2	20	66.7	
Three miscarriages	20	26.3	13	28.3	7	23.3	0.390[ns]
More than three miscarriages	12	15.8	9	19.6	3	10.0	

ns = not significant; p value reached from Chi square test

Table II. Association between endometrial cavity with timing of miscarriages (N=76)

Timing of miscarriages	Total		Endometrial cavity				P Value
			Normal(n= 46)		Abnormal(n=30)		
	n	%	n	%	n	%	
First trimester	62	81.6	38	82.6	24	80.0	0.774[ns]
Second trimester	14	18.4	8	17.4	6	20.0	

ns = not significant; p value reached from Chi square test

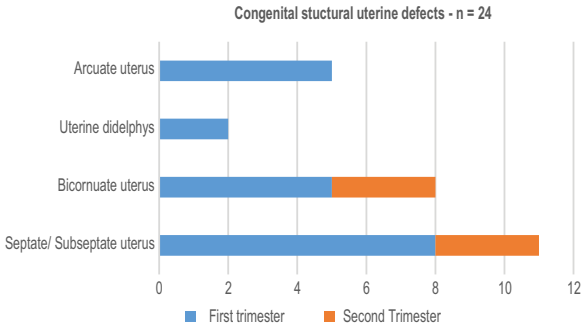

Figure 1. Distribution of the study population by congenital structural uterine defects

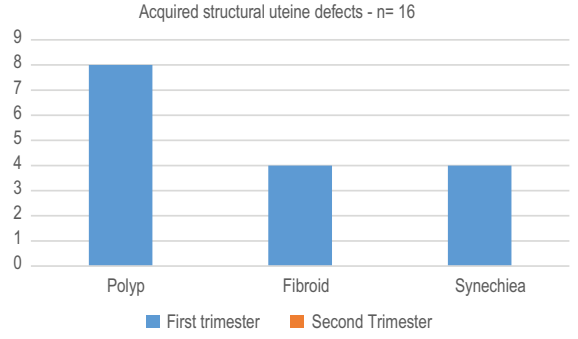

Figure 2. Distribution of the study population by acquired structural uterine defects

DISCUSSION

This cross-sectional observational study was carried out to assess the association of structural anatomical anomalies of the uterus with repeated pregnancy loss among Bangladeshi women. Based on the result of the study, the commonest age for women to present with repeated pregnancy loss was 31 to 35 years (47.4%) followed by 26 to 30 years (32.0 %). According to Bangladesh demographic and health survey (2017)[7], the average age of first marriage of female population in Bangladesh is 16.3 years only. So, it is understandable that most Bangladeshi women may already have history of multiple miscarriages by the time they are between 31 to 35 years old.

This study followed the ESHRE criteria of RPL which included loss of two or more pregnancies. So, a total of 44 patients with history of two and 20 patients with history of three miscarriages were included in the study. Only 12 patients had more than three miscarriages. (Table I)

Regarding the timing of miscarriages, this study revealed 62 women had history of repeated first trimester and 14 women had repeated second trimester miscarriages among the study population (Table II). This study further confirmed that miscarriage is more common during first trimester than second trimester. This study also revealed that neither timing nor number of miscarriages had any positive correlation with the structural uterine abnormalities on hysteroscope. This is in contrast to a similar study by Souza and Schmitz where they a positive correlation between anatomical abnormalities and the number of miscarriages ($r = 0.31$, $P=0.02$).[8]

Nearly two-thirds of patients in this study had normal cavity on hysteroscopy and 39.5% had some form of structural uterine defects. Ventolini and Zhang in a small study of 23 patients in 2004 also reported similar incidence (39.1%) of SUD in their study population with RPL.[9] More recently, a study conducted on 80 patients at Al-Azhar University, Cairo showed that 52.5% of study population had a normal finding which is more than our study result.[10] In contrast, Habib and Mufti in their study (2019) showed a much higher number of (67.5%) abnormal hysteroscopy findings in RPL where only 32.5% patients had normal endometrial cavity.[11] This higher uterine abnormality findings may be explained by the fact that they included patients with three or more miscarriages following the RCOG criteria of repeated pregnancy loss.

