

A survey on infertility in men and its relation to risk factors in selected provinces of Iran

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ABSTRACT

Objective: Infertility in men cause significant morbidity and mortality, unfortunately there is not enough information about it due to the lack of a registry in the country. The purpose of this study was to determine the frequency of infertility in men and its association with risk factors.

Methods: This cross-sectional study used data from a nation-wide project on reproductive morbidities among males in Iran in 2007. 2,293 men aged 25-60 years were selected from four provinces across the country including, Golestan Province in the North, Hormozgan Province in the South, Kermanshah Province in the West, and Isfahan Province by cluster sampling scheme. Then, we determined the frequency of infertility in married men, and related risk factors such as smoking, infection, trauma, etc.

Results: Of the 2,293 men interviewed, 2,076 were married, 78 were infertile; current primary and secondary infertility was estimated at 3.75%. The incidence of infertility in urban areas was significantly higher than in rural areas (p value<0.003), and finally the clinically male infertility was estimated at 2%.

Conclusions: We need to explain that this project was a cross-sectional study. Therefore, it is recommended that more studies be conducted for accurate estimates of infertility in Iranian men.

Keywords: infertility, morbidity, survey, risk factors

INTRODUCTION

Infertility is the lack of pregnancy in a sexually active couple who do not use contraceptives for 2 years. In about 25% of couples who do not get pregnant within a year, 15% of them seek treatment, and less than 5% of them do not have any children. Male causes account for 50% of the cases. Reduced fertility in men can be the result of congenital or acquired reproductive disorders such as genital tract infection, increased scrotal heat (varicocele), endocrine disorders, genetic disorders and immunological factors. In 30-35% of the cases, there is no cause (idiopathic), but seminal fluid is abnormal. After that, varicocele has the highest prevalence (12.3%), and genital tract infections (about 7%) are in the next category. The main factors affecting infertility are its duration, which increases the likelihood of infertility, primary or secondary infertility, the result of semen analysis, age, and the fertility status of the spouse (Jungwirth *et al.*, 2012). A complete physical examination by an urologist for the treatment and follow up of infertility is important because infertility may be a symptom of a systemic illness that has not been previously detected.

It is also important to consider the patient's medical history, such as systemic diseases, genetics, surgery, reproductive history, sexual history, family history, drug use, alcohol and smoking, occupation, disruptive drugs of ejaculation including antihypertensives, antipsychotics,

and antidepressants. In physical examination, attention to the testis and scrotum is important for finding varicoceles, congenital anomalies (CAVD), prostate and penile disorders. Testosterone, FSH, LH and prolactin hormones are also included in the lab evaluation along with urinalysis in some cases (Turek, 2004). Over the past few decades, the quality of sperm and fertility has dropped dramatically in human societies, which could be due to environmental issues such as pesticides, lead, and cigarette smoking. A study showed that nicotine interferes with spermatogenesis and causes testicular atrophy in mice (Arabi & Anand, 2002). There are different reports about the prevalence of infertility in Iran. A study by Nojoomi *et al.* (2002) estimated that infertility affects at least 10% of couples in Tehran, and at least 2% of them have not been treated. In addition, the statistics showed that the prevalence of infertility in the country and in the county are 2.5% and 1.6%, respectively (Vahidi *et al.*, 2009).

The aim of this comprehensive study was to determine the frequency of infertility in Iranian men and its relation to risk factors, in order to plan for the management and improve health of this group, and reduce the economical and psychological costs.

MATERIALS AND METHODS

This research is a cross-sectional study, a systematic cluster sampling with a sample size of 2,293 individuals from four province -cities and rural areas around them- of different climates (Figure 1). Regarding the selection of provinces, four provinces, including Kermanshah, Golestan, Isfahan and Hormozgan, were randomly selected. Then, in each province, three counties were randomly selected, and according to the composition of urban and rural population of 25-60 years old men, the sample sizes from city and village were separately selected. At first, the midwives and general practitioners (GPs) at the participant's house filled out the questionnaires. The husbands were referred to the urologist if the couple had a history of infertility. Clinical examinations were performed and some tests including semen analysis, FSH and testosterone were requested if necessary.

