Mini Review

Endocrine Dysfunction Leads to Increase Risk of Developing Infertility in Nepalese Male Population

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Abstract

Present study includes hormonal profile and semen analysis in two clinically diagnosed male infertile azoospermic and oligospermic cases. Male infertility, affecting 15%-20% of couples globally and there a need for comprehensive assessment to explore the etiopathology of disease. A cross-sectional study involving (n=100) individuals having age group 24 to 50 selected for hormonal profiles such as Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), and Testosterone using an immunoassay. Findings reveals, increased level of FSH and LH levels but decreased testosterone level in azoospermic cases, suggesting, hormonal imbalances may lead to affect spermatogenesis. Significant variations and correlation analyses in azoospermic and oligospermic revealed intricate relationships between age, hormone levels, and semen analysis outcomes, enriching our understanding of male reproductive health complexities.

Keywords: Male infertility; Hormonal assay; Azoospermia; Oligospermia; Spermatogenesis

Introduction

Infertility is usually described as the failure to conceive after at least a year of regular unprotected intercourse and 15%-20% of couples are affected by reproductive disorder [1]. Globally, estimated 72.4 million people are affected and WHO estimates that 9% of couples worldwide struggle with fertility issues. In 50% of couples are solely responsibility 30% in male and 20% in female factor [2]. Etiopathology of male infertility is a complex phenomenon affecting approximately 7% of the global human population with wide range of heterogeneous phenotypes, from congenital or acquired urogenital reproductive disorders, endocrine dysfunction including immunological factors during spermatogenesis [3]. Epidemiological data available over the past twenty years revealed that about 30% of cases shows abnormal pathology, therefore, the male factor is at least partly responsible in about 50% of infertile couples [4].

At present includes physical examination, semen analysis, biochemical examination, hormonal assay, immunological, radiological investigations, cytogenetic and testicular biopsy [5]. Gonadotrophins (FSH, LH) and testosterone are the prime regulators of germ cell development. The successful and complete male germ cell development depends on the balanced endocrine interplay of hypothalamus, pituitary and the testis. Episodic secretion of Gonadotrophin Releasing Hormone (GnRh) by the hypothalamus elicits the pulsatile release of gonadotrophins i.e. FSH and LH [6,7]. These hormones play an important role in steroidogenesis

for male gonads. In the testes, LH is the exclusive steroidogenic hormone acting for the regulation of interstitial cells of Leydig, and FSH acts for Sertoli cells. FSH binds with receptors in the Sertoli cells and stimulate spermatogenesis. LH stimulates the production of testosterone in Leydig cells and Sertoli cells for differentiation of peritubular cells of the seminiferous tubules regulating spermatogenesis [7]. Testosterone can be metabolized in peripheral tissue to the potent androgen in the form of dihydrotestosterone and act as the potent estrogen. These androgens and estrogens act independently to modulate the activity of LH secretion [5]. Isolated rise in FSH is an important and sensitive biomarker for the differentiation of the germinal epithelium. The increased FSH level in men with azoospermia or severe oligozoospermia (< 5million sperm/ml) is indicator a symptomatic damage of seminiferous tubule [8]. The failure of pituitary to secret FSH and LH will result in disruption of testicular function followed by hypogonadotropic hypogonadism leads to decreased sperm counts [9].

Materials and Methods

The analytical cross-sectional study aimed to investigate male infertility, specifically focusing on azoospermic and oligospermic cases in comparison to age-matched normozoospermia act as controls. A total of (n=100) individuals aged between 24 to 50 years, that comprise 50 case samples suspected with male infertility (azoospermic and oligospermic primary infertile) and equal number of control subjects (males of proven fertility) were recruited for the study. Moreover, the female partner of the respective individual male subject was not having any causes related to infertility. Total (5.0 ml) of venous blood was collected from each subject, following the acquisition of informed consent and collection of relevant information. Quantitative analysis of hormone profiles, including Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), and Testosterone was performed using Immunoassay analyzer (Access 2 Immunoassay Analyzer, Beckman Coulter, Inc. USA).

