Health Science Reports

WILEY

Health Science Reports
Open Access

ORIGINAL RESEARCH OPEN ACCESS

Comprehensive Assessment of Genital Infections and Reproductive Health in Women Visiting a Fertility Clinic in Warangal, India—A Case-Control Study

Naresh Patnaik[1] | Uttam Sarkar[2] | Malathi Jojula[3] | Hema Vaddiraju[4] | Ruchi Jain Dey[1]

[1]Department of Biological Sciences, Birla Institute of Technology and Science, Pilani, Hyderabad Campus, Hyderabad, Telangana State, India | [2]Department of Animal Genetics and Breeding, West Bengal University of Animal and Fishery Sciences, West Bengal, India | [3]Department of Microbiology, Sri Shivani College of Pharmacy, Warangal, Telangana State, India | [4]Curewell Hospital, Warangal, Telangana State, India

Correspondence: Ruchi Jain Dey (ruchij80@hyderabad.bits-pilani.ac.in)

Received: 18 July 2024 | **Revised:** 4 January 2025 | **Accepted:** 21 March 2025

Funding: This was supported by the Birla Institute of Technology and Science, Pilani, for Open Access Publication support, Indian Council of Medical Research (ICMR), Govt. of India, Senior Research Fellowship (RBMH/FW/2019/13) awarded to Naresh Patnaik (2019-2022), Research Initiation Grant (RIG) and Centre for Human Disease Research (CHDR) programs intramurally funded by Birla Institute of Science and Technology (BITS) Pilani, Hyderabad campus, India to Ruchi Jain Dey (June 2018- March 2023), Ramalingaswami Re-entry fellowship (BT/RLF/Re-entry/18/2016) awarded to Ruchi Jain Dey (May 2018- April 2023).

Keywords: endometrial disorders | female genital tuberculosis (FGTB) | female infertility | genital infections | menstrual disorders | PCOS & PCOD

ABSTRACT

Background: Female infertility is a global health issue however, its link with genital infections is often overlooked due to asymptomatic nature of infections. Delayed diagnosis and treatment due to absence of reliable point-of-care (POC) tools result in long-term pathological consequences and infertility. This pilot-scale study aims to identify the most noteworthy prognostic symptoms of genital infections that exhibit a significant correlation with reproductive tract disorders and infertility.

Methods: We designed a detailed questionnaire and conducted a case-control, observational study with 100 female patients, categorized into infertile (n1 = 62) and healthy groups (n2 = 38) followed by statistical analysis.

Results: This study highlights an early onset of infertility (18-25 years). Approximately 27% of the infertile female patients are symptomatic for genital infections, and ~42% exhibit menstrual irregularities. Polycystic ovarian syndrome/disease (PCOS/PCOD, ~30%) appears to be the most predominant disorder, followed by endometrial disorders (~10%) and tubal damage (~8%) in infertile patients. A multivariate correlation analysis revealed a highly significant ($p \leq 0.05$) and strong association ($0.15 < \Phi \leq 1.0$) between menstrual disorders, endometrial disorders, uterine/tubal blockage, and hormonal disruption with infection-associated symptoms, e.g. vaginitis, cervicitis, pelvic inflammatory disorder (PID), dyspareunia or infections like tuberculosis (TB) & urinary tract infection (UTI).

Conclusions: Our study shows a significant contribution of genital infections to female infertility. Nevertheless, a substantial 73% of infertile patients are ineligible for confirmatory diagnosis due to the absence of classical infection symptoms. This underscores the pressing requirement for comprehensive screening strategies for timely management of reproductive health and fertility.

Patient or Public Contribution: This study was performed in line with the principles of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines (Supporting Information 1) [1]. The study was performed following an ethical approval of the Institutional Human Ethics Committee. All individuals who participated in the study were fully informed about various aspects, including the study's objectives, methodologies, sources of funding, potential conflicts of

interest, institutional affiliations of the researcher, anticipated benefits, potential risks, and the discomfort they might experience. Their participation was contingent on obtaining their informed consent (See Supporting Information 2 for patient consent form). Furthermore, to safeguard patient confidentiality, we took measures to de-identify patient information. This included the removal of exact ages, which were replaced with age ranges, and the omission of exact dates or photographs during presentation of the data.

1 | Introduction

Infertility and menstrual disorders are significant global health concerns, with an estimated 17.5% of women affected by infertility according to the WHO [2–4]. This issue spans low-, middle-, and high-income countries, underscoring the urgency of expanding reproductive healthcare and research [3, 4].

Infertility, defined as the inability to conceive after a year of unprotected sexual intercourse, affects both genders due to genetic, environmental, infectious, and lifestyle factors [3–5]. Limited access to care and societal stigma result in delayed diagnosis and treatment, causing emotional and financial stress [3]. High medical costs can lead to healthcare-induced poverty during infertility treatments [3, 6–8].

In regions like India, where infectious diseases, such as tuberculosis, are prevalent, infectious agents play a prominent role in infertility [6, 9–11]. Genital infections may cause a wide spectrum of conditions/symptoms like vaginitis, cervicitis, dyspareunia, and PID [12, 13], endometriosis and other endometrial disorders [6, 14], PCOS/PCOD, ovarian atresia or cysts, and anovulation [15, 16]. These infections become chronic if left undiagnosed and untreated, resulting in long-lasting inflammation and irreversible reproductive tract scarring, leading to sub-fertility, infertility, and various adverse outcomes [6, 10, 11]. Female genital tuberculosis (FGTB) alone is responsible for a significant proportion of female infertility cases in India [6, 17–20]. The success rate of the anti-TB drug regimens in improving fertility (~30%) suggests that early detection and effective antimicrobials, along with adjunct therapies to reduce inflammation may thus help in reversing reproductive tract damage and restoring fertility [21–23]. Bacterial vaginosis (BV) is also linked to PID and endometritis, further contributing to infertility [12, 14], reducing pregnancy chances by 40% in women with subclinical PID [13]. In addition, genital infections with *Chlamydia trachomatis* and *Ureaplasma urealyticum* and its serovars have also been identified to be associated with women infertility in 13.5% and 20% cases, respectively [24–26].

Current diagnostic approaches for asymptomatic or subclinical genital infections rely on advanced methodologies such as molecular diagnostics (e.g., NAATs, qPCR) [27–29], serological tests [30], and microbial cultures [29], which are highly sensitive and effective for pathogen detection. Techniques like endometrial biopsy combined with NAAT [31] or next-generation sequencing (NGS) [32] have further enhanced the detection of infections and dysbiosis [33, 34] that are often missed by conventional methods and could potentially be linked to pre-term births, recurrent abortions, or infertility. Imaging methods, including transvaginal ultrasound, laparoscopy, hysterosalpingography (HSG) [35], magnetic resonance imaging (MRI) [35], and pelvic doppler ultrasound, are currently used in identifying subclinical PID, pelvic infections, abscesses, or tubal damage that may contribute to unexplained infertility [35]. However, these techniques are often inaccessible in resource-limited settings, presenting a huge challenge to diagnose asymptomatic women. Over the past few years, our lab has concentrated on developing rapid point-of-care diagnostic tools. However, during clinical validation, we observed that genital infections in women can be low in bacterial count and persist chronically without symptoms, often remaining undetected and untreated. This oversight can lead to severe complications and infertility. Remarkably, without obvious signs of infection, these women aren't routinely screened for genital infections. This prompted us to conduct a comprehensive case-control, observational study among infertile patients in rural India, where challenges such as poor hygiene and limited access to diagnostic services exacerbate the issue. To explore infertility and the impact of genital infections on female reproductive health, we devised a detailed questionnaire and conducted a one-time survey among infertile women in Warangal, India. The major goal was to develop a method essentially to stratify women based on detailed analysis of menstrual and reproductive anomalies, identifying those with subtle indications of infection. This systematic stratification can help prioritize women at-risk for advanced diagnostic testing, thereby bridging the diagnostic gap and improving outcomes in fertility management.

2 | Materials and Methods

2.1 | Study Design

This study was conducted as a case-control, observational survey, adhering to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) (Supporting Information 1) [1, 36] guidelines for reporting epidemiological studies.

2.2 | Study Setting

The study was carried out in a fertility clinic (Curewell Hospital) located in a rural setting in Warangal, India.

2.3 | Study Timeline

The study was a one-time assessment, conducted at a single time-point for each participant.

