



## Original article

## Prevalence of hysteroscopic alterations in patients with recurrent pregnancy loss

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## ABSTRACT

**Objective:** To determine the prevalence of uterine malformations and endometrial disorders diagnosed through office hysteroscopy in women with recurrent pregnancy loss (RPL).

**Methods:** Retrospective analysis of medical records of 114 patients referred to a tertiary academic hospital in Belo Horizonte, Brazil, between January 2014 and August 2022, due to a history of two or more miscarriages (RPL group) and 1144 women preparing for in vitro fertilization due to couple infertility (control group). All the participants underwent a diagnostic office hysteroscopy in the proliferative phase of the menstrual cycle. The prevalence of hysteroscopic alterations was compared between the RPL and control groups and between women with two versus three or more miscarriages, using the chi-square test.

**Results:** In comparison with the control group, the RPL group had a higher prevalence of uterine malformations (15.8% vs. 4.6%,  $p < 0.001$ ), endometrial adhesions (12.3% vs. 3.3%,  $p < 0.001$ ) and endometritis (10.5% vs. 3.7%), and a lower prevalence of endometrial polyps (6.1% vs. 14.9%,  $p = 0.01$ ). Congenital malformations were present in 18/114 patients (15.9%), of which 11 cases (9.7%) were a septate/bicornuate uterus. There was no difference between the prevalence of hysteroscopic alterations in patients with two versus three or more miscarriages (35.3% versus 42.8%,  $\chi^2 = 0.395$ ,  $p = 0.529$ ).

**Conclusion:** The frequency of uterine malformations and endometrial disorders can be high in patients with RPL, including those with only two previous miscarriages. This finding supports the investigation of uterine disorders in women with a history of RPL.

## Introduction

Recurrent pregnancy loss (RPL), defined as the loss of two or more pregnancies [1], is a clinical condition that affects 1–2% of women worldwide [2]. A pregnancy loss (miscarriage) is the demise of a pregnancy at a gestational age that is incompatible with neonatal survival, by convention less than 24 weeks gestation [1]. The latest definition of RPL comprehends both spontaneous pregnancies and those obtained through assisted reproductive technology (ART) but excludes molar and ectopic pregnancies, as well as implantation failures [3].

RPL has been associated with chromosomal anomalies in the couples or the embryo, maternal thrombophilias, environmental factors, maternal immune dysfunctions, endocrine disorders, and uterine structural alterations [4–7], but about 50% of the cases remain idiopathic after exhaustive investigation [3]. Uterine structural alterations can be divided into congenital malformations and acquired conditions. The septate uterus is the most common congenital malformation and it is the most

frequently associated with RPL [8,9]. Acquired structural alterations include endometrial polyps, submucosal myomas, and intrauterine adhesions [8].

Uterine factor investigation varies among guidelines, considering the availability and the cost of diagnostic tests in different settings. The Royal College of Obstetricians and Gynaecologists recommends a two-dimensional pelvic ultrasound for initial screening and, in case of abnormal findings, a specific diagnosis can be pursued using three-dimensional (3D) pelvic ultrasound, hysteroscopy, sonohysterography or laparoscopy [9]. The European Society of Human Reproduction and Embryology (ESHRE) recommends a 3D pelvic ultrasound in the initial screening of uterine abnormalities [10], while the last American Society for Reproductive Medicine (ASRM) guideline concludes that the screening of uterine anatomy in the assessment of RPL may include a sonohysterogram, a hysterosalpingogram, and/or a hysteroscopy [2].

Hysteroscopy is considered the gold-standard method for endometrial cavity evaluation and can be performed both for diagnostic and

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therapeutic indications. A hysteroscope is a telescope that is inserted into the uterus via the vagina and cervix to visualize the endometrial cavity. It provides direct visualization of the cavity as well as the tubal ostia, the cervix, and the vagina. Hysteroscopy is one of the best methods for evaluation of the endometrial cavity, since it enables a direct, amplified and tridimensional view of the uterine cavity, endometrium and cervix [1]. It also has the advantage that it can be performed in outpatient clinics, although it is not available in every service.

The prevalence of anatomical uterine alterations in women with RPL varies from 15 to 42% according to different populations previously studied [11–17], and this apparent discrepancy likely reflects not only methodological and conceptual differences between studies but also epidemiological differences between populations. Thus, the purpose of this study was to evaluate the prevalence of uterine anomalies in Brazilian women with two or more consecutive pregnancy losses assisted in a tertiary reference center, based on hysteroscopic findings obtained in their investigation, and to compare the prevalence of uterine anomalies in patients with two versus three or more miscarriages.

## Methods

We did a retrospective analysis of medical records of 114 patients referred to a tertiary academic hospital in Belo Horizonte, Brazil, between January 2014 and August 2022, due to a history of two or more miscarriages (RPL group) and 1144 women preparing for in vitro fertilization (IVF) due to couple infertility (control group). The Project was approved by the Research Ethics Committee of Universidade Federal de Minas Gerais (protocol 58024219.3.0000.5149).

