Original paper

Incidence of intrauterine abnormalities in Pakistani women with unexplained infertility diagnosed via saline infusion sonography

Rubina Izhar[1], Samia Husain[1], Suhaima Tahir[2], Sonia Husain[1]

[1] *Department of Gynaecology And Obstetrics, Abbasi Shaheed Hospital & Karachi Medical and Dental College, Karachi, Pakistan*
[2] *Dow Medical College, Dow University of Health Sciences, Karachi, Pakistan*

Correspondence: Samia Husain, Department of Gynaecology And Obstetrics, Abbasi Shaheed Hospital & Karachi Medical and Dental College, 3-D, 25/20, Nazimabad No. 3, Karachi, Pakistan; tel.: +923453120015, e-mail: samiahusain_scorpio@hotmail.com

Abstract

Objective: To determine the frequency of intrauterine abnormalities in women with unexplained infertility using saline infusion sonography. **Material and methods:** This was a retrospective cohort study conducted at Aziz medical centre, Karachi, Pakistan between January and December 2015. The study population comprised of women with unexplained infertility who underwent saline infusion sonography as a part of their diagnostic workup. The frequency of uterine abnormalities in these women was determined and the relationship between these pathologies and patient age and body mass index was assessed. **Results:** Of the 769 women included, 202 (26.3%) had uterine abnormalities. Endometrial polyp (118 cases, 15.3%) was the most common abnormality, followed by submucous fibroids (54, 7%), intrauterine adhesions (20, 2.6%), and septae (10, 5%). Intrauterine pathologies were more common in women with primary infertility (71.8% versus 28.2%, $p = 0.002$). Uterine abnormalities were most common in the age group 30–34 years ($n = 80$, 39.6%) and in overweight patients ($n = 95$, 47%). The distribution of abnormalities differed significantly in various age groups ($p = 0.009$) and among women with different BMI ($p = 0.029$). **Conclusions:** A significant number of women with unexplained infertility present with unsuspected uterine abnormalities; therefore an assessment of the uterine cavity should be performed in all cases.

Introduction

According to estimates from the United Kingdom, infertility affects 1 in 7 heterosexual couples. Unexplained infertility accounts for about 30% of these cases[1]. Unexplained infertility refers to a situation when a couple is unable to conceive after 2 years of unprotected intercourse provided both male and female preliminary infertility workup is normal. This workup includes evidence of ovulation and patent fallopian tubes in females and semen analysis which should correspond to the reference limits described by World Health Organization in males[2].

After this workup, the couple is offered three choices, i.e. wait and watch, undergo artificial reproductive techniques or adoption[3,4]. Artificial reproductive techniques are an expensive mode of treatment which are not commonly provided in public sector hospitals in our country[5]. This label of unexplained infertility generally leaves less hope for patients in most setups countrywide[6].

The preliminary workup performed prior to designating a category to these women does not take into account the uterine cavity. Traditional transvaginal pelvic ultrasound may overlook up to 50% of abnormalities[7]. The uterine cavity plays a significant role in the im-

plantation of the developing embryo. The presence of subtle unsuspected abnormalities can hinder implantation and reduce the chances of conception. It has been postulated that success of In Vitro Fertilization (IVF) is also affected by uterine abnormalities[8]. These abnormalities remain "masked" during traditional workup.

A study on the usefulness of hysteroscopy prior to artificial reproductive techniques found that 31.8% of women with unexplained infertility had intrauterine abnormalities; with the highest proportion of polyps[9]. Unfortunately, international institutions, such as the Royal College of Gynaecologists and Obstetricians (RCOG) and the European Society for Human Reproduction and Embryology (ESHRE), have not included an assessment of uterine cavity in their proposed guidelines[10,11]. The reason stated for this recommendation is the fact that the treatment of these abnormalities has not been justified. Evidence is gradually accumulating that the elimination of these abnormalities may improve pregnancy rates[12].

Regardless of guidelines, many societies have incorporated an assessment of the uterine cavity in their fertility workup. Their analyses show the presence of such abnormalities in approximately 11 to 45% of women[13–15]. They suggested that these pathologies should be treated to increase pregnancy rates. However, most of this evidence lacks quality[13,14].

Congenital anomalies and acquired diseases of the uterus can affect endometrial receptivity, which results in implantation failure and may manifest as recurrent pregnancy loss or infertility. In Pakistan, no data was available on the presence of these abnormalities in women with unexplained infertility or their possible associations, if any. The aim of this study was to determine the frequency and characteristics of women with these abnormalities in the region.