Finally, we used the SPSS 11.5 to analyze the data. We analyzed the quantitative variables (age, height, weight, etc.) using the independent T-test. We used the Chi-square test to determine the relationship between qualitative variables. We used the Pearson's correlation coefficient to examine the correlation between variables. The ethics committee of the Shahid Beheshti University of Medical Sciences approved the project and we received consent from all participants.

RESULTS

Demographic characteristics

In total, 2,293 men in the age range of 25-60 years were interviewed, clinical and lab evaluations were carried out. The dispersion of samples in each province, by segments of urban and rural areas, is shown in Figure 1.

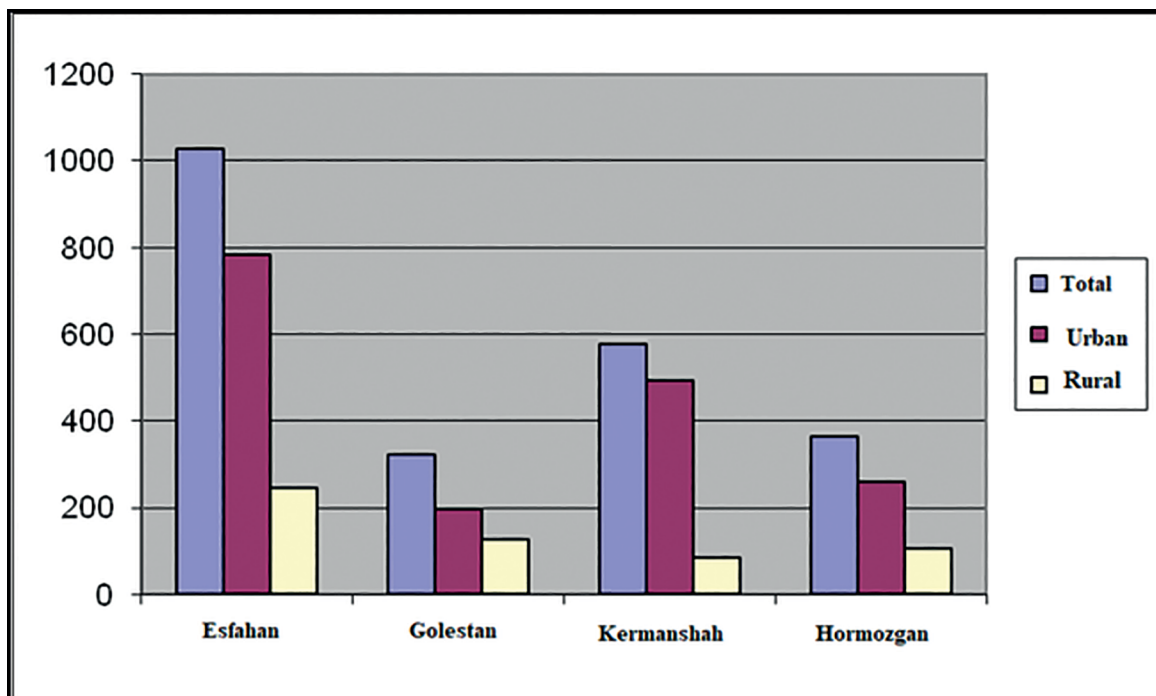


Figure 1. Dispersion of samples from each province in urban and rural areas.

75.5% of the men lived in urban areas, and 24.5% lived in rural areas.