RPL was defined as a history of at least two clinical pregnancies (i.e. confirmed by ultrasound and/or clinical examination) consecutive or not, interrupted spontaneously before 20 weeks gestation. Ectopic pregnancies were not considered. All patients were submitted to the following screening tests: serum thyroid stimulating hormone (TSH), couple's karyotype, lupus anticoagulant antibody, anticardiolipin antibodies (IgM and IgG), anti- $\beta_2$  glycoprotein 1, serum prolactin (if clinical suspicion of hyperprolactinemia) and transvaginal ultrasound.

Diagnostic office hysteroscopy was performed in the follicular phase, preferably between the 7th and the 10th day of the menstrual cycle. In women who presented with amenorrhea, pregnancy was excluded with a serum pregnancy test. Women with any type of vaginal bleeding were rescheduled since the proper visualization of the endometrial cavity could have been impaired. The selected technique was vaginoscopy or touchless hysteroscopy. A rigid hysteroscope of narrow gauge (<4 mm) was introduced into the vaginal introitus without the use of a vaginal speculum. The labia minora were manually closed to contain the distending medium. The cervix was visualized and the hysteroscope was directed through the endocervical canal to the uterine cavity, which was distended with 0.9% saline and a maximal pressure of 70 mmHg. Then, the endocervical canal, the isthmus, the whole uterine cavity (fundus, corpus, lateral, anterior e posterior walls), cornual regions, tubal ostia and endometrium were analyzed.

Anatomical alterations were described and categorized into congenital (septate uterus, arcuate uterus) or acquired (polyps, submucosal fibroids, adhesions and endometritis). Uterine polyps were defined as rounded or oval structures, with a reddish appearance, pedunculated or sessile, soft and friable when touched by the hysteroscope. In contrast, fibroids were identified as firm rounded structures, especially white in color, with superficial vessels. They were classified according to the European Hysteroscopy Society (EHS) system that evaluates the extension of myometrial involvement of the fibroids: Type 0 – completely inside the endometrial cavity; Type I – extends less than 50% into the myometrium; Type II – extends 50% or more into the myometrium [18].

Intrauterine adhesions were defined as tracks of fibrotic tissue formed inside the endometrial cavity. The severity of the disease could vary from thin tissue threads to complete obliteration of the cavity. Mucosal

**Table 1**

Clinical characteristics of the study participants.

	RPL (n = 114)	Control (n = 1144)	p value
Age (years)	33.9 $\pm$ 5.6	35.4 $\pm$ 4.7	0.002
Previous gestations	3.57 $\pm$ 1.63	0.47 $\pm$ 0.79	<0.001
Previous miscarriages	3.08 $\pm$ 1.51	0.29 $\pm$ 0.55	<0.001
Time of pregnancy loss			
Only first trimester	93/114 (82%)	–	
Only second trimester	2/114 (2%)	–	
First and second trimester	19/114 (16%)	–	
Screening tests (altered, %)			
Serum TSH	9/88 (10%)	–	
Serum prolactin	5/71 (7%)	–	
Karyotype	18/89 (20%)	–	
Autoantibodies	3/91 (3%)	–	
Transvaginal ultrasound	43/86 (50%)	180/1144 (16%)	<0.001

**Table 2**

Frequency of hysteroscopic findings.

	RPL (n = 114)	Control (n = 1144)	p value
Uterine malformations	18 (15.8%)	53 (4.6%)	0.0001
Endometrial adhesions	14 (12.3%)	38 (3.3%)	0.0001
Endometrial polyps	7 (6.1%)	170 (14.9%)	0.0110
Submucous fibroids	5 (4.3%)	44 (3.8%)	0.9760
Endometritis	12 (10.5%)	42 (3.7%)	0.0010
Any alteration <sup>a</sup>	45 (39.5%)	337 (29.5%)	0.0266

<sup>a</sup> This number is smaller than the sum of specific alterations because some patients had more than one diagnosis.

adhesions were the same color as the endometrium and fragile while fibrotic adhesions were pale and strong. The diagnosis of chronic endometritis was based of observational findings such as focal or diffuse endometrial hyperemia, mucosal edema and micropolyps (<1 mm) [19].

## Statistical analysis

Continuous data were reported as mean  $\pm$  SD and range (minimum–maximum). The categorical variables were described as percentages and the chi-square test or Fisher's exact test was performed. Two-sided  $p < 0.05$  was considered statistically significant.

Forty-nine subjects in each arm of the study were needed to achieve a power of 80% with an alpha = 0.05 to detect an increase of 25% in the frequency of abnormal hysteroscopic findings, according to previous studies [20].

## Results

As shown in Table 1, the RPL group included 114 participants with a mean age of 33.9  $\pm$  5.6 years (range 20–46 years). The mean number of previous losses was 3.08  $\pm$  1.51 (range 2–11) and the number of previous pregnancies varied from two to eleven (mean 3.57  $\pm$  1.63). Seventy-two patients were nulliparous. Most losses occurred in the first trimester (Table 1). The control group had a mean age of 35.4  $\pm$  4.7 years (range 19–49 years) and the mean number of previous miscarriages was 0.29  $\pm$  0.55 (Table 1).

