ISSN 2795-1952 | eISSN 2976-1107
DOI: https://doi.org/10.3126/mjmms.v4i7.71233

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ORIGINAL RESEARCH Open Access

Mullerian Anomalies and Reproductive Performance among Infertile Women in Nepal

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Received: 23 January 2024
Revised: 03 March 2024
Accepted:11 April 2024

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Funding details: Self

Citation:
Pandey K, Giri M, Rijal B, Shahi A. Mullerian Anomalies and Reproductive Performances among Infertile Women in Nepal. MedS. J. Med. Sci.2024;4(7):04-09

Abstract:

Introduction: On average, one in five couples struggle with infertility, which is one of the biggest public health issues in the world. A congenital abnormality is too common for uterine abnormalities. Female children grow two distinct uteri during the time they develop inside the womb, which melds together before birth. Studying Mullerian abnormalities and reproductive performance in Nepalese infertile women was one of the study goals.

Materials and Methods: A cross-sectional study design was used to evaluate Mullerian duct anomaly among infertile women. The study was conducted on infertile women who were receiving services from the infertility clinic of the Hospital for Advanced Medicine and Surgery [HAMS], Kathmandu, Nepal, during the year 2019–2020 AD. The study population included reproductive-aged women [aged 18–40 years] who had primary and secondary infertility. A hospital patient registry book was used to obtain the relevant information for the purpose of the study. An approval was obtained from the hosting hospital to proceed with the study. The "ASRM Mullerian Anomalies Classification 2021" was adopted for the classification of anomalies among women.

Results: A total of 300 participants were included, among whom 61% [n = 183] had primary infertility and 39% [n = 117] had secondary infertility. The study revealed that 4.67% [n = 14] of pregnancies ended in miscarriage, 16.33% [n = 49] in preterm labor, 50.66% [n = 152] in normal spontaneous delivery [NSD], 27.67% [n = 83] in lower segment cesarean section [LSCS], and 0.7% [n = 2] in intrauterine fetal death [IUFD]. The current study attempted to identify the following methods of achieving pregnancy: spontaneous ovulation, 15% [n = 45]; ovulation induction, 54% [n = 162]; intrauterine insemination, 15% [n = 47]; IVF/ICSI, 14% [n = 42]; and not conceiving, 1.3% [n = 4].

Conclusions: The present study showed that primary infertility affected 61% [n = 183] of participants, whereas secondary infertility affected 39% [n = 117]. A complete picture of Mullerian abnormalities cannot be drawn from the few studies available here; therefore, well-designed prospective studies are needed. Despite the fact that infertility has a medical basis, infertile women are nonetheless victims of all aspects of their social and personal lives in contemporary society in Nepal. To change the KAP among people in Nepal regarding infertility, BCC must be addressed.

Keywords
Infertility, Mullerian duct anomaly, Pregnancy outcome, Uterine malformation

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INTRODUCTION

The first representative of the female reproductive system is the uterine duct. Hundreds of years ago, in the 1800s, Cruveilhier and Von Rokitansky coined the phrase "uterine dysfunction," which was subsequently the subject of numerous studies. Differentiation, migration, fusion, and canalization of the Müllerian duct are distinctive features of the complex and particular processes that make up normal female reproductive tract development. The aberrant development of Mullerian duct[s] during embryogenesis prevents the development of a normal uterus, resulting in uterine malformation, which is a female genital tract abnormality. Uterine malformations are sometimes referred to as Mullerian anomalies (MAs). The term 'septate uterus/uterine septum' uterus with a single uterine fundus and with a uterine cavity divided into two parts without measurable criteria of deformity degree are also considered malformations of the uterus [1].

Uterine malformations can occur due to birth defects. During the development period inside the womb, female infants develop two separate halves of their uterus, which merge together before birth. Sometimes two halves fail to merge completely because a woman may be born with a malformed uterus. Uterine malformations make up a diverse group of congenital anomalies that can result from various alterations in the normal development of the Mullerian ducts [2]. The common types of malformation include an absent uterus, an accurate uterus, a bicornuate uterus, a septated uterus, a didelphys uterus, a unicornet uterus, etc. [2].

