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Research Article

Sperm Disorders and Aetiologies of Male Infertility in Pakistan: Meta-Analyses and Review

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Abstract

A few studies reported spermatogenic abnormalities and factors of infertility in Pakistani men with variable results. Therefore, performing meta-analysis was required to generalize the results. The present study is a composite of meta-analyses and review of various aspects of male infertility. Fixed and random effect models were used to analyze the data. We searched international and national electronic databases up to October 2013 including PubMed, Google Scholar and PakMediNet; screened reference lists. We assessed 13 cross-sectional studies addressing the prevalence of spermatogenic disorders and factors of infertility among men. The prevalence of primary and secondary infertility in infertile men was 78.19% and 21.81%, respectively. Rates of overall sperm count abnormalities were 34.97% (95% CI=24.98, 44.96) among infertile men. Oligospermia was the greatest problem 22.92% (95% CI=16.01, 29.83) followed by asthenospermia 18.78% (95%CI=6.52, 31.04) and azoospermia 18.33% (95% CI=14.78, 21.88). Morphological sperm abnormalities were prevalent in 13.61% (95% CI=1.68, 25.54) in infertile men. The major factor of male infertility was a stringent physical activity (35.9%) followed by iatrogenic cause (26.65%). Smoking is another significant factor 25.90% (95% CI=19.23, 32.56) followed by various infections 23.85% (95% CI=17.93, 29.78). Congenital testicular disorders were prevalent in 17.41%, while 12.69% (95% CI=6.11, 19.26) of the men had inguinal/abdominal surgery or trauma in the past. Varicocele was a cause of infertility in 9.74% (95% CI=4.33, 15.14) of infertile men and drug addiction was prevalent in 88.36% (95% CI=2.62, 14.09). Data showed 1.93% men with sperm abnormalities had one or more azoospermia factor regions deleted on Y-chromosome. A total of 72% respondents reported previous infections of the urinary tract, 24% reported smoking, 65% reported psychological stress, 58% reported obesity and 13% reported stringent exercise could be the factors of infertility. Sperm count, physical activity, iatrogenic effects and smoking are the major factors of male infertility in Pakistan.

Keywords: Male Infertility; Sperm Disorders; Reproductive Health; Azoospermia; Oligospermia

Introduction

Infertility is a common problem affecting about 21.9% of the Pakistani population with 3.5 primary and 18.5% secondary infertility. Both partners are found to be infertile in 30% of the cases, while male factor is responsible of infertility in 20 to 25% of the couples [1,2].

Infertility and sub-fertility can be caused by various factors such as chromosomal and genetic disorders, physical and mental stress, obesity, malnutrition, smoking, drug abuse, cryptorchidism, Sexually Transmitted Diseases (STDs), contraceptive procedures, accessory gland infections, germ cell malignancies, and testicular cell calcification, disorders of ejaculation, varicocele, endocrine disruption and autoimmunity [3-5].

Infertility affects mental and physical health of couples often leading them to the separation. A few studies regarding prevalence of spermatogenic abnormalities and etiological factors of infertility in Pakistani men have been conducted. But these studies have conflicting results. Here, we provided a review along with meta-analysis of prevalence of sperm abnormalities and factors in infertility in Pakistani infertile men.

Methods

Study design

Present study is a composite of meta-analysis and review of various aspects (sperm counts, motility, morphology and their possible etiologies) of male infertility in Pakistan.

Definition: Infertility is a state of failure to conceive in a year of unprotected intercourse with the same partner. Definitions of various spermatogenic abnormalities have been adopted from standard protocol [6].

Inclusion criteria: The meta-analysis included 13 cross sectional articles reporting the prevalence of sperm disorders in infertile male subjects and related etiological factors in only clinical setting [7-19]. Cohort studies were excluded along with studies having ambiguous or repeating data from the same author in different journals. However, data on prevalence of sperm abnormalities have been extracted from case-control studies.