Material and methods

This was a retrospective cohort study conducted at Aziz medical centre. Consent for the study was obtained from the administrator and the head of department gave the consent to use the data. A total of 1231 case records of women undergoing saline infusion sonography (SIS) at Aziz medical Centre between January 2015 and December 2015 were compiled and analysed. Patients with unexplained infertility, defined as 24 months of regular unprotected sexual intercourse where semen analysis was normal according to the WHO criteria and hysterosalpingogram was unremarkable, which means both fallopian tubes were patent and uterine cavity had no visible abnormalities, were included. This was assessed by a radiologist at a reputed diagnostic centre with 15 years of experience. Patients with evidence of regular spontaneous ovulation, i.e. serum progesterone at mid luteal phase of 30 nmol, were included. Women undergoing SIS for other indications and in whom the procedure was advised but not completed due to cervical stenosis or pain during procedure were excluded. Also, case files which did not clearly indicate the three

Fig. 1. *Cervix visualized and 5 French foley catheter inserted*

Fig. 2. *Saline infused into uterine cavity through a 5 French catheter*

mentioned criteria for unexplained infertility were excluded. Women with uterine anomalies, medical disorders such as diabetes, thyroid disorder and smokers were also excluded.

All saline sonography procedures were performed in an outpatient setting. The procedure was as follows: in all cases after all aseptic measures a speculum was introduced vaginally and up to 20–30 mL of sterile saline solution was infused into the uterine cavity through a 5 or 7 French foley's catheter to distend the endometrial cavity (Fig. 1, Fig. 2, Fig. 3).

A Mindray DP-2200 scanner with a 5 to 7.5 MHz frequency transvaginal transducer was used to scan the uterine cavity. All scans were performed by a specialist with 10 years of experience. The findings of saline infusion sonography were recorded.

A proforma was used to collect the data. The demographic data included patient age, height and weight. Past obstetric history regarding infertility duration and type was also analyzed. The presence or absence as well as the type of abnormalities on saline sonography were also recorded.

There is no formal ethical review committee in the hospital. Therefore, instead of a formal ethics committee, the principles of the Helsinki Declaration were followed. Data was coded and confidentiality was ensured.

Data was entered and analysed using SPSS version 15. Shapiro-Wilk test was used to assess normality of data distribution. Quantitative variables such as age and duration of infertility were not normally distributed and were represented by median and range. Variables such as height and weight were used to calculate the body mass index (BMI). Variables such as BMI and age were recoded into body mass index range and age range. The BMI ranges were as follows: less than 18.5 (underweight), 18.5–24.5 (normal weight), 25–29.5 (overweight) and greater than 30 (obese). Age ranges were as follows: < 24 years, 25–29 years, 30–34 years, 35–39 years and > 40 years. Frequency and percentages were calculated for qualitative variables such as age range, BMI range, type of infertility and the presence or absence of abnormalities. Effect modifiers were controlled through stratification of women's age and BMI range to identify their effects on the outcome variables. Post stratification chi square test was used with p-value ≤ 0.05 considered statistically significant.

Results

In 2015, a total of 1231 women underwent SIS in the infertility clinic, including 814 patients undergoing SIS due to unexplained infertility. Of these 814 women, 769 fulfilled all inclusion criteria.

Most women (310, 40.3%) were 30–34 years old and either had normal BMI range (n = 323, 42.2%) or were overweight (n = 337, 44%). In the study population, 481 (62.5%) women had primary infertility. The median duration of infertility was 3 years (2 to 9 years).

Of the 769 women included, 202 (26.3%) had uterine abnormalities. Endometrial polyp was the most common pathology (118, 15.3%), followed by submucous

Fig. 3. *A polyp delineated against saline background*

Characteristics (n = 769)		n (%)
Age range (years)	less than 24	86 (11.2%)
	25–29	217 (28.2%)
	30–34	310 (40.3%)
	35–39	102 (13.3%)
	Greater than 40	54 (7.0%)
BMI	Less than 18.5	63 (8.2%)
	18.5–24.9	323 (42.2%)
	25–29.9	337 (44.0%)
	greater than 30	43 (5.6%)
Abnormalities	none	567 (73.7%)
	yes	202 (26.3%)
Type of abnormality	endometrial polyp	118 (58.4%)
	intrauterine adhesions	20 (9.9%)
	submucous fibroid	54 (26.7%)
	septae	10 (5.0%)
Type of infertility	primary	481 (62.5%)
	secondary	288 (37.5%)
Duration of infertility in years (median, range)		3 (2–9)

Tab. 1. *Characteristics of the study population*

fibroids in 54 (7%), intrauterine adhesions in 20 (2.6%), and septae in 10 (1.3%) patients (Tab. 1).