The etiologies of uterine malformations are still unclear, although they could be multifactorial and composed of genetic and environmental factors. Studies have linked uterine anomalies to abnormalities in gene expression. Several genes, such as Pax, Lim1, Emx2, Wnt4, and Wnt9b, are involved in the development of Mullerian ducts during morphogenesis. Along with Wnt7a, a subset of homeobox genes regulates the differentiation of Müllerian ducts [3]. Many studies have suggested that adverse reproductive outcomes that are associated with septate uteri include infertility, pregnancy loss, and poor obstetrical outcomes, such as malpresentation and preterm delivery. However, many women with uterine septa do not experience any reproductive consequences. Unsuspected uterine malformations may present as impaired intrauterine fetal growth due to abnormal placentation or abnormal fetal positioning related to mechanical factors in the shape of the uterine cavity, often resulting in an increased rate of early pregnancy loss. The diagnosis of uterine malformations is crucial for determining the association between miscarriage and infertility [4]. Malformations of the uterus negatively affect the reproductive performance of the uterus, leading to an increased incidence of abortion and preterm delivery, especially in women with unicornuate, bicornuate, didelphys or septate uteruses [2]. The prevalence of uterine malformation in the general population is estimated to be 6.7%, which is slightly greater in the population with infertility and significantly greater in the population of women with a history of recurrent miscarriages [2]. Moreover, uterine malformation tends to negatively impact full-term pregnancy. A study mentioned that approximately 1 in 4 women who had recurring miscarriages or who delivered prematurely had a uterine malformation [2]. Hysterosalpingography and transvaginal ultrasonography have been utilized to evaluate the pelvis and upper genital organs during nonsurgical pelvic and genital examinations. Hysterosalpingography is the initial and most popular method used to examine these diseases (HSGs).

The diagnostic strategy for the pelvic cavity has been dramatically revolutionized by transvaginal sonography (TVS) [5]. Infertility is a public health problem worldwide and affects an average of approximately one in five couples. The prevalence of Mullerian malformation in women with a history of miscarriage is 13.3%, and miscarriage is associated with infertility 24.5%; 5.5% of the general population has a uterine anomaly diagnosed by an optimal test globally [6]. However, very few studies have evaluated uterine malfunction to determine the accuracy of uterine malformation problems and its consequences for reproductive preformation. The true prevalence of congenital uterine anomalies is difficult to assess because there are no universally agreed upon standardized classification systems or best diagnostic techniques. Diagnoses of uterine anomalies are difficult because many cases are undetected because of the interest and awareness of the physician. Reproductive malfunction depends on each malformation type and recurrence in successive pregnancies, and the proposed corrective measures are not uniform.

Because of the widespread gender discrimination in Nepal, people with Mullerian malformations face severe societal stigma. More frequently than not, Mullerian anomalies in women result in social stigma. Compared to the average household's income, the cost of anomaly correction is also fairly high [7]. Each person has a unique presentation of Mullerian duct anomalies. The ability and willingness of the doctor, as well as the available technology, determine the diagnosis and treatment in various and individual ways. In a similar vein, it is crucial to consider the patient party's decision

for management control, which is influenced by their awareness and socioeconomic status [7]. In impoverished nations such as Nepal, women's status frequently depends on their ability to reproduce. If they fail to do so for any reason, they will experience social and cultural consequences. According to WHO statistics, primary and secondary infertility affect more than 180 million couples in developing nations. Infertility issues affect 132 out of 1784 women in the reproductive age range, or 7.4%, according to a survey performed in eight districts of Nepal [8]. Due to the limited or complete lack of studies in Nepal, it is challenging to estimate the burden of Mullerian duct anomalies. Most likely, for the context of Nepal, this is the first study with the aim of examining the various subtypes of Mullerian duct anomalies. The study also outlined the traits of women who were infertile. The study's conclusions serve as compelling justification for the creation of a case management strategy and for the regulation of the early identification and elimination of earlier stages of unneeded burden.

METHODS AND MATERIALS

Study design and setting

A retrospective cross-sectional study design was used to evaluate the reproductive performance of infertile women with uterine malformations. The study was conducted between 2019 to 2020 with a cohort of women who had undergone hysterectomy and laparoscopy as a part of the initial infertility workshop using a retrospective observational technique at Hospital for Advanced Medicine and Surgery (HAMS), Kathmandu, Nepal.