In total, 90.5% were married, 8% were single, 0.8% were divorced and 0.4% were widows. In addition, the mean age of marriage was 24.14 ± 4.07 years. In terms of social habits, over the past year, about 68.11% of the people have not smoked at all, 6.41% smoked sometimes, and 25.39% smoked every day. About 9% of the subjects were exposed to smoking daily and 18.5% were only occasionally exposed to it. In terms of drinking alcohol, about 94% said they had not consumed alcoholic drinks; 5.39% said occasionally and only 0.3% refused to respond. The average duration of alcohol consumption was 11.1 ± 8.9 years and the period of drinking was between 1 and 47 years. In terms of narcotic drugs, 7% used occasionally, 4% daily, and 0.3% refused to respond and, the method of administration were smoking (8.29%); (0.1%) injection and (2%) other methods. About 92% of the participants did not take any psychotic medication, and about 8% used it. In terms of referral to the psychiatrist, about 92% did not mention any referrals. Other medical records from the participants included 0.14% with Parkinson's disease; 2% had history of seizure; 0.7% a history of stroke; 11.5% had hyperlipidemia; 3.6% had a history of cardiovascular drugs; 29% had a history of taking h2-blockers; 1.83% used antipsychotic medications; and 4.82% had used antidepressants. The results of the response from 2076 couples to this question: "Do you have any child from your spouse?" including: 8.8% had no offspring; 91% said yes; 0.3% used treatment to have pregnancy and 0.2% did not respond. The results of the interview showed that, 41% of the patients had a history of hospitalization or surgery; 16.4% mumps, 1.18% mumps with orchitis; 5.14% undescended testes (UDT); 4.5% diabetes; 6% hypertension; 1.4% had thyroid disease; 12.5% allergic disease; 4.1% testicular trauma; 0.82% testicular infection; 1.9% varicocele; 0.6% orchiopexy; 5.8% hernia repair; 0.8% hydrocelectomy; 24.51% exposure to heat and 14.52% chemical agents. Figure 2 shows the family history of infertility by province in urban and rural areas.

Regarding the fact that 224 (10.8%) couples tended to have children and 78 of them had been trying pregnancy for more than 12 months, and the total number of married persons was 2,076 (Table 1). The percentage of current primary and secondary infertility were estimated at 3.75%, but the definitive clinical diagnosis of current infertility was documented only in 2% of the subjects. Table 2 shows the distribution of infertility in urban and rural areas. The difference we found between urban and rural areas is statistically significant ($p=0.02$).

Tables 3, 4 and 5 show the difference between fertile and infertile people with respect to different risk factors. It should be explained that in all the comparison tables for each of the studied morbidity, this type of morbidity was compared to healthy subjects (those who did not have a disease).

DISCUSSION

Given the importance of men's role in social and economic issues, their health information is important in every context. About 25% of the couples do not get pregnant within a year; 15% of them seek treatment; and less than 5% of them are without children (Jungwirth et al., 2012; Tanagho & McAninch, 2004; Arabi & Anand, 2002). In most cases, the prevalence of primary infertility in the world is 13-19%, with an untreated portion of 2.49%, and the frequency of the secondary type (having at least one child) is about 5-10% (Borjian Boroujeni et al., 2018). Another study that has been conducted by the Royan Institute has been investigating a large number of different causes for infertility such as marriage age rising, increasing the use of contraceptives, the freedom of abortion and the inappropriate economic situation (Moieni et al., 1999). In a cross-sectional study on 12,000 Iranian women aged 19-49 years of age, a history of primary infertility was 24.9%. According to this study, about one quarter of Iranian couples experience primary infertility during their lifetime (Nojomi et al., 2002). In our cross-sectional study, out of 2,076 men under investigation, 78 were infertile. The frequency of infertility found was 3.75%. In addition, in other studies, the rate of infertility in Iran is estimated to be about 1.6% to 3.4% (Jungwirth et al., 2012; Nojoomi & Ashrafi,