2.4 | Study Population

The study included female patients aged 18-45 years who were seeking infertility treatment at the clinic, along with their male partners.

2.5 | Inclusion Criteria

Patient recruitment for the study was done based on the gynaecologist's assessment. Patients were enrolled in the study based on the inclusion/exclusion (I/E) criteria. In this study, female patients (18-45 years) visiting the clinic for infertility treatment (along with their male partners) were enrolled. Patients (couples) with complaints of infertility (not getting conceived for a duration of ≥ 12 months) were classified into the infertile group.

2.6 | Exclusion Criteria

Female patients outside the age group of 18-45 years were excluded from this study. Female patients with history of HIV/HCV were excluded.

2.7 | Sample Size Calculation

The sample size (n = 97) was determined by the help of formula $n = [DEFF * Np(1-p)]/[(d^2/Z^2_{1-\alpha/2}*(N-1) + p(1-p)]$, where n = sample size, DEFF = design effect, N= population size (10^7), p = estimated proportion (6.7% ± 5), q = 1-p, d = desired absolute precision (5%) or absolute level of precision, achieving a confidence level of 95% [37, 38].

2.8 | Sampling Methods/Techniques

A total of 100 female patients were enrolled based on the inclusion/exclusion criteria and provided informed consent. The patients were categorised into case and control based on their health assessment done by the concerned gynaecologist using a questionnaire designed by the researchers. Infertile patients were further stratified into primary (no live birth) and secondary infertility cases (at least one live birth). Females with regular menstrual cycles and no recent history of infertility or genital infection were classified into the healthy control group.

2.9 | Study Procedure

A total of 100 female patients were enrolled for this study based on I/E criteria defined above, following their informed consent. These patients were further allocated into groups (infertile and healthy) based on their fertility status (Figure 1 for study outline). The patients in each group were assessed at a single time-point using a detailed questionnaire. The questionnaire (Supporting Information 2), designed to collect a comprehensive data on the female patients, includes a variety of 45 parameters (Table S1, Supporting Information 3). The study solely assessed the existing information provided by the patients (including previous test reports verified by the gynaecologist) and did not involve collection of any new samples or performance of any new tests.

2.10 | Ethics and Consent

This study was performed in line with the principles of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines (Supporting Information 1) [1, 36]. The study was performed following an ethical approval of the Institutional Human Ethics Committee (IHEC approval number: BITS-HYD/IHEC/2022/01). All participants were informed about the "aims, methods, sources of funding, possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study, and the discomfort it may involve". Participants were enrolled only after obtaining their informed consent (See Supporting Information 2 for patient consent form).

2.11 | Data Management

Data was collected using a questionnaire and digitally recorded in Microsoft Excel sheet using a Google Form.

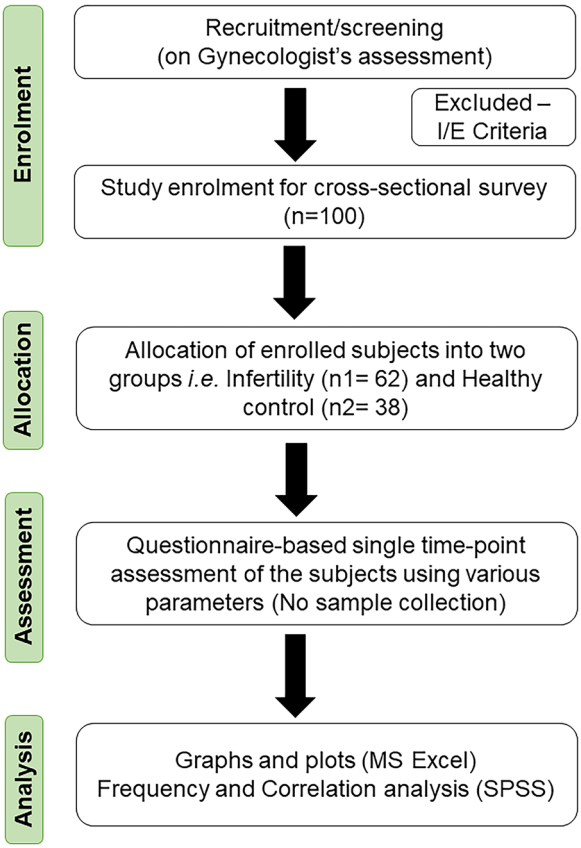

FIGURE 1 | Study design flowchart. Figure depicts an outline of the case control survey conducted in infertile and healthy women to understand various parameters influencing female fertility. In this study, 45 parameters (listed in Table S1) were assessed to determine frequency and correlation between different parameters (as described in Table S2A-D and Figure 5, respectively).

2.12 | Data Analysis

For the purpose of analysis, the data sets were simplified into a multinomial format (Yes/No/No data). Data analysis was performed using Microsoft Excel and IBM SPSS Statistics software (Version 25.0, IBM Corp., Chicago, IL). Analytical graphs were plotted using Microsoft Excel. Statistical analyses such as frequency distribution, likelihood ratio test, multivariate logistic regression, and multivariate correlation analysis (Phi coefficient) were conducted to assess the relationships between various parameters. The analysis followed the STROBE guidelines for reporting (Supporting Information 1) [1, 36].

3 | Results

3.1 | Landscape of Female Infertility and Other Reproductive Health-Related Conditions

A comprehensive questionnaire-based case-control, observational study is carried out to identify the most significant parameters associated with subfertility, infertility (primary and secondary), or conditions like pre-term birth, spontaneous abortions, medical termination of pregnancy, and ectopic pregnancy in females. Out of the 100 patients assessed, 62 were categorized into the infertile group and 38 were healthy patients with no history of infertility or menstrual disorders (Figure 1). Amongst the infertile group, only-female infertility (39%) with healthy and fertile male spouses, predominated the assessed population (Figure 2A, Table 1A). Infertility due to only-male factors with apparently healthy/fertile females represented mere 2% of the study population (Figure 2A, Table 1A). Female infertility is seen in 60% of the total study population including 21% of cases contributed by both male and female infertility (Figure 2A, Table 1A). Out of the total 62 infertility cases, 90% are diagnosed with primary infertility, rest 10% are cases of secondary infertility (Figure 2B, Table 1B). Our study highlights an early onset of female infertility as young as ≤ 20 years of age (Figure 2C, Table 1B), with predominance of both primary and secondary infertility in the age group of 21-30 years (Figure 2C, Table 1B). Among 62 infertility cases, ~74% failed to conceive even once, and a large proportion of ~23% suffered from spontaneous abortions or have undergone medical termination of pregnancy (MTP) (Figure 2D, Table 1C). Ectopic pregnancies were observed in ~3% of cases, however, no pre-term birth cases were observed in this study population (Figure 2D, Table 1C). Age distribution of these failed pregnancies reveals an early occurrence in the age group of 21-25 years (Figure 2E, Table 1C).

3.2 | Genital Infections—A Major but Neglected Contributor to Female Infertility

Among the various parameters assessed in females belonging to the infertility group, incidence of genital infections were thoroughly investigated in this study, using (a) most recurring symptoms of infections such as vaginitis (vaginal itching, burning and discharge), cervicitis (cervical inflammation), dyspareunia (painful intercourse), PID, and symptoms of UTI (painful micturition/burning sensation on micturition), and (b) laboratory confirmed cases of infections such as UTI (urine examination), TB positivity (based on tuberculin test/QuantiFERON-TB Gold/TB molecular diagnosis using PCR or TB culture test) (Table S1 and S2A, Supporting Information 3). Surprisingly, a large proportion of ~27% of infertile females show one or more signs of infection-related symptoms (Figure 3A, Table S2A, Supporting Information 3). The major symptoms observed in these patients are vaginitis (~18%), PID (~26%), dyspareunia (~11%), and 2 confirmed cases of pulmonary TB (~3.2%) (Figure 3B, Table S2A, Supporting Information 3). Interestingly, the analysis of questionnaire data reveals that confirmatory detection of infections has largely been overlooked and is not typically included in the routine check-ups involved in infertility management. Hence, the rest ~73% of the patients were rendered ineligible for infection-screening in the absence of classical signs of infection. As the diagnosis is simply based on visible signs of genital infections listed above, asymptomatic but chronic genital infections cases go unnoticed/undetected and hence, left untreated. Therefore, detection of genital infections may prove to be highly valuable for early management of infection-associated female infertility.

