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# A Meta-Analysis of The Prevalence and Etiology of Infertility in Iran

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#### Abstract .

Infertility is a serious health issue in the world affecting approximately 8-10% of couples worldwide. The meta-analysis study was performed to assess the prevalence and etiologic factors associated with infertility in Iran. We made sure that the implementation of study and reporting the results were consistent with the MOOSE and PRISMA guidelines, respectively. All stages of the research were conducted by two authors, and the disagreement at each stage of the research was resolved by consensus. On January 1, 2020, we started a detailed literature search on international online databases, and Iranian Online databases, as well as specialized journals, several authentic international publishers and Google Scholar. We reviewed the reference list of identified articles for missed articles and then searched online for them. Data analysis was performed to estimate the prevalence using a random effects model. The lifetime infertility prevalence was found to be 11.3% [95% confidence interval (CI): 8.6-14.7] and the current infertility was evaluated to be 3.7% (95% CI: 3.2-4.3). The prevalence of primary infertility (based on 45 articles consisting of 51,021 samples) as well as secondary infertility (based on 13 articles consisting of 35,683 samples) in Iran were estimated to be 18.3% (95% CI: 15.4-21.6) and 2.5% (95% CI: 1.6-4.0), respectively. The prevalence of female, male, both and unexplained causes was estimated to be 32.0% (95% CI: 27.6-36.8), 43.3% (95% CI: 38.2-48.6), 12.5% (95% CI: 9.6-16.2) and 13.6% (95% CI: 10.2-17.8), respectively. The prevalence of causes related to ovulation, uterine tubes, and endometriosis in infertile women was estimated to be 54.0% (95% CI: 45.6-62.2), 15.5% (95% CI: 11.3-21.0), 6.2% (95% CI: 3.5-10.6), and 5.4% (95% CI: 2.5-11.3), respectively. In summary, the estimate of infertility burden in Iran did not change between 1990 and 2017 and its prevalence remains high. This research presents a unified and up-to-date overview regarding the burden of infertility in Iran.

Keywords: Etiology, Infertility, Iran, Prevalence

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## Introduction

Infertility is a serious worldwide health problem affecting almost 8-10% of couples global (1). According to the World Health Organization (WHO), 186 million ever-married women in sexual age in developing countries are affected by infertility (2). This serious problem requires urgent action, especially where most infertility cases are avoidable. According to the latest global described as failure to reach clinical pregnancy after regular unprotected intercourse for twelve months omore. Having regular sexual intercourse is a key factor in pregnancy. Primary infertility is the lack of ability to give birth either because of not having the ability to get pregnant or carry a baby till live birth, which can encompass miscarriage or stillbirth. Secondary infertility is the lack of ability to conceive or give birth despite a

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previous pregnancy or a live birth (3).

Infertility is a very important part of sexual health and

efforts that have often been ignored (4) in this regard.

Failure to give birth to an infant influences many couples

around the world. The United State Centers for Disease Control and Prevention emphasize that infertility is

beyond just a problem that affects the quality of life with

significant consequences for public health, such as mental

discomfort, social stigma, economic stress and marital

separation. According to the results comparing stressful

life events, after mother's death, father's death and

spouse's infidelity, infertility is ranked as fourth stressful

life event (5). Not considering the emotional afflictions

of infertile men and women and secondary signs of infertility (interpersonal problems, marital discontent and

loss of libido) may lead to a flawed cycle that increases infertility incidence (6). On the other hand, in recent years, factors such as changes in women's role in social activities, delaying marriage, changes in childbearing age, increasing use of contraceptive methods, liberal abortion laws, and undesirable economic status have decreased fertility rates and increased infertility (7).

There are over one million infertile couples living in Iran, and since childbearing is so important in the religious, historical, and cultural context of Iranian society, infertility can be one of the causes of divorce (8). Gaining accurate information about the prevalence, and infertility trends is the first main step in providing evidence-based measures and policies for decreasing the difficulties of this issue worldwide. There have been numerous studies in Iran on the prevalence and etiology of infertility and the results vary widely (9-43), and a systematic review of the original studies now seems necessary. The metaanalyses combine various studies with similar objectives, which involves increasing the number of samples and decreasing the confidence interval, and this can provide a more reliable estimate (44, 45). The purpose of this metaanalysis was to assess the prevalence and etiologic factors associated with infertility in Iran.

## Materials and Methods

## **Study protocol**

Theprotocolofthepresentstudy wasposted on International Prospective Register of Systematic Reviews (PROSPERO 2020) prior to implementation (CRD42020170926 Available from: https://www.crd.york.ac.uk/prospero/ display\_record.php?ID=CRD42020170926). We made sure that the implementation of study and reporting the results were consistent with the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) (46) and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, respectively (47). All stages of the research were conducted by two authors, and the disagreement at each stage of the research was resolved by consensus.

