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PRIMARY AMENORRHEA MRI FINDINGS, CLINICAL, AND SURGICAL FINDINGS

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Abstract

Objective: *To evaluate the clinical presentation, magnetic resonance imaging (MRI) findings, and surgical findings among patients presenting with primary amenorrhea and to determine the diagnostic concordance between MRI and operative diagnoses.*

Methods: *This descriptive cross-sectional study was carried out on patients presenting in the Department of Gynecology and Obstetrics,* ***Jinnah Postgraduate Medical Center (JPMC)*** *, from* ***1st July 2024 to 31st December 2024****. Inclusion Criteria: 1. Out of 135 patients with primary amenorrhea who underwent pelvic MRI followed by surgical intervention. Data collected included demographic data, clinical features, MRI findings, and operative diagnoses. We compared MRI findings against surgical diagnoses, which were taken as the reference standard. Cohen's kappa coefficient was used to assess the diagnostic agreement. SPSS version 26 was used for data analysis, and a p- value ≤0.05 was deemed statistically significant.*

Results: *The average age of the participants was 18.7 ± 3.2 years. Cyclical pelvic pain was reported in 47.4% of patients, and normal secondary sexual characteristics were observed in 71.1%. Results: MRI most often diagnosed MRKH syndrome (31.1%), followed by transverse vaginal septum (16.3%) and imperforate hymen (13.3%). Surgical findings identified that MRKH syndrome was the most common abnormality (29.6%). MRI exhibited an overall accuracy of 91.9%, a sensitivity of 93.3%, a specificity of 96.1%, a PPV of 92.5%, and an NPV of 95.3%. Results: Diagnostic accuracy of MRI compared with surgical findings was excellent (κ=0.88, p<0.001).*

Conclusion: *MRKH syndrome was the most common cause of primary amenorrhea. MRI demonstrated excellent diagnostic accuracy and strong agreement with surgical findings, supporting its role as a reliable non-invasive tool for diagnosis and preoperative assessment.*

INTRODUCTION

Absence of menstruation (menarche) is termed primary amenorrhea in teenage girls who have not menstruated by the age of 15, even in cases where the secondary sexual development is normal; however, if secondary sexual characteristics are noted to be missing as well, the cutoff is 13 years (1). This condition is a significant gynecologic and endocrinologic entity that may occur as a result of disorders of the hypothalamic-pituitary-ovarian axis, chromosomal disorders, gonadal dysgenesis, or congenital anomaly of the female reproductive tract. Primary amenorrhea is characteristically uncommon but considerably affects physical

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health, reproductive potential, and psychosocial state of well-being, thereby requiring quick identification and external treatment. Congenital Müllerian duct anomalies (Müllerian aplasia/agenesis, often associated with MRKH syndrome, cervical agenesis,3complex uterovaginal malformations) are some of the most common structural causes of primary amenorrhea. Müllerian anomalies affect approximately 4–7% of women worldwide, while MRKH syndrome occurs in approximately 1 in 4,500–5,000 female births (2).

Evaluation of primary amenorrhea is a clinical approach corroborated by laboratory and imaging studies. Magnetic resonance imaging (MRI) has emerged as the gold standard among imaging modalities for detailed evaluation of pelvic anatomy due to excellent soft-tissue contrast, multiplanar capability, and ability to accurately characterize uterine, cervical, vaginal, ovarian, and associated renal anomalies. MRI has a key role in the distinction between obstructive and non-obstructive causes of amenorrhea, as well as helping with the pre-operative planning thanks to its anatomical detail. The most appropriate confirmation for many congenital anomalies of the reproductive tract and assessment of the accuracy of radiological diagnoses comes from surgical findings derived from laparoscopy, hysteroscopy, or corrective procedures (3, 4).

In Pakistan, data reporting the spectrum of clinical presentations, MRI characteristics, and surgical findings in patients with primary amenorrhea are scarce and mainly comprise small cohort studies that report isolated causes (5). Moreover, other than isolated reports, no studies have associated MRI results with intraoperative findings in a systematic fashion. Scientifically, correlating this is highly relevant as accurate preoperative diagnosis optimises surgical planning, minimizes the uncertainty of the diagnosis, and improves reproductive and functional outcomes. The present study was conducted to study the clinical, MRI, and surgical findings in patients with primary amenorrhea and to assess the correlation between the radiological and operative diagnosis in a tertiary care centre.