Result

In this study, the distribution of azoospermia, oligospermia, and those with normozoospermia act as controls were studied according to age groups. The majority of azoospermia cases fall within the 30-40 age group, whereas, controls are more evenly distributed across the 30-40 and 40-50 age groups (Table 1). Oligospermia cases are observed across all age groups, mostly in the 30-40 age group. In the study, individuals with azoospermia exhibited significantly elevated levels of mean FSH (17.94±14.14), mean LH (9.92±7.42), and lower mean testosterone (3.54±1.63) compared to the control group (mean FSH: 5.85±2.41, mean LH: 5.42±2.74, mean testosterone: 5.35±2.05), while those with oligospermia demonstrated intermediate values (mean FSH: 6.95±4.88, mean LH: 4.85±2.33, mean testosterone: 3.96±1.79) (Figure 1). The median and Interquartile Range (IQR) of Hormonal Levels (FSH, LH, and Testosterone) based on semen analysis reveal notable differences between azoospermia, oligospermia, and control groups. Azoospermia cases exhibit higher FSH levels as compared to controls, indicating a potential dysfunction in spermatogenesis (Table 2).

Table 1: Age wise distribution of semen analysis in different groups.

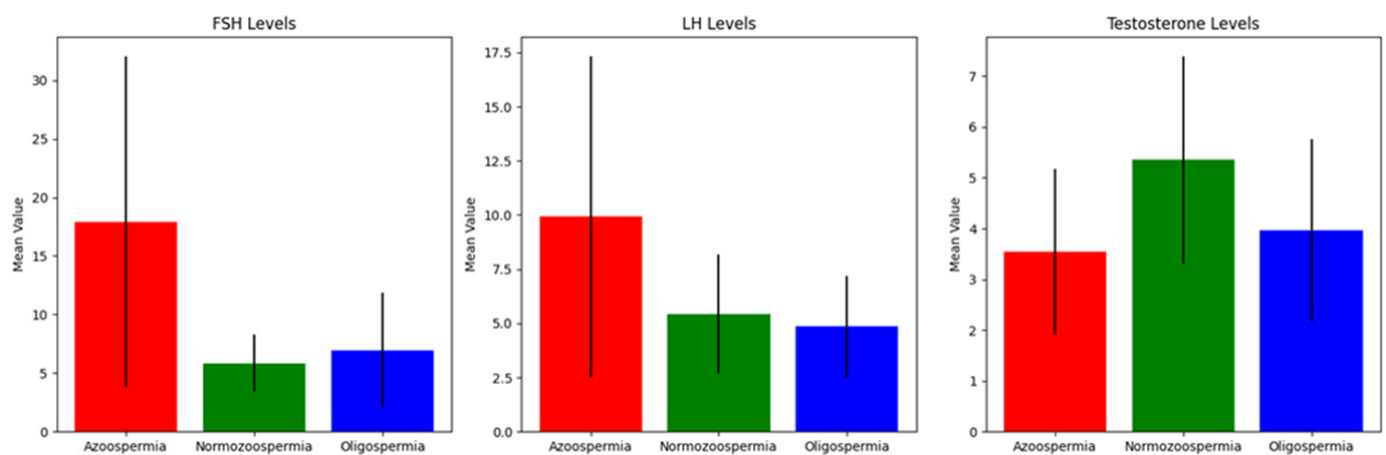| Semen Analysis	Age Groups			Total
	20-30 (years)	30-40 (years)	40-50 (years)	
Azoospermia	7	7	4	18
Controls (Normozoospermia)	8	25	17	50
Oligospermia	6	18	8	32

Figure 1: Bar diagram representing mean value of hormone levels based on semen analysis.

Table 2: Statistical analysis showing significant association between hormone profile and semen analysis.