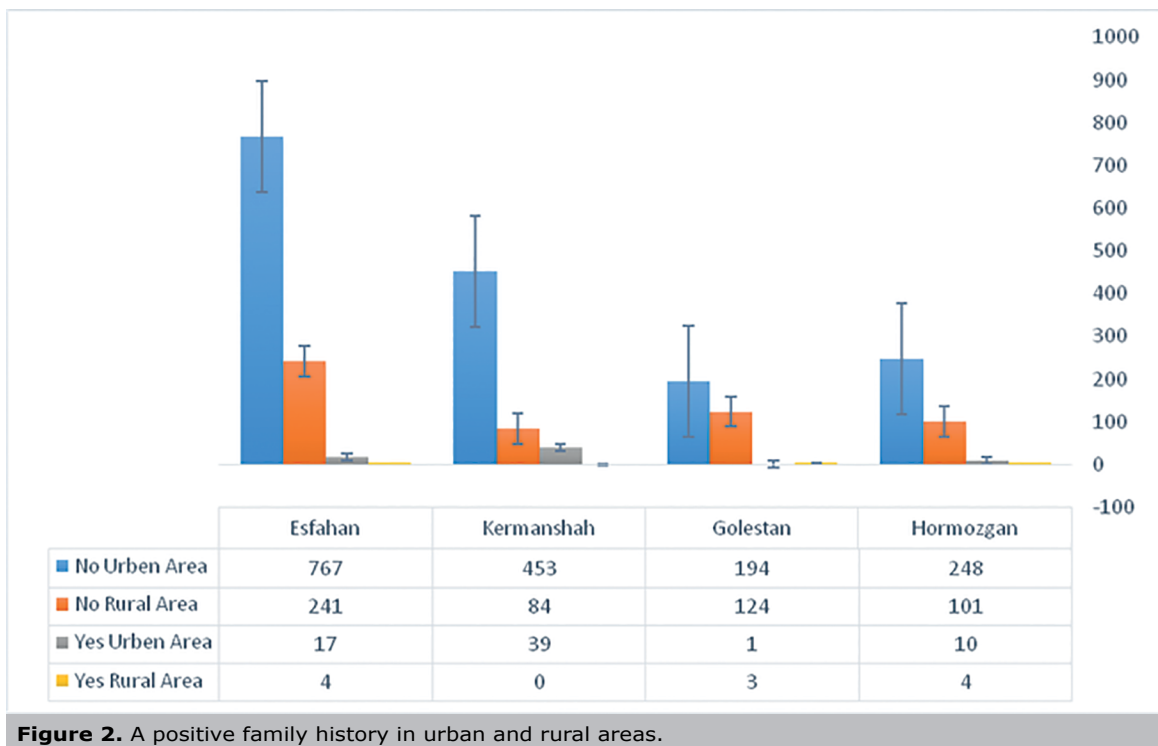


Figure 2. A positive family history in urban and rural areas.

Percentage (%)	Frequency	Marital status
8	184	Single
90.5	2076	Married
0.7	17	Divorced
0.4	10	Widow
0.3	6	Not Response
100	2293	Total

2001; Direkvand Moghaddam et al., 2016). The reason for the discrepancy between the frequency of infertility in our study and other surveys is that previous studies have been carried out mainly in urban areas and, as discussed later, the frequency of infertility in urban areas is significantly higher than villages. In our study, 2,076 people were surveyed, with a population of 1,562 people living in urban areas and 514 people living in rural areas. Of the urban population, 67 men (4.30%) and of the rural population 11 men (2.10%) were included in the definition of infertility. The results show that, the frequency of infertility in urban areas was significantly higher than in rural areas in Iran (Table 2). In our study, infertility in different age groups of marriage showed a significant difference (in all samples, between urban areas and rural areas) (Table 3).