3.3 | Menstrual Health—A Noninvasive Prognostic Marker of Infertility

Menstrual irregularities appear to be the predominant symptoms observed in the case of females in the infertile group (~42%, Figure 4A, Table S2A and B, Supporting Information 3). Menstrual irregularities were further stratified into various categories such as menorrhagia (heavy and prolonged bleeding), dysmenorrhoea (painful periods with cramps), amenorrhoea (absence of periods), metrorrhagia (spot bleeding in between the periods), and oligomenorrhoea (irregular periods or inconsistent blood flow). Among these symptoms, amenorrhoea (~13%), metrorrhagia (~8%), and oligomenorrhoea (~15%) are evident only in the case of infertile patients (Figure 4B, Table S2A and B, Supporting Information 3). However, symptoms such as menorrhagia (~34% vs. ~24% in infertile vs. healthy) and dysmenorrhoea (~65% vs. ~29% in infertile vs. healthy) are observed both in healthy and infertile patients, though a larger proportion is observed in the infertile group (Figure 4B, Table S2A and B, Supporting Information 3).

3.4 | Spectrum of Reproductive Tract Anomalies in Infertile Females

We next assessed the spectrum of anomalies in the female reproductive tract in infertile patients. Among the various anomalies, PCOS and PCOD are the most prominent pathological sequelae observed in infertile patients ($n = 19$, ~31%) (Figure 4C, Table S2A, Supporting Information 3). The other prominent symptoms include fallopian tube blockage ($n = 5$, ~8%) and a variety of endometrial disorders, such as secretory/proliferative/thickened endometrium/hyperplasia/cysts ($n = 4$; ~7%), and endometriosis ($n = 2$, ~3%) (Figure 4C, Table S2A, Supporting Information 3). Unlike these symptoms, only one case of anovulation and ovarian teratoma is observed in the infertile group (Figure 4C, Table S2A, Supporting Information 3).

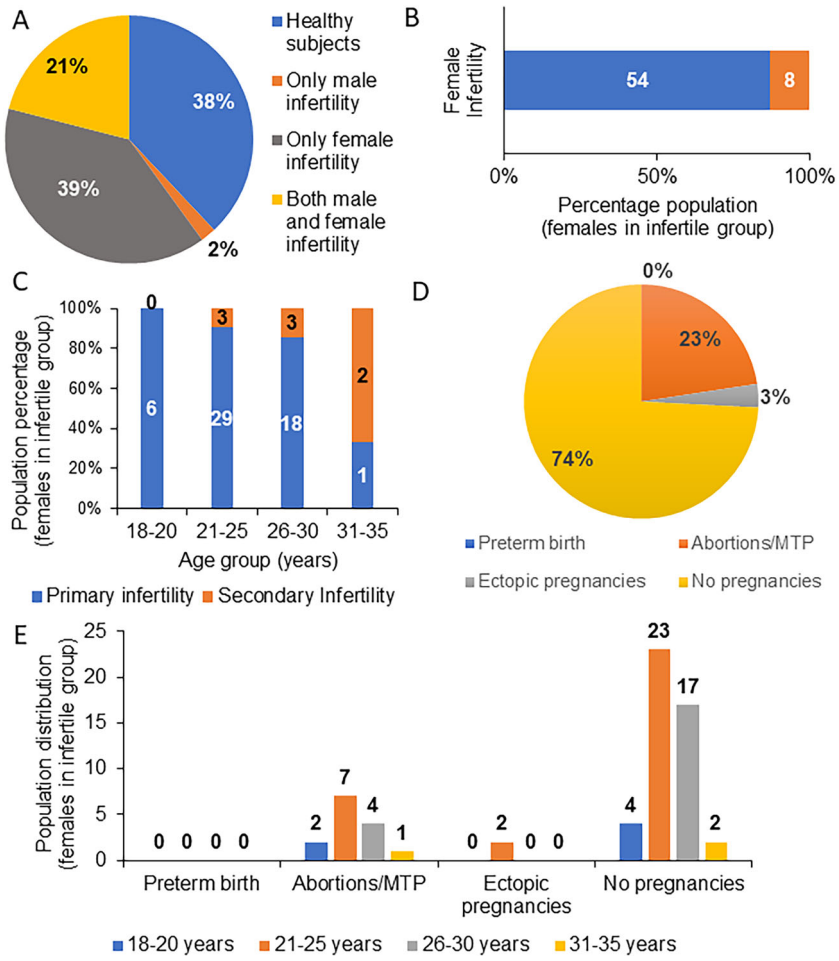

FIGURE 2 | Population distribution and pattern analysis of female infertility and other reproductive conditions. (A) Pie-chart shows the population distribution of infertility amongst the assessed patients ($n = 100$, 62 infertile couples and 38 healthy patients). Out of 62 infertile couples, 60 cases were found to be associated with female infertility (39 cases of only female infertility and 21 cases of both male and female infertility), while 2 cases were identified as only male infertility leading to failure in conception. (B) Histogram shows the percentage distribution of primary and secondary infertility amongst the 62 cases of infertility. (C) Histogram shows the age-based population distribution (females) of primary and secondary infertility amongst 62 cases of infertility. (D) Pie chart shows percentage population of preterm birth, spontaneous abortions/medical termination of pregnancy (MTP), ectopic pregnancy, and no conception amongst infertile females ($n = 62$). (E) Age-based population distribution of females ($n = 62$) experiencing preterm birth, spontaneous abortions/MTP, ectopic pregnancy, and no conception.

3.5 | Multivariate Correlation Analysis Among Various Parameters

The major objective of this analysis is to identify the most significant parameters (Table S1, Supporting Information 3) that impact fertility and reproductive health in females. We also wanted to assess if changes in these critical female parameters co-occur/correlate with the reduced sperm/semen quality in males, which can happen as a consequence of male genital infection [39, 40]. We stratified the parameters into various categories such as (a) menstrual disorders (Table S2A and B, Supporting Information 3), (b) reproductive tract anomalies such as endometriosis, other endometrial disorders (eg thickened/secretory/proliferative endometrium/hyperplasia/cysts), fallopian tube or uterine blockages, PCOS/PCOD, anovulation and ovarian cysts/teratoma (Table S2A, Supporting Information 3), (c) genital infection associated symptoms/confirmed diagnosis of infections like TB/UTIs (Table S2A, Supporting Information 3), (d) physiological parameters such as reproductive hormones (FSH, LH, Prolactin, AMH) (Table S2D, Supporting Information 3 and 4), (e) physical parameters and lifestyles, such as weight, height, BMI and exercise routine (Table S2A and C, Supporting Information 3 and 4) and (f) male sperm and semen abnormalities (Table S2A, Supporting Information 3 and 4). To derive the correlations between various parameters, we performed multivariate correlation analysis (Phi correlation) [41–43].

We observe a highly significant and very strong correlation between parameters related to genital infection-associated symptoms (or confirmed diagnosis) and menstrual disorders such as oligomenorrhoea, amenorrhoea, metrorrhagia, and dysmenorrhoea. (Figures 5 and 6). Further, a very strong and significant correlation is observed between genital infections and perturbations in the female reproductive hormones such as LH (Figures 5 and 6). For more details on comparisons and categorization of the LH, FSH, AMH and prolactin hormonal profiles in the infertile patients, see Figure S1A and B in Supporting Information 4. The presence of infection-associated symptoms also is strongly correlated with the occurrence of

TABLE 1 | Demographic variables of the study population.

A. Demographic distribution of fertility status of couples amongst study population based on gender (corresponding to the analytical graph provided in Figure 2A).

Fertility status of the couple	No. of Patients (Represents percentage as well against to total study population)
Healthy individuals	38
Only male infertility	2
Only female infertility	39
Both male and female infertility	21

B. Demographic distribution of the infertile study population based on categorisation into primary and secondary infertility (corresponding to the analytical graph provided in Figure 2B and C). Percentages in the brackets are represented against the infertile study population.

Age group in years	Primary infertility	Secondary Infertility
18-20	6 (10%)	0 (0%)
21-25	29 (46%)	3 (5%)
26-30	18 (29%)	3 (5%)
31-35	1 (2%)	2 (3%)
Total	**54 (87%)**	**8 (13%)**

C. Demographic distribution of the infertile study population based on outcomes of infertility (corresponding to the analytical graph provided in Figure 2D and E). Percentages in the brackets are represented against the infertile study population.

