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Sociodemographics and Risk Factors of Secondary Infertility in Pakistan: A Case-Control Study

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Abstract: Infertile couples fail to achieve a clinical pregnancy after engaging in regular unprotected sexual intercourse for 12 months. Primary infertility refers to their inability to conceive without any previous successful pregnancies. Secondary infertility is the inability to conceive for a period of one year after conceived at least once. This study aimed to explore the risk factors and sociodemographics of secondary infertility. This case-control study was conducted at the University Institute of Public Health using data from the Gilani Ultrasound Center. The data were collected 18 months after the approval of the synopsis, examining a total of 690 females (345 cases and 345 controls). All females in the case group participated if they were 20–45 years of age, had any parity, and had a confirmed diagnosis of secondary infertility. The study occurred after getting permission from the institutional review board. Every participant in the study provided written informed consent, indicating their voluntary agreement to participate in the research and use their data for study purposes and publication. This study applied independent sample t-test and chi-square test. Working females, obese females, females living in the joint family system, cousin marriage, relationship difficulties with husband, violence during previous pregnancy by husband, history of diabetes, hypertension, polycystic ovary syndrome, pelvic inflammatory disease, endometriosis, uterine fibroids, menorrhagia, intermenstrual bleeding, history of abortion, history of breastfeeding, and history of urinary tract infection are associated with secondary infertility. The identified risk factors of secondary infertility are mostly modifiable, and managing these risk factors can prevent them.

Keywords: secondary infertility, socio-demographics, risk factors, pelvic inflammatory disease, polycystic ovarian syndrome.

巴基斯坦繼發性不孕症的社會人口統計和危險因子：病例對照研究

摘要：不孕夫婦在定期無保護性交 12 個月後未能達到臨床懷孕。原發性不孕症是指以前沒有成功懷孕過而無法懷孕。繼發性不孕症是指至少受孕一次後一年內無法懷孕。本研究旨在探討繼發性不孕症的危險因子和社會人口統計。這項病例對照研究是在大學公共衛生研究所使用吉拉尼超音波中心的數據進行的。數據是在概要批准後 18 個月收集的，總共檢查了 690 名女性（345 名病例和 345 名對照組）。病例組中所有年齡在 20-45 歲、有過產次且確診為繼發性不孕症的女性都參加。這項研究是在獲得機構審查委員會的許可後進行的。研究的

每位參與者都提供了書面知情同意書，表明他們自願同意參與研究並將其數據用於研究目的和發表。本研究採用獨立樣本 t 檢定及卡方檢定。職業婦女、肥胖女性、合併家庭女性、表親婚姻、與丈夫關係困難、丈夫懷孕期間有暴力行為、糖尿病史、高血壓、多囊性卵巢症候群、骨盆腔炎、子宮內膜異位症、子宮肌瘤、月經過多、經間期出血、流產史、哺乳史、泌尿道感染史與繼發性不孕有關。已確定的繼發性不孕症的風險因素大多是可以改變的，管理這些風險因素可以預防它們。

关键词：繼發性不孕症、社會人口統計、危險因子、骨盆腔發炎、多囊卵巢综合征。

1. Introduction

Infertility is typically defined as a couple's failure to conceive after 12 months of unprotected sexual activity [1, 2]. Infertility has two types: primary and secondary infertility. Primary infertility occurs when a woman has never given birth despite having sex without using contraception and being exposed to the chance of pregnancy for 12 months [3]. Secondary infertility occurs when a woman has previously experienced a pregnancy but is unable to achieve another pregnancy despite engaging in unprotected intercourse for a continuous period of twelve months, raising the possibility of conception [4]. Owing to a lack of understanding of the reasons for infertility and a lack of healthcare-seeking behavior, the population of Pakistan, a nation with a low-middle income, has a high incidence of this medical condition. According to reports, infertility is 22% common in Pakistan, with 4% of all instances being primary infertility [5, 6]. Globally, the prevalence of secondary infertility is reported from 2.1%6 to 65% [7-9]. In low-income countries such as Pakistan, the status of women with infertility issues continues to be awful. They continue to be affected by these circumstances, which may cause psychological and physical issues [10]. Hence, estimates of infertility are crucial in helping governments and healthcare decision-makers adopt the right social and economic policies [11].