## Data sources and search strategy

On January 1, 2020, we started a detailed literature search on international databases of Web of Science (ISI), Ovid, Scopus, EMBASE, PubMed/Medline, Cochrane Library, EBSCO, CINAHL, and Iranian Online databases Scientific Information Database (SID), elmnet, Civilica, Regional Information Center for Science and Technology (RICST), , IranDoc , Magiran Barakat Knowledge Network System, and Iranian National Library, as well as specialized journals, several authentic international publishers including Wiley online library, Science Direct, and Springer and search engines such as Google Scholar. We reviewed the reference list of identified articles for missed articles and then searched online for them.

The following search strategy is an example of what was used in PubMed: ("prevalence" OR "frequency" OR

"incidence" OR "rate" OR "epidemiology" OR "etiology" OR "cause") AND ("infertility") AND Iran.

## **Study selection**

After excluding duplicate studies, the two writers reviewed the title and abstract of the studies independently. In case of disagreement, a third author was consulted or it resolved through consensus. Then, the full text of each study was reviewed based on the target inclusion criteria (Fig.S1, See Supplementary Online Information at www.ijfs.ir).

## Inclusion and exclusion criteria

Eligible studies according to PECOS (population, exposure, comparison/comparator, outcome and study type) criteria: i. Population: Iranian population, ii. Exposure: infertility, iii. Comparison/comparator: type of infertility and its cause, iv. Outcome: prevalence of infertility, and v. Study type: cross-sectional study.

## Definition

Infertility was defined as failure to achieve pregnancy after unprotected intercourse for 12 months. Primary infertility was defined as not experiencing a previous pregnancy and secondary infertility was defined as having a previous pregnancy (48). Infertility is considered as lifetime when a couple has experienced infertility in their whole lives. However, current infertility is defined as having the problem of infertility at present (49).

## Data extraction

Two researchers extracted the required data from all studies based on data encryption list. The following variables were obtained for each article: i. Study information (authors, publication year, place of study and completion year), ii. Design of the study, iii. Sample selection, iv. Reliability coefficient of the instrument, v. Sample size, vi. Prevalence (lifetime infertility, current infertility, primary infertility, secondary infertility, and etiology of infertility).

## Qualitative evaluation

Newcastle-Ottawa Scale adapted for cross-sectional research was used to assess the quality of articles (50). The highest achievable score was 9. Three categorizations were defined for the quality of studies with a score of less than 6, 6-7, and 8-9 as low, medium and high quality, respectively.

## Data analysis

The program used here was Comprehensive Metaanalysis Software ver. 2, and the results were shown as forest plot. The heterogeneity of the data was evaluated using I<sup>2</sup> index. This test evaluates the percent of variability in estimating the effect of heterogeneity. Significant heterogeneity exists if I<sup>2</sup> values are above 50% (51). Meta-analysis was performed to estimate the prevalence using a random effects model by DerSimonian and Laird

## Results

### Study selection process and study characteristics

## The infertility prevalence

The lifetime infertility prevalence (in 14 studies with

46,466 samples) (Table 1) was 11.3% (95% CI: 8.6-14.7) and current infertility (in 34 studies with 30,069 samples) estimated to be 3.7% (95% CI: 3.2-4.3) (Fig.1).

### Subgroup analysis of infertility

The subgroup analysis regarding the prevalence of lifetime infertility according to the region (P=0.069), year (P=0.069) and studies quality (P=0.069) was insignificant (Fig.S2, See Supplementary Online Information at www.ijfs.ir). Subgroup analysis of current infertility prevalence was significant based on year (P<0.001) but not significant based on region (P=0.321) and studies quality (P=0.593, Fig.S3, See Supplementary Online Information at www.ijfs.ir).