Age group in years	Preterm birth	Spontaneous abortions/MTP	Ectopic pregnancies	No pregnancies
18-20 years	0 (0%)	2 (3%)	0 (0%)	4 (7%)
21-25 years	0 (0%)	7 (11%)	2 (3%)	23 (37%)
26-30 years	0 (0%)	4 (7%)	0 (0%)	17 (27%)
31-35 years	0 (0%)	1 (2%)	0 (0%)	2 (3%)
Total	**0 (0%)**	**14 (23%)**	**2 (3%)**	**46 (74%)**

PCOS and PCOD, uterine and tubal blockage, ovarian cysts, and endometrial disorders (Figures 5 and 6).

We next assessed if female genital infection factors correlate/co-occur with male infection factors, such as abnormalities in the semen and sperm profile. Our study suggests a very strong and significant correlation of female genital infections with the occurrence of teratozoospermia, pyospermia, and hyper viscosity of semen, and a strong correlation with asthenozoospermia. The abnormalities observed in male partners of infertile females in this study concur well with the previously reported sperm abnormalities during male genital infections [39, 40], however, no confirmatory diagnostic reports were available to verify the nature of infections in these males (Figures 5 and 6, Figure S2 A and B in Supporting Information 4). Another key finding is a very strong and significant correlation between male semen/sperm abnormalities characteristic of infections, such as low sperm DNA integrity, asthenozoospermia, teratozoospermia, pyospermia and hyper viscosity with female disorders such as occurrence of PCOS and PCOD, uterine and tubal blockage, oligomenorrhoea, amenorrhoea, metrorrhagia & dysmenorrhoea (Figures 5 and 6, Figure S2A and B in Supporting Information 4). These observations highlight that transmission of genital infections between sexual partners could potentially influence female menstrual health and fertility in both males and females. Male factors are also strongly correlated with hormonal perturbations in infertile females such as FSH, LH, and AMH (Figures 5 and 6).

Among other parameters, we observe a strong and significant correlation between reproductive tract anomalies such as PCOS and PCOD with the occurrence of menstrual disorders such as amenorrhoea (Figures 5 and 6). We also observe endometrial disorders to impact menstrual health and are significantly correlated with menorrhagia. We next assessed if the reproductive tract anomalies are linked with reproductive hormones. We observe a strong and significant correlation between ovarian cysts with AMH and anovulation with FSH, LH, and prolactin (Figures 5 and 6). In addition, uterine and tubal blockage are strongly correlated with prolactin, LH, and AMH levels (Figures 5 and 6). However, one limitation of the data collected was the presence of reports corresponding to female reproductive hormones only in a limited number of patients (Figure S1A and B, Supporting Information 4 and Table S2D, Supporting Information 3).

Peculiarly, we observe a very strong and significant correlation between BMI in females and genital infection-associated

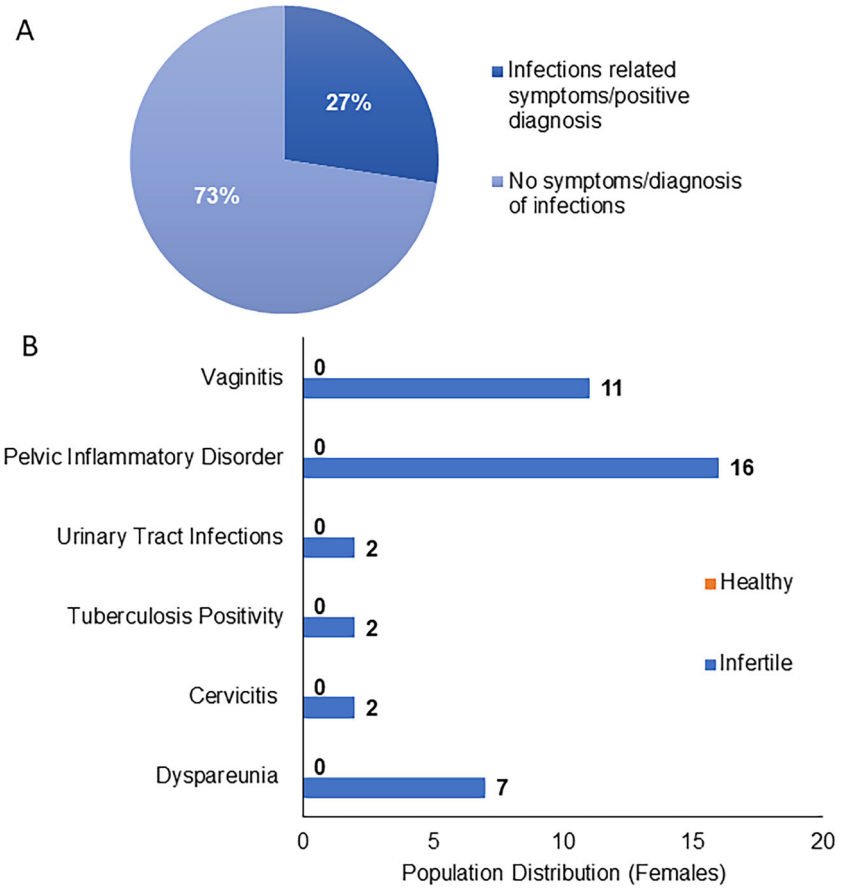

FIGURE 3 | Contribution of genital infections to female infertility. (A) The Pie chart shows percentage of infertile females experiencing symptoms of genital infections or confirmed diagnosis of infection. Reports suggest tuberculosis infection (based on PPD tests) in 2 cases out of 62 patients, while other infections are not identified during diagnosis. (B) Histogram shows population distribution of various genital infection related symptoms in females belonging to infertile group ($n = 62$, all cases of infertility) and healthy group ($n = 38$). Healthy females do not show any symptoms of infection; hence their bar is represented as "0".

symptoms (such as dyspareunia/cervicitis/vaginitis), menstrual disorders (such as menorrhagia), and reproductive hormones (such as LH) (Figures 5 and 6). For more details on contribution of lifestyle and BMI see Figure S1 C and D in Supporting Information 4.

3.6 | Predictors of Infertility Identified by Multivariate Logistic Regression Analysis

The multivariate logistic regression analysis identified several predictors associated with infertility, with likelihood ratios calculated for each. Additionally, regression coefficient values (β) were determined to indicate the direction and strength of association. Parameters with a likelihood ratio greater than 1 and positive regression coefficients included: TB positivity, confirmed UTI or visible symptoms of UTI, vaginitis and oligospermia (Table 2). Pyospermia in the male spouse showed a positive regression coefficient value as well (Table 2). However, for these parameters, p-values were found to be greater than 0.9, suggesting that while there is a positive predictive association with infertility (as indicated by $\beta > 0$), these results are not statistically significant in this analysis (Table 2). The following parameters also showed a significant positive association with infertility, indicated by likelihood ratios greater than 1, such as menstrual irregularities -oligomenorrhea ($p < 0.05$) and dysmenorrhea ($p < 0.05$), anovulation, endometrial abnormalities, ovarian cysts, PID ($p < 0.05$), hormonal markers (prolactin and AMH) and abnormal BMI ($p < 0.05$) (Table 2). Among these, parameters with notably high likelihood ratios (> 10, $p < 0.05$), demonstrating a very strong association with infertility, were PCOS/PCOD, repeated abortions/MTP and abnormal FSH levels (Table 2).

These findings suggest that while multiple factors are associated with infertility, certain conditions—particularly PCOS/PCOD, a history of abortion/MTP, and abnormal FSH—exhibit the strongest association in this study population.

4 | Discussion

Our pilot-scale investigation revealed that genital infections are often overlooked during fertility assessment in women of reproductive age, indicating a glaring gap in current healthcare practices and a significant lack of robust POC diagnostic tools in rural areas for detecting genital infections, including TB.