In gynecological clinics, secondary infertility is a significant problem. Usually, some controllable risk factors should be thoroughly examined [12]. The most frequent reason for female infertility is ovulatory failure or disorder [13, 14]. The other causes of infertility differ depending on the age of the couple and the age of the marriage. Although polycystic ovarian syndrome (PCOS) is the most common cause, infections are also a significant cause of tubal factor infertility, and 1/3 of the cases remain unsolved [15]. So, individualized therapy should be provided because the etiology of infertility exhibits local diverse epidemiological features [16].

Secondary infertility in developing countries is mostly attributable to modifiable risk factors. There is a dearth of information on the prevalence and causes of secondary infertility in Pakistan. As per our knowledge and search, literature is not widely available on the local population in the recent past, specifically on secondary infertility. Therefore, this study was designed to explore the risk factors for secondary infertility in a local population. This study aimed to discuss sociodemographic and medical risk factors and to raise awareness among married couples. Females with such factors are at high risk of secondary infertility, and by controlling modifiable risk factors or by treating the conditions; we can reduce or minimize the risk of secondary infertility.

2. Methods

2.1. Study Design

This case-control study included two groups: cases of females having secondary infertility and controls of females who have more than one child and have never been diagnosed with infertility. Samples collection used non-probability consecutive sampling, and the study was conducted at the University Institute of Public Health 18 months after approval of the synopsis, taking data from Gilani Ultrasound Center, Feroz Pur Road, Lahore. A total of 690 females (345 cases and 345 controls) participated, and the sample size estimation used a two-proportion formula using WHO software, where P1 = proportion of adverse pregnancy outcome in females with secondary infertility= 32%. 17 and P2 = proportion of adverse pregnancy outcome in controls = 20% 17, using a 95% confidence level and 5% margin of error.

2.2. Eligibility Criteria

Inclusion criteria for cases were females aged 20–45 years and diagnosed with secondary infertility (as per operational definition). Inclusion criteria for control females were an age of 20–45 years and having parity >1, and females visiting for routine antenatal USG or who have never been diagnosed with infertility. Exclusion criteria were cases and control couples who had not lived together for at least 12 months, couples with male factor infertility, and infertile females with H/O tuberculosis or any organic lesion (fibroids, etc.).

2.3. Data Collection Tools

The institutional review board of the Faculty of Allied Health Science, University of Lahore, approved this study. After approval of the synopsis, females with secondary infertility who fulfilled the inclusion and exclusion criteria participated in the study, informed of their entitlement to discontinue their participation at any point. We collected sociodemographic data from all cases and controls, including age and social and domestic issues. Complete history and examination were performed and recorded. All females underwent a physical examination, with measurements of weight, height, and body mass index (BMI). All cases diagnosed as having secondary infertility by gynecologists and visited for further investigation on USG were asked about their current or past obstetrical, clinical, and family history of different conditions and diseases. All controls who were pregnant and were visiting for routine antenatal USG or other reasons were also asked about their current or past obstetrical, clinical, and family history of different conditions and diseases. For condition based on ultrasonographic diagnoses, a senior sonologist diagnosed it in a selected setting for both cases and controls. Performa recorded on and analyzed all information.

2.4. Statistical Analysis

All data were entered and analyzed using the SPSS program. In descriptive analysis, for quantitative data mean ± S.D or in case of non-normality of data median ± IQR was used. For categorical data, frequency (%) was used. Independent sample t-test and chi-square test were used by taking p-value ≤ 0.05 as significant.

2.5. Informed Consent Form

Each participant in the study provided written consent, indicating their willingness to participate in the research and allowing their data to be used for the purposes of the study and publication. All participants received comprehensive information about the study protocol, including detailed explanations of the procedures involved, such as ultrasonography.