In a study ran by Collodel et al. (2010), the effects of smoking on semen parameters in two groups of idiopathic infertile men were examined, and there were significant disturbances in the smoker group compared to the control group. Sperm concentration and fertility index in heavy smokers were significantly reduced compared to other smokers and non-smokers. Collodel et al. (2010) investigated the effects of smoking on sperm parameters. Sperm samples were taken from 25 fertile smokers, 21 fertile non-smokers, 23 infertile smokers and 32 infertile non-smokers, and then sperm analysis was performed.

The study found that smoking had an effect on sperm parameters, although this effect was not statistically significant (Colagar et al., 2007). Cigarette smoking seems to play a role in reducing the quality of semen and increasing the risk of male idiopathic infertility (Ranganathan et al., 2018). In our study, out of 1,414 non-smoker men, 57 were infertile/ and from 660 smokers, 21 men were infertile. This difference was not statistically significant, and smoking did not play a role in increasing the prevalence of infertility (Table 4). In this study, smokers were divided into two groups, 614 men who smoked less than 20 cigarettes a day, and those who smoke 20 or more cigarettes a day were 24, but there was no significant difference ($p=0.54$) (Table 4).

Concerning the association of alcohol consumption with male infertility, Dunphy et al. showed no association between alcohol and infertility in 258 couples referred to the infertility clinic (Dunphy et al., 1991). The results from Aboulmaouahib et al. presented the highest values of DNA fragmentation and chromatin decondensation (31% and 39%) in the smoking and the alcohol/smoking group (Aboulmaouahib et al., 2018). In our study, with 112 men who consumed alcohol, the number of infertile men were 2 (1.8%); while among 1,956 men who did not consume alcohol, 76 were infertile and there was no statistically significant ($p=0.43$) relationship between the two groups (Table 3). On the other hand, in our study, out of 78 drug-addicted males, eight were infertile; and among 1,991 non-addicted men, 208 were infertile. There was no significant difference ($p=0.96$) between the two groups. Of course, the drug cannot be evaluated as an independent factor. Because it is mainly associated with smoking and alcohol, and addicts have a lack of family support and very risky sexual behaviors, which are associated with a history of STD in these people.

Several studies have investigated the effects of Selective Serotonin Reuptake Inhibitor on infertility and showed that these drugs disrupt motility and sperm concentration, which is a reversible effect (Tanrikut & Schlegel, 2007). We generally considered psychiatric drugs in two categories of

Table 2. Comparison of infertility in urban and rural areas.

Comparison of infertility in urban and rural areas	Fertile (frequency and %)	Infertile (frequency and %)	Total
Urban	1945 95.70%	67 4.30%	1562 100%
Rural	503 97.90%	11 2.10%	514 100%
Total	1998 96.20%	78 3.80%	2076 100%

p value<0.003.

Table 3. Infertility in different age groups of marriage.

Infertile (frequency and %)	Fertile (frequency and %)	Different age groups
<20	209 97.2%	6 2.8%
20-25	921 96.5%	33 3.5%
25-30	688 95.6%	32 4.4%
30-40	174 96.7%	6 3.3%
>40	5 83.3%	1 16.7%

p value<0.003.

antipsychotic and antidepressant medications in the questionnaire. In our study, out of 1,985 men who did not use any psychiatric drugs, 76 were infertile; and from 87 persons who used drugs, only 2 were infertile, and we could not find any association ($p=0.46$) between psychiatric drugs and infertility (Table 4).

Trauma of the testes can lead to complete testicular atrophy (Katz *et al.*, 2017). In our study, from 1,973; 66 men with no history of testicular trauma were infertile, while out of 85 men with a positive history, 9 were infertile. There was a statistically significant difference ($p=0.001$) between testicular trauma and infertility (Table 4). Of course, the severity, type, unilateral or bilateral trait of the trauma was not included in this study.