Ref.	First author, Published Year	Year	Place	Number	Lifetime infertility	Current infertility	Method	Quality
(9)	Badr et al., 2009	2004	Tabriz	3183	104	88	15- to 49-year-old couples	Moderate quality
(10)	Vahidi et al., 2006	2004-5	East Azarbaijan	610		14	19- to 49-year-old women	Moderate quality
			West Azarbaijan	502		5	19- to 49-year-old women	Moderate quality
			Ardabil	236		4	19- to 49-year-old women	Moderate quality
			Isfahan	675		18	19- to 49-year-old women	Moderate quality
			Ilam	114		8	19- to 49-year-old women	Moderate quality
			Bushehr	149		8	19- to 49-year-old women	Moderate quality
			Tehran	1730		58	19- to 49-year-old women	Moderate quality
			Chaharmahal and Bakhtiari	147		5	19- to 49-year-old women	Moderate quality
			Khorasan	1197		45	19- to 49-year-old women	Moderate quality
			Khuzestan	741	30	19- to 49-year-old women	Moderate quality	
			Zanjan	205		10	19- to 49-year-old women	Moderate quality
			Semnan	86		3	19- to 49-year-old women	Moderate quality
			Sistan-Baluchestan	330		20	19- to 49-year-old women	Moderate quality
			Fars	742		26	19- to 49-year-old women	Moderate quality
			Qazvin	290		15	19- to 49-year-old women	Moderate quality
			Qom	136		8	19- to 49-year-old women	Moderate quality
			Kurdistan	254		8	19- to 49-year-old women	Moderate quality
			Kerman	371		8	19- to 49-year-old women	Moderate quality
			Kermanshah	384		7	19- to 49-year-old women	Moderate quality
			Kohkiluyeh and Boyer Ahmad	90		2	19- to 49-year-old women	Moderate quality

#### Table 1: Summary of characteristics in studies into a meta-analysis

Ref.	First author, Published Year	Year	Place	Number	Lifetime infertility	Current infertility	Method	Quality
			Golestan	261		8	19- to 49-year-old women	Moderate quality
			Guilan	427		19	19- to 49-year-old women	Moderate quality
			Lorestan	317		7	19- to 49-year-old women	Moderate quality
			Mazandaran	545		13	19- to 49-year-old women	Moderate quality
			Markazi	219		7	19- to 49-year-old women	Moderate quality
			Hormozgan	208		20	19- to 49-year-old women	Moderate quality
			Hamedan	292		7	19- to 49-year-old women	Moderate quality
			Yazd	148		2	19- to 49-year-old women	Moderate quality
(11)	Mohammad Baygi, 2002	2002	Sanandaj	902	166		15- to 49-year-old women	Moderate quality
(12)	Kamali et al., 2007	1995-2001	Tehran-Royan institute		2492		Infertile couples	High quality
(13)	Bakhtiari, 1999	1999	Babol –Fatematazah- ra		920		Infertile couples	High quality
(53)	Karimpour Malekshah et al., 2011	2003-8	Mazandaran- clinics		3734		consecutive couples	High quality
(15)	Moghaddam et al., 2000	1999	Mazandaran	2953	389		15- to 49-year-old couples	Moderate quality
(16)	Esmailzadeh et al., 2002	1996-8	Babol –Fatematazah- ra		2169		Infertile couples	Moderate quality
(17)	Sadegh Moghadam et al., 2008	2006	Gonabad	380	45		15- to 49-year-old women	Moderate quality
(18)	Ardalan et al., 2010	2004–2005	Iran	10783	1592		19- to 49-year-old women	High quality
(19)	Sedaghat Siahkal et al., 2003	2001	Tehran	1987	173	50	25- to 49-year-old women	High quality
(20)	Parsanezhad and Alborzi, 1998	1993	Shiraz	1430	159		15- to 49-year-old couples	Moderate quality
			Shiraz		693		20- to 49-year-old women	Moderate quality
(21)	Barouti et al., 1999	1997	Tehran	1784			19- to 49-year-old women	Moderate quality
(22)	Nojomi et al., 2002	2000	Tehran	1174	141	49	40- to 50-year-old women	High quality
(23)	Moini and Yazdan Panah, 1999	1990-5	Tehran-Royan Institute		4360			High quality
(14)	Karimpour et al., 2005	2001-3	Sari		657	37	Infertile couples	High quality
(24)	Delpishe et al., 2014	2013	Ilam- clinics	1013	117	44		High quality
(25)	Shagheibi et al., 2018	2014-15	Sanandaj-hospital		579		Infertile couples	High quality
(26)	Kazemijaliseh et al., 2015	1998	Tehran	1067			18- to 57-year-old couples	High quality
(27)	Noorbala, 2001	2001	Iran	10418		292		High quality
(28)	Shafi et al., 2016	2012	Babol	1081			20- to 45-year-old women	High quality

