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Original research article

Prevalence of Mullerian Anomaly among infertile patients

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Abstract

Background: To evaluate the prevalence of Müllerian anomalies (MAs) among infertile women came for fertility treatments (intrauterine insemination or IVF (In vitro fertilization) cycles. Aim: To calculate the prevalence of mullerian anomaly and each subtype among infertile women. Methods: This is a retrospective observational study based upon a cohort of infertile women, who underwent hysteroscopy and laparoscopy as part of the basic infertility workup from 2018 to 2019, at department of Reproductive Medicine in IGIMS, Patna. Results: A total of 160 women were included in the study. The prevalence of mullerian anomaly was 8.13% (n=13). The prevalence of different subtypes among women with mullerian anomaly were: septate uterus 53.85% (n = 7), arcuate uterus 23.08% (n = 3), bicornuate uterus 7.69% (n = 1), unicornuate uterus 7.69 % (n = 1) and didelphys uterus 7.69% (n = 1). We did not find any case of uterine hypoplasia/agenesis or unclassified type. Women with mullerian anomaly who achieved pregnancy were: 38.46% (n = 5). Highest pregnancy rate was associated with septate uterus after hysteroscopic correction, at 42.86% (3/7). Conclusions: The prevalence of mullerian anomaly among infertile women may be considered as low. The most common mullerian anomaly is septate uterus in women with infertility.

Keywords: Müllerian anomalies; intrauterine insemination;In vitro fertilization; infertility; prevalence

1. Introduction

Normal female reproductive tract development involves differentiation, migration, fusion and canalization of the Müllerian duct [1,2]. Alterations in the embryonic development of the Müllerian ducts results in mullerian anomalies , potentially affecting the morphology of the uterus, fallopian tubes, cervix and vagina. Sometimes, MAs may be associated with ovarian, urinary tract, skeletal, or other organ anomalies [3–7]. Previously attempts were taken at systematically classifying MAs, first in 1907; and later, many other classifications of MAs were proposed [8]. In 1979, based on female genital tract development, Buttram and Gibbons developed a classification system [9]. In 1988, this classification was reviewed and modified by The American Society of Reproductive Medicine (ASRM), categorizing seven different MA types [10]. ASMR classification of MAs is focusing on uterine anomalies in relation with fertility and is well established, due to its overall simplicity [3,4]. However, in 2004, based on the embryologic origin of the different genital tract organs, , another classification system was proposed [11,12]. MAs are associated with higher risk of obstetric complication, including recurrent pregnancy loss (RPL), preterm delivery, and higher perinatal morbidity

and mortality [13–15]. Any causal relationship has not yet been demonstrated between role of MAs and the pathophysiology of female infertility [16,17]. Sometimes, MAs are diagnosed accidentally in multiparous women during routine investigations [18]. It is currently difficult to estimate the real prevalence of MAs because of the rarity of MAs, the lack of a universally accepted classification system, and the different diagnostic strategies in common use (with variable diagnostic accuracy) [19–22]. A recent systematic review reported a prevalence of 5.5% in the general population, while about 8% among infertile women. The limitations of this review, by Chan et al. [19], were related to the applied diagnostic tests, the substantial heterogeneity of the patients, and the classification systems used. Thus, we aimed to determine the prevalence of MAs and its subtypes (classified according to the ASRM classification) in a consecutive cohort of infertile women who underwent diagnostic hysteroscopy and laparoscopy as a basic infertility workup. Secondarily, we also evaluated the reproductive outcomes of these patients during the study period.

2. Materials and Methods

2.1. Study Design and Ethical Approval : This retrospective observational study was performed at Department of Reproductive Medicine, in IGIMS,Patna. All women who underwent a hysteroscopy and laparoscopy during their infertility evaluation at our infertility clinic between 2018 and 2019 were included. Data were obtained from clinical records, excluding incomplete files. Ethical approval was taken from Institutional Ethical Committee.

2.2. Study Objectives

1) To assess the prevalence of MAs and its subtypes in the study cohort.
2) To evaluate the percentage of women with MAs who achieved pregnancy. 2.3.