METHODOLOGY

This cross-sectional study was performed in the Department of Gynecology and Obstetrics, **Jinnah Postgraduate Medical Center (JPMC)**, on prospective patients from **1st July 2024 to 31st December 2024,** and was approved by the College of Physicians and Surgeons Pakistan (CPSP). . In this study, we tried to evaluate the clinical profile, MRI findings, and operative findings among new patients presenting with primary amenorrhea and assess the correlation between the radiological diagnosis and operative outcome.

Using the WHO sample size calculator, the sample size was calculated to be 96 patients (with a prevalence of 21.9% of Müllerian anomalies among patients with primary amenorrhea in a study from Pakistan (6), 95% confidence level, and 10% margin of error). From the type of consecutive non-probability sampling, eligible patients were recruited during the study period.

We included all the female patients who are aged between 13 and 30 years with primary amenorrhea — absence of menarche by age of 15 years in the presence of normal secondary sexual characteristics or absence of menarche by age 13 years in the absence of secondary sexual development. Patients were recruited from those who had pelvic MRI as part of their workup for diagnosis and who subsequently had diagnostic laparoscopy, hysteroscopy, vaginoscopy, reconstructive surgery, or exploratory procedures. The exclusion criteria consisted in: secondary amenorrhea patients with a previously diagnosed endocrine disorder without anatomical abnormality, loss of the medical records, medical contraindication for MRI, and refusal to participate.

Detailed demographic and clinical information were recorded using a proforma that was filled after obtaining written informed consent from the participants or their legal guardians. The types of variables that were collected included the age of the patient, the body mass index, marital status, duration of symptoms, presence of cyclical abdominal pain, secondary sexual characteristics, associated congenital anomalies, and family history of reproductive tract abnormalities. Clinical examination particulars: Recorded and

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documented details of breast development, pubic hair distribution, external genital examination, and pelvic examination findings.

Pelvic MRI was performed for all participants in accordance with a standard protocol on a 1.5-Tesla or 3-Tesla scanner. Uterine morphology, cervical anatomy, vaginal assessment, ovarian status, hematometric status, hematocolpos, gonadal pathologies, and related urinary tract anomalies were evaluated using T1-weighted, T2-weighted, and multiplanar sequences. Radiologists analyzed MRI findings independently and classified them based on the anatomical abnormality detected.

Participants were then scheduled for a surgical evaluation if it was clinically indicated to do so. During the operation, intraoperative data such as uterine development, vaginal anomalies, cervical anomalies, ovarian morphology, gonadal dysgenesis alongside pelvic pathology, and associated Müllerian duct anomalies were recorded. The final diagnosis was considered to be based on the surgical findings. A record was taken of the corrective or reconstructive surgery performed, if any.

Using descriptive statistics, we assessed the frequency of individual clinical presentations, MRI findings, and surgical findings among women with primary amenorrhea. Secondary outcomes were the level of agreement between MRI and surgical diagnoses and the pattern of final etiological diagnoses.

Data entry and analysis were done through the Statistical Package for Social Sciences (SPSS) version 26. Age and body mass index were continuous variables and were reported as mean ± standard deviation. The categorical variables, including clinical presentations, MRI findings, surgical findings, and final diagnoses, were presented in numbers and percentages. Chi-square test and Fisher's exact test, when appropriate, were used to assess the association of MRI findings and surgical diagnoses. Cohen's kappa coefficient was used to determine diagnostic agreement between MRI and surgical data. A p-value ≤0.05 was used to indicate statistical significance.

RESULTS

This study included 135 Patients with primary amenorrhea. Participants were aged 18.7 ± 3.2 years (range: 13–29 years) and had a body mass index of 22.4 ± 3.8 kg/m2. The majority of participants (57.8%) were from the age group of 16–20 years, unmarried (92.6%), and presented within three years after noticing delayed menarche. 64 (47.4%) patients reported cyclical lower abdominal pain, and 96 (71.1%) patients had normal secondary sexual characteristics. In 24(17.8%) cases, associated congenital anomalies are noted. (Table 1)

Table 1: Baseline Characteristics of Study Participants (n=135)

