Epidemiology and Etiology of Infertility in Iran, Systematic Review and Meta-Analysis

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Abstract

Background: Epidemiological study of infertility might let the related policy makers to make accurate decisions regarding the potential users’ requirements for infertility workup or management. The objective of this study was to find the incidence and etiologic factors for infertility in Iranian population.

Methods: an internet based search through PubMed, Google Scholar, Iran Medex, magiran and SID with the search terms including; “Iran” and “infertility” and “epidemiology” or “etiology” or “cause” and university library archives was performed that was restricted to the publications in the recent 25 years (since 1987-2012) in English or Persian. This project included all of the studies that were designed by random cluster sampling with face to face interviews at home from the Iranian population. Life time infertility was defined as inability to conceive after 12 months of unprotected intercourse. For analyzing the causes of infertility we included the published articles that were designed by Iranian infertility clinics and evaluated the causes of infertility by appropriate diagnostic techniques. Independent data extraction was performed by two observers and meta-analysis was done. Random affects meta-analyses, forest plot and Sata graph, publication bias and sensitivity analyses were performed.

Results: Twelve studies that were designed to evaluate the prevalence rate of infertility were identified and meta-analysis was performed to integrate the findings of the separate studies. The average rate of infertility was; 10.9% (95% CI 7.4-14.4), Primary infertility; 10.6% (95% CI 5.3-16.0), secondary infertility; 2.7% (95% CI 1.9-3.5) and current infertility; 3.3% (95% CI 2.7-3.8). Causes of infertility were picked up from seven qualified studies. Male factor was; 34.0% (95%CI 26.9- 42.0), female factor; 43.5% (95% CI 35.5- 51.7), both male and female factors; 17.1% (95% CI 11.4- 21.9) and unexplained cause; 8.1% (95% CI 5.6-11.5), respectively.

Conclusions: Prevalence rate of life time infertility was 10.9%. The most common cause was female factor.

Keywords
Infertility; Epidemiology; Etiology; Iran

Introduction

Infertility is defined as one year unprotected intercourse without pregnancy [1]. Cycle fecundability is the probability that a cycle will result in pregnancy that is about 20% in normal individuals. Subfertility is defined when pregnancy occurs after 12 months of trying to conceive [2]. Evidence shows that the incidence of infertility has not changed during the past thirty years and is even declining in some populations [3]. However Total Fertility Rate (TFR) that is the average number of children born to a woman in her lifetime is decreasing in the world. The decline in TFR has several causes such as; changing values, delayed child bearing, and successful family planning for an ideal smaller family size [4,5]. It is estimated that almost 72.4 million couples around the world experience primary or secondary infertility [6]. The reported infertility rates for different countries range from almost 5-30% [7] and the reported causes of infertility in the couples include; male problems (35%), tubal and pelvic pathology (35%), ovulatory dysfunctions (15%), unexplained infertility (10%) and unstudied problems (5%) [6]. Here we review the data about the prevalence and causes of infertility in every population is very important. Epidemiological national data and knowledge about the geographic differences can help the organizations and policy makers to understand the trends of public health in each area, to advance the health preventive programs and to program for allocation of resources.

The objective of this study was to review the existing literature to answer these questions: 1) What is the prevalence of infertility in Iranian population?, 2) What are the etiologic factors of infertility in Iran?

Data Sources and Method of Selection

To estimate the epidemiology and etiology of infertility in Iran we performed an internet based search through PubMed, Google Scholar, Iran Medex, magiran and SID with the search terms including; “Iran” and “infertility” and “epidemiology” or “etiology” or “cause”. The last searching performed on 25.02.2012. There are Persian published studies that were not accessible by using the ordinary electronic searching methods and they were found in the university libraries and were included only if they had all the inclusion criteria. The studies which were performed in the recent 25 years were included. In order to have a more accurate estimation of the epidemiology of infertility, the samples should be representative of the condition in the general population in Iran. Therefore, we included only the epidemiological studies that were performed by random cluster sampling of the targeted regions and face to face interviews at home. In order to perform these kind of studies the targeted areas are divided to smaller population-based residency areas and according to the number of houses and their populations the sample sizes are assessed in each area by expert epidemiologists. In the next step the randomly selected houses in each geographic area is knocked by the trained staff and the questionnaires are completed by face to face interview. However for evaluation of the etiology of infertility we included the studies that were performed in Iranian different infertility clinics that appropriate evaluations could be performed to investigate and find the cause of infertility.