Types	Azoospermia	Controls (normozoospermia	Oligospermia	p-Value
FSH(µIU/mL)	10.3 (31.03 - 5.92)[a]	5.625 (7.08 - 4.20)[a]	5.635 (8.75 - 3.77)[a]	0.005[c]
LH(µIU/mL)	6.705 (15.22 - 4.50)[a]	4.825 (6.10 - 3.59)[a]	4.265 (6.08 - 3.54)[a]	0.034[c]
Testosterone(ng/mL)	3.54±1.63[b]	5.35±2.05[b]	3.96±1.79[b]	0.0004[d]

Furthermore, the Kruskal-Wallis test demonstrates statistically significant differences in FSH and LH levels among azoospermia, oligospermia, and control groups. This suggests that hormonal variations are associated with different semen analysis outcomes. One-way ANOVA analysis of testosterone levels also revealed statistically significant differences. In the azoospermia group, there is a negative correlation was observed between age and testosterone, while FSH and LH show positive correlations with each other and a negative correlation with testosterone. In the oligospermia group, age shows a positive correlation with FSH and LH, and negative correlation with testosterone. In the control group, age is positively correlated with FSH and negatively correlated with testosterone, while FSH and LH show a positive correlation with each other and with testosterone (Figure 2).
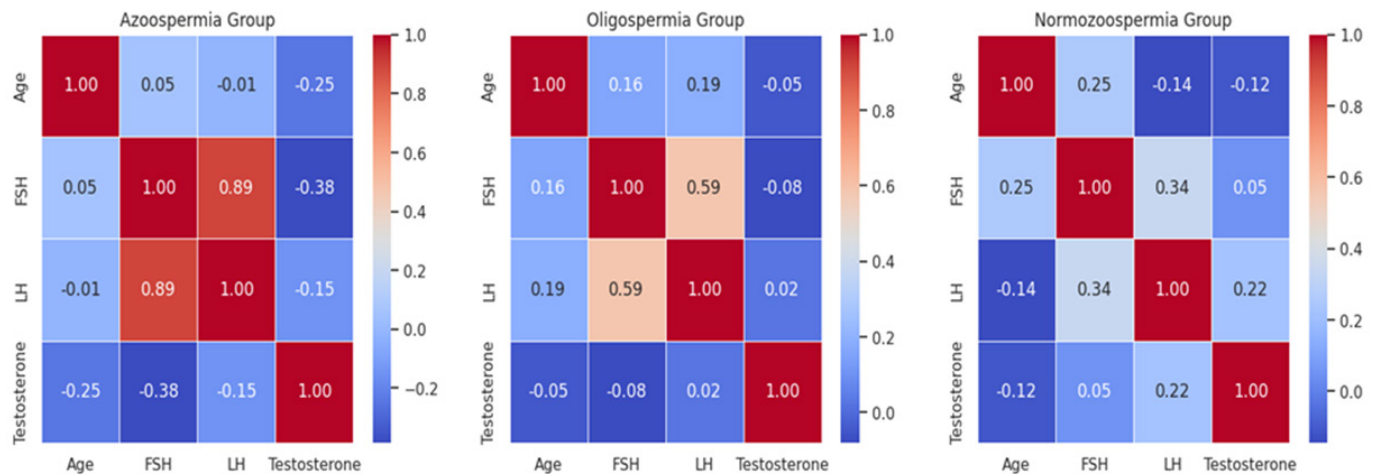

Figure 2: Correlation between different variables such as azoospermia, oligospermia and control (normozoospermia).

Discussion

Present study aimed to investigate endocrinological variations in male infertility within Nepalese population in azoospermic and oligospermic cases and compared with to age-matched normozoospermia individuals act controls with confirm fertility. The results reveal several key findings that contribute to the understanding of male reproductive health. The age-wise distribution of infertility cases demonstrated a higher prevalence of azoospermia in the 30-40 age group, while normozoospermia cases were more evenly distributed across the 30-40 and 40-50 age range. In oligospermia cases, on the other hand, were observed across all age groups, with a majority in the 30-40 age group. This age-specific distribution underscores the importance of considering age-related factors when evaluating in male infertility.

