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Clinical and Laboratory Characterization of Male Infertility in five Familial and Sporadic Cases

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Abstract

Introduction: Male infertility is a complex reproductive disorder influenced by abnormalities in sperm characteristics, hormonal imbalance, and various genetic and environmental factors. Semen analysis is an essential diagnostic tool for evaluating male reproductive health and identifying abnormalities associated with infertility. The present study was conducted in District Malakand, Khyber Pakhtunkhwa, Pakistan, to investigate semen parameters among infertile males from familial and unrelated cases. **Methodology:** A total of 53 infertile males were included in the study, comprising 16 individuals from five families and 37 unrelated infertile individuals. Semen samples were collected under standardized laboratory conditions and analyzed according to the World Health Organization (WHO) guidelines. Parameters including semen volume, sperm count, motility, morphology, viability, and the presence of pus cells were evaluated to assess semen quality among the participants. **Results**: The results revealed considerable variation in semen quality among the affected individuals. Azoospermia was observed in 24.32% of unrelated infertile males, indicating the complete absence of sperm in semen. Several individuals exhibited oligospermia characterized by reduced sperm concentration. Normospermia with functional impairment was detected in 24.32% of cases, suggesting that normal semen parameters do not always guarantee fertility. Teratospermia and hypospermia were identified in 13.51% and 10.81% of individuals, respectively. Familial analysis also showed that some affected members had normal sperm concentration but reduced motility and increased dead sperm percentage. **Conclusion**: In conclusion, abnormalities in sperm concentration, motility, morphology, and viability were strongly associated with infertility in the studied population. Comprehensive semen evaluation is essential for accurate diagnosis, and further clinical and molecular studies are recommended to better understand the genetic and environmental factors contributing to male infertility.

Introduction

Infertility is a global health disorder defined as the inability of a couple to achieve conception after 360 days of regular, unprotected sexual intercourse (Nouriani, 2006). It represents a multifactorial condition involving both male and female partners. Male factors are estimated to contribute to nearly half of all infertility cases, while approximately 30% remain idiopathic with no clearly identifiable cause (Vicdana at al., 2004; Yang at al., 2005). Male infertility constitutes a major reproductive health concern worldwide, including in Pakistan (Khan et al., 2011). According to a World Health Organization report, infertility affected approximately 48.5 million couples globally in 2010. It has been reported that 1.9% of women aged 20–44 years who desired children were unable to achieve their first live birth, while 10.5% were unable to conceive a second child even after five years of continuous attempts. Overall, infertility is estimated to affect nearly one in six couples worldwide. In Pakistan, infertility is a significant public health issue. Although Pakistan ranks among the most populous countries in the world, the prevalence of infertility is reported to be 21.9%, of which 3.5% constitutes primary infertility and 18.4% secondary infertility (Khan et

al., 2011). Primary infertility refers to couples who have never achieved pregnancy despite regular unprotected intercourse without contraception. It may also include cases where repeated miscarriages prevent successful continuation of pregnancy (Nouriani, 2006). Secondary infertility refers to difficulty in conceiving after previously achieving at least one pregnancy. Approximately 40% of infertility cases are attributed to male factors, 40% to female factors, and 20% remain unexplained (Access, 1996).

Subfertility represents a reduced level of fertility characterized by delayed conception within one year. Most conceptions occur during early reproductive cycles, with nearly 80% of pregnancies achieved within the first six fertile cycles. Failure to conceive beyond this period increases the likelihood of subfertility, affecting approximately 10–12% of couples (Access, 1996). Varicocele, defined as abnormal dilation and tortuosity of the pampiniform plexus veins within the scrotum, is a common condition associated with male infertility. It affects approximately 10–15% of men and is most frequently observed in adolescents and young adults, particularly during the second and third decades of life (Thomas, 1997). Male genital tract infections represent another important cause of infertility, accounting for nearly 12% of male infertility cases. These include infections of the prostate gland, epididymis, and testes (orchitis). Among these, prostate-related disorders are particularly significant due to the prostate's essential role in semen production and sperm function (Dohle, 2003).

MATERIALS AND METHODS

Biological Samples Collection

Periphral Blood and semen samples were collected under aseptic conditions. Blood was used to assess reproductive hormones, and semen was analyzed for volume, concentration, morphology, motility, pH, and liquefaction time following WHO guidelines (2010).

Semen Analysis

Macroscopic semen features (volume, color, pH, liquefaction time) were recorded. Microscopic examination was performed at 200× magnification to assess sperm morphology, motility, aggregation, and presence of non-sperm cells.

Sperm Concentration and Motility

The sperm concentration and motility were carefully determined using a hemocytometer and phase-contrast microscopy. Hoewere, the percentages of progressively motile, non-motile, and sluggish sperm were calculated from 100 spermatozoa across three fields per sample.