Participant, sample size, and sampling technique

The reproductive aged group of fertile as well as infertile (primary and secondary both) women (18-40 years) who had delivered their child at HAMS without hypoplastic uterus or Mayer-Rokitansky-Kuster-Hauser syndrome were the participants of the study. The sample size was determined by using an estimation sample size calculation formula for the finite population with 95% confidence interval. The calculated sample size for the study was 300. The registry book of the hospital from the infertility clinic for the years 2019–2020 was used to obtain a sampling frame where 1200 patients who met the inclusion criteria for the study were recorded. Among the 1200 patients, 300 were included in the study.

Data collection procedure and study variables

The "ASRM Mullerian Anomalies Classification 2021" is widely practiced in Nepal. There are nine categories of classification, which is convenient in the context of Nepal. The tools were developed by adopting this classification. The dissertation supervisor closely supervised the tool's development, and changes were made based on the supervisor's feedback [7]. The data were gathered using a closed-ended checklist. Information was collected in accordance with the variables listed on the checklist using the hospital's registration book from the infertility clinic for the years 2019–2020. The researcher herself cross-checking to maintain the quality of the data.

Statistical analysis and data management

The information from the checklist was entered into the IBM Statistical Package for Social Sciences (SPSS) version 27 software. Continuous variables are expressed as the mean ± standard deviation, and categorical variables are expressed as absolute frequencies and percentages according to the data distribution. Prevalence was calculated with a 95% confidence interval.

Ethical Consideration

For the purpose of the study, ethical review board (ERB) approval was obtained from the hosting hospital. In addition, permission from the gynecology and administration departments of the hospital was obtained to provide consent.

RESULTS

This descriptive cross-sectional study included 300 participants. Different variables were used to study Mullerian anomalies in Nepal among infertile women

Table 1| Sociodemographic information of the patient (n=300)

Characteristics	Mean (SD)	Min-Max
Age (in years)	30.26 (4.93)	19-44
Weight (in kg)	85.20 (9.78)	40-152
Height (in cm)	158 (8.02)	138-262
Address	**Frequency**	**Percent**
Province No. 1	26	8.70
Province No. 2	32	10.70
Bagmati Province	107	35.70
Gandaki Province	45	15.00
Lumbini Province	27	9.00
Karnali Province	33	11.00
Sudurpashhim Province	30	10.00
Marital Status		
Married	298	99.30
Single	2	0.70
Year of Experience		
Less than 5 years	136	45.30
6-10 years	110	36.70
11-15 years	43	14.30
More than 16 years	11	3.70
Occupation		
Housewife	120	40.00
Self employed	113	37.70
Business	44	14.70
Service/Job	18	6.00
Other	5	1.70

Table 2|Clinical information (n = 300)

Characteristics	Frequency	Percent
Type of infertility		
Primary infertility	183	61.00
Secondary infertility	117	39.00
Uterine anomaly		
Normal uterus	66	22.00
Dysmorphic uterus	60	20.00
Septate uterus	112	37.30
Dysfused uterus (including dysfused 'septate')	28	9.30
Unilaterally formed uterus	26	8.70
Aplastic/dysplastic	4	1.30
Unclassified malformations	4	1.30
Cervical anomaly		
Normal cervix	226	75.30
Septate cervix	54	18.00
Double 'normal' cervix	13	4.30
Unilateral cervical aplasia	1	0.30
Cervical aplasia	6	2.00
Vaginal anomaly		
Normal vagina	227	75.70
Longitudinal nonobstructing vaginal septum	49	16.30
Longitudinal obstructing vaginal septum	18	6.00
Transverse vaginal septum and/or imperforate hymen	2	0.70
Vaginal aplasia	4	1.30