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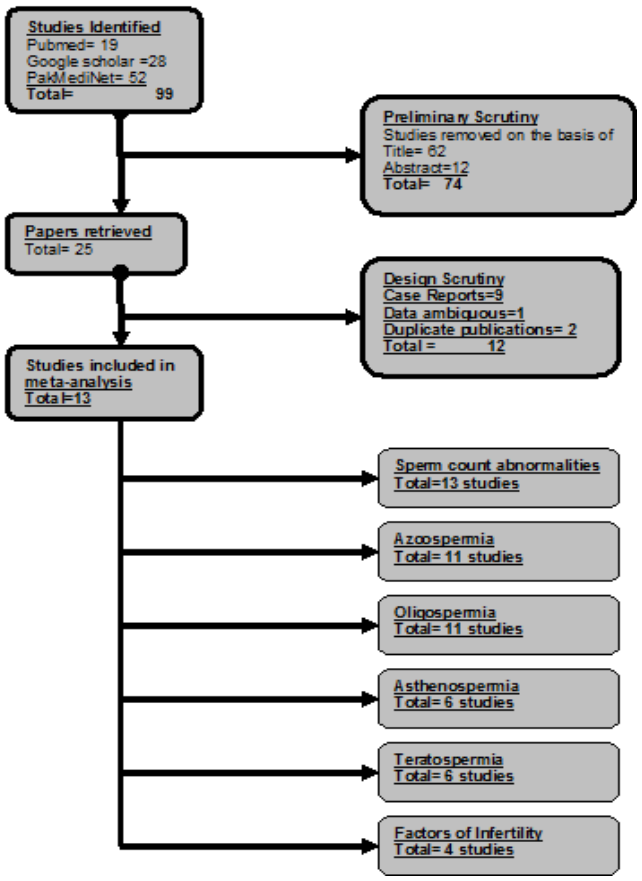

Figure 1: Flowchart of selection and Inclusion of Studies in the Meta-analysis.

Literature search: Articles were searched in PubMed, Google Scholar and PakMediNet (for non-indexed Pakistani journals), by using the keywords: prevalence of male infertility in Pakistan, status of sperm disorders in infertile male in Pakistan, spermatogenic disorders in Pakistan, azoospermia in Pakistan, oligospermia in Pakistan, causes of sperm disorders in Pakistan and etiological factors of male infertility in Pakistan.

Data extraction: Title and abstracts of retrieved articles were screened by two authors to decide on which studies met the inclusion criteria. Then the full text of short listed articles was reviewed and data were extracted, pooled and entered into an electronic data sheet after reversing percentages into frequencies where ever required. The total 99 different articles/reports were obtained from the literature search, of that 13 published from 1992 to 2013 were included in this study (Figure 1). The selected studies were arranged with respect to study area (provinces and cities). There were 3 studies from the Federal Capital Territory, Islamabad, 5 from Punjab province, 4 studies from Sindh province while only one study was available from Khyber Paktunkhawa. All the data of all parameters from the selected studies were obtained and meta-analysis was performed unless single study remained in any subgroup.

Data items: The present study is composite of analysis of data about the prevalence of various sperm abnormalities (count, motility and morphology) and factors of infertility in Pakistani infertile men.

Data analysis

Prevalence: Prevalence rates of sperm abnormalities and aetiologies in infertile men were calculated along with 95% Confidence Interval.

Heterogeneity assessment: Statistical heterogeneity was assessed by using the chi-squared (χ^2) test at the 5% significance level (P<0.05). We also calculate Q-statistic for this purpose by using following formula 1 [20].

$$Q = \sum(Weight \times Outcomes^2) - \frac{[\sum(Weight \times Outcome)]^2}{\sum Weight} \quad (1)$$

By using formula 2, I^2 statistic was calculated to assess inconsistency between the results of different studies [21].

$$I^2 = \frac{(Q - df)}{Q} \times 100 \quad (2)$$

In addition, between-study variance was estimated by using tau-squared (Tau^2) statistic (formula 3) and funnel plot was used to investigate publication bias [22].