Definition of infertility in all of these studies was as inability to conceive after 12 months of unprotected intercourse. Primary infertility was defined when no previous pregnancy had occurred and...
secondary infertility was defined when there was a prior pregnancy [2]. Life time infertility is when a couple had experienced infertility sometime in their life. However current infertility is defined when the couple has infertility at the present time [8]. The search was restricted to the studies that were published in peer reviewed English or Persian journals. Independent data extraction was performed by two observers and discrepancies were solved by re-evaluation of the discrepant material in a joined meeting with presence of the two observers and considering the reason for exclusion.

Data Analysis

Meta-analysis was performed to integrate the findings of the separate studies. The pooled estimates accompanied by 95% C.I were calculated by DerSimon and Laird random effect model. Inconsistency across the studies was tested by Cochrane’s Q test. The I^2 statistics (= 100(Q-df)/Q), was calculated to describe the variation across the studies that is due to heterogeneity rather than chance. The presence of publication bias was assessed by Begg and Egger test. Sensitivity analyses were performed and showed that elimination of a single study does not induce a significant influence on the final result.

The P-value less than 0.05 were considered significant. Analysis was concluded using NCSS and STATA statistical software.

Results

There were twelve studies that had been published by random cluster sampling and home-interviews that were included for epidemiologic analysis and estimation of the prevalence rate of infertility and classification of primary and secondary infertility in Iranian population [9-20]. Meta-analysis that was performed by using data of these studies showed heterogeneity among the studies and concluded that the total average rate of infertility in Iran is 10.9% (95% CI 7.4-14.4), primary infertility is 10.6% (95% CI 5.3-16.0), secondary infertility is 2.7% (95% CI 1.9-3.5) and current infertility is 3.3% (95% CI 2.7-3.8). The estimates are presented as percents in the basic tables (Table 1).

Table 1: Studies included for calculation of the prevalence rate of infertility in Iran.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study-Year</th>
<th>Study-region</th>
<th>Sample-size</th>
<th>lifetime infertility n(%)</th>
<th>Primary infertility</th>
<th>Secondary infertility</th>
<th>Current infertility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parsanezhad ME [9]</td>
<td>1993</td>
<td>Shiraz</td>
<td>1430</td>
<td>159 (11.1)</td>
<td>83 (5.8)</td>
<td>76 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Barouei E. et al. [10]</td>
<td>1997</td>
<td>Tehran</td>
<td>1784</td>
<td>381 (21.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moghadam AE et al. [11]</td>
<td>1999</td>
<td>Mazandaran</td>
<td>2953</td>
<td>389 (13.2)</td>
<td>351 (11.9)</td>
<td>38 (1.3)</td>
<td>118 (4.0)</td>
</tr>
<tr>
<td>Nojomi M et al. [12]</td>
<td>2000</td>
<td>Tehran-west</td>
<td>1174</td>
<td>141 (12.0)</td>
<td>98 (8.3)</td>
<td>43 (3.7)</td>
<td>49 (4.2)</td>
</tr>
<tr>
<td>Siahkal MS et al. [13]</td>
<td>2001</td>
<td>Tehran</td>
<td>1987</td>
<td>173 (8.7)</td>
<td>145 (7.3)</td>
<td>28 (1.4)</td>
<td>50 (2.5)</td>
</tr>
<tr>
<td>Noorbalaa AA [14]</td>
<td>2001</td>
<td>Iran</td>
<td>10418</td>
<td>1653 (76.2)</td>
<td>5200</td>
<td>16 (9.2)</td>
<td>107 (2.0)</td>
</tr>
<tr>
<td>Mohammad baygi R et al. [15]</td>
<td>2002</td>
<td>Sanandaj</td>
<td>902</td>
<td>166 (18.4)</td>
<td>130 (14.4)</td>
<td>36 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Ahmadi Asr Badr Y et al. [16]</td>
<td>2004</td>
<td>Tabriz</td>
<td>3183</td>
<td>104 (3.3)</td>
<td>62 (2.0)</td>
<td>39 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Moghadam LS [17]</td>
<td>2004</td>
<td>Gonabad</td>
<td>380</td>
<td>45 (11.9)</td>
<td>25 (6.6)</td>
<td>20 (5.4)</td>
<td></td>
</tr>
<tr>
<td>Vahidi S et al. [18]</td>
<td>2004</td>
<td>Iran</td>
<td>11370</td>
<td>2829(24.9)</td>
<td>385(3.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ardalan A et al. [19]</td>
<td>2004-5</td>
<td>Iran</td>
<td>10783</td>
<td>1592(14.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aflatoonian et al. [20]</td>
<td>2004-5</td>
<td>Yazd</td>
<td>5200</td>
<td>2775(53)</td>
<td>170(3.3)</td>
<td>1072(2.0)</td>
<td></td>
</tr>
<tr>
<td>Total Average (%) (95% C.I)</td>
<td></td>
<td></td>
<td></td>
<td>10.9 (7.4-14.4)</td>
<td>10.6 (5.3-16.0)</td>
<td>2.7 (1.9-3.5)</td>
<td>3.3 (2.7-3.8)</td>
</tr>
<tr>
<td>Cochrans’s Q</td>
<td></td>
<td></td>
<td></td>
<td>858.4 (&lt;0.001)</td>
<td>2884.8 (&lt;0.001)</td>
<td>85.8 (&lt;0.001)</td>
<td>20.4 (&lt;0.001)</td>
</tr>
<tr>
<td>I^2 statistic</td>
<td></td>
<td></td>
<td></td>
<td>99.1</td>
<td>99.7</td>
<td>91.8</td>
<td>80.4</td>
</tr>
</tbody>
</table>