aged 18–40 years. The following tables try to describe the results of the study. Table 1 shows the sociodemographic characteristics of the subjects included in the study. According to the table, the average age of the participants was 30.26 years, with a minimum age of 19 years and a maximum age of 44 years. Similarly, the average weight and height of the participants were 85.2 kg and 158 cm, respectively. According to the above table, the majority of service takers were from Bagmati Province (35.7%, n = 107), followed by Gandaki Province (15.7%, n = 45), Karnali Province (11%, n = 33), and Province No. 1 (8.7%, n = 26). Furthermore, 45.3% (n = 136) of the participants had experienced infertility for less than 5 years, 36.7% (n = 110) had experienced infertility for 5-10 years, 14.3% (n = 43) had experienced infertility for 10-15 years, and 3.7% (n = 11) had experienced infertility more than 15 years. According to the study, the majority of service takers were housewives: 40% (n = 120), 37% (n = 113) were self-employed, 14.7% (n = 44) were involved in business, and 6% (n = 18) were involved in service or job activities, with only a small number of participants (1.7%, n = 5) engaged in other occupations. Table 2 presents clinically relevant information about the study subjects. According to the table, 61% (n = 183) had primary infertility, while 39% (n =117) had secondary infertility. The table shows that 22% (n = 66) had a normal uterus, 20% (n = 60) had a dysmorphic uterus, 37.3% (n = 112) had a septate uterus, 9.3% (n = 28) had a dysfused uterus (including a dysfused "septate" uterus), 8.7% (n = 26) had a unilaterally formed uterus, 1.3% (n = 4) had aplastic or dysplastic uterus, and 1.3% (n = 4) had unclassified malformations. As shown in the table 2, 75% (n = 226) of the women had a normal cervix, 18% (n = 54) had a septate cervix, 4.3% (n = 13) had a double "normal" cervix, 0.3% (n = 1) had unilateral cervical aplasia, and 2% (n = 6) had cervical aplasia. Similarly, the study attempted to

Table 3| Outcome of the pregnancy-related information

Characteristics	Frequency	Percent
Methods used to achieve pregnancy		
Spontaneous	45	15.0
Ovulation Induction	162	54.0
Intrauterine Insemination	47	15.7
IVF/ICSI	42	14.0
Not conceived	4	1.3
Outcome of the pregnancy		
Miscarriage	14	4.7
Preterm labor	49	16.2
Normal Spontaneous Delivery (NSD)	152	50.7
Lower Segment Caesarian Section (LSCS)	83	27.7
Intrauterine Fetal Death IUFD	2	0.7
Ectopic Pregnancy	0	0.0

classify vaginal anomalies as follows: 75.7% (n = 227) had a normal vagina, 16.3% (n = 49) had a longitudinal non-obstructing vaginal septum, 6% (n = 18) had a longitudinally obstructing vaginal septum, 0.7% (n = 2) had a transverse vaginal septum and/or imperforate hymen, and 1.3% (n = 4) had vaginal aplasia.

Table 3 shows the pregnancy-related outcomes of the participants in the study. According to the methods listed in Table 3, 15% of the participants (n = 45) became spontaneously pregnant. Similarly, 54% (n = 162) of the participants used ovulation induction methods, 15.70% (n = 47) used intrauterine insemination techniques, 14% (n = 42) used IVF/ICSI, and 1.3% (n = 4) were unable to conceive. Similarly, the following table was used to determine the pregnancy outcome: 4.67% (n = 14) had a miscarriage, 16.33% (n = 49) had experienced preterm labor, 50.66% (n = 152) had a normal spontaneous delivery (NSD), 27.67% (n = 83) had a lower segment cesarean section (LSCS), and 0.80% (n = 2) had intrauterine fetal death (IUFD). The study revealed that there was no effect of ectopic pregnancy.

DISCUSSION

This study investigated the reproductive performance status of infertile women with Mullerian malformation in Nepal. The results of the study showed that 61% (n = 183) had primary infertility and 39% (n = 117) had secondary infertility. The study showed that the role of hysteroscopic removal of Mullerian anomalies in improving the reproductive outcomes of pregnant patients was as follows: 4.67% (n = 14) ended in miscarriage, 16.33% (n = 49) in preterm labor, 50.66% (n = 152) in normal spontaneous delivery (NSD), 27.67% (n = 83) in lower segment cesarean section (LSCS), and 0.7% (n = 2) in intrauterine fetal death (IUFD); moreover, the study revealed that there were no effects of ectopic pregnancy. However, hysterosalpingograms (HSGs), laparoscopy, and 3D ultrasound are widely used to diagnose anomalies. Similarly, the study showed that the following methods were used to achieve pregnancy: spontaneous ovulation, 15% (n = 45); ovulation induction, 54% (n = 162); intrauterine insemination, 15% (n = 47); IVF/ICSI, 14% (n = 42); and not conceiving, 1.3% (n = 4). Nepal is a nation that is still developing. Couples experience tragedy when they are unable to have children, feeling a sense of loss, failure, or marginalization due to societal problems. Research has demonstrated that for many people, infertility can be a severe experience with considerable negative effects on their social and psychological well-being, leading to a serious life crisis. In some parts of Nepal, infertile women feel betrayed because they are married and always see themselves as inferior in front of others. Nevertheless, in some parts of Nepalese society, husbands and in-laws made it difficult for women to live together if they were diagnosed with infertility; they had two options: either accept torture and violence or leave their husband's house. However, women cannot leave their husbands infertile, accept that misfortune is a part of their lives, are childless for the rest of their lives, and care for their husbands and families. A husband often threatens his wife with their next marriage, even though he knows he has a problem. If they are fertile, most men are willing—or their families force them to have a second marriage [9, 10]. However, the National Civil (Code) Act 2017 of Nepal clearly mentions that multiple marriages are not conclusive and are punishable [11].