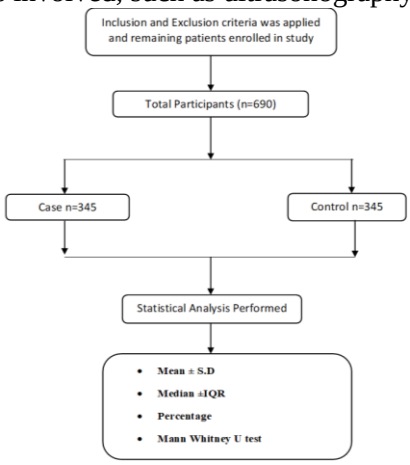

Fig. 1 Methodology flowchart

3. Results

The mean age of cases (females with secondary infertility) and controls was 33.08 ± 4.17 years and 31.37±4.36 years, respectively. The mean education of females in the case and control groups was 11.61 ± 5.72 years and 11.47 ± 5.43 years, respectively. The average monthly income was 64.05±84.20 in cases and was 72.52±106.85 in the control group. Age, education, and monthly income were statistically the same in the cases and controls, p-value > 0.05. In this study, few significant factors were found as follows. The 128 (37.1%) working females and 217 (62.9%) were housewives in cases, whereas in control groups were 97 (28.1%) working and 248 (71.9%) were housewives. The number of working females was statistically higher in cases than controls, p-value < 0.05 (Table 1).

Table 1 Comparison of current sociodemographic and anthropometric variables

Variables		Mean ± S.D	Median ±IQR	Z-test [a]	*P*-value
Current age (years)	Cases	33.08±4.17	34.0±6	-5.20	<0.001**
	Controls	31.37±4.36	30.0±7		
	Total	32.22±4.35	32.0±6		
Age at marriage (years)	Cases	24.33±4.76	25.0±6	-2.98	0.003*
	Controls	24.59±2.96	25.0±5		
	Total	24.46±3.96	25.0±6		
BMI	Cases	27.61±4.27	27.64±7.56	-5.60	<0.001**
	Controls	25.52±4.30	24.77±6.73		
	Total	26.56±4.41	25.86±7.01		
Education (years)	Cases	11.61±5.72	14.0±6	-1.09	0.273
	Controls	11.47±5.43	12.0±5		
	Total	11.54±5.58	13.0±6		
Monthly income *1000 (Rs.)	Cases	64.05±84.20	45.0±30	-1.06	0.289
	Controls	72.52±106.85	32.0±50		
	Total	68.28±96.22	45.0±43		

There were 104 (30.1%) obese and 241 (69.9%) non-obese females in the cases, and there were 79 (22.9%) obese and 266 (77.1%) non-obese females in the control groups. The proportion of obesity was statistically higher in cases than in controls (p-value < 0.05). As per type of family, 210 (60.9%) females of the case group and 128 (37.1%) females of the controls were living in joint families, and 135 (39.1%) females

in cases and 217 (62.9%) in controls were living in nuclear families. Females from the joint family system were higher in cases than controls, p-value < 0.05. The proportion of cousin marriages was higher in cases (64.9%) than in controls (56.8%), p-value < 0.05.

According to the family and social support system, there was an association between infertility and relationship difficulties with husbands, i.e., 11.9% of infertile females had relationship difficulties with husbands and only 5.5% of the females of controls had relationship difficulties with husbands, p-value < 0.05. Domestic violence during previous pregnancy by husband was also higher in infertile females (14.5%) than 9% females of controls, p-value < 0.05. There was an association between the study groups and history of diabetes (15.9% versus 8.7%), history of hypertension (26.1% versus 18.6%), history of polycystic ovary (17.7% vs. 9.6%), pelvic inflammatory disease (7.2% versus 2.0%), history of endometriosis (15.4% versus 9.3%), uterine fibroids (23.2% versus 16.2%), history of menorrhagia (15.4% versus 7.2%), intermenstrual bleeding (11% versus 5.8%), history of abortion (49.9% versus 15.9%), and history of breast feeding to child (47% versus 32.5%), p-value < 0.05 Table 2. The Anxiety and Depression Index among participants is as follows. 8 (3.9%) participants had no anxious depression, 56(27.5) had subclinical anxiety, 122 (60.0) had minor anxious depression, and 17 (8.3) had major anxious depression.