Intrauterine abnormalities were more common in women with primary infertility. A total of 145 (71.8%) women with pathologies suffered from primary infertility compared to 28.2% with secondary infertility ($p = 0.002$). Uterine abnormalities were most common in the age group 30–34 years ($n = 80$, 39.6%) and in overweight patients ($n = 95$, 47%) (Tab. 2).

Characteristics		Abnormalities		p value†
		no (n = 567)	yes (n = 202)	
Type of infertility	primary	336 (59.3%)	145 (71.8%)	0.002*
	secondary	231 (40.7%)	57 (28.2%)	
Age range (years)	Less than 24	62 (10.9%)	24 (11.9%)	0.705
	25–29	158 (27.9%)	59 (29.2%)	
	30–34	230 (40.6%)	80 (39.6%)	
	35–39	73 (12.9%)	29 (14.4%)	
	Greater than 40	44 (7.8%)	10 (5.0%)	
BMI ranges	Less than 18.5	52 (9.2%)	11 (5.4%)	0.169
	18.5–24.9	242 (42.9%)	81 (40.1%)	
	25–29.9	242 (42.9%)	95 (47.0%)	
	Greater than 30	28 (5.0%)	15 (7.4%)	

† chi square test
* The p value is significant at the 0.05 level

Tab. 2. *Comparison of women with abnormalities and those without abnormalities*

The type and distribution of abnormalities differed significantly in various age ranges ($p = 0.009$). The majority of polyps occurred in patients aged 25–29 years (41, 34.7%) and 30–34 years (39, 33.1%). All other pathologies were more common in the age range 30–34 years: intrauterine adhesions (12, 60%), submucous fibroids (24, 44.4%) and septae (5, 50%) (Tab. 3).

The types of abnormalities also differed significantly among women with different BMI ($p = 0.029$). Polyps were more common in women with normal BMI range (53, 44.9%) and those overweight (49, 41.5%). Submucous fibroids were most common in overweight patients with BMI = 25–29.9 ($n = 36$, 66.7%). Intrauterine adhesions and septae were most common in women with normal BMI (Tab. 3).

Discussion

Infertility is a common reason for referral to a gynecologist in all setups[1]. Unexplained infertility becomes a challenge not only due to the self-explanatory description implied by the term but also the subsequent

management commonly suggested. IVF is not affordable for the majority of women reporting to public sector hospitals. Furthermore, the chances of success are only 30 to 33%. Even artificial reproductive techniques fail in the case of uterine pathologies as implantation is heavily dependent on the uterine environment[8].

These abnormalities may be either congenital or acquired; acquired abnormalities are generally treatable and can lead to conception in some cases[12]. Women conceived especially after polypectomy, but strict follow up data was not maintained for the entire cohort. Further research to assess the effect of intervention in such cases needs to be conducted. Improved fertility would establish a cause-effect relationship and help modify clinical practice.

The present paper presents the findings from a retrospective analysis of women with unexplained infertility. This is the first ever study reporting data from Pakistan on this subject utilizing saline infusion sonography as a diagnostic tool.

Saline infusion sonography has evolved as a major diagnostic tool in the evaluation of intrauterine abnormalities worldwide[16,17]. Low cost and easy accessibility render this technique far more applicable than the gold standard, i.e. hysteroscopy. SIS has been shown to be equal to hysteroscopy for the detection of intrauterine abnormalities.

About 26% of women in our study had some intrauterine abnormality revealed by SIS. The most common abnormality was represented by polyps. Our study showed fewer abnormalities than Shokeir *et al.*, who reported pathologies in 40% of their subjects, with polyps being the dominant finding[18]. Nayak *et al.* reported 18% of abnormalities diagnosed by hysteroscopy[19].