Table 2: Studies that evaluated the causes of infertility in Iran.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Center</th>
<th>Total</th>
<th>Primary infertility</th>
<th>Secondary infertility</th>
<th>Male factor n(%)</th>
<th>Female factor n(%)</th>
<th>Both factors n(%)</th>
<th>Unexplained n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moini A et al. [21]</td>
<td>1990-5</td>
<td>Tehran-Royan Institute</td>
<td>4360</td>
<td>3719 (85.3)</td>
<td>641 (14.7)</td>
<td>220 (50.6)</td>
<td>200 (45.9)</td>
<td>-</td>
<td>153 (3.5)</td>
</tr>
<tr>
<td>Parsanezhad et al. [9]</td>
<td>1991-3</td>
<td>Shiraz, Clinics</td>
<td>693</td>
<td>453 (65.4)</td>
<td>240 (34.6)</td>
<td>140 (20.2)</td>
<td>464 (67.0)</td>
<td>-</td>
<td>89 (12.8)</td>
</tr>
<tr>
<td>Esmaizadeh S et al. [22]</td>
<td>1996-8</td>
<td>Babol – Fatematazahra</td>
<td>2169</td>
<td>1653 (76.2)</td>
<td>516 (23.8)</td>
<td>755 (34.8)</td>
<td>678 (33.1)</td>
<td>475 (23.3)</td>
<td>136 (6.7)</td>
</tr>
<tr>
<td>Baktiari A [23]</td>
<td>1999</td>
<td>Babol – Fatematazahra</td>
<td>920</td>
<td>707 (76.8)</td>
<td>213 (23.2)</td>
<td>208 (22.6)</td>
<td>398 (43.3)</td>
<td>250 (27.2)</td>
<td>64 (7.0)</td>
</tr>
<tr>
<td>Kamali M et al. [24]</td>
<td>1995-2001</td>
<td>Tehran-Royan institute</td>
<td>2492</td>
<td>2245 (90.1)</td>
<td>247 (9.9)</td>
<td>1258 (50.5)</td>
<td>713 (28.6)</td>
<td>289 (11.6)</td>
<td>232 (9.3)</td>
</tr>
<tr>
<td>Aflatoonian et al. [20]</td>
<td>2004-5</td>
<td>Yazd - Clinics</td>
<td>174</td>
<td>116 (66.7)</td>
<td>58 (33.3)</td>
<td>44 (25.3)</td>
<td>100 (57.5)</td>
<td>14 (8.0)</td>
<td>16 (9.2)</td>
</tr>
<tr>
<td>Karimpour Malekshah AK et al. [25]</td>
<td>2003-8</td>
<td>Mazandaran- clinics</td>
<td>3734</td>
<td>2941 (78.7)</td>
<td>793 (21.3)</td>
<td>1453 (38.9)</td>
<td>1296 (34.7)</td>
<td>545 (14.6)</td>
<td>441 (11.8)</td>
</tr>
<tr>
<td>Total Average (%) (95% C.I)</td>
<td></td>
<td></td>
<td></td>
<td>78.4 (72.1-83.7)</td>
<td>21.6 (16.3-27.9)</td>
<td>34.0 (26.9-42.0)</td>
<td>43.6 (35.5-51.7)</td>
<td>17.1 (11.4-21.9)</td>
<td>8.1 (5.6-11.5)</td>
</tr>
<tr>
<td>Cochrans’s Q (p-value)</td>
<td></td>
<td></td>
<td></td>
<td>389.7 (&lt;0.001)</td>
<td>389.7 (&lt;0.001)</td>
<td>677.1 (&lt;0.001)</td>
<td>580.6 (&lt;0.001)</td>
<td>162.9 (&lt;0.001)</td>
<td>208.8 (&lt;0.001)</td>
</tr>
<tr>
<td>I^2 statistic</td>
<td></td>
<td></td>
<td></td>
<td>99.2</td>
<td>98.2</td>
<td>99.1</td>
<td>98.9</td>
<td>97.8</td>
<td>97.1</td>
</tr>
</tbody>
</table>
It can be concluded from these data that the prevalence of infertility in the United States of America is reported to be 11.2% in 1965, declining from 11.2% in 1965 to 9% (range: 3.5%-16.7%) in 2007. These studies used different classification methods and are hardly comparable. These data is in agreement with the calculated percentages as measured by the Royal Commission for New Reproductive Technologies [33].