Patients and Procedures

All subfertile patients were enrolled, defined as the incapability to achieve a pregnancy after12 months of sexual intercourse without contraceptives [23]. Inclusion criteria were subfertile woman having submitted to hysteroscopy and laparoscopy as basic infertility workup. Exclusion criteria were suspected MAs by means of sonohysterography (SHG) only, without hysteroscopy/laparoscopy, and incomplete medical records.

All women underwent following tests: fasting glucose, thyroid function test, hormonal tests (LH (Luteinizing hormone), FSH (Follicle-stimulating hormone), estradiol, prolactin), vaginal culture, Chlamydia trachomatis detection by PCR, urea plasma urealyticum and mycoplasma hominis culture, endovaginal ultrasound, followed by a hysterosalpingography (HSG). In some cases, an SHG was performed. Data were collected from medical records about general patient features and information on patients' follow-up. We systematically recorded the following variables: Age, weight, height and body mass

index (BMI) calculated using the equation: weight (kg)/height (m2), type of infertility, number of previous gestations and miscarriages. Pregnancy was defined as a positive pregnancy test, plus the identification of a gestational sac at the ultrasound examination and/or the presence of an embryo with heartbeat. Immediately after diagnostic workup, hysteroscopic correction was performed with a laparoscopy operative guide, using hysteroscopic scissors, monopolar energy and/or bipolar energy (VersaPoint

system. Gynecare; Ethicon Inc., NJ, USA) [5,10,24]. Many women spontaneously conceived after correction. All the women were followed up until January 2019.

2.4. Definition and Diagnosis of Müllerian Anomalies

MAs were defined as congenital anomalies of the Müllerian duct, affecting uterus, tubes, cervix and/or vaginal morphology [1]. Reference standard for diagnosis was hysteroscopy

and laparoscopy, performed in the operating room under general and were differentiated according to ASRM classification [10].

2.5. Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences Software (SPSS V.15, Chicago, IL, USA). Continuous variables were expressed as mean _ standard deviation, and categorical variables as absolute frequencies and percentages, according to data distribution. Prevalence was calculated with a 95% confidence interval.

3. Results

A total of 160 subfertile women were submitted for hysteroscopy and laparoscopy between 2018 to 2019. Out of 160, 13 women (8.13%) were diagnosed with MA. The majority of patients with MA were having primary infertility (n = 9, 69.23%). Table 1 shows the general characteristics of women with a diagnosis of MA.

Table 1: Characteristics of Subfertile women with Müllerian anomalies.

Characteristics	**n = 13**
Age (years)	27.9 ± 4.3
Weight (kg)	65.4 ± 9.7
Height (m)	1.45 ± 0.7
BMI (kg/m2)	26.7 ± 3.7
Primary infertility	69.23% (n=9)
Secondary infertility	30.77% (n=4)

MA: Müllerian Anomalies; BMI: body mass index. Data are expressed as mean ± SD or absolute frequency (%).

Septate uterus was the most prevalent type of MA (n = 7, 53.85%). The other MA types diagnosed were arcuate uterus (n = 3, 23.08%), bicornuate uterus (n = 1, 7.69%), unicornuate uterus (n = 1, 7.69%), didelphys uterus (n = 1, 7.69%). We did not find any case of uterine hypoplasia/agenesis, and unclassifiable type according to the ASRM system.

Hysteroscopic corrections (metroplasty) were performed in 8 women (61.54%) using hysteroscopic scissors. Out of 13 women diagnosed with MA, 30.77% (n = 4) achieved pregnancy within 1 year. The MA types associated with higher pregnancy rates were septate uterus (42.86%), and arcuate (33.3%) uterus.

4. Discussion

In the present study, the MA prevalence was found to be 8.13%. In the present study, hysteroscopy and laparoscopy were used for diagnosing MA, currently considered the gold standard for the diagnosis of MAs [15]. Previously many studies had been performed to know the prevalence of MA among subfertile women and general population. Raga et al. found 4% uterine malformations in their study population based on evaluation of the morphology of uterus by hysterosalpingography (HSG) and laparoscopy/laparotomy. Incidences of MA were higher in infertile women (6.3%), compared to fertile (3.8%) and sterile (2.4%) ones [26]. However, Acien et al. reported a considerably higher prevalence of MA (16%) in the Spanish population based on transvaginal ultrasound and HSG, and only 28% of diagnoses were confirmed by laparoscopy/laparotomy, potentially increasing the rate of false positive diagnoses. [25]. The sensitivity of different diagnostic methods were considered in a systematic review by Saravelos et al.. Studies were grouped into three classes: Class Ia

