Dose-Dependent Effect of Smoking on Fertility Status among Men in Gaza Strip, Palestine

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\textbf{Keywords}  
Primary infertility · Tobacco smoking · Men · Gaza strip · Palestine

\textbf{Abstract}

\textbf{Introduction:} Tobacco smoking is constantly increasing mainly in developing countries and accounts for many morbidities and mortalities. Several studies have addressed the effect of smoking on male reproductive mechanism, particularly semen quality, but the effect of smoking behavior remained inconclusive. The aim of this study was to explore the relationship of tobacco smoking status, intensity, and duration between infertile and fertile men and other accompanying genitourinary conditions. \textbf{Methods:} Through a case-control study, 160 infertile couples were recruited from in vitro fertilization centers in Gaza Strip. Correspondingly, another 160 fertile couples were selected from governmental clinics and residentially matched with cases. The probable stratified random technique for 2017/2018 patient’s registries was performed. Both cases and controls were interviewed with a self-constructed questionnaire. Descriptive analysis, logistic regression, and the Cochran-Mantel-Haenszel test were deployed statistically with a significant level set on $p = 0.05$. \textbf{Results:} The mean age of cases and controls was $35.7 \pm 10$ and $34.9 \pm 5$ years, respectively, where 70 and 59%, respectively, were refugees; 52 and 43%, respectively, had university education; and 10.6% compared to 5.6%, respectively, earn $>USD \ 720$/month. Active smoking was detected among 38% of infertile men and 42.5% of fertile men. Nevertheless, passive smoking (52.5% infertile and 37.5% fertile) and smoking duration $>2$ years (85.2% infertile and 69.1% fertile) showed a positive significant relationship ($p = 0.007$ and $p = 0.030$, respectively). Furthermore, 34 and 49% of all infertile smokers showed a dose-dependent effect (odds ratio [OR]: 2.98, $p = 0.023$ for 6–10 cig/day and OR: 3.68, $p = 0.004$ for $>10$ cig/day), mainly in nonobstructive causes (OR: 4.26, $p = 0.040$ for 6–10 cig/day and OR: 5.52, $p = 0.004$ for $>10$ cig/day). Varicocele was more likely to occur among passive smokers ($p = 0.024$), smoking $>10$ cig/day ($p = 0.038$), and for $>2$ years ($p = 0.024$). Recurrent genitourinary tract infection was 3 times more among infertile passive smokers (OR: 2.96, 95% confidence interval: 1.38–6.32, and $p = 0.005$). Adjustment for age and refugee status showed 3.5 times risk for passive smoking, more than 9 times risk for former smokers, and 2.8 risk when smoking $>5$ cig/day. \textbf{Conclusion:} Smoking more than 5 cigarettes/day and for $>2$ years duration or exposure to passive smoking hold an increased risk on the fertility status of men. More global and national efforts need to be directed to controlling and eliminating tobacco smoking.

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Introduction

Tobacco smoking is one of the largest global public health problems, which is frankly consumed by over 1.1 billion people around the world. A yearly estimate stated that around 8 million people die from different forms of tobacco exposure. More than 7 million people die yearly from direct tobacco use, while around 1.2 million are the result of second-hand smoking [1]. One in 5 adults in the world smoke tobacco [2], and typically more men (35% of men globally) than women (6% of women globally) are known as active users [2, 3]. The increasing prevalence is most commonly witnessed in the eastern Mediterranean and African Region [4]. The fact that tobacco smoking holds a detrimental effect on health in general [5], and the impact on the male reproductive system has long been a special concern of many scientists and researchers [6].

Inhaled cigarette smoke contains various toxic substances other than nicotine, including carbon monoxide, benzopyrene, naphthalene, meth naphthalene, radioactive polonium, dimethyl benzanthracene, and dimethyl nitrosamine, that were suggested to harm the male reproductive system [7, 8]. Primary infertility is defined clinically in both males and females as the inability to achieve pregnancy for >1-year duration of unprotected intercourse [9]. Many different medical conditions and/or risks can be related to fertility problems in men. Infertility problems could be related to more than one cause or factor; others could assume one cause or factor, while some cases are identified as idiopathic [10]. Although most studies discussed the relationship between tobacco smoking and infertility among men in the respect of their semen parameters, some reported contradictory results. A recent meta-analysis concluded that tobacco smoking is associated with lower sperm count and more morphological abnormalities, while the sperm motility, semen pH, and reproductive hormones were not affected [11]. On the other hand, another systematic review and meta-analysis reported that cigarette smoking has an overall negative impact on all semen parameters [12]. Scarce research was found discussing the intensity and duration of smoking along with accompanied genitourinary health conditions and their effect on the fertility status among men, especially those living in Gaza Strip, Palestine. Accordingly, the aim of this study was to explore the relationship of tobacco smoking status, intensity, and duration between infertile and fertile men and other accompanying genitourinary conditions.