No significant publication bias was seen. By removing each study the sensitivity analyses showed a negligible change in the pooled estimates.

There were five studies that accurately sub classified the causes of female infertilities [9,20,21,23,24]. These studies used different classification methods and are hardly comparable. These data is presented in Table 3. It can be concluded from these data that ovulatory factor was the most frequent cause diagnosed in all of these studies followed by tubal factor.

**Discussion**

Reproduction is one of the naturally desired human goals and mandatory for survival of every society. Infertility can affect social health of the couples, and decreases their sense of self confidence and life satisfaction [26]. The prevalence of infertility is different between regions. The prevalence of infertility in the Middle East is estimated to vary between 10-15% [27]. However on the so called “infertility belt” in the central and southern parts of Africa almost one-third of couples are not able to conceive after one year [28]. The present meta-analysis showed that the average prevalence rate of life time infertility is 10.9% in Iran and 3.3% of the population have current infertility. Similarly designed studies performed in other countries reported almost similar results. Data show that almost 10-15% of couples in the United Kingdom have difficulty to conceive [29,30] and 2.4% of them have unresolved current infertility [31]. However the incidence of infertility in the United States of America is reported to be declining from 11.2% in 1965 to 9% (range: 3.5%-16.7%) in 2007 [6]. The prevalence of Infertility is considered to be almost 8.5% in Canada as measured by the Royal Commission for New Reproductive Technologies [33].

Meta-analysis of the etiology of infertility among the referees to the different infertility clinics of Iran showed that 78.4% of the couples suffer from primary and 21.6% from secondary fertility problems. 34% of them have male factor, 43.5% female factor and 17% both male and female factors and 8.1% have no determined cause for their infertility. These calculated percentages are in agreement with the published estimates of the major causes of infertility in the textbooks [4,30].

Total fertility rate is decreasing universally. Europe has the lowest fertility rate in the world. Instability of partnerships, increasing participation of women in higher education and employment, delayed childbearing, value changes and economic pressures are considered to have major impact on fertility rates [5]. TFR in Iran was 7.7 children per woman in 1966, 5.5 in 1988, 2.17 in 2000 and 1.88 in 2011, respectively [34-36].

Decreasing the fertility rate does not mean that infertility has increased. Although there are reports about increasing the rate of infertility in some areas in the world but evidence show that overall incidence of infertility did not have a significant change during the past thirty years [4].