$$\tau^2 = \left(\frac{Q - df}{C}\right) \quad (3)$$

where, C was calculated by using formula 4.

$$C = \sum Weight - \frac{\sum Weight^2}{\sum Weight} \quad (4)$$

Egger statistical tests to quantify the publication bias (formulae 5-7) [23].

$$E[z_i] = \beta_\circ + \beta_1 prec_i \quad (5)$$

$$z_i = \frac{Outcome}{S.D.} \quad (6)$$

$$prec_i = \frac{1}{S.D.} \quad (7)$$

Meta-analysis was performed on the prevalence of sperm abnormalities and their causes in infertile men. The results were reported using a random effect model with 95% CI.

Results

Types of infertility

The pooled prevalence of primary and secondary infertility in infertile men from two studies was 78.19% and 21.81%, respectively [9,15].

Total sperm count disorders

Characteristics of studies: Characteristics of 13 studies included in meta-analysis such as duration, location, title and method are given in (Table 1).

Cumulative meta-analysis: Thirteen studies included a total of 6508 male infertile participants of which 1961 had sperm count disorders [7-19]. Data showed that rates of overall sperm count abnormalities were 34.97% (95% CI=24.98, 44.96) among infertile men. Between studies heterogeneity was considerably high (χ^2 = 669.50 df =12 p = 0.00; and I^2 = 98.14). We used a randomized design to analyze the data which reduced the heterogeneity (I_v^2 = 21.59). Publication bias assessed by using the funnel plot, and Begg and Egger tests that confirmed absence of publication bias. Within studies heterogeneity was low as tau^2 statistics had small value equal to 0.01 (Figure 2, Table 2).

Subgroup analysis: i. Islamabad: Three studies from Islamabad

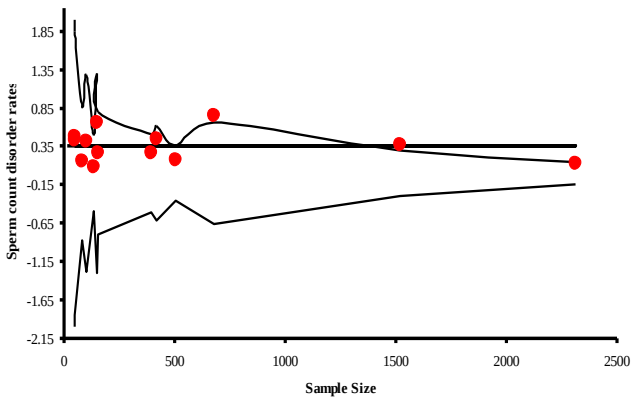

Figure 2: Funnel plot for assessing publication bias in the studies included in cumulative meta-analysis for estimating the prevalence rate of sperm count abnormalities in infertile men.

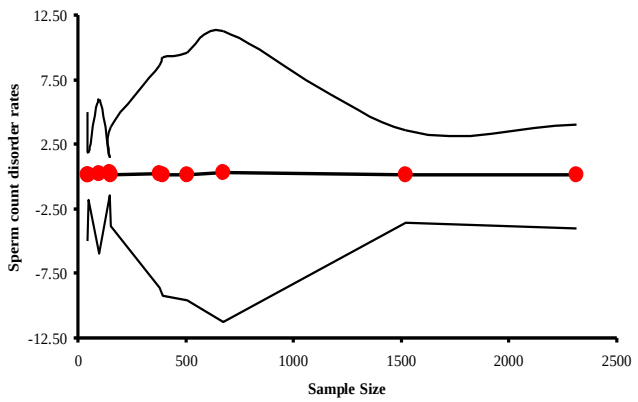

Figure 3: Funnel plot for assessing publication bias in the studies included in cumulative meta-analysis for estimating the prevalence rate of azoospermia in infertile men.

included 2054 male infertile participants (766 with sperm count disorders). [11,14,15] Data showed that sperm count abnormalities were observed in 36.10% (95% CI=27.72, 44.48) infertile men from Islamabad (Table 3).