Likewise, infertility can also cause severe strain in a couple's relationship if childlessness is a major theme in their life, if children are highly desired, if parenthood is culturally needed, or if childlessness is socially unacceptable. This study revealed that the majority of service takers were from Bagmati Province (35.7%, n = 107), followed by Gandaki Province (15.7%, n = 45), Karnali Province (11%, n = 33), and Province No. 1 (8.7%, n = 26). The majority of them were most likely from higher-income families. However, in the context of Nepal, most couples who have struggled with infertility have poor socioeconomic status and seek treatment from hospitals and traditional healers. Many Nepaleses people visited traditional healers for 2–3 years on the advice of in-laws and friends. Traditional treatments such as astrologic and sacred offerings used to cost a great deal of money. This could have occurred due to the inaccessibility of fertility services in their area and their lack of knowledge. A study conducted in Spain mentioned that many people who corrected their Mullerian anomalies did not attempt to conceive [12]. However, this study revealed that all the women and couples came to the hospital, and their main concern was reproduction. This could be because having children is a social status symbol in Nepalese culture. Likewise, this may have happened because women who came to the capital city to obtain infertility services from outside the city followed the full instructions and supervision of the doctor. A case study conducted in Nepal on Mullerian digenesis revealed that girls were born by their parents. Parents started to worry about when the female child did not start menstruating after developing secondary sexual characteristics. All were considered healthy by their body and not to have any health consequences [13].

The study was conducted to complete the partial fulfillment of a "Master's Degree in Biotechnology of Human Assisted Reproduction and Embryology." The study time was limited, so a descriptive cross-sectional design was developed to study Mullerian anomalies and reproductive performance among infertile women in Nepal, which limited the analysis to associations among

the methods used to achieve delivery and pregnancy outcomes.

CONCLUSION

This study aimed to measure the prevalence of the subtypes of Mullerian malformations. The study states that a significant level (61%) of women is affected by primary infertility; the rest of the women are found to have secondary infertility (39%). Likewise, a study found that half of women resulted in normal spontaneous delivery (50.66%) as their outcome of pregnancy. Moreover, it has been found that very few (0.7%) resulted in intrauterine fetal death (IUFD). The study also revealed that ectopic pregnancy has no consequences. Likewise, the majority of women had normal cervix and vagina (75% and 75.7%), respectively. A complete picture of Mullerian abnormalities cannot be drawn from the few studies on this topic that have been performed in Nepal. Therefore, to more accurately examine these correlations, well-designed prospective studies are needed. Additionally, only interventional studies will allow for a proper evaluation of the contributions that hysteroscopic excision of Mullerian abnormalities, hysterosalpingograms (HSGs), laparoscopy, and 3D ultrasonography make to enhancing reproductive outcomes. Despite the fact that infertility has a medical basis, infertile women are nonetheless victims of all aspects of their social and personal lives in contemporary society. To improve the knowledge, attitudes, and practices of people in Nepal's society, public education and behavioral change communication must be addressed.

ADDITIONAL DETAILS AND DECLARATIONS

Acknowledgments: The authors would like to thank all individuals who provided their direct and indirect inputs and participation in this study.

Funding: Self-Funding.

Competing interest: The authors declare no competing interests.

Author Contributions: Concept and design: **KP;** data collection and statistical analysis: **KP and MG**; writing of the manuscript: **MG and AS;** monitoring and supervising the research finalizing the manuscript: **BR**; and all authors read and agreed with the contents of the final manuscript.

Availability of data and materials: The datasets used and analyzed for the study are available from the corresponding author upon reasonable request

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