Hence, infertile women are typically not treated for infections unless there are visible signs. As a result, asymptomatic females remain undiagnosed for infections and do not receive appropriate

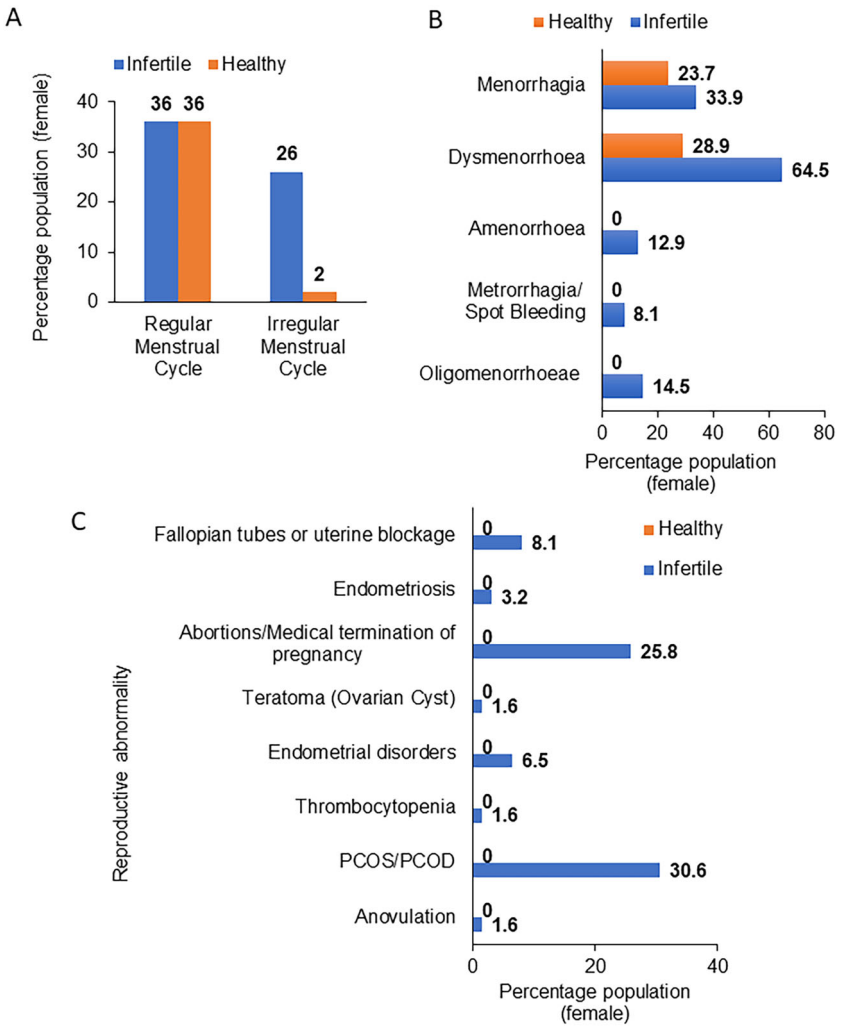

FIGURE 4 | Menstrual disorders and anatomical abnormalities of the reproductive tract in female infertility. (A) Histogram shows the percentage population distribution of females with respect to their menstrual health based on the regularity of the menstrual cycle. (B) Histogram shows population distribution of various menstrual disorders among females belonging to infertile ($n = 62$, all cases of infertility) and healthy group ($n = 38$). (C) Histogram shows population distribution of various anatomical abnormalities of the female reproductive tract in infertile ($n = 62$, all cases of infertility) and healthy group ($n = 38$). Infertile [%] = [No. of patients with symptoms/Total infertility cases]*100. Healthy [%] = [No. of healthy patients with symptoms/Total no. of healthy patients]*100.

health care promptly. This prolonged lack of diagnosis and treatment can lead to chronic infections and consequential pathological sequelae, ultimately resulting in infertility.

Our study reveals an early onset of infertility in females between 18 and 25 years of age, suggesting possibly occurrence of undiagnosed and untreated chronic infections postpuberty. Importantly, a substantial portion of these patients exhibited classical signs of infection (27%), while 73% were rendered ineligible for confirmatory diagnostic tests due to a lack of classical symptoms of infections. This underscores the urgent need for more comprehensive screening strategies. We observed in our study that infertile females present heterogenous symptoms such as, menstrual disorders, PCOS/PCOD, tubal blockage, endometriosis, anovulation, uterine fibroids, and ovarian cysts, making it extremely challenging for the clinicians to establish a clear link between these reproductive disorders and genital infections.

Furthermore, we observed a very strong and significant correlation of genital infections with physiological parameters (hormonal profiles and BMI) and pathological impact on female reproductive health (reproductive anomalies and menstrual disorders) and sperm/semen quality in the case of their respective spouses [44, 45].

While causation between pelvic infections and PCOS remains unestablished and requires further experimental validation in animal models, existing literature suggests a plausible indirect relationship mediated by inflammation, insulin resistance, hormonal imbalances, and menstrual disorders. González et al. demonstrated that chronic low-grade inflammation, characterized by elevated cytokines like TNF-α and adipocytokines, significantly contributes to insulin resistance and PCOS pathogenesis [46]. Supporting this, Juber et al. reported higher infection susceptibility among women with PCOS compared to those without the condition [47]. Furthermore, studies such as Azat and Rasim highlight the role of pelvic infections in disrupting hormonal balance, altering estrogen-to-androgen ratios, and contributing to menstrual irregularities and infertility, with partial recovery of ovarian function observed following

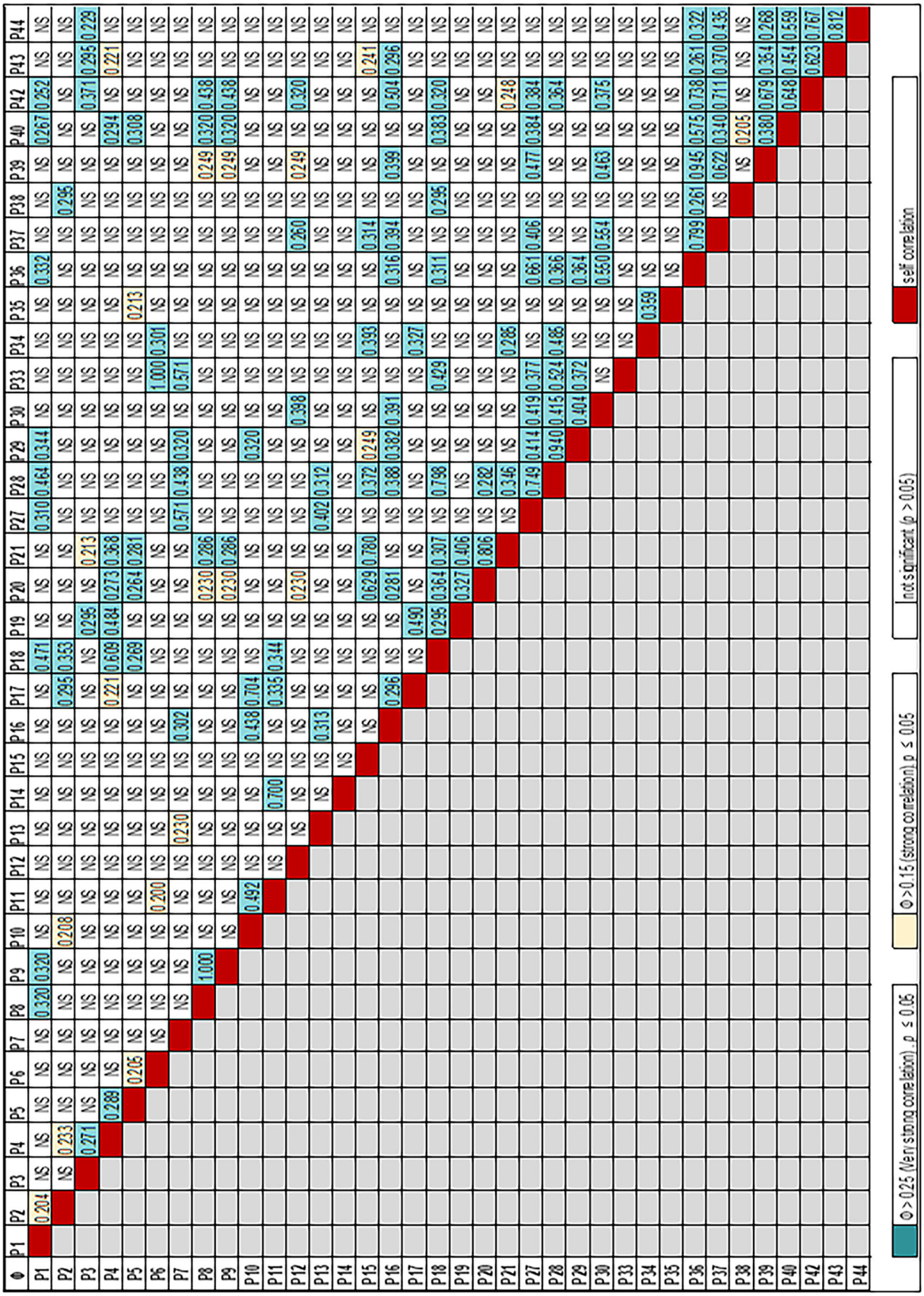

FIGURE 5 | Correlation heat map. The data gathered by questionnaire-based assessment of female patients is used for finding out the correlation amongst the various parameters used for the assessment. A multivariate correlation values (Phi correlation with significance of correlation $p \leq 0.05$) used for generating this correlation heat map. (P1-P45 are the various parameters assessed in this study; for description see Table S1).