ii. Punjab: Five studies from Punjab included 3025 male infertile subjects of which 455 had sperm count disorders [7,9,12,13,16]. Data showed that sperm count disorders were observed in 19.60% (95% CI=11.74, 27.47) (Table 3).

iii. Sindh: Four studies from Sindh had 753 male infertile patients, of which 230 were with sperm count abnormalities [8,10,17,18]. Data showed that sperm count disorders were observed in 43.43% (95 CI=15.16, 71.70) (Table 3).

iv. Khyber Pakhtunkhawa: A study from Khyber Pakhtunkhawa had 676 infertile male subjects of which 510 were with sperm count disorders [19]. The study showed that 75.44% (95 CI=68.90, 81.99) of infertile male patients had sperm count abnormalities (Table 3).

Azoospermia

Cumulative meta-analysis: Eleven studies included a total of 6291 male infertile participants of which 1024 were reported with azoospermia [8-15,17-19]. The studies showed that 18.33% (95% CI=14.78, 21.88) of infertile male had azoospermia. Two studies reported that testicular failure is a cause in 55.09% azoospermia cases, while obstruction is a cause in 44.91% azoospermic men. Between studies heterogeneity was considerably high (χ^2 = 92.2973 df=10 p=0.0000; and I^2 =89.16). We used a randomized design to analyze the data which reduced the heterogeneity (I_v^2 = 24.45). Publication bias assessed by using the funnel plot, and Begg and Egger tests that confirmed absence of publication bias. Within studies heterogeneity was low as tau^2 statistics had small value equal to 0.00 (Figure 3, Table 4).

Subgroup analysis: i. Islamabad: Three studies from Islamabad included 2054 male infertile subjects of which 318 had azoospermia [11,14,15]. Azoospermia was observed in 17.24% (95% CI=10.20, 24.28) infertile men from Islamabad (Table 5).

ii. Punjab: Four studies from Punjab included 2808 male infertile men, of which 363 had azoospermia [9,12,13]. The data showed that 14.97% (95% CI=7.83, 22.12) of infertile men had azoospermia (Table 5).

iii. Sindh: Three studies from Sindh included 753 infertile men, of which 149 had azoospermia [8,10,17,18]. Data showed that 19.30% (CI=12.26, 26.34) of infertile men had azoospermia (Table 5).

iv. Khyber Pakhtunkhawa: A study from Khyber Pakhtunkhawa showed that 28.70% (95% CI=24.66, 32.74) of a total 676 infertile men had azoospermia [19] (Table 5).

Oligospermia

Cumulative meta-analysis: Eleven studies included a total of 3688 male infertile participants of which 937 had oligospermia [7,9-12,14-17,19]. The studies showed that 22.92 (95% CI= 16.01, 29.83) of infertile men had oligospermia. Between studies heterogeneity was considerably high (χ^2 = 179.95 df=10 p=0.0000; and I^2 =94.44). We used a randomized design to analyze the data which reduced the heterogeneity (I_v^2 = 3.37). Publication bias assessed by using the funnel plot, and Begg and Egger tests that confirmed absence of publication bias. Within studies heterogeneity was low as tau^2 statistics had small value equal to 0.00 (Figure 4, Table 6).

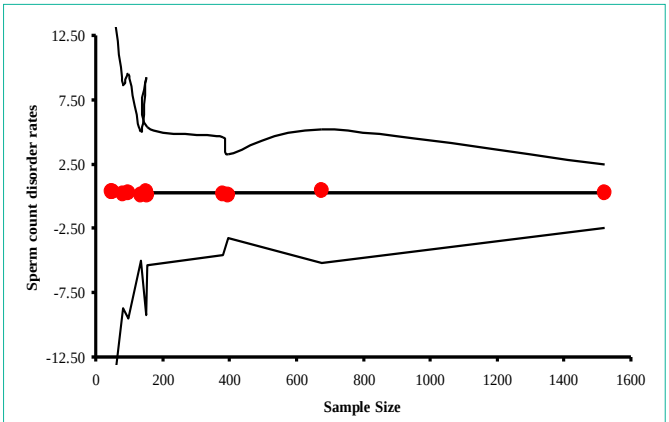

Figure 4: Funnel plot for assessing publication bias in the studies included in cumulative meta-analysis for estimating the prevalence rate of oligospermia in infertile men.