Table 2 Comparison of risk factors and study groups

Factors		**Groups**		***p*-value**
		Cases	**Controls**	
Sociodemographic factors	Obesity	104 (30.1%)	79 (22.9%)	0.03*
	Working profession	128 (37.1%)	97 (28.1%)	0.01*
	Urban Residential status	222 (64.3%)	232 (67.2%)	0.42
	Joint type of family	210 (60.9%)	128(37.1%)	<0.001**
	Cousin marriage	224 (64.9%)	196 (56.8%)	0.03*
Difficulty relationships	Relationship difficulties with the husband	41 (11.9%)	19 (5.5%)	0.003*
	Relationship difficulties with any member of the law	64 (18.6%)	56 (16.2%)	0.42
	Bad language/abuses of Husband during previous pregnancy	42 (12.2%)	48 (13.9%)	0.50
	Bad language/abuses of anyone during previous pregnancy	75 (21.7%)	85 (24.6%)	0.37
	Domestic violence during previous pregnancy by husband	50 (14.5%)	31 (9%)	0.03*
History of different conditions	History of diabetes mellitus	55 (15.9%)	30 (8.7%)	0.004*
	History of hypertension	90 (26.1%)	64 (18.6%)	0.02*
	History of thyroid	13 (3.8%)	20 (5.8%)	0.21
	History of kidney disease	9 (2.6%)	7 (2.0%)	0.61
	History of PCOS	61 (17.7%)	33 (9.6%)	0.002*
	History of PID	25 (7.2%)	7 (2.0%)	0.001*
	History of endometriosis	53 (15.4%)	32 (9.3%)	0.02*
	History of premature ovarian failure	28 (8.1%)	20 (5.8%)	0.23
	Uterine fibroids	80 (23.2%)	56 (16.2%)	0.02*
	Irregular menses	115 (33.3%)	111 (32.2%)	0.75
	Menorrhagia	53 (15.4%)	25 (7.2%)	0.001*
	Dysmenorrheal bleeding	16 (4.6%)	11 (3.2%)	0.33
	Intermenstrual bleeding	38 (11%)	20 (5.8%)	0.01
	Use of hormones to regulate menstruation	28 (8.1%)	21 (6.1%)	0.30
	Premature delivery	24 (7%)	15 (4.3%)	0.14
	History of abortion	172 (49.9%)	55 (15.9%)	<0.001**
	History of breast feeding to the child	162 (47%)	112 (32.5%)	<0.001**
	Cracked nipple	31 (9%)	35 (10.1%)	0.61
	Breast engorgement	45 (13%)	51 (14.8%)	0.51
	Lactation mastitis	12 (3.5%)	13 (3.8%)	0.84
	Plugged ducts	11 (3.2%)	6 (1.7%)	0.22
	Breast abscess	26 (7.5%)	32 (9.3%)	0.41
	Family planning history	120 (34.8%)	128 (37.1%)	0.53
Personal gynecological risk factors	History of urinary tract infection	113 (32.8%)	37 (10.7%)	<0.001**
	Abnormal uterine bleeding	25 (7.2%)	7 (2%)	0.33
	Tumor in the reproductive system	7 (2%)	5 (1.4%)	0.56
	Diabetes mellitus	63 (18.3%)	55 (15.9%)	0.42
	Hypertension	79 (22.9%)	77 (22.3%)	0.86
	Kidney disease	47 (13.6%)	51 (14.8%)	0.66
	Thyroid disease	63 (18.3%)	56 (16.2%)	0.48