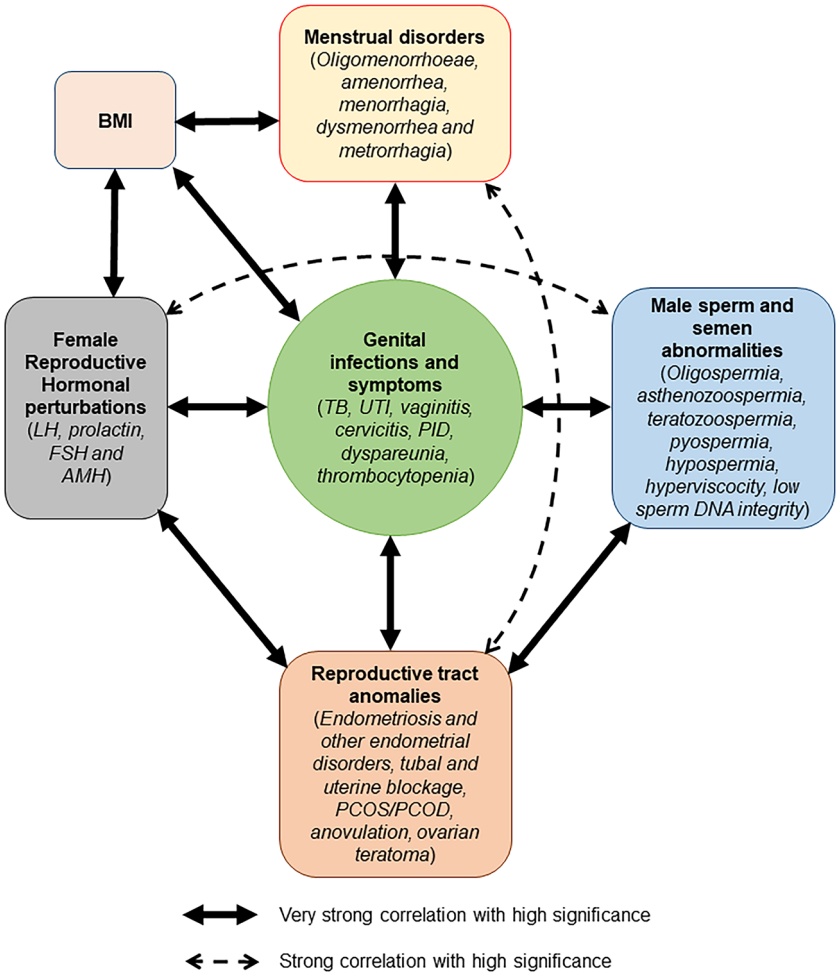

FIGURE 6 | Schematic diagram showing correlation between various fertility parameters and their association with the incidence of genital infections. The correlation between various parameters is depicted schematically with the help of bidirectional arrows of varying thickness corresponding to the strength of correlation between these parameters. The correlations are deduced from the multivariate correlation analysis (Phi correlation and the significance of the correlation). For details, refer to the correlation heat map shown in Figure 5.

antibiotic treatment [48]. The heterogeneity in the impact of pelvic infections on PCOS and menstrual disorders suggests a complex interplay, where factors like diabetes and obesity may predispose certain women to these conditions leading to dysbiosis and higher risk of infection with pathogenic species [49].

Hence, regular screening and treating these infections is crucial not only for improving female reproductive health but also for enhancing the success rate of fertility treatments, including assisted reproductive technologies (ART). Thus, our study emphasizes on the necessity of a POC for the detection of genital infections as a primary regular screening tool, especially in the rural settings, wherein, it is often challenging to diagnose asymptomatic and the regular culture tests may fail in efficiently diagnosing such cases [14, 21–26, 50]. A comprehensive questionnaire-based assessment followed by POC molecular diagnosis screening methods may aid in validating the clinical suspicion of genital infections and may further address the gap in reproductive health care [21–23, 51, 52].

The statistical analysis provides a comprehensive view of the factors associated with infertility. TB positivity, UTI symptoms, vaginitis, pyospermia, and oligospermia were found to have positive regression coefficients ($\beta > 0$), suggesting a directionally positive association with infertility. However, with p-values greater than 0.9 for these parameters, these findings are statistically nonsignificant in this study. Although these factors could theoretically influence reproductive health, the lack of statistical significance indicates that future studies with larger sample sizes could clarify these associations further.

The study also reaffirms the significance of menstrual irregularities, endometrial abnormalities, and ovarian factors as contributors to infertility. The strong likelihood ratios for PCOS/PCOD, repeated abortions, and abnormal FSH levels highlight their critical role in the etiology of infertility. PCOS/PCOD remains a prominent risk factor due to its hormonal and metabolic implications, which disrupt normal ovarian function [53]. The high likelihood ratio for repeated abortions/MTP with secondary infertility observed in our study could possibly originate from uterine scarring, sepsis, peritonitis, visceral injuries, and hormonal effects incurred during these surgical procedures as shown previously [54]. Abnormal FSH has also been previously found to be the biological basis of infertility due to consequent diminished ovarian reserve [55], which corroborates with our findings and underscores the

TABLE 2 | Multivariate logistic regression analysis of the various parameters associated with infertility in females.

	Likelihood ratio test		Regression coefficients (β)	
Paramater	**Chi-Square**	**Significance value**	**β value**	**Significance**
P1	4.598	0.032	−17.007	NS
P2	13.227	0	−17.527	0.993
P3	0.895	0.344	−15.674	NS
P4	0.895	0.344	−15.193	NS
P5	5.414	0.02	−1.134	0.023
P6	0.83	0.362	−0.426	0.368
P7	1.08	0.299	−15.965	NS
P8	0	NS	−15.539	NS
P9	0	NS	0	NS
P10	0.759	0.384	−15.539	NS
P11	2.827	0.093	−16.341	0.992
P12	1.427	0.232	−16.341	NS
P13	17.821	0	−16.124	0.984
P14	0	0.998	0	NS
P15	6.872	0.009	−15.792	0.989
P18	8.091	0.017	16.483	0.997
P19	0	1	15.247	0.997
P20	4.288	0.038	−18.086	0.995
P21	0	1	1.43	1
P27	25.658	0	−11.788	0.995
P28	0	1	−0.279	1
P29	5.541	0.063	−0.488	1
P30	2.384	0.304	−15.256	0.99
P33	2.784	0.249	−0.629	0.321
P34	8.256	0.041	−0.126	0.881
P35	0.508	0.476	0.425	0.48
P36	9.263	0.01	−13.189	0.994
P37	0	1	0.563	1
P38	0	0.995	NR	NR
P39	0.982	0.612	−10.344	0.996
P40	NR	NR	NR	NS
P41	0	1	0	1
P42	0	1	1.524	0.999
P43	0	1	NR	NR
P44	0	1	NR	NR
P45	NR	NR	NR	NR

Abbreviations: NR, No results obtained in the statistical analysis; NS, No significance.

indirect effect of infections with hypothalamic secretions and effect on fertility [15]. In addition, elevated prolactin and AMH levels observed in infertile patients in our study also highlight the role of hormonal dysregulation in fertility issues, aligning with existing knowledge about their role in reproductive health and increase during infections [56–59].

5 | Conclusion

In conclusion, this study highlights the significant association between genital infections and infertility, emphasizing the critical need for improved diagnostic and management approaches, particularly in rural areas. Our findings reveal a high

prevalence of genital infections among infertile women and underscore the potential benefits of integrating self-assessment questionnaires and point-of-care (POC) molecular diagnostic tools to facilitate timely diagnosis and intervention. Such measures could improve reproductive health outcomes and increase the success rates of fertility treatments. In addition to infectious factors, the study confirms that hormonal and pathological abnormalities—particularly PCOS/PCOD, repeated abortions/MTP, and abnormal FSH levels—are strong predictors of infertility, reinforcing the importance of a multifactorial approach in infertility risk assessment. Future research should further explore the links between infections and reproductive health, focusing on tailored interventions to address both infectious and noninfectious contributors to infertility.