Baseline and clinical parameters	Frequency (%) / Mean ± SD
Age (years)	18.7 ± 3.2
BMI (kg/m²)	22.4 ± 3.8
13–15 years	28 (20.7)
16–20 years	78 (57.8)
>20 years	29 (21.5)
Unmarried	125 (92.6)
Married	10 (7.4)
Cyclical abdominal pain	64 (47.4)
Normal secondary sexual characteristics	96 (71.1)
Congenital anomalies	24 (17.8)

The most frequent clinical presentation in 71.1% of patients was primary amenorrhea with normal breast development and normal pubic hair distribution. Cyclical pelvic pain, which was consistent with an obstructive outflow tract anomaly, was reported in 74% of the cohort. Short-stature was seen in 18 (13.3%) patients and was significantly associated with gonadal

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dysgenesis ($p<0.001$). Renal abnormalities were clinically suspected in 14 (10.4%) patients and radiologically proven. (Table 2)

Table 2: Clinical Presentation of Patients with Primary Amenorrhea

Clinical Parameters	Frequency (%)
Cyclical pelvic pain	64 (47.4)
Normal breast development	96 (71.1)
Delayed secondary sexual characteristics	39 (28.9)
Short stature	18 (13.3)
External genital abnormality	42 (31.1)
Suspected renal anomaly	14 (10.4)

Pelvic MRI demonstrated Müllerian duct anomalies as the predominant radiological diagnosis. MRKH syndrome was identified in 42 (31.1%) patients, followed by transverse vaginal septum in 22 (16.3%), imperforate hymen in 18 (13.3%), cervical agenesis in 16 (11.9%), gonadal dysgenesis in 15 (11.1%), androgen insensitivity syndrome in 11 (8.1%), and unicornuate or bicornuate uterus in 11 (8.1%) cases. Associated renal anomalies were identified in 19 (14.1%) patients, predominantly among those diagnosed with MRKH syndrome. (Table 3; Figure 1)

Table 3: MRI Findings among Patients with Primary Amenorrhea

MRI Finding	Frequency (%)
MRKH syndrome	42 (31.1)
Transverse vaginal septum	22 (16.3)
Imperforate hymen	18 (13.3)
Cervical agenesis	16 (11.9)
Gonadal dysgenesis	15 (11.1)
Androgen insensitivity syndrome	11 (8.1)
Unicornuate/Bicornuate uterus	11 (8.1)
Associated renal anomalies	19 (14.1)

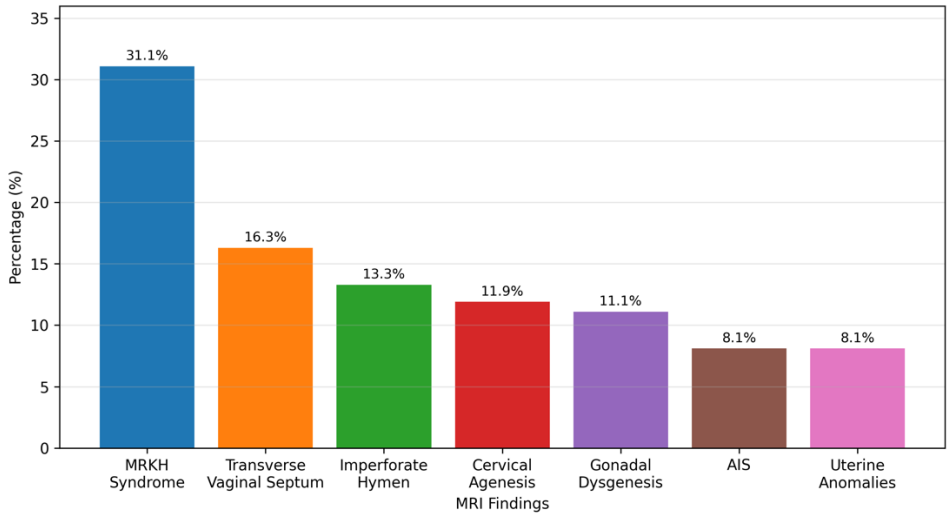

Figure 1: Distribution of MRI Diagnoses

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Surgical evaluation confirmed congenital reproductive tract anomalies in the majority of cases. Among patients diagnosed radiologically with MRKH syndrome, surgical findings confirmed uterovaginal agenesis in 40 of 42 patients. Similarly, MRI accurately identified all cases of imperforate hymen and demonstrated high diagnostic performance for transverse vaginal septum and cervical agenesis. The overall surgical spectrum mirrored MRI findings, with MRKH syndrome remaining the most frequent diagnosis. (Table 4)