Materials and Methods

Sampling and Study Participants

A case-control study design was conducted with the participation of fertile and infertile married couples in Gaza Strip, Palestine. Infertile couples were defined according to the clinical definition of the World Health Organization for primary infertility: inability to achieve pregnancy despite exposure to the risk for 1 year or more of unprotected intercourse [9]. Cases were selected from those that were registered at 5 in vitro fertilization centers for treatment and were chosen from each center through the stratified random sampling technique. Controls were defined as those who achieved at least 2 normal pregnancies with no history of any means of assistive reproductive techniques. They were matched with the cases according to their residential area. As a population setting, controls were chosen from governmental primary healthcare centers, by tracing couples who were married and receiving antenatal care, postnatal care, or family planning services and who were congruent with the predetermined criteria. Sample size was calculated through Epi-info 7 calculator with a two-sided confidence interval (CI) of 95%, power of study of 80%, percentage of exposed controls of 50% (because information about the risk of exposure among the control group was limited), odds ratio (OR) of 2, and ratio of cases to controls of 1. The final sample size was 320 total study populations.

Study Instrument and Data Collection

The researchers developed and self-constructed a face-to-face interview questionnaire that fully achieved the study objectives and was typically suitable for the study population context. We were committed to acquire an informed consent form prior to each participation. The consent form explained the aim of the study and the expected benefits of the research along with emphasizing that confidentiality is highly implemented and that taking part in the study is voluntary with their right to withdraw participation at any time. An ethical approval was obtained from the Palestinian Health Research Council and an administrative approval was acquired from the Al-Quds University.

Data collection was performed through 2 nurses with high-qualified medical and practical background. They were chosen upon having adequate expertise in the research field. Prior to data collection, the data collectors had a comprehensive training on the structure of the instrument and the data collection process to minimize interobserver variation and eventually ensure research reliability. An iterative pilot study as a cognitive qualitative testing was performed on 10% of total sample size, and appropriate minimum modification on the instrument was applied.

Statistical Analysis

Analysis was conducted through IBM SPSS Statistics 24 package. Data were cleaned and coded where appropriate. Descriptive analysis was deployed to produce crude distribution of variables (percentage and frequency), and further bivariate analysis was performed to calculate the OR through the $\chi^2$ cross-tabulation. This procedure was used for the demographic variables, to calculate the risk of active smoking, passive smoking, former smoking, smoking intensity, and smoking duration of selected subjects. Also, it was used to show the risk of smoking among different causes of infertility (Fisher Exact test) and different accompanied genitourinary conditions (Cochran-Mantel-Haenszel test). Finally, to examine
the size of change in the risk between statistically significant independent variables and tobacco smoking, we used binary logistic regression analysis with the best fit module. The statistically significant level was set as \( p < 0.05 \).

**Results**

Table 1 shows the general characteristics of the study population. From a total of 160 infertile men, 47 (29.4%) were more than 30 years age than 27 (16.9%) fertile men \( (p = 0.008) \). Marital duration of >5 years was reported among 68 (42.5%) infertile men, compared to only 23 (14.4%) of their counterpart. More than two-thirds of the infertile group (70%) were Palestinian refugees \( (p = 0.036) \). Almost half of them (51.9%) had a university degree compared to nearly the same distribution being noticed among those who completed 10–12 years of schooling (34.3 and 39.4%, respectively) and those who gained <10 years (13.8 and 17.5%, respectively). The controls were double the cases when comparing a monthly income of USD 441–720 for both groups \( (p = 0.007) \); otherwise the same distribution was noticed among those who gain less than USD 440 a month.