Author Contributions

Naresh Patnaik: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, software, validation, visualization, writing – original draft, writing – review and editing. **Uttam Sarkar:** formal analysis, software, validation, visualization, writing – review and editing. **Malathi Jojula:** data curation, investigation, resources, validation, visualization. **Hema Vaddiraju:** data curation, investigation, resources, validation, visualization. **Ruchi Jain Dey:** conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, visualization, writing – original draft, writing – review and editing.

Acknowledgments

Source of financial support in the form of grants: Birla Institute of Technology and Science, Pilani, for Open Access Publication support, Indian Council of Medical Research (ICMR), Govt. of India, Senior Research Fellowship (RBMH/FW/2019/13) awarded to Naresh Patnaik (2019-2022)Research Initiation Grant (RIG) and Centre for Human Disease Research (CHDR) programs intramurally funded by Birla Institute of Science and Technology (BITS) Pilani, Hyderabad campus, India to Ruchi Jain Dey (June 2018- March 2023), Ramalingaswami Re-entry fellowship (BT/RLF/Re-entry/18/2016) awarded to Ruchi Jain Dey (May 2018- April 2023).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Transparency Statement

The lead author Ruchi Jain Dey affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

References

1. STROBE. CONSORT CHECKLIST. 2010, https://www.strobe-statement.org/.

2. M. Halleran, A. Chernoff, and J. L. Gordon, "Fertility Knowledge Among Women Struggling to Conceive Without Medical Intervention: A Brief Report," *Frontiers in Global Women's Health* 3 (2022): 828052.

3. P. Njagi, W. Groot, J. Arsenijevic, S. Dyer, G. Mburu, and J. Kiarie, "Financial Costs of Assisted Reproductive Technology for Patients in Low- and Middle-Income Countries: A Systematic Review," *Human Reproduction Open* 2023, no. 2 (2023): hoad007.

4. WHO. 1 in 6 People Globally Affected by Infertility: WHO. 2023, https://www.who.int/news/item/04-04-2023-1-in-6-people-globally-affected-by-infertility#:~:text=Large%20numbers%20of%20people%20are,report%20published%20today%20by%20WHO, accessed 4th April 2023.

5. J. Wu, D. Li, X. Liu, et al., "IDDB: A Comprehensive Resource Featuring Genes, Variants and Characteristics Associated With Infertility," *Nucleic Acids Research* 49, no. D1 (2020): D1218–D1224.

6. J. Sharma, S. Dharmendra, S. Agarwal, and E. Sharma, "Genital Tuberculosis and Infertility," *Fertility Science and Research* 3, no. 1 (2016): 6.

7. P. Deshpande and A. Gupta, "Causes and Prevalence of Factors Causing Infertility in a Public Health Facility," *Journal of Human Reproductive Sciences* 12, no. 4 (2019): 287.

8. J. E. Allsworth and J. F. Peipert, "Prevalence of Bacterial Vaginosis: 2001–2004 National Health and Nutrition Examination Survey Data," *Obstetrics and Gynecology* 109, no. 1 (2007): 114–120.

9. S. J. Dyer and M. Patel, "The Economic Impact of Infertility on Women in Developing Countries-A Systematic Review," *Facts, Views & Vision in ObGyn* 4, no. 2 (2012): 102–109.

10. K. Saigal, B. Dhawan, J. Rawre, N. Khanna, and R. Chaudhry, "Genital Mycoplasma and Chlamydia Trachomatis Infections in Patients With Genital Tract Infections Attending a Tertiary Care Hospital of North India," *Indian Journal of Pathology and Microbiology* 59, no. 2 (2016): 194.

11. B. Dhawan, S. Khullar, J. Rawre, S. Gupta, and N. Khanna, "Prevalence of Genital Chlamydia Trachomatis At a Tertiary Care Hospital in North India: A 10-year Observational Study," *Indian Journal of Sexually Transmitted Diseases and AIDS* 44, no. 1 (2023): 104–105.

12. C. L. Haggerty, P. A. Totten, G. Tang, et al., "Identification of Novel Microbes Associated With Pelvic Inflammatory Disease and Infertility," *Sexually Transmitted Infections* 92, no. 6 (2016): 441–446.

13. H. C. Wiesenfeld, S. L. Hillier, L. A. Meyn, A. J. Amortegui, and R. L. Sweet, "Subclinical Pelvic Inflammatory Disease and Infertility," *Obstetrics and Gynecology* 120, no. 1 (2012): 37–43.

14. E. Cicinelli, M. Matteo, R. Tinelli, et al., "Prevalence of Chronic Endometritis in Repeated Unexplained Implantation Failure and the IVF Success Rate After Antibiotic Therapy," *Human Reproduction* 30, no. 2 (2015): 323–330.

15. P. R. Jirge, S. M. Chougule, A. Keni, S. Kumar, and D. Modi, "Latent Genital Tuberculosis Adversely Affects the Ovarian Reserve in Infertile Women," *Human Reproduction* 33, no. 7 (2018): 1262–1269.

16. P. R. Jirge, "Effect of Genital Tuberculosis on Ovarian Reserve," *US Endocrinology* 16 (2020): 104–108.

17. J. B. Sharma, E. Sharma, S. Sharma, and S. Dharmendra, "Recent Advances in Diagnosis and Management of Female Genital Tuberculosis," *Journal of Obstetrics and Gynecology of India* 71, no. 5 (2021): 476–487.

18. D. Zahoor, M. M. Bhat, F. Kanth, and A. Farhana, "Prevalence of Genital Tuberculosis in Infertile Women: A Study From a Tertiary Care Center in North India," *International Journal of Contemporary Medical Research [IJCMR]* 6, no. 6 (2019): F1–F3.

19. S. Agarwal, J. Chauhan, A. Vacchani, and K. K. Ahir, "A Study on Co-Relation of Infertility and Female Genital Tuberculosis," *National Journal of Medical Research* 6, no. 02 (2016): 151–154.

20. D. Sharma, A. Depan, K. Yadav, S. Narayan, and A. Sharma, "Prevalence of Female Genital Tract Tuberculosis in Suspected Cases Attending Gynecology OPD At Tertiary Centre by Various Diagnostic Methods and Comparative Analysis," *International Journal of Reproduction, Contraception, Obstetrics and Gynecology* 8, no. 6 (2019): 2286–2293.

21. J. B. Sharma, E. Sharma, S. Sharma, and S. Dharmendra, "Female Genital Tuberculosis: Revisited," *Indian Journal of Medical Research* 148, no. Suppl 1 (2018): S71–S83.

22. S. N. Tripathy and S. N. Tripathy, "Infertility and Pregnancy Outcome in Female Genital Tuberculosis," *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics* 76, no. 2 (2002): 159–163.

23. S. Tripathy, *Tuberculosis Manual for Obstetricians & Gynecologists* (JP Medical Ltd, 2015).

24. B. Dhawan, J. Rawre, A. Ghosh, et al., "Diagnostic Efficacy of a Real Time-Pcr Assay for Chlamydia Trachomatis Infection in Infertile Women in North India," *Indian Journal of Medical Research* 140, no. 2 (2014): 252–261.

25. B. Dhawan, N. Malhotra, V. Sreenivas, et al., "Ureaplasma Serovars & Their Antimicrobial Susceptibility in Patients of Infertility & Genital Tract Infections,"*Indian Journal of Medical Research* 136, no. 6 (2012): 991–996.

26. N. Arif, J. Rawre, S. Patra, V. Sreenivas, N. Khanna, and B. Dhawan, "Increase in Prevalence of Ureaplasma Spp. in Patients With Genital Tract Infections in a Tertiary Care Hospital of North India," *Indian Journal of Dermatology, Venereology and Leprology* 84 (2018): 457.

27. B. Dhawan, J. Rawre, A. Ghosh, et al., "Diagnostic Efficacy of a Real Time-Pcr Assay for Chlamydia Trachomatis Infection in Infertile Women in North India," *Indian Journal of Medical Research* 140, no. 2 (2014): 252–261.

28. A. Krishnan, S. Sabeena, P. V. Bhat, et al., "Detection of Genital Chlamydial and Gonococcal Infection Using Urine Samples: A Community-Based Study From India," *Journal of Infection and Public Health* 11, no. 1 (2018): 75–79.