hysteroscopy and laparoscopy, Ib only hysteroscopy, II; HSG or 2D ultrasound and III; magnetic resonance imaging (MRI) and physical examination during pregnancy or delivery. The prevalence of MA was reported to be 7.3% (95% CI 6.7–7.9) in women with infertility of class Ia and Ib; however, the prevalence of MA in class II was 10.8% [20].

In the present study, the most frequent MAs in women with subfertility were septate (53.85%), arcuate (23.08%) and bicornuate (7.69%) uterus. Raga et al. found that the most frequent MA were septate (33.6%), arcuate (32.8%) and bicornuate (20.3%) uterus [26]; Saravelos et al.also reported the same MA in a proportion of 4:2:1, respectively [20]. The review by Chan et al. reported canalization defects (including septate and subseptate uterus) as the most common MA, with a prevalence in the general population of 2.3% (95% CI 1.8–2.9) but no significantly higher MA rates in infertile women (3.0%; 95% CI 1.3–6.7; p = 0.422) were reported. However, the prevalence of MAs was higher in women with an RPL and infertility (15.4%; 95% CI 12.5–19.0) and RPL history (5.3%; 95% CI 1.7–16.8; p = 0.021). The second and third most common types of MA among infertile women were arcuate uterus (1.8%; 95% CI 0.8–4.1) and bicornuate uterus (1.1%; 95% CI 0.6–2.0), respectively [19]. These results are similar to those of our study.

The association between RPL and MAs is well established [27,28]; however, its association with infertility is controversial [29,30]. In a study by Chan et al. no difference in pregnancy rates were found when comparing women with MAs and women with normal uteri (RR: 0.87 95% CI 0.68–1.11; p = 0.25) [16]. The meta-analysis by Venetis et al. reported that septate uterus was the only MA associated with a significant decrease in the natural conception rate (RR: 0.86; 95% CI; 0.77–0.96) [31]. However, in the absence of a control group, no direct inferences between MAs and infertility can be drawn but the prevalence of septate uterus in the present study was considerably higher, compared to other data in the general population, potentially suggesting an association with infertility. In the present study, 30.77% of women with MAs and subfertility achieved pregnancy, with a higher percentage among women with septate uterus (42.86%). It should be mentioned that these women underwent a septum resection by hysteroscopy before achieving pregnancy. In 2013, Valle et al. reported a pregnancy rate of 67.8% (95% CI 62.5–72.8), with a live birth rate of 53.5% (95% CI 43.4–57.1) after septum resection in women with infertility [32]. Pregnancy rates in women who underwent ART were found to be similar in women with an arcuate uterus (54.5%), major uterine anomalies (70%) and normal uterus (43.4%) in a study by Jayaprakasan et al. [33]. In the present study, the pregnancy rate was found to be lower than in previous studies. The strengths of our study are the use of laparoscopy and hysteroscopy in all patients and the homogeneity of the study population (i.e., only patients with a diagnosis of subfertility**.**

Conclusions

Based on hysteroscopy and laparoscopy, we found prevalence of MAs to be 8.13% among subfertile patients. This systematic review highlights the potential clinical importance of mullerian anomalies for the reproductive performance of women. As most of the available studies are retrospective and do not adequately control for potential confounders, there is significant gap. Thus, well-designed prospective studies are needed to assess these associations with more accuracy. Also, the role of hysteroscopic removal of a uterine septum in improving reproductive outcome can be properly assessed only through a large randomized controlled trial. Currently, the best available evidence suggests that the presence of certain types of MA might be associated with a detrimental effect on the probability of pregnancy achievement, spontaneous abortion and on the obstetric outcome of each pregnancy. Furthermore, hysteroscopic removal of a septum seems to reduce the probability of a

spontaneous abortion. Thus these findings should be considered when deciding on the optimal management of patients with MA.

Conflicts of Interest: The authors declare no conflict of interest.

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