Sperm Morphology

The morphology of 100 spermatozoa per sample was carefully evaluated, and the percentages of normal and abnormal forms were calculated according to WHO principle and criteria.

RESULTS

The present investigation was conducted in District Malakand, Khyber Pakhtunkhwa, Pakistan. A total of five families were studied, comprising 16 infertile male individuals and 21 unaffected individuals. In addition, 37 unrelated infertile males from different regions of District Malakand were recruited for comparative semen analysis. Semen samples were collected from affected individuals after informed consent. For familial cases, pedigrees covering three to four generations were constructed to assess inheritance patterns and the presence of consanguineous marriages. Family MIF-01 belonged to Dargai, District Malakand, and consisted of 19 members across three generations. Two infertile males (MIF-01/III-8 and MIF-

01/III-10) were identified in the third generation. Both affected individuals showed normal semen volume and sperm concentration. However, increased sluggish and dead sperm percentages were observed, along with mild infection. While, family MIF-02 belonged to Thana and included two infertile males (MIF-02/II-1 and MIF-02/II-2) in the second generation. Consanguineous marriage was observed in this family. Both individuals had normal semen volume and sperm concentration; however, significantly reduced motility and high dead sperm percentage were observed, indicating severe impairment and infection. **Family MIF-03** Two infertile males (MIF-03/III-4 and MIF-03/III-9) were identified in this non-consanguineous family. Both individuals had normal semen volume and sperm count, but reduced motility and increased dead sperm percentage were observed, suggesting impaired sperm viability. **Family MIF-04** Three infertile males (MIF-04/III-4, MIF-04/III-6, and MIF-04/III-8) were identified in the third generation of this non-consanguineous family. Normal semen volume and sperm concentration were observed in all subjects. However, two individuals exhibited reduced motility and increased dead sperm percentage, indicating compromised sperm viability. **Family MIF-05** Four infertile males were identified in this family across multiple generations, with consanguineous marriages present. Severely impaired semen quality was observed in this family. One individual exhibited extremely low semen volume, while two individuals showed absence of motile sperm and very high dead sperm percentage. **Among 37** independent infertile males, multiple semen abnormalities were observed including azoospermia, oligospermia, hypospermia, and teratospermia. Overall semen parameters showed significant deviation from normal reference values.

Table 3.1 Semen Parameters of Family MIF-01 Compared with Reference Values

Parameter	Reference Value	MIF-01/III-8	MIF-01/III-10
Semen color	Whitish	Turbid white	Turbid white
Semen volume (mL)	≥2.0	2.0	2.5
Motile sperm (%)	≥45	60	42
Sluggish sperm (%)	0–5	30	30
Dead sperm (%)	0–5	10	28
Sperm count (million/mL)	20–130	80	55
Pus cells	0–5	10–15	8–10

Table 3.2 Semen Parameters of Family MIF-02 Compared with Reference Values

Parameter	Reference Value	MIF-02/II-1	MIF-02/II-2
Semen color	Whitish	Turbid white	Turbid white
Semen volume (mL)	≥2.0	2.8	2.5
Motile sperm (%)	≥45	10	25
Sluggish sperm (%)	0–5	10	30
Dead sperm (%)	0–5	80	45
Sperm count (million/mL)	20–130	65	40
Pus cells	0–5	10–15	8–10

Table 3.3 Semen Parameters of Family MIF-03 Compared with Reference Values

Parameter	Reference Value	MIF-03/III-4	MIF-03/III-9
Semen color	Whitish	Turbid white	Turbid white
Semen volume (mL)	≥2.0	2.0	2.5
Motile sperm (%)	≥45	20	40
Sluggish sperm (%)	0–5	10	15
Dead sperm (%)	0–5	70	45
Sperm count (million/mL)	20–130	55	65
Pus cells	0–5	0–1	4–5

Table 3.4 Semen Parameters of Family MIF-04 Compared with Reference Values

Parameter	Reference Value	MIF-04/III-4	MIF-04/III-6	MIF-04/III-8
Semen color	Whitish	Turbid white	Turbid white	Turbid white
Semen volume (mL)	≥2.0	2.0	2.5	2.2
Motile sperm (%)	≥45	68	35	40
Sluggish sperm (%)	0–5	20	25	15
Dead sperm (%)	0–5	12	40	45
Sperm count (million/mL)	20–130	40	55	40
Pus cells	0–5	2–3	3–4	2–5

Table 3.5 Semen Parameters of Family MIF-05 Compared with Reference Values

Parameter	Reference Value	MIF-05/01	MIF-05/02	MIF-05/03
Semen color	Whitish	Turbid white	Turbid white	Turbid white
Semen volume (mL)	≥2.0	3.0	2.5	0.1
Motile sperm (%)	≥45	0	25	0
Sluggish sperm (%)	0–5	0	0	15
Dead sperm (%)	0–5	100	60	0
Sperm count (million/mL)	20–130	0.2	—	80
Pus cells	0–5	1–2	1–2	4–5