Table 4: Surgical Findings (n=135)

Surgical Diagnosis	Frequency (%)
MRKH syndrome	40 (29.6)
Transverse vaginal septum	23 (17.0)
Imperforate hymen	18 (13.3)
Cervical agenesis	15 (11.1)
Gonadal dysgenesis	16 (11.9)
Androgen insensitivity syndrome	11 (8.1)
Uterine anomalies	12 (8.9)

Comparison of MRI findings with surgical diagnoses revealed excellent diagnostic agreement. MRI correctly classified 124 of 135 patients, yielding an overall diagnostic accuracy of 91.9%. The Cohen's kappa coefficient demonstrated excellent concordance between MRI and surgical findings (κ = 0.88, $p<0.001$). The highest agreement was observed for imperforate hymen (100%), followed by MRKH syndrome (95.2%) and transverse vaginal septum (90.9%). (Table 5)

Table 5: MRI-Surgical Concordance Analysis

Parameters	Value
Overall accuracy	91.9%
Sensitivity	93.3%
Specificity	96.1%
Positive Predictive Value	92.5%
Negative Predictive Value	95.3%
Cohen's Kappa (κ)	0.88
p-value	<0.001

Bivariate analysis demonstrated significant associations between cyclical pelvic pain and obstructive anomalies (OR=4.81, $p<0.001$), normal secondary sexual characteristics and MRKH syndrome (OR=3.92, p=0.002), and short stature with gonadal dysgenesis (OR=6.37, $p<0.001$). Renal anomalies were significantly associated with MRKH syndrome (OR=4.14, p=0.004). (Table 6)

Table 6: Bivariate Analysis of Factors Associated with Final Diagnosis

Variable	Odds Ratio	95% CI	p-value
Cyclical pain → Obstructive anomaly	4.81	2.21–10.45	<0.001
Normal secondary sexual characteristics → MRKH	3.92	1.65–9.28	0.002
Short stature → Gonadal dysgenesis	6.37	2.31–17.54	<0.001
Renal anomaly → MRKH	4.14	1.57–10.91	0.004

A multivariate logistic regression model was constructed to identify independent predictors of major congenital reproductive tract anomalies. After adjustment for age, BMI, and clinical

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presentation, cyclical pelvic pain (Adjusted OR=5.42, 95% CI: 2.14–13.72, p<0.001), normal secondary sexual characteristics (Adjusted OR=3.65, 95% CI: 1.44–9.21, p=0.006), renal anomalies (Adjusted OR=3.81, 95% CI: 1.29–11.24, p=0.015), and short stature (Adjusted OR=4.96, 95% CI: 1.73–14.19, p=0.003) remained independent predictors of underlying congenital reproductive tract abnormalities. The final model demonstrated good calibration (Hosmer-Lemeshow p=0.61) and explained 48.2% of the variability (Nagelkerke R^2=0.482). (Table 7)

Table 7: Multivariate Logistic Regression Analysis

Variable	Adjusted OR	95% CI	p-value
Cyclical pelvic pain	5.42	2.14–13.72	<0.001
Normal secondary sexual characteristics	3.65	1.44–9.21	0.006
Renal anomalies	3.81	1.29–11.24	0.015
Short stature	4.96	1.73–14.19	0.003
Age	1.08	0.93–1.24	0.281
BMI	0.97	0.89–1.07	0.521