4. Discussion

After 12-24 months of consistent, unprotected intercourse, couples that cannot conceive are infertile. Infertility varies among individuals. In both men and women, the fertility process is complex. Approximately 10%–15% of all couples experience infertility [18]. The single most significant factor affecting both spontaneous and treatment-related conception is female sex. The threshold for advanced reproductive age lacks a universally agreed-upon definition; however, 35 years marks a significant point in terms of fertility [19]. In this study, patients presenting with secondary

infertility were of age 33.08 ± 4.17 years. A study conducted in 2010 [20] reported that the mean age in secondary infertility was 32, while [21] reported a mean age of mean years in secondary infertility. The current study described all the concerned risk factors associated with secondary infertility. The findings of this study will help the nation overcome or minimize these risk factors, which will eventually lead to a decline in the ratio of secondary infertility. There are different risk factors of secondary infertility, such as lifestyle-related factors, such as obesity, diet, smoking, alcohol consumption, and chemical environments, and secondary factors related to human infertility, such as unsafe methods of childbirth and post-partum period as well as symptoms of sexually transmitted diseases [22]. The other common factors responsible for infertility in females are anovulatory disorder, tubal factors, PCOS, peri-tubovarian adhesions, endometriosis, uterine and cervical factors, etc. [23-25]. Healthy development of female reproductive functions depends on adipose tissue. An association between fat and hyperinsulinemia, hyperandrogenism, and abnormal hormone production, including leptin cause numerous reproductive issues seen in infertile women [26]. Factors related to nutrition and lifestyle that impact fertility includes conditions such as anemia, weight imbalances, and smoking. The American Society for Reproductive Medicine emphasizes that 12% of infertility instances arise from being either underweight or overweight [27]. According to the current study, women with obesity had 1.45 times higher chances of secondary infertility. A study found that BMI was significantly higher in females with secondary infertility [28]. However, research in China has indicated that the highest incidence of infertility in women is observed among those who are underweight [29]. Tubal disease accounts for approximately 40% of secondary infertility [30], and the most prevalent causes of tubal factor infertility are pelvic inflammatory disease and acute salpingitis. The incidence of tubal damage after one episode of pelvic infection is approximately 12%, 23% after two episodes, and 54% after three episodes [31]. However, the causes of infertility may be different in different geographic areas [32]. Pelvic inflammatory disease refers to a group of infections affecting the pelvic organs caused by various microorganisms such as bacteria and inflammatory illnesses that can lead to infertility [33]. In the current study, females with PID were associated with secondary infertility (p-value < 0.05, same results have been reported by [34] followed by PCOS (2.03 times), endometriosis (1.78 times), and uterine fibroids (1.56 times. By comparing our results with those of other studies, PCOS, endometriosis, and uterine fibroids were also found to be the cause of secondary infertility [20]. Sultana and her team documented parallel results in a local study, noting occurrences of ovulation failure in 60% of cases, PCOS in 32%, bilateral tubal occlusion in 8%, and pelvic adhesions in 24% [35] There is a strong reason for infertility and PCOS, as in PCOS, the ovaries generate a large quantity of androgens, primarily testosterone, resulting in amenorrhea or oligomenorrhea. Because of the increased androgen synthesis in PCO, there are high levels of luteinizing hormones and low levels of follicle stimulating hormones, preventing follicles from generating mature eggs [33]. Another interesting finding of our study was the significant association of abortion with secondary infertility. In a study conducted in Nigeria, induced abortion and post-abortion sepsis were the most important risk factors for secondary infertility [36] Few more studies found an association between abortion and secondary infertility [17, 37]. Our study highlights several significant factors associated with secondary infertility. Female age, particularly after 35 years of age, emerges as a crucial determinant of fertility. Lifestyle-related factors such as obesity and diabetes also play a notable role. In addition, conditions such as PCOS, endometriosis, and uterine fibroids contribute to secondary infertility.

Moreover, tubal disease, often linked to pelvic inflammatory disease, is a major cause of secondary infertility. Importantly, abortion-related complications were found to significantly increase the risk of secondary infertility. In addition, a history of breastfeeding was associated with a higher likelihood of experiencing secondary infertility. These findings underscore the complexity of secondary fertility issues and emphasize the importance of considering multiple factors in understanding and addressing secondary infertility.

5. Conclusion

This study identified that the age of the female, age at marriage, sociodemographics, and medical health factors are the main causes of couple infertility. A number of studies have been conducted on secondary infertility, but this study focused on broad-spectrum risk factors of secondary infertility. By managing sociodemographic factors and improving health conditions, the risk of secondary infertility can be reduced. Hence, the identified risk factors of secondary infertility are mostly modifiable and can be prevented or treated in the future.

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