Reviewing the literature shows that there are discrepancies between definitions for infertility in different studies that can induce misunderstanding in the real status of the condition [37]. National Institute for Health and Clinical Excellence guideline 2004 defined...
infertility as failure to conceive after 2 years of regular unprotected intercourse [38] while the American Society for Reproductive Medicine (ASRM) considers a couple as infertile if pregnancy does not happen after 12 months of regular unprotected intercourse [39]. Evidence shows that among the couples who do not conceive after 12 cycles there are at least 10% who are moderately or seriously subfertile and 50% of them will conceive spontaneously in the next 36 months. However among the couples who had not conceived after 48 months only sporadic spontaneous conceptions will happen in the future and is suggested to be considered as equivalent of sterility [40,41]. We included only the studies with the definition of 12 months duration. Therefore we excluded even several well designed studies with more than 12-month measure from this analysis (such as Safarinejad study [42]. There were also variations in definition of women’s reproductive age ranging from (15-44), (19-49), (15-49), (20-49) and (25-45) years used in different studies that were ignored in this analysis.

This meta-analysis showed that 78.4% of the couples in Iran

![Figure 2: Meta-analysis of infertility rate in Iran produced by Stata program.](image-url)
suffered from primary infertility compared to 21.6% for the secondary infertility. The etiologic cause of infertility for 43.5% of the couples was a female factor. Among the female causes of infertility ovulatory dysfunction was the most frequent etiologic factor reported by all of the centers followed by tubal factor.

Some etiologic factors for infertility are more dominant in special geographic areas. Tuberculosis of female genital tract in Iran is presenting with infertility as its most common presenting clinical symptom and is mostly seen among Afghan immigrants [43,44].

Evidence shows that male fertility has decreased in some populations. It is suggested that it may be linked to inferior semen quality, more aneuploidy and early loss. Male infertility may develop because of occupational or environmental factors that may cause genetic derangements in gonadal cells [45,46]. As an environmental etiologic factor of infertility exposure to toxic materials has always been considered. Several Iranian people were exposed to toxic-chemicals during recent Iraq-war. There is one study on the prevalence of infertility in the individuals that were exposed to mustard-gas in one or both partners in Iran and did not show a significant effect [47].

Management of infertility is important because it affects not only the fertile couple but also the offspring and the next generations. Unexplained infertility is an especial category in this topic. Couples with unexplained infertility may have the lower extremes of fertility or it may reflect the limitations of current diagnostic technologies [2]. The diagnosis of unexplained infertility depends on the evaluation strategies to show the occult causes of infertility. The rate of unexplained infertility is reported to range between 10-30%. The average rate of unexplained infertility calculated in this meta-analysis was 8.1% (95% CI 5.6-11.5). Recently laparoscopy is reported to be a cost effective approach for more accurate diagnosis and management for this group of patients [48,49]. Performing laparoscopy for this group of patients may help to explain the cause of infertility in a couple and may help for a more appropriate management.

Considering the psychosocial burden of infertility evidence shows that performing psychological consultations for these couples and their close relatives may help them to cope with the condition [50].

However we must remember the significant limitation and disadvantage of systematic reviews and meta-analyses that is reflected by the classification and selection bias that may be present in each individual study.

Table 3: Etiologic factors for female infertility.

<table>
<thead>
<tr>
<th>Author</th>
<th>Ovulatory dysfunction</th>
<th>Tubal factor</th>
<th>Endometriosis</th>
<th>Tuboperitoneal factor</th>
<th>Cervical factor</th>
<th>Uterine factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moiri A, et al. [21]</td>
<td>(21.4)</td>
<td></td>
<td></td>
<td>(18.9)</td>
<td>(3.6)</td>
<td>(1.9)</td>
</tr>
<tr>
<td>Parsanezhad [9]</td>
<td>313(45.16)</td>
<td>91(13.1)</td>
<td>9(1.3)</td>
<td>34(4.9)</td>
<td>17(2.45)</td>
<td></td>
</tr>
<tr>
<td>Bakhtiari A [23]</td>
<td>420(45.7)</td>
<td>31(3.4)</td>
<td></td>
<td>42(4.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alfatoonian [20]</td>
<td>67(58.6)</td>
<td>28(24.6)</td>
<td>1(0.88)</td>
<td>9(7.9)</td>
<td></td>
<td>(4.13)</td>
</tr>
<tr>
<td>Kamali M [24]</td>
<td>(20.38)</td>
<td>(12.64)</td>
<td>(1.28)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Author Disclosure Statement

No competing financial interests exist.

References


36. People Statistics > Total fertility rate by country.