Table 3.6 Summary of Semen Parameters in 37 Infertile Individuals

Parameter	Reference Value	Lowest	Highest	Mean
Semen volume (mL)	≥2.0	0.1	3.5	2.27
Motile sperm (%)	≥45	0	75	34
Sluggish sperm (%)	0–5	0	30	9.73
Dead sperm (%)	0–5	5	80	21
Sperm count (million/mL)	20–130	0	80	60.17
Pus cells	0–5	1–2	10–15	2.48–3.73

Table 3.7 Distribution of Sperm Abnormalities

S/No	Abnormality	Number of Patients
1	Azoospermia	9
2	Oligospermia	3
3	Hypospermia	4
4	Normospermia (with functional defect)	9
5	Teratospermia	5

DISCUSSION

Male infertility is a multifactorial condition influenced by hormonal balance, spermatogenesis, and semen quality. Evaluation of semen parameters together with key reproductive hormones such as follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, and testosterone plays a crucial role in identifying the underlying causes of infertility. Previous investigations, including the study by Brook et al. (1999), emphasized that combined hormonal and seminal analysis provide a more reliable assessment of male reproductive function. In the present study, semen characteristics were examined in infertile males from different families and unrelated individuals to understand the contribution of sperm abnormalities to infertility.

Azoospermia, defined as the complete absence of spermatozoa in semen, is a significant contributor to male infertility and is reported to account for approximately 10% of infertile male cases. In the current investigation, two individuals from Family MIF-05 (MIF-05/01 and MIF-05/02) were found to be azoospermic. Among the unrelated infertile individuals, seven out of thirty-seven subjects were diagnosed with azoospermia, representing 24.32% of the study population. These findings indicate a relatively higher prevalence compared with general estimates, suggesting possible genetic, environmental, or physiological influences within the studied population. Previous work by Olatinwo et al. (2002) reported that 58.8% of infertile males exhibited oligospermia, characterized by low sperm concentration. In the present study, several individuals including II-3, II-5, III-4, III-6, and IV-1 demonstrated reduced sperm counts, confirming the presence of oligospermia as another major factor contributing to male infertility.

Normospermia refers to the condition in which semen parameters such as sperm count, motility, and morphology fall within normal reference ranges despite infertility. Earlier studies, including Oghagbon (2004), reported that approximately 24.6% of infertile males exhibit normal semen characteristics, while Abduhadi et al. (2007) observed normospermia in about 25% of infertile patients. The findings of the present study are consistent with these reports, as 24.32% (9 out of 37) of the infertile individuals showed normal semen parameters yet remained infertile. This suggests that factors beyond routine semen analysis, such as functional sperm defects, genetic abnormalities, or hormonal imbalance, may contribute to infertility in these individuals.

Sperm morphology is another critical determinant of male fertility, as structural abnormalities in spermatozoa can impair motility, fertilization capacity, and overall reproductive success. Previous research by Teruaki et al. (2007) indicated that approximately 80–90% of infertility cases are associated with abnormal semen parameters, including defective sperm morphology. In the present study, teratospermia (abnormal sperm morphology) was observed in 13.51% (5/37) of infertile individuals, while hypospermia (reduced semen volume) was detected in 10.81% (4/37) of the cases. Although the frequency observed in this study was lower than previously reported, abnormal morphology and reduced semen volume were still significant contributors to impaired fertility among the studied population. These

findings highlight the importance of detailed semen evaluation in diagnosing and understanding male infertility.

CONCLUSIONS

The present study concludes that male infertility in the investigated population is primarily associated with abnormalities in semen parameters, including sperm concentration, motility, morphology, and viability. A significant proportion of individuals were diagnosed with azoospermia and oligospermia, indicating impaired spermatogenesis. The occurrence of teratospermia and hypospermia further emphasizes the role of structural and quantitative abnormalities in male reproductive failure. Familial clustering of infertility and the presence of consanguinity in some cases suggest possible genetic involvement. Overall, semen analysis proved to be a fundamental diagnostic tool for evaluating male infertility.

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CONFLICT OF INTEREST STATEMENT

The authors confirmed that they have no relevant financial or non-financial competing interest to reveal.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are available from the agreeing authors on reasonable request for research purpose only.

ETHICS STATEMENT

This study was approved by the Institutional Bioethics Committee at Government Postgrdaduate College Dargai, Malakand (BEC No. 195), thereby upholding the highest ethical standards. Prior to participation, a written informed consent was obtained from all recruited family elders and guardians."

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