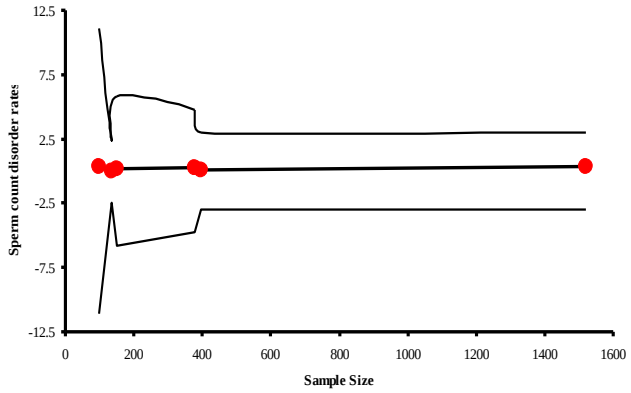

Figure 5: Funnel plot for assessing publication bias in the studies included in cumulative meta-analysis for estimating the prevalence rate of asthenospermia in infertile men.

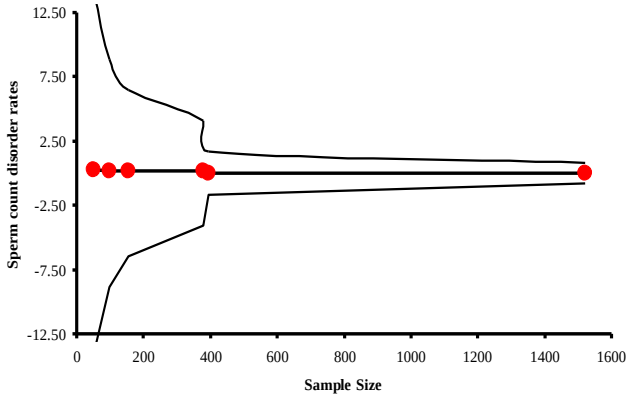

Figure 6: Funnel plot for assessing publication bias in the studies included in cumulative meta-analysis for estimating the prevalence rate of teratospermia in infertile men.

Subgroup analysis: i. Islamabad: Three studies from Islamabad included 2054 infertile men, of which 448 had oligospermia [11,14,15]. Data showed that oligospermia was observed in 18.76% (95% CI=12.45, 25.08) of infertile men from Islamabad (Table 7).

ii. Punjab: Four studies from Punjab included 712 infertile men, of which 92 had oligospermia [7,9,12,16]. The data showed that 13.75% (95% CI=7.73, 19.73) of infertile men had oligospermia in Punjab (Table 7).

iii. Sindh: Three studies from Sindh included 246 infertile men, of which 81 had oligospermia [10,17,18]. Data showed that 32.80% (95% CI=23.22, 42.39) of infertile men had oligospermia in Sindh (Table 7).

iv. Khyber Pakhtunkhawa: A study from Khyber Pakhtunkhawa showed that 46.75% (95% CI=41.59, 51.90) of a total 676 infertile men had oligospermia (Table 7) [19].

Sperm motility disorders

Cumulative meta-analysis: Six studies included total 2681 infertile men, of which 721 had asthenospermia. Data showed that rate of asthenospermia was 18.78% (95% CI=6.52, 31.04) in infertile men [7;9;12;14,15;18]. Between studies heterogeneity was considerably high (χ^2=309.05 df=5 p=0.0000 and I^2 =98.23). Randomized design reduced the heterogeneity and homogeneity was achieved (I_v^2 = 0.00). Publication bias assessed by using the funnel plot, and Begg and Egger tests that confirmed absence of publication bias. Within studies heterogeneity was low as tau^2 statistics had small value equal to -0.01 (Figure 5, Table 8).