The incidence of primary endocrine defects in sub-fertile men is less than 3% and is rare in men with sperm concentrations greater than 5 million per ml [10]. This study assessed the endocrine environment in relation to spermatogenesis and sperm maturation. The serum FSH, LH and testosterone levels were estimated in infertile azoospermic, oligospermic males and age matched normozoospermic fertile cases (controls). The mean FSH and LH levels had significant rise in azoospermic males in contrast to oligospermic and normozoospermic males. The findings of this study had significantly elevated gonadotropins (FSH and LH) levels in azoospermic males than that of ologospermic and normozoospermic in accordance with the earlier studies [10-16] with mean LH and FSH levels, 9.92mIU/mL and 17.94mIU/mL in azoospermic males were also in concordance.

The higher FSH have been reported to be associated with human subfertility by different studies [14,17,18]. Various studies have also highlighted elevated serum FSH levels are associated with azoospermia [18-20]. The abnormal spermatogenesis may have a normal serum FSH, but a marked elevation in serum FSH is clearly indicative of abnormality in spermatogenesis [21]. In this study, the median and Interquartile Range (IQR) of hormonal levels (FSH, LH, and Testosterone) based on semen analysis reveal notable differences between azoospermia, oligospermia, and normozoospermia (control) groups. Azoospermia cases exhibit higher FSH levels compared to normozoospermia cases, indicating a potential endocrine dysfunction during spermatogenesis. It has been reported that, in addition to FSH secreting pituitary adenoma or testicular failure, hyperactivity of the FSH axis, could also be due to mutations of FSH receptor gene [22].

The data from the Kruskal-Wallis test and one-way ANOVA also confirmed statistically significant differences in FSH, LH, and testosterone levels among azoospermia, oligospermia, and normozoospermia groups. These variations suggest that hormonal dysregulation is associated with different semen analysis outcomes, supporting the evidence that endocrine disorders contribute significantly to male infertility [23-25]. The correlation analysis revealed intriguing patterns in different semen analysis groups. In the azoospermia group, a negative correlation was observed between age and testosterone, while FSH and LH showed positive correlations with each other and negative correlations with testosterone. In the oligospermia group, age exhibited a positive correlation with FSH and LH, while testosterone showed a negative correlation with age. In the normozoospermic group, age positively

correlated with FSH and negatively correlated with testosterone, and FSH and LH exhibited positive correlations with each other and with testosterone. These correlations highlight the complexity of the interplay between age, hormonal levels, and semen analysis outcomes, providing valuable insights for further research [26,27]. The variation in the hormone profile and semen analysis may be either due to genetic heterogeneity of folate metabolism regulatory methylene tetrahydrofolate C677T gene polymorphism in oligozospermic cases or genetic factor that increase "risk factor" for developing infertility in male [28].

Conclusion

The findings conclude the highlight the relevance of hormonal analysis in understanding male reproductive health. The elevated FSH and LH levels appear to be associated with azoospermia, emphasizing the potential role of hormonal dysfunction leads to abnormal spermatogenesis. These results contribute valuable insights knowledge of complexity between age, hormonal levels, and semen analysis outcomes, providing a foundation for further research in male fertility. The important component of evaluating male infertility is to quantifying the hormones of the hypothalamus-pituitary-gonadal axis. A patient's abnormalities in the production of certain hormones, such as FSH, LH, and Testosterone, can be used as a diagnostic biomarker to determine the etiopathology of their azoospermia/oligospermia patients. These findings have implications for clinical practice, emphasizing the importance of incorporating hormonal analysis alongside traditional semen analysis in the evaluation of male infertility. The identified correlations between age, hormonal levels, and semen analysis outcomes pave the way for further research in the field of male reproductive health. Understanding these complex relationships is crucial for developing targeted interventions and personalized treatment strategies for individuals having male infertility. The limitations of this study include its cross-sectional design, sample size and the need for further longitudinal research to validate the observed associations. Additionally, exploring the cytogenetic aspects of infertility could provide a more comprehensive understanding of the underlying mechanisms. Future studies should aim to elucidate the genetic and environmental factors influencing endocrinological and cytogenetic variations in male infertility.

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