29. B. Dhawan, V. Gupta, N. Khanna, M. Singh, and R. Chaudhry, "Evaluation of the Diagnostic Efficacy of PCR for *Ureaplasma Urealyticum* Infection in Indian Adults With Symptoms of Genital Discharge," *Japanese Journal of Infectious Diseases* 59, no. 1 (2006): 57–58.

30. C. M. Mangione, M. J. Barry, W. K. Nicholson, et al., "Serologic Screening for Genital Herpes Infection: US Preventive Services Task Force Reaffirmation Recommendation Statement," *Journal of the American Medical Association* 329, no. 6 (2023): 502–507.

31. L. Chaubey, D. Kumar, V. Prakash, and G. Nath, "Menstrual Blood Versus Endometrial Biopsy in Detection of Genital Tuberculosis by Using Nested Polymerase Chain Reaction in an Endemic Region," *Journal of Human Reproductive Sciences* 12, no. 1 (2019): 35–39.

32. I. Moreno and C. Simon, "Deciphering the Effect of Reproductive Tract Microbiota on Human Reproduction," *Reproductive Medicine and Biology* 18, no. 1 (2019): 40–50.

33. S. G. Vitale, F. Ferrari, and M. Ciebiera, et al, "The Role of Genital Tract Microbiome in Fertility: A Systematic Review," *International Journal of Molecular Sciences* 23, no. 1 (2021): 180, https://doi.org/10.3390/ijms23010180.

34. U. Gudnadottir, J. W. Debelius, J. Du, et al., "The Vaginal Microbiome and the Risk of Preterm Birth: A Systematic Review and Network Meta-Analysis," *International Journal of Molecular Sciences* 12, no. 1 (2022): 7926.

35. L. A. Mattos, L. J. Sauer, R. Blasbalg, C. A. Petta, R. M. Pereira, and L. F. P. Carvalho, "Hysterosalpingography Using Magnetic Resonance Imaging for Infertility Patients," *JBRA Assisted Reproduction* 25, no. 3 (2021): 403–411.

36. M. Assel, D. Sjoberg, A. Elders, et al., "Guidelines for Reporting of Statistics for Clinical Research in Urology," *BJU International* 123, no. 3 (2019): 401–410.

37. S. Patra Female Infertility in India: Causes, Treatment, and Fertility Impairment in High Prevalence Districts. Paper presented at: PAA 2017 Annual Meeting 2017.

38. R. L. Scheaffer, W. Mendenhall, III, R. L. Ott, and K. G. Gerow, *Elementary Survey Sampling* (Cengage Learning, 2011).

39. E. Moretti, S. Capitani, N. Figura, et al., "The Presence of Bacteria Species in Semen and Sperm Quality," *Journal of Assisted Reproduction and Genetics* 26 (2009): 47–56.

40. M. Solomon and R. Henkel, "Semen Culture and the Assessment of Genitourinary Tract Infections," *Indian Journal of Urology* 33, no. 3 (2017): 188.

41. H. Akoglu, "User's Guide to Correlation Coefficients," *Turkish Journal of Emergency Medicine* 18, no. 3 (2018): 91–93.

42. Z. Hosseinzadeh-Shanjani, K. Hajimiri, B. Rostami, S. Ramazani, and M. Dadashi, "Stress, Anxiety, and Depression Levels Among Healthcare Staff During the COVID-19 Epidemic," *Basic and Clinical Neuroscience Journal* 11, no. 2 (2020): 163–170.

43. B. M. Kerur, B. V. Bhat, B. N. Harish, S. Habeebullah, and C. U. Kumar, "Maternal Genital Bacteria and Surface Colonization in Early Neonatal Sepsis," *Indian Journal of Pediatrics* 73 (2006): 29–32.

44. S. Sedighi, S. A. A. Akbari, M. Afrakhteh, T. Esteki, H. A. Majd, and Z. Mahmoodi, "Comparison of Lifestyle in Women With Polycystic Ovary Syndrome and Healthy Women," *Global Journal of Health Science* 7, no. 1 (2015): 228.

45. S. S. Lim, S. K. Hutchison, E. Van Ryswyk, R. J. Norman, H. J. Teede, and L. J. Moran, "Lifestyle Changes in Women With Polycystic Ovary Syndrome," *Cochrane Database of Systematic Reviews* 2019, no. 3 (2019): CD007506, https://doi.org/10.1002/14651858.CD007506.pub4.

46. F. González, "Inflammation in Polycystic Ovary Syndrome: Underpinning of Insulin Resistance and Ovarian Dysfunction," *Steroids* 77, no. 4 (2012): 300–305.

47. N. F. Juber, A. Abdulle, A. Ahmad, et al., "Associations Between Polycystic Ovary Syndrome (Pcos) and Antibiotic Use: Results From the Uaehfs," *Antibiotics (USSR)* 13, no. 5 (2024): 397.

48. A. A. Rasimovich and A. R. Mindrakhmanovich, "The Effect of Inflammatory Diseases Associated With Opportunistic Urogenital Infection on the Hormonal Function of the Female Reproductive System," *International Journal of Reproductive Biomedicine* 16, no. 11 (2018): 697.

49. S. Zheng, H. Chen, H. Yang, et al., "Differential Enrichment of Bacteria and Phages in the Vaginal Microbiomes in PCOS and Obesity: Shotgun Sequencing Analysis," *Frontiers in Microbiomes* 2 (2024): 1229723.

50. M. F. Gallo, M. Macaluso, L. Warner, et al., "Bacterial Vaginosis, Gonorrhea, and Chlamydial Infection Among Women Attending a Sexually Transmitted Disease Clinic: A Longitudinal Analysis of Possible Causal Links," *Annals of Epidemiology* 22, no. 3 (2012): 213–220.

51. K. A. Workowski, G. A. Bolan, and P. Centers for Disease Control and, "Sexually Transmitted Diseases Treatment Guidelines, 2015," *MMWR. Recommendations and Reports: Morbidity and Mortality Weekly Report. Recommendations and Reports* 64, no. Rr–03 (2015): 1–137.

52. H. C. Wiesenfeld, L. A. Meyn, T. Darville, I. S. Macio, and S. L. Hillier, "A Randomized Controlled Trial of Ceftriaxone and Doxycycline, With or Without Metronidazole, for the Treatment of Acute Pelvic Inflammatory Disease," *Clinical Infectious Diseases* 72, no. 7 (2021): 1181–1189.

53. R. R. S. Saini, S. Gupta, M. Tyagi, S. Agrawal, and B. K. Gupta, "Clinical, Hormonal and Ovarian Morphological Correlation in Women With Polycystic Ovary Syndrome," *International Journal of Reproduction, Contraception, Obstetrics and Gynecology* 11, no. 4 (2022): 1102–1109.

54. S. Gadappa and R. Pardeshi, "Life-Threatening Complications of MTP/Abortion." *Principles of Critical Care in Obstetrics: Volume II* (Springer, 2016), 295–307.

55. H. Abdalla, "An Elevated Basal Fsh Reflects a Quantitative Rather Than Qualitative Decline of the Ovarian Reserve," *Human Reproduction* 19, no. 4 (2004): 893–898.

56. A. Wdowiak, D. Raczkiewicz, P. Janczyk, I. Bojar, M. Makara-Studzińska, and A. Wdowiak-Filip, "Interactions of Cortisol and Prolactin With Other Selected Menstrual Cycle Hormones Affecting the Chances of Conception in Infertile Women," *International Journal of Environmental Research and Public Health* 17, no. 20 (2020): 7537.

57. A. Montero, O. A. Bottasso, R. Luraghi, A. G. Giovannoni, and L. Sen, "Association Between High Serum Prolactin Levels and Concomitant Infections in HIV-Infected Patients," *Human Immunology* 62, no. 2 (2001): 191–196.

58. D. N. Nguyen, L. Huyghens, J. Schiettecatte, J. Smitz, and J.-L. Vincent, "High Prolactin Levels Are Associated With More Delirium in Septic Patients," *Journal of Critical Care* 33 (2016): 56–61.

59. R. Scherzer, P. Bacchetti, G. Messerlian, et al., "Impact of CD 4+ Lymphocytes and HIV Infection on Anti-Müllerian Hormone Levels in a Large Cohort of HIV-Infected and HIV-Uninfected Women," *American Journal of Reproductive Immunology* 73, no. 3 (2015): 273–284.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.