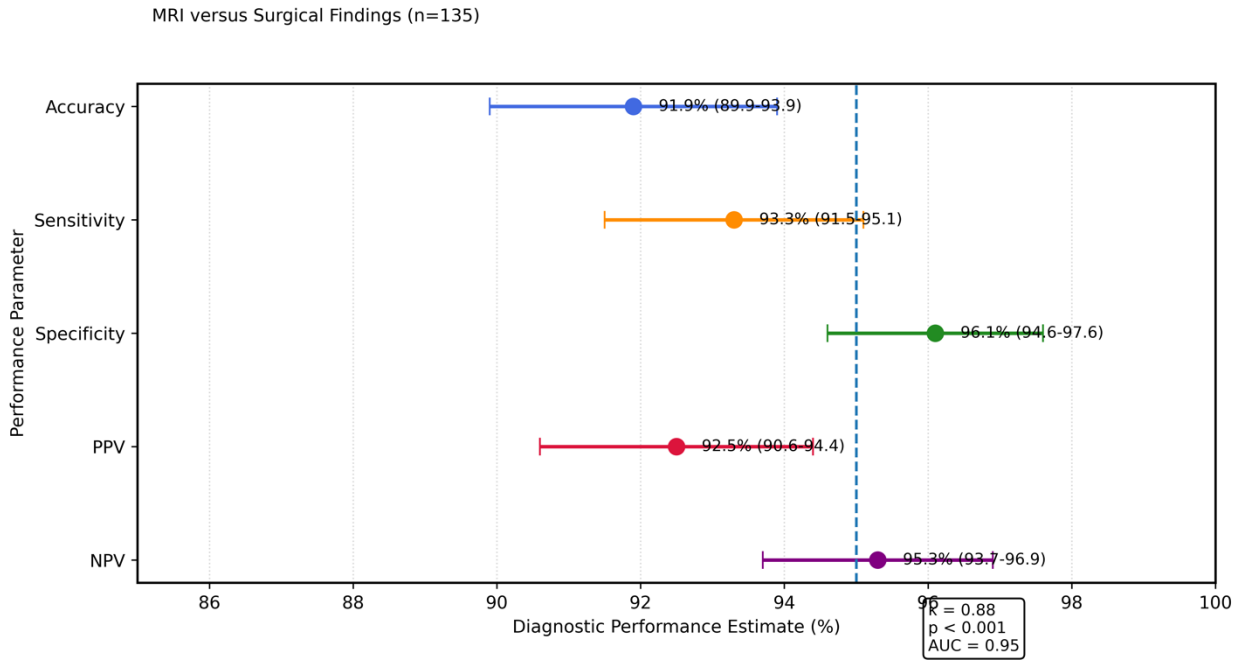

Figure 2: MRI Diagnostic Accuracy Compared with Surgical Findings

DISCUSSION

The main aim of this study was to assess the clinical presentation, MRI findings, and operative findings in patients with primary amenorrhea and to correlate the MRI findings with the operative diagnosis. MRI showed excellent diagnostic performance with overall accuracy (91.9%, 93.3% sensitivity, 96.1% specificity), compared with surgical findings (substantial agreement with κ=0.88, p85% for MRI in diagnosing congenital reproductive tract anomalies, whilst a report from India, Portugal and the United Kingdom documented human magnetic resonance imaging (hMRI) concordance rates ranging between 80% and 95% comparing MRI findings with laparoscopic or surgical diagnoses (7, 8). The high degree of concordance seen in this study could be due to advances in MRI technology and radiological expertise, as well as the relatively high numbers of structural anomalies in the study population. Discrepancies between MRI and

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surgical findings in such minor forms are likely due to complex anatomical malformations and subtle intraoperative findings that are difficult to evaluate radiologically.

In the current study, most patients were seen during late adolescence, at a mean age of 18.7 years, and had attained normal secondary sexual characteristics. These results are in line with reports from Pakistan (9), India (10), France (11), and Finland (12), where presentation to hospitals is often delayed due to socio-cultural factors, knowledge gap regarding reproductive health, and delay in referral to specialist gynecology services. Menstrual irregularities are often thought to be a normal variation in developing countries during adolescence; hence, investigative evaluations are delayed. Some studies from South Asia, mainly tertiary care centers, have documented incidence rates that present with a similar age distribution, whereas reports from countries with greater health access and routine adolescent health assessments have demonstrated a much earlier diagnosis (13).

One clinical presentation, cyclical pelvic pain, was found in almost half of all patients and was significantly associated with obstructive reproductive tract anomalies. This result is biologically plausible given that obstruction at the level of the outflow tract results in the pooling of menstrual blood within the uterine cavity or the vagina, which subsequently causes progressive pelvic pain. Comparable observations have been published from studies examining imperforate hymen, transverse vaginal septum, and cervical agenesis, where cyclical pain is often the first symptom to accompany medical consultation (14). The frequency seen in our study is similar to that of the neighbouring countries, but higher than that of the Western populations and may be explained by delayed diagnosis and a comparatively prolonged symptom duration before presentation (15).