| General characteristics | Cases \((n = 160)\) | Controls \((n = 160)\) | OR (95% CI) | \( p \) value |
|-------------------------|------------------|------------------|-------------|--------------|
| Age, years              |                  |                  |             |              |
| \( \geq 30 \)           | 47    | 29.4            | 27    | 16.9         | 2.049 (1.20–3.50) | 0.008* |
| \( \\\\leq 30 \)      | 113   | 70.6            | 133   | 83.1         |               |              |
| Marital duration, years |                  |                  |             |              |
| <5                      | 68    | 42.5            | 23    | 14.4         | 6.182 (2.62–14.61) | <0.001** |
| 5–10                    | 54    | 33.8            | 79    | 49.4         | 1.429 (0.64–3.17) | 0.379 |
| 11–15                   | 27    | 16.9            | 35    | 21.9         | 1.613 (0.67–3.88) | 0.283 |
| >15                     | 11    | 6.9             | 23    | 14.4         | Ref.           |              |
| Refugee status          |                  |                  |             |              |
| Refugees                | 112   | 70.0            | 94    | 58.8         | 1.638 (1.03–2.60) | 0.036* |
| Nonrefugees             | 48    | 30.0            | 66    | 41.3         |               |              |
| Education level         |                  |                  |             |              |
| 0–9 years               | 22    | 13.8            | 28    | 17.5         | 0.653 (0.34–1.24) | 0.193 |
| 10–12 years             | 55    | 34.3            | 63    | 39.4         | 0.726 (0.45–1.18) | 0.192 |
| 13+ years               | 83    | 51.9            | 69    | 43.1         | Ref.           |              |
| Monthly income, USD     |                  |                  |             |              |
| \( \leq 440 \)          | 127   | 79.4            | 118   | 73.8         | 0.570 (0.24–1.33) | 0.188 |
| 441–720                 | 16    | 10.0            | 33    | 20.6         | 0.257 (0.09–0.70) | 0.007* |
| >720                    | 17    | 10.6            | 9     | 5.6          | Ref.           |              |

OR, odds ratio; CI, confidence interval. * Significant level \( p = 0.05 \). ** Highly significant level \( p < 0.001 \). Ref., reference used to breakdown \( >2 \times 2 \) contingency table.

Table 2 demonstrates the smoking status, intensity, and duration in both groups. Results showed that nearly half the infertile men were exposed to passive smoking compared to only 37.5% of the fertile group \((p = 0.007)\). Former smokers were more among infertile men (37%) than fertile ones (27.5%), but the relationship did not reach a statistically significant level. Frequency of active smokers among infertile men (38%) was less than those in the fertile group (42.5%), but the smoking intensity among the 2 groups showed a dose-dependent effect when smoking 6–10 cigarettes per day \((OR: 2.98 \text{ and } p = 0.023)\) and more than 10 cigarettes per day \((OR: 3.68 \text{ and } p = 0.004)\). Furthermore, smoking for more than 2 years was 2.5 times more likely among the infertile group \((p = 0.03)\).

Table 3 presents the distribution of tobacco smoking variables by causes of infertility among men. Passive smoking was detected more among infertile men with nonobstructive causes \((OR: 1.7, 95\% \text{ CI: 1.05–2.88, and } p = 0.032)\) and those with obstructive causes \((OR: 5.0, 95\% \text{ CI: 1.30–19.20, and } p = 0.014)\) than fertile men. Furthermore, a positive dose-dependent association was observed among smokers with nonobstructive causes. The coefficient increased gradually from 4.263 for 6–10 ciga-
rettes/day to 5.523 for >10 cigarettes/day. Idiopathic causes showed no relationship with all forms of smoking behavior except for passive smoking ($p = 0.014$).

Table 4 presents the distribution of tobacco smoking variables by accompanying genitourinary conditions among the study population. The genitourinary conditions included were unilateral or bilateral varicocele and recurrent genitourinary infection (>5 times in the past 2 years). Passive smoking ($p = 0.024$), smoking more than 5 cigarettes per day ($p = 0.038$ for 6–10 and $p = 0.035$ for >10 cig/day), and smoking for >2 years ($p = 0.024$) were more among infertile men with unilateral or bilateral varicocele. Passive smoking was also significantly higher among infertile men with recurrent
Table 4. Relationship between tobacco smoking and various genitourinary conditions in infertile and fertile men (Cochran-Mantel-Haenszel test)

|                        | Unilateral/bilateral varicocele | OR | p value | Recurrent genitourinary infection | OR | p value |
|------------------------|---------------------------------|----|---------|-----------------------------------|----|---------|
|                        | cases (n = 77)                  |    |         | controls (n = 20)                 |    |         |
| Passive smoking        |                                 |    |         |                                  |    |         |
| Yes                    | 41                              | 3.42| 0.024*  | 35                                | 2.96| 0.005*  |
| No                     | 36                              | 15 |         | 18                                | 25 |         |
| No. of cig/day         |                                 |    |         |                                  |    |         |
| 1–5                    | 1                               | 3 | Ref.    | 2                                | 8 | Ref.    |
| 6–10                   | 7                               | 1 | 21.0     | 0.038*                           | 7 | 3       | 9.33    | 0.028*  |
| >10                    | 20                              | 6 | 10.0     | 0.035*                           | 17 | 16     | 4.25    | 0.082*  |
| Duration of smoking, years |                         |    |         |                                  |    |         |
| >2                     | 24                              | 5 | 6.0      | 0.024*                           | 20 | 18     | 1.67    | 0.412   |
| ≤2                     | 4                               | 5 |          | 0.024*                           | 6 | 9       |