The prevalence of uterine alterations detected in office hysteroscopy is described in Table 2. In total, uterine alterations were found in 39% of the women with RPL. Congenital anomalies were present in 18/114 RPL patients (15.8%), of which 11 cases (9.6%) were a septate or a bicornuate uterus. Twenty-six patients presented isolated acquired abnormalities: 14 patients (12.3%) had intrauterine adhesions, seven (6.1%) had endometrial polyps, five (4.4%) had submucous fibroids and 12 (10.5%) had hysteroscopic signs of chronic endometritis. In comparison

**Table 3**Prevalence of hysteroscopic findings in the RPL group ( $n = 114$ ) according to the reproductive history.

	Frequency of hysteroscopic alterations	$\chi^2$	$p$ value
<i>Previous losses</i>			
Two ( $n = 51$ )	18 (35.3%)	0.395	0.529
Three or more ( $n = 63$ )	27 (42.9%)		
<i>Trimester of previous losses</i>			
Only first ( $n = 93$ )	35 (37.6%)	0.358	0.549
First and/or second ( $n = 21$ )	10 (47.6%)		

with the control group, the RPL group had a higher prevalence of uterine malformations, endometrial adhesions and endometritis, and a lower prevalence of endometrial polyps (Table 2).

As shown in Table 3, there was no difference between the prevalence of hysteroscopic alterations in patients with two versus three or more miscarriages (35.3% versus 42.8%,  $\chi^2 = 0.395$ ,  $p = 0.529$ ) or according to the gestational trimester of the pregnancy losses (Table 3).

## Discussion

The presence of alterations in the genetic and metabolic screening of couples with RPL does not rule out the possibility of an associated uterine factor, therefore uterine evaluation is essential in all patients with RPL [11,21]. Hysteroscopy is considered gold-standard in the diagnosis of uterine cavity malformations and acquired anomalies [14].

The prevalence of uterine anatomical anomalies in patients with RPL is highly variable depending on the studied population. Our results are in line with previous studies based on hysteroscopic screening, in which about 40% of the patients had uterine alterations [11,15]. This prevalence is twice as high as that observed when the patients were screened with three-dimensional sonohysterography, followed by a hysteroscopy only in cases where the first test showed some anomaly [8].

In the present study, uterine malformations were found in patients with RPL three times more frequently than in the control group composed by women preparing to IVF, confirming previous studies that also suggested an association between RPL and uterine congenital anomalies [11,14,15]. The prevalence of submucosal fibroids in our study was 4.3%, which matches a systematic review where the prevalence of submucosal and cavity-distorting myomas in women with two or more pregnancy losses was 4.1% [22]. Endometrial polyps were found in 6.1% of our patients with RPL, which is similar to previous reports, although there is no clear evidence that this condition increases the risk of repeated losses [11–17]. We also detected endometrial adhesions in 12.3% of the RPL group, which coincides with previous studies [14] and contrasts with the 3.3% prevalence of this hysteroscopic finding in our control group.

The hysteroscopic findings did not vary comparing women with two versus women with three or more losses, which corroborates previous studies performed in other populations [14,17]. Weiss et al. found that 22% of patients with two consecutive miscarriages had Müllerian anomalies and 12% had acquired anomalies, whereas patients with three or more miscarriages had a 17% prevalence of Müllerian anomalies and 11% prevalence of acquired anomalies [17].

Chronic endometritis is defined as chronic inflammation of endometrial lines. Patients with chronic endometritis usually are asymptomatic, but they may present with symptoms such as pelvic pain, dyspareunia, abnormal vaginal bleeding or vaginal discharge [23]. In our study, the prevalence of chronic endometritis in women with RPL was 10.5%, while in other retrospective studies it varied from 13% to 56% [24,25]. Although the gold-standard diagnosis of endometritis demands the histological identification of plasmatic cells in the endometrial stroma through immunohistochemical evaluation [23], the hysteroscopic diagnosis also has a reasonable sensitivity and specificity when endometrial biopsy is not promptly available [26,27].

The main limitation of this study is the retrospective design, which increases the possibility of imprecision and incompleteness of the data; this was minimized using objective information registered in standard forms by the attending physicians throughout the study period. Another limitation is the participant selection, which was all performed in a tertiary hospital center and therefore does not represent the general population or the epidemiological scenario of primary care.

In conclusion, the frequency of uterine malformations and endometrial disorders can be high in patients with RPL, including those with only two previous miscarriages. This finding supports the investigation of uterine disorders in women with a history of RPL, due to the possible role of anatomical abnormalities in pregnancy losses and the availability of treatments to repair most of these conditions.

## Authors' contributions

Conceptualization: ECFO  
 Methodology: ECFO, IKC, FMR  
 Investigation: ECFO, BCQ, CSM  
 Formal analysis: FMR  
 Data curation: ECFO, CSM  
 Writing – original draft: ECFO  
 Writing – review & editing: FMR  
 Supervision: IKC, FMR

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## Conflict of interest

The authors report no conflicts of interest.

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