Most women in the analyses were overweight and belonged to the age group of greater than 30–34 years. Being overweight reduces chances of conception and is generally associated with other health hazards such as diabetes, hypertension and coronary disease[20]. Our study further shows that the risk of abnormalities was higher in overweight women ($n = 95$, 47%).

The presence of uterine abnormalities even in patients with normal BMI ($n = 81$, 40.1%) was another concerning finding. Polyps were more common in women with normal BMI range (53, 44.9%) and those overweight (49, 41.5%). This finding is in stark contrast with previously reported findings indicating that endometrial polyps were most common in overweight women[21].

Submucous fibroids were most common in overweight patients with BMI = 25–29.9 ($n = 36$, 66.7%). This finding has been reported previously. Intrauterine adhesions and septae were not correlated with greater BMI as their pathogenesis does not correlate with weight gain.

Characteristics		Type of abnormality				
		Endometrial polyp ($n = 118$)	Intrauterine adhesions ($n = 20$)	Submucous fibroid ($n = 54$)	Septae ($n = 10$)	*p* value[†]
Age (years) range	Less than 24	19 (16.1%)	3 (15.0%)	2 (3.7%)	0 (0%)	0.009*
	25–29	41 (34.7%)	4 (20.0%)	10 (18.5%)	4 (40.0%)	
	30–34	39 (33.1%)	12 (60.0%)	24 (44.4%)	5 (50.0%)	
	35–39	14 (11.9%)	1 (5.0%)	13 (24.1%)	1 (10.0%)	
	Greater than 40	5 (4.2%)	0 (0%)	5 (9.3%)	0 (0%)	
BMI	Less than 18.5	8 (6.8%)	1 (5.0%)	2 (3.7%)	0 (0%)	0.029*
	18.5–24.9	53 (44.9%)	10 (50.0%)	11 (20.4%)	7 (70.0%)	
	25–29.9	49 (41.5%)	8 (40.0%)	36 (66.7%)	2 (20.0%)	
	Greater than 30	8 (6.8%)	1 (5.0%)	5 (9.3%)	1 (10.0%)	

† chi square test
* The *p* value is significant at the 0.05 level

Tab. 3. *Types of abnormalities as distributed across different age groups and BMI ranges*

Age is generally considered a factor negatively correlated with conception[22]. Similarly, more women aged > 30 years presented to the clinic with unexplained infertility. The probability of identifying an unsuspected uterine abnormality increases with patient's age, as also shown in other studies[23]. Our study showed that polyps were more common in women aged < 35 years with only 5 (4.2%) polyps diagnosed in women aged 40 years and over. Submucous fibroids were more common in women aged 30 years and over. Intrauterine adhesions were also less common in patients aged 35 and above.

Abnormalities were more common in women with primary infertility than secondary infertility (71.8% versus 28.1%, $p = 0.002$). This finding is in contrast to that reported by Ajayi *et al.*, who showed that pathologies were more common in secondary infertility[24]. This may be associated with different types of abnormalities. Intrauterine adhesions were the most common type of abnormality in their analysis, whereas polyps were most common in our study. Intrauterine adhesions are mostly secondary to uterine trauma.

Our study showed that although uterine abnormalities are more common in patients aged > 30 years and BMI > 25, no age group is immune. Therefore, an assessment technique for uterine cavity that is both cost effective and efficient is urgently needed. Groszmann *et al.* have proposed transvaginal ultrasound and sonohysterography as a "one stop shop" for a complete evaluation of an infertile patient[25].

Large sample size is the major advantage of our study. Another strong point is that the outcome reported and its association with both age and BMI in women with unexplained infertility has never been reported from this region. The study's main limitation is the retrospective design. There is no follow-up data to assess the pregnancy rates in the two groups, i.e. those with abnormalities and those without abnormalities.

Further well-designed studies on the subject with prospective design and follow-up data are needed to assess the effects of these abnormalities on reproductive outcomes in women with unexplained infertility.

Conclusions

In conclusion, our study shows that a significant number of women with unexplained infertility have unsuspected uterine abnormalities and an assessment of uterine cavity is needed in all cases. Although these pathologies are more common in certain groups of the population, no age group or BMI range is immune to their presence.

Conflicts of interest

None.

Funding

None.

Ethical approval

The study used data records of the patients who underwent SIS. The hospital does not have a formal ethical review committee. Instead of a formal ethics committee, the principles of the Helsinki's Declaration were followed. Data was coded and confidentiality was ensured. The Head of the hospital granted permission for the study.

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