In their study, Tsvetkov investigated 27 men with a history of mumps and fertility problems. There was unilateral testicular destruction in 21 patients, and bilateral in six patients. The researchers divided these patients into two groups: the first one who had suffered from orchitis before the age of 10 years; and the second group, who had suffered from orchitis after the age of 10 years. The spermogram revealed azoospermia in both groups of patients with bilateral orchitis (Tsvetkov, 1990). In our study, out of 296 patients who had a positive history of mumps, 10 were infertile. The obtained numbers were compared with the prevalence of infertility in a control group without history of mumps and orchitis, there was no significant difference, $p=0.91$ and $p=0.73$, respectively (Table 4).

On the other hand, in our survey, out of 17 individuals with a history of testicular infections (epididymo orchitis), two were infertile; and in comparison with the control group, there was a significant association ($p=0.07$) between infections and infertility (Table 4).

In an investigation by Romeo & Santoro, varicocele was one of the main causes of male infertility. Their findings indicated that varicocele reduced fertility (Romeo & Santoro, 2009). Several review articles demonstrated that spermatozoa abnormalities in patients with varicocele may be

multifactorial, and oxidative stress seems to be one of the main causes of this problem (Agarwal *et al.*, 2009; Roque & Esteves, 2018; Sönmez & Haliloğlu, 2018). In our study, varicocele was considered with a history of varicocele surgery. Among 40 men with a history of varicocele surgery, 10 had a history of infertility - which was statistically significant ($p<0.001$) in comparison with the control group (Table 4). However, in this study, the effects of varicocele treatment before and after surgery on infertility are not judicious. In addition, of the 17 men who had a history of hydrocelectomy, there was one infertile men who did not show a significant difference ($p=0.64$) compared to 76 infertile men from 1,968 without a history of hydrocelectomy as a control group (Table 4).

A study by Paul *et al.* found evidence that sperm production with DNA disorders could result from incomplete DNA repair or environmental effects such as heat-induced stress (Paul *et al.*, 2008). In our study, out of 507 men with a history of heat exposure, 27 were infertile, which was statistically significant ($p=0.02$) in comparison with the control group (Table 4).

Podzimek *et al.* (2005) found that heavy metals could have a negative effect on the fertility system and lead to immune responses. The results showed that more than 50% of the patients responded to mercury, aluminum and silver with lymphocyte activation. In our study, there were 15 infertile men who had a history of contact with chemicals (285), and there was no significant difference ($p=0.17$) in comparison with the control group (Table 4).

Normal thyroid function is very important for the proper development and momentous for the maintenance of male reproduction (Patel & Kashanian, 2016; Ceccarelli *et al.*, 2008; Sawka *et al.*, 2008). In our study, 30 patients had thyroid disease, and only one case had infertility recorded (Table 4).

In the article by McPherson & Lane (2015), the prevalence of overweight and obesity in reproductive-aged men is increasing worldwide, and it was associated with

Table 4. Differences between healthy and infertile people with respect to risk factors.

Risk Factors	Fertile (frequency and %)	Infertile (frequency and %)	p*
Smokers -/+	1357/639 (96%/96.8%)	57/21 (4% - 3.2%)	0.34
≤0 cigarettes daily->20 cigarettes daily	596/24 (96% - 97.10%)	18/1 4% - 2.90%	0.54
Alcoholic -/+	1880/110 96.1% - 98.2%	76/2 3.9% - 1.8%	0.43
Addicted -/+	1783/208 96.2% - 96.3%	70/8 3.8% - 3.7%	0.96
Psychiatric Medication user -/+	1909/85 96.2% - 97.7%	76/2 3.8% - 2.3%	0.46
Testicular trauma -/+	1907/76 96.7% - 89.4 %	66/9 3.3% - 10.6%	<0.0001
Mumps -/+	1457/286 96.7% - 96.6%	49/10 3.3% - 3.4%	0.91
Mumps orchitis -/+	1778/21 96.7% - 95.5%	60/1 3.3% - 4.5%	0.73
Testicular infections -/+	1980/15 96.4% - 88.2%	73/2 3.6% - 11.8%	0.07
Varicocele surgery -/+	1960/30 96.6% - 75.0%	68/10 3.4% - 25.0%	<0.0001
Hydrocelectomy -/+	1968/16 96.3% - 94.1%	76/1 3.7% - 5.9%	0.64
Exposed to heat -/+	1512/480 96.9% - 94.7%	49/27 3.1% - 5.3%	0.02
Exposed to chemical agents -/+	1705/285 96.6% - 95.0%	60/15 3.4% - 5.0%	0.17
Thyroid disorders -/+	1959/29 96.2% - 97.7%	77/1 3.8% - 3.3%	0.89
Hyperlipidemia -/+	1670/236 96.3% - 98.7%	65/3 3.7% - 1.3%	0.04
UDT -/+	1846/101 96.3% - 97.1%	70/3 3.7% - 2.9%	0.68
Orchiopexy in the UDT patients -/+	100-1 97.1% - 100.0%	3/0 2.90% - 0.00%	1.00
Orchiopexy -/+	1975/10 96.3% - 76.9%	75/3 3.7% - 23.1%	<0.0001
Family history of infertility -/+	1643/332 96.5% - 95.1%	59/17 3.5% - 4.9%	0.21