OR, odds ratio; cig/day, cigarettes per day. * Significant level p = 0.05. † Mantel-Haenszel 2-tailed p value. Ref., reference used to breakdown >2 × 2 contingency table.

Table 5. Predictors of primary infertility among independent tobacco smoking variables (binary logistic regression)

| Independent variables             | OR | 95% CI       | p value |
|-----------------------------------|----|--------------|---------|
| Age                               | 1.003 | 0.960–1.048 | 0.894   |
| Continuous                        |    |              |         |
| Refugee status                    | 1.260 | 0.541–2.935 | 0.592   |
| Nonrefugee = reference            |    |              |         |
| Passive smoking                   | 3.455 | 1.491–8.009 | 0.004*  |
| No = reference                    |    |              |         |
| Former smoker                     | 9.498 | 2.975–30.320| <0.001**|
| No = reference                    |    |              |         |
| Smoking intensity                 | 2.788 | 1.080–7.197 | 0.034*  |
| ≤5 cigarettes/day = reference     |    |              |         |
| Smoking duration                  | 2.324 | 0.810–6.669 | 0.117   |
| ≤2 years = reference              |    |              |         |
| Constant                          | 0.015 | <0.001**    |         |

OR, odds ratio; CI, confidence interval. Model coefficient $\chi^2 = 23.84$; $p = 0.001$; Nagelkerke $r^2 = 0.225$; membership for cases. * Significant at $p < 0.05$. ** Highly significant at $p < 0.001$.

genitourinary infection than fertile men with the same condition ($p = 0.005$).

Table 5 illustrates binary logistic regression of the positively associated independent variables with primary infertility in men. After adjustment for age and refugee status, passive smoking was >3 times more likely among infertile men than their counterpart ($p = 0.004$); former smokers held >9 times risk ($p < 0.001$), and smoking more than 5 cigarettes per day was more than twice among infertile men ($p = 0.034$).

**Discussion/Conclusion**

In this study, we evaluated the relationship between tobacco smoking in both men with normal fertility status and men suffering from primary infertility. The study revealed that passive smoking among all participants is way more among infertile (52.5%) than fertile men (37.5%) ($p = 0.007$). Passive smoking occurs when an individual inhales the smoke that is produced from the burning end of the cigarette (sidestream smoke), which represents
90% of the smoke in the area surrounding the smoker and another 10% produced from the exhaled smoke (mainstream smoke) [13]. According to a biomarker that detects exposure to tobacco smoke, around 50% of non-smokers are passive smokers [14]. Usually, passive smokers exhale large amounts of superoxide and hydrogen peroxide [13] that form most of the sidestream smoke and that affect sperm motility [15–17], sperm chromatin integrity [18], and that may result in impaired oocyte fertilization [19].

Being a case-control study that had recruited infertile couples from fertility centers and who were under some sort of medical consultation, investigation, or even management for their infertility problem, many men were already enduring lifestyle modification as a preliminary management plan like losing excess weight and cessation of smoking. In addition, some men might have voluntarily stopped any unhealthy habits for the sake of childbearing which might have also included quitting of smoking. These suggestions may explain the decreased frequency of active smokers among infertile men in relation to their counterpart in relation to former smokers. Moreover, exploring the intensity of tobacco use per day revealed a dose-response effect among infertile men. Several research studies confirmed the reverse dose-dependent effect between the amount of cigarette consumption and semen parameters in men [20–22]. In a large cross-sectional study that included 2,542 men, Ramlau-Hansen et al. [20] conducted 7 semen quality studies to evaluate the association between current smoking and semen quality. Researchers observed a reverse dose-dependent association between smoking and total sperm count, semen volume, and the number of motile sperms. However, the study reported that ever-smokers had values of total sperm count and sperm concentration in between never-smokers and currently smoking men, suggesting a partly irreversible effect of tobacco smoking. However, prospective studies with appropriate controls need to be conducted to rule out reversibility from otherwise.