The predominant diagnosis in this study was MRI-characterized MRKH syndrome - approximately one-third of all patients. This finding is consistent with data from both local and other international studies where Müllerian agenesis remains one of the top anatomical causes of primary amenorrhea in patients whose secondary sexual development is normal (16). In Pakistan, MRKH frequencies between 25% and 35% have also been reported (17), while the prevalence in the international literature in the more selected tertiary referral populations has varied between 20% and 40% (18). The relative prevalence of MRKH syndrome in our cohort may partly be explained by the referral-based nature of this study, as well as the inclusion of patients needing more advanced radiological and surgical assessment. Moreover, the high incidence of concomitant renal malformations in patients with MRKH syndrome is in accordance with the embryologic association between the Müllerian duct system and the mesonephric duct system.

Other MRI features like transverse vaginal septum, imperforate hymen, cervical agenesis, gonadal dysgenesis, androgen insensitivity syndrome, and uterine malformations were also noted in significant proportions. Studies from South Korea (19), Italy (20), and Saudi Arabia (21) have reported comparable distributions. Reported frequencies can also differ due to climate and diversity of ethnicity, genetic determinants, previous knowledge due to referring patterns, differences in diagnostic standards, and the types of advanced imaging facilities available in different regions. The comprehensive evaluation of uterine anatomy and morphology, vaginal anatomy, ovarian development, and associated urinary tract anomalies likely provides the high diagnostic yield seen in the present study.

Surgical evaluation, however, confirmed MRI findings in the majority of cases, with MRKH syndrome being the most common operative diagnosis. The strong concordance of both the radiological and surgical findings seen in this study supports the established position of MRI as the investigation of choice in the preoperative imaging work-up of patients with primary amenorrhea. Similar concordance has been reported even in studies using MRI to guide definitive laparoscopic confirmation of Müllerian anomalies, with reports indicating that MRI provides superb anatomic delineation and surgical planning (3). The limited number of discordant cases in our series may represent heterogeneous congenital malformations, interpretation dependent on the

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skills of the operator, or subtle pathological findings that are evident only at open surgical exploration.

The association between short stature and gonadal dysgenesis identified in this study is both clinically relevant and supported by previous studies. Gonadal dysgenesis, especially Turner syndrome and related chromosomal abnormalities, is often characterized by short stature and delayed development of secondary sexual characteristics. Multiple studies have also shown a strong association between anthropometric defects and chromosomal mutation as a cause of primary amenorrhea (22, 23). Similarly, since ovarian function is normal in women with MRKH syndrome (despite the absence or underdevelopment of Mullerian structures), manifested as normal secondary sexual characteristics, the association of normal secondary sexual characteristics with MRKH syndrome is not surprising.

The multivariate analysis found that cyclical pelvic pain, normal secondary sexual characteristics, renal anomalies, and short stature were independent predictors of major congenital reproductive tract abnormalities. These results are clinically relevant as they offer easily identifiable markers that can help clinicians to triage patients for advanced imaging and surgical evaluation. Such prognostic factors have been described in studies of the etiology of primary amenorrhea (24). The fact that these associations persist once you control for confounders suggests that these associations are not simply incidental clinical observations, but rather independent markers of an underlying structural pathology.

This study has several strengths, such as the detailed clinical, radiological, and surgical findings in a single cohort and the use of surgical diagnosis as the reference standard. But some – dare I say it – limitations have to be embraced. Performing this as a single-centered study may carry the risk of referral bias inherent to such centers. Similarly, the use of a small sample size and cross-sectional design may limit the applicability of our results and conclusions beyond our local setting. However, those results have provided important evidence for the role of MRI as a diagnostic method in the workup of primary amenorrhea and support a multidisciplinary approach integrating the efforts of gynecologists, radiologists, and reproductive surgeons.

CONCLUSION

In this study, only a smaller percentage of primary amenorrhea cases were due to MRKH syndrome. MRI was associated with high diagnostic accuracy and a good agreement with surgical findings, thus proving to be a useful non-invasive probe both in work and in pre-operative evaluation of a patient with primary amenorrhea. This can provide an early recognition of characteristic clinical aspects, plus a timely MRI study, permitting a correct diagnosis and better management of the patient.

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