Subgroup analysis: i. Islamabad: Two studies from Islamabad included 1900 infertile men, of which 621 had asthenospermia [14,15]. Data showed that asthenospermia was observed among 29.08% (95% CI=16.85, 41.31) of infertile men from Islamabad (Table 8).

ii. Punjab: Three studies from Punjab included 631 infertile men, of which 71 had asthenospermia [7,9,12]. The data showed that 12.51% (95% CI=2.17, 22.86) of infertile men had asthenospermia in Punjab (Table 8).

iii. Sindh: A study from Sindh showed that 13.33% (95% CI=7.49, 19.18) of a total 150 infertile men had asthenospermia (Table 8) [18].

Sperm morphological disorders

Cumulative meta-analysis: A total of six studies included total 2599 infertile male participants, 170 of them had teratospermia [9,11,12,14,15,17]. Data showed that morphological sperm abnormalities were prevalent in 13.61% (95% CI=1.68, 25.54) in infertile men. "Between studies" heterogeneity was considerably high (χ^2 =86.25 df=5 p=0.0000 and I2 =99.19). Within studies heterogeneity was low as tau^2 statistics had small value equal to -0.01Randomized design reduced the heterogeneity and gained homogeneity (Iv2 = 0.00). Publication bias was assessed by using the funnel plot, and Begg and Egger tests that confirmed absence of publication bias. (Figure 6, Table 9).

Subgroup analysis: i. Islamabad: Three studies from Islamabad included 2054 infertile men, of which 126 had teratospermia [11,14,15]. Data showed that teratospermia was observed in 11.95% (95% CI=-22.80, 46.71) of infertile men from Islamabad (Table 9).

ii. Punjab: Two studies from Punjab included 495 infertile men, of which 31 had teratospermia [9,12]. The data showed that 11.40% (95% CI=-31.29, 54.08) of infertile men had teratospermia in Punjab (Table 9).

iii. Sindh: A study from Sindh showed that 26% (95% CI=11.87, 40.13) of a total 50 infertile men had teratospermia (Table 9) [17].

Multiple sperm disorders

Oligoasthnospermia was observed in 7.99% of infertile men in Pakistan while 2.06% in Punjab [11,12,17,18]. Asthenoteratospermia was observed in 17.53%, oligoasthenoteratospermia in 11.69%, necrospermia in 1.32% and polyspermia in 1.91% [11,14,15].

Factors of male infertility

Varicocele: Four studies included 1204 infertile men, of which 81 had varicocele. Data showed that varicocele may be a cause of infertility in 9.74% (95% CI=4.33, 15.14) of infertile men (Table 10) [12,15,17,19].

Inguinal or abdominal surgery/Trauma: Two studies showed that inguinal or abdominal surgery/trauma was found responsible of

infertility in 12.69% (95% CI=6.11, 19.26) of total 1055 infertile men (Table 10) [15-19]. A study from Islamabad showed that the surgery/trauma is prevalent in 10.81% of infertile men out of them 4.49% men had inguinal surgery, 5.01% had inguinal trauma, and 1.32% men had gone through abdominal surgery previously [15].

Congenital testicular disorders: A study from Islamabad showed that congenital testicular disorders were prevalent in 17.41% infertile men out of them 3.17% men had undescended testis, 12.66% had ectopic testis, 1.06% had single testis and 0.53% had retractile testis [15].

Infections: According to data from three studies, different infections were prevalent in 23.85% (95% CI=17.93, 29.78) of 1105 infertile men (Table 10) [15,17,19]. These infections included urinary tract infections (25.88%), mumps (8.96%) and tuberculosis (2.11%) [11,15,17,19]. Semen culture had infections, including 2.4% Neisseria gonorrhea, 1.2% E. coli, 0.59% Proteus spp., and Providencia spp., each in infertile men [19].