After adjustment for age and refugee status, our study revealed that men who were exposed to passive smoking were about 3.5 times more likely to have primary infertility, former smokers had 9 times the risk, and men who smoke >5 cigarettes per day had twice the risk. When some researchers found that smoking is associated with both reduced sperm quality and idiopathic infertility [23, 24], particularly in heavy long-term smokers [25, 26], some research studies suggested no relationship exists [27–29]. Possible explanations for such opposing and confusing results could be related to the different metric measures used and the difficulty in adjusting confounding factors that could be existing such as chronic medical diseases, passive smoking, environmental toxins, and socioeconomic status [8].

In our study, causes of infertility among men recruited for the study were categorized into 3 types as follows: nonobstructive causes, obstructive causes, and idiopathic etiology. Nonobstructive causes included abnormal spermatogenesis, antisperm antibodies, low sperm motility, high semen viscosity, varicocele, oligospermia, azoospermia, necropermia, and necrozoo spermia. Obstructive causes were found to include ejaculatory disorders, epididymal obstruction, prostatic enlargement, obstructive oligospermia, and obstructive azoospermia. Analysis revealed another positive dose-dependent relationship between infertile men with nonobstructive causes and fertile men in relation to the number of cigarettes consumed per day. The coefficient increased from 4.26 (95% CI: 1.19–15.25) among 6–10 cigarettes/day consumers to 5.52 (95% CI: 1.63–18.72) among >10 cigarettes/day consumers. This can confirm what has been discussed before about the effect of tobacco smoking on semen parameters and its direct relationship with infertility among men. However, a recent systemic review and meta-analysis that was conducted with 10,823 infertile men found that oligospermia was significantly higher among infertile smokers, while teratospermia, azoospermia, and asthenospermia did not show a significant relationship. Reproductive-related hormones: testosterone, prolactin, and follicular stimulating hormone were found not related to these hormones through the varicosed internal spermatic vein [30].

For intense scrutinizing, the effect of tobacco smoking on the fertility status of men and accompanying genitourinary conditions were compared within the 2 groups. Based on our results, unilateral or bilateral varicocele seemed to be more likely to occur among passive smokers, those who smoke >5 cigarettes per day, and those who remained active smokers for >2 years. Research studies suggested that oligospermia incidence among smokers with varicocele is ten times greater than among non-smokers. This could be explained by the increased secretion of adrenal catecholamines, influenced by the nicotine component of cigarettes, which in turn leads to seminiferous tubule damage due to the retrograde flow of these hormones through the varicosed internal spermatic vein [31]. Others suggested that oxidative stress inducing
a significantly higher level of plasma protein carbonyls in spermatic veins among smokers with varicocele than nonsmoker varicocele patients is a significant marker [32]. Moreover, our findings revealed that genitourinary tract infection of >5 times in the past 2 years was more among passive smokers and among those who smoke >5 cigarettes per day. However, the role of tobacco smoking on the renal system has not been extensively reviewed. In 1 case-control study, smokers were found more likely to suffer from nephrolithiasis than nonsmokers (OR: 2.06, 95% CI: 1.06–4.01, and \( p = 0.03 \)) [33], but other hospital-based study found that the relationship was weak to be identified as a risk factor [34], although some suggested that tobacco smoking decreases urinary output and aggravate oxidative stress which in turn are related to nephrolithiasis [35, 36].

In conclusion, studying smoking status alone in men is not typically indicative to pursue the hazardous effect of tobacco on the male reproductive state. Exploring passive smoking, former smoking, the cumulative effect of tobacco consumption examined through the amount of use per day, and the duration of being an active smoker provided substantially indicative findings. From the attained results, global tobacco control efforts need to outline the specific hazards of tobacco smoking on health in general and on the reproduction system in particular.

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Statement of Ethics

The study followed the Declaration of Helsinki and the ethical approval was obtained from the Palestinian Health Research Council in Gaza Strip, Number PHRC/HC/548/19 Dated 2019/04/09 before conducting the study. All participants signed a written informed consent that was attached to each questionnaire to participate in this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.D. developed the concept and the design of the work, prepared the study proposal with hypothesis statements and research questions, performed data entry, statistical analysis, and results interpretation. Y.A. critically reviewed and substantially advised on the methodology and statistical analysis, assisted in results analysis and interpretation, and supervised the whole study. A.D. wrote the manuscript, and Y.A. provided feedback and helped shape the analysis and the manuscript. Both the authors reviewed and agreed on the final version of the manuscript.

Availability of Data and Material

The data that support the findings of this study are openly available in “figshare” at 10.6084/m9.figshare.14628474 [37].

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