-: Without history of risk factors. +: With history of risk factors. *Fisher exact test was used to calculate the p-value. Fisher exact test

male subfertility, reducing sperm counts, increasing oxidative sperm DNA damage and changing the epigenetic status of sperm. In our study, out of 239 men with hyperlipidemia, three were infertile, which was statistically significant ($p=0.04$) in comparison to the control group (Table 4).

Thorup & Cortes (2009) and Vikraman *et al.* (2016) concluded that an undescended testis (UDT) is associated with an increased risk of infertility and cancer; and it has been shown that early treatment of UDT reduces the risk of infertility and cancer. In an article by Bonney *et al.* (2009), UDT has been raised as a cause of infertility and cancer, and their recommendation is to perform orchiopexy. In our study, out of 104 patients with UDT, three were infertile, which was not statistically significant ($p=0.68$) in comparison to the control group. On the other hand, there was no statistically significant difference in the subjects with UDT

between those that had orchiopexy and those that had not been treated (Table 4).

In this study, out of 349 couples with family history of infertility, 17 cases were found, which was not statistically significant ($p=0.21$) (Table 4).

In a study by Hofny *et al.* (2010), the increase in BMI causes abnormalities in sperm morphology, LH, serum leptin, testosterone and sperm motility. Tamer Erel & Senturk (2009) suggest that obesity also affects ART. In our study, infertility in different BMIs was not significantly different ($p=0.44$) (Table 5). Of course, it is necessary to explain that in most papers, the effect of obesity as a disturbance in the quality and quantity of sperm as well as changes in endocrine status has been mentioned, while in our study, the fertility criterion was having a child.

In summary, according to the results of this study, in relation to infertility, the following is cited:

Table 5. Infertility in different groups of body mass index (BMI).

BMI	Fertile (frequency and %)	Infertile (frequency and %)
<20	175 95.6%	8 4.4%
20-25	823 96.1%	33 3.9%
25-27.5	436 95.60%	20 4.4%
27.5-30	307 98.1%	6 1.9%
30-40	222 96.5%	8 3.5%

p value=0.44.

- Of the 2,293 men interviewed, 2,076 were married, 78 were infertile, resulting in an estimated primary and secondary infertility of 3.75%.
- The frequency of infertility in urban areas was significantly higher than in rural areas of Iran.
- The frequency of infertility in addicted people was not higher.
- Mumps, orchitis, testicular trauma, varicocele, exposure to heat and hyperlipidemia increases the risk of infertility.

We need to explain that this project was performed as a cross-sectional study, and current clinically male infertility was estimated at 2%. Therefore, we need to conduct such studies in the future.

Limitation

According to the financial constraints of the project, which led to a relatively low number of samples, we suggest that larger studies be conducted on male morbidity.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

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