Smoking: Three studies included 1105 infertile men, of which 254 were smokers [15,17,19]. Data showed that smoking was prevalent in 25.90% (95% CI=19.23, 32.56) in infertile men (Table 10) while tobacco chewer were 8.95 in infertile men [17,19].

Drug addiction: Three studies included 1105 infertile men, of which 100 were drug addicts [15,17,19]. Drug addiction was prevalent in 8.36% (95% CI=2.62, 14.09) of infertile men (Table 10). Marijuana addicts were 3.55% [19] and alcohol addicts were 3.26% among infertile men [15,17].

Genetic mutations: Three studies reported work on Y-chromosomes micro-deletions and cumulative data showed 1.93% of infertile men had micro-deletions [24-26]. A study from Islamabad reported 5.88% men with sperm abnormalities had one or more azoospermia factor regions deleted on Y-chromosome. Complete AZF regions were deleted in 1.96% of the subjects, AZFb and AZFc were deleted in 1.96% men, and AZFc was also deleted in 1.96% infertile men. Moreover, all the deletions were found in men with non-obstructive azoospermia [24]. Second study could not find any Y-chromosome micro-deletions in 53 infertile men [25]. However, another study carried out in three most populated provinces (Punjab, Sindh and Khyber Pakhtunkhwa) showed that 2.86% individuals with severe oligozoospermia and 5.5%. Azoospermic males had deletions in the AZFc region [26].

Environmental effects: A study found that heat exposure was responsible of infertility in 6.6% and chemical exposure in 5.28% of men [15].

Occupational effects: A study from Khyber Pakhtunkhawa found that 35.9% infertile men were doing hard work as labors or farmers, 12.8% had less physical activities (such as clerks, tailors and shopkeepers), 16.3% teachers, 9.9% drivers, 8.4% belonged to the armed forces, 4.4% mechanics, 1% doctors, 1% engineer, and 9.9% were unemployed19.

Iatrogenic effects: A study showed that 26.65% infertile men may have use of medicine as an underlying cause. Herbal medicine users were 12.41% and allopathic medicine users were 10.03%, while both types of medicines were reported in 4.49% infertile men [15].

Immunological effects: According to data from two studies (not included in meta-analysis), 8.25% of male infertile subjects had anti-sperm antibodies in their blood while a study showed that 8.06% infertile male patients had anti-sperm antibodies in their seminal plasma also [27,28]. Furthermore, 48.43% infertile men had pus cells in their semen [15,19].

Others causes: Impotence, diabetes and herniopathy each were observed in 2% infertile men [17]. Hydrocele was observed in 0.53% of infertile men while underdeveloped external genitalia and underdeveloped secondary sex characteristics were observed in 1.06 and 0.79% of infertile men [15].

Social aspects of male infertility

Studies showed that 76.09% infertile men had single marriage, 9.83% had multiple marriages [17,19], 0.53% men were unmarried [15], and 10.87% had divorced [17].

Awareness of male infertility

According to a study carried in Karachi (Sindh) on awareness about infertility, 55% respondents reported infertility as disease, 94% believed in medical remedies, only 20% think that husband must be investigated first for infertility, 72% respondents thought that the previous infections of the urinary tract were responsible of male infertility. A total of 24% respondents reported smoking, 65% reported psychological stress, 58% reported obesity and 13% reported stringent exercise could be the factor of male and female infertility. Some of the respondents also believed in black magic (38%) and supernatural creatures (30%) as factors of infertility. A total of 41% respondents believed that husband infertility may lead to divorce while only 4% respondents believed that the husband is blamed for infertility in society [29]. It was observed that 42.45% infertile men had major depression and 23.5% had minor depression [30].