Our study also revealed that among the women with abnormal uterine cavity (n=30), 24 women had some form of congenital SUDs and 16 women had some form of acquired SUDs. Among the abnormal group (n=30), ten women had both congenital and acquired SUDs. Elaine *et al* from Brazil also showed in their study that, the RPL group can have various types of SUDs and the incidence of uterine malformation (15.8% vs. 4.6%) endometrial adhesions (12.3% vs. 3.3%) and endometritits (10.5% vs. 3.7%) were more than the control group. They concluded that the frequency of uterine malformations and endometrial disorders can be high in patients with RPL, including those with only two previous miscarriages.[12] But despite the presence of different congenital and structural anomalies in patients with RPL, our study did not find any significant statistical association between number of miscarriages with endometrial cavity abnormality.

Regarding the congenital SUDs, septate/ sub-septate uterus was the commonest type in our study (11 out of 24 patients). This was followed by bicornuate uterus (8 out of 24 patients). Both anomalies were found in both first and second trimester miscarriages. Arcuate uterus was another anomaly found in 5 patients. Uterus didelphys was present in 2 patients only. Ventolini also had similar observations in his studied subjects where the association of septate uterus with RPL was 8.7% which was the commonest among the defects.[9] Habib *et al* also found that septate uterus was the commonest (25%) anomaly in their study.[11] Sayed and Ahmad from Cairo in 2022 reported in their study that congenital anomalies were found in 14 out of 80 cases (17.5%) with arcuate uterus 7 (8.8%) being the commonest followed by septate uterus 2 (2.5%).[10] Brazilian study also showed that congenital malformations were present in 18 out of 114 patients (15.9%), of which 11 cases (9.7%) were a septate/bicornuate uterus.[12] Different other studies also revealed that septate uterus is the congenital malformations most commonly associated with RPL, being found in 6%-16% of cases.[13-15] This correlate with our study and may result from imperfect implantation of the embryo on a poorly vascularized septum. Further study also showed that uterine septum could alter the pre- and post-ovulatory changes of the

endometrium under the influence of estradiol and progesterone, uterine contractility and /or disruption the physiology of endometrial factors like endothelial growth factor.[16] Even though arcuate uterus was found to be common in study result, association of this minor structural anomaly with repeated pregnancy loss is not clear.

In women with acquired anomalies, endometrial polyp was the commonest anomaly. Twenty nine percent women had sub mucous fibroids on hysteroscopy and 23% women had uterine synechiea. All these acquired defects were found only in women with first trimester abortions. Habib *et al* had found 20% patients with submucous fibroids and 12.5% patients with polyps in their study.[11] The Cairo group also reported 20% patients with polyps and 7.5% patients with fibroids in their study population.[10] These studies were in agreement with present study. This is in contrast with study finding of Ventolini where the prevalence of intrauterine adhesions is more than polyp and was present in 1.8% of patients with SUD.[9] So, we can conclude that even though there is a worldwide uniformity regarding congenital SUDs , acquired defects can vary from country to country. Further study is required to find out the cause of variation the acquired causes of RPL.

Conclusion

The prevalence of uterine anomalies in patients with recurrent miscarriages is 39.5% in our study with septate uterus being the most common anomaly. For this reason uterine anomalies should be systematically assessed by hysteroscopy in patients with recurrent miscarriage. We conclude that hysteroscopy should be routinely used as a tool to diagnose the cause of repeated pregnancy loss even though no correlation is found between different types of structural uterine abnormalities with the timing or number of miscarriages in our study.

Limitations of the study

It was conducted in a specialized fertility clinic and consecutive study subjects were selected with relatively small sample size. Further multi-centric study with a larger sample size could be done to determine the validity of the findings of the present study.

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