Discussion

Reproduction is essential for the continuation of the genome of individuals and species including human. The desire of survival and continuation of the genome is strong enough that the human individuals fail to reproduce have poor social, mental and physical health. For the remedies of the condition, estimation of prevalence and factors are pre-requisite. A few studies reported prevalence of sperm disorders and factors of male infertility in Pakistan with variable results. Therefore, the present meta-analysis was done to generalize the results. However, there were still some heterogeneities such as the definition of the outcomes, inclusion criteria or time periods. Furthermore, the sperm characteristics vary according to the methodology used to collect semen [31]. Most of the studies did not contain information of the ethnic group, socioeconomic status, and method of data collection, etc. that reduced the homogeneity of the studies. In spite of these limitations, our study is giving a better picture of sperm disorders and their etiologies in Pakistan that will be helpful in making policies for remedies and management of the male infertility.

According to the present study, prevalence of primary and secondary infertility in infertile men was 78.19% and 21.81%, respectively, that is comparable to the findings of a meta-analysis of studies on the infertile Iranian couples [32]. It is already established that the most of the male infertility problems are sperm count based.

However, a positive correlation has been found between normal sperm count and normal sperm morphologies. The azoospermia, 18% reported by the present study is comparable to 10 to 15% azoospermia in infertile Indian males [33]. The sperm count disorders may correspond to economic development, as the prevalence of azoospermia reported by us was higher than Italy (4.7%), Siberia (8.6%), South Africa (9%) and Indonesia (12%) but lower than Mexico (19.9), Mongolia (20%), Zimbabwe (24%) and Ethiopia (26%) [33-40]. Similarly, the prevalence of oligospermia (20.53%) reported in this study was less than Nigeria (60.9%) but higher than India (1.8%), Saudi Arabia (5.7%), USA (18%) [41-43]. However, prevalence of asthenospermia (18.78%) in this study is higher than Nigeria (17.4%) but less than India (60%), Saudi Arabia (35.5%) and USA (51%) [41-44]. Morphological sperm abnormalities were prevalent in 13.63% of infertile men that are higher than Serbia (2.2%), Nigeria (8.7%) and less than USA (14%) [40,41,44].

The overall sperm abnormalities were more prevalent in the infertile men from Khyber Pakhtunkhwa, the least developed province included in the present study, followed by Sindh, and Punjab. Similarly, sperm count abnormalities (azoospermia & oligospermia) were more prevalent in the infertile men from Khyber Pakhtunkhwa. The reason behind is that socioeconomic status and formal literacy rate are low and most of the people are hand workers in Khyber Pakhtunkhwa. The major factor of male infertility, reported in a study from Khyber Pakhtunkhwa was a stringent physical activity [19]. While, the rates of oligospermia, asthenospermia and teratospermia were the least in the province of Punjab.

The major factor of male infertility was a stringent physical occupational activity followed by iatrogenic cause, smoking, infections, congenital testicular, inguinal/abdominal surgery or trauma, varicocele, drug addiction and azoospermia factor regions deleted on Y-chromosome as reported previously [45-51]. Furthermore, impotence, diabetes and herniopathy were observed in 2% of infertile men.

Studies about awareness of male infertility revealed that 20% of people think that husband must be investigated first for infertility, 72% respondents thought that the previous infections of the urinary tract were responsible of male infertility. A total of 24% respondents reported smoking, 65% reported psychological stress, 58% reported obesity and 13% reported stringent exercise could be the factor of infertility. A total of 41% respondents believed that husband infertility may lead to divorce while only 4% respondents believed that the husband is blamed for infertility in society.

Conclusion

Present meta-analysis showed that sperm count abnormalities, oligospermia followed by azoospermia, were more prevalent in infertile men as compared to other sperm abnormalities. Furthermore, physical occupational activity, incorrect use of medicines and smoking were among major etiological factors of infertility (sperm disorders) in Pakistani men. The study also indicated a difference in the distribution of sperm disorders in various provinces and regions of Pakistan, though insufficient published data were available. All the studies concerned had various shortcomings i.e. definition of infertility, no partner screening or its description, defining sperm disorders, hospital based data, and less sample size. Therefore, it is needed to carry out a well-structured population based study to report correct frequencies of male infertility, sperm disorders and factors with respect to sociodemographic description.

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