### Table 1: Continued

Ref.	First author, Published Year	Year	Place	Number	Lifetime infertility	Current infertility	Method	Quality
(29)	Vizheh et al., 2015	2014	Tehran		123		infertile couples	High quality
(30)	Esfahani Shahsavari et al., 2010	2008-9	Jahrom		169		infertile couples	Moderate quality
(31)	Aflatoonian et al., 2009	2004-5	Yazd	5200	333		Couples	High quality
(32)	Rostami Dovom et al., 2014	2008-10	Iran	888	256	57	non-menopausal women age 18-49	High quality
(33)	Masoumi et al., 2015	2010-2011	Hamadan		1200		infertile couples	High quality
(35)	Akhondi et al., 2013	2010-2011	Iran	13750	2819		20- to 40-year-old women	High quality
(36)	Sepidarkish et al., 2016	2014-15	Iran-Royan Institute		405		infertile patients	High quality
(37)	Taghavi et al., 2011	2005-2010	Mashhad		2000		Infertile males	Moderate quality
(38)	Farmani et al., 2016	2016	Qom		100		Infertile males	Moderate quality
(39)	Hossein Rashidi B, 1998	1998	Tehran		1293		infertile couples	Moderate quality
(40)	Yousefi Z, 2001	1999-2000	Mashhad		1846		Infertile couples	Moderate quality
(41)	Natami M, 2016	2016	Bandar Abbas		151		Infertile males	Moderate quality
(42)	Mirzaei et al., 2018	2014-2015	Yazd	2611	135		20-69 years old people	High quality
(43)	Ershadi, 2006	2006	Gonabad	212	25	88	15- to 49-year-old women	Moderate quality

#### Table 1: Continued

## Prevalence of primary and secondary infertility

The primary infertility prevalence (in 45 studies with 51,021 samples) and secondary infertility (in

13 studies with 35,683 samples) in Iran was 18.3% (95% CI: 15.4-21.6) and 2.5% (95% CI: 1.6-4.0), respectively (Fig.2).

А

Study name		Statist	ics for ea	ich study		<u>)</u>			
	Event rate	Lower limit	Upper limit	Z-Value	p-Value			Rela	ative ∋ight
Ahmadi Asr Badr Y, 2006	0.033	0.027	0.039	-33.982	0.000			7	7.14
Mohammad baygi R, 2002	0.184	0.160	0.211	-17.332	0.000			7	<i>.</i> 19
Moghaddam A, 2000	0.132	0.120	0.144	-34.657	0.000			7	.29
Sadegh Moghadam L, 2008	0.118	0.090	0.155	-12.644	0.000			6	3.82
Ardalan A, 2010	0.148	0.141	0.154	-64.584	0.000			7	.34
Siahkal MS, 2003	0.087	0.075	0.100	-29.533	0.000			7	.22
Parsanezhad ME, 1998	0.111	0.096	0.129	-24.711	0.000			7	.20
Nojomi M, 2002	0.120	0.103	0.140	-22.182	0.000			7	7.18
Delpisheh A, 2014	0.115	0.097	0.137	-20.710	0.000			7	7.14
Aflatoonian A, 2009	0.064	0.058	0.071	-47.350	0.000			7	.29
Rostami Dovom M. 2014	0.288	0.259	0.319	-12.198	0.000			7	.23
Akhondi MM, 2013	0.205	0.198	0.212	-64.156	0.000			7	7.35
Mirzaei M, 2018	0.052	0.044	0.061	-32.916	0.000			7	7.18
Ershadi F, 2006	0.118	0.081	0.169	-9.449	0.000			6	3.44
	0.113	0.086	0.147	-13.483	0.000	👅			
Heterogeneity: I <sup>2</sup> = 98.99%, P	P< 0.001					0.00	0.50	1.00	

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Fig.1: Prevalence of infertility. A. Lifetime infertility and B. Current infertility. Red rhombus; Overall estimate.

### Subgroup analysis of primary and secondary infertility

Subgroup analysis of primary infertility prevalence was significant based on year (P<0.001) and studies quality (P=0.069) but not significant based on region (P=0.430) (Fig.S4, See Supplementary Online Information at www.ijfs.ir). Subgroup analysis of secondary infertility prevalence according to region (P=0.321), and studies quality (P=0.593) was not significant, but was significant based on year (P<0.001, Fig.S5, See Supplementary Online Information at www.ijfs.ir).

#### The etiology of infertility

The prevalence of female, male, both and unexplained causes was estimated to be 32.0% (95% CI: 27.6-36.8), 43.3% (95% CI: 38.2-48.6), 12.5% (95% CI: 9.6-16.2) and 13.6% (95% CI: 10.2-17.8), respectively (Fig.3).

## Female etiology

The prevalence of causes related to ovulation, uterine tubes, and endometriosis in infertile women was estimated to be 54.0% (95% CI: 45.6-62.2), 15.5% (95% CI: 11.3-21.0), 6.2% (95% CI: 3.5-10.6), and 5.4% (95% CI: 2.5-11.3), respectively (Fig.4).

#### Semen analysis

Abnormal semen analysis was estimated to be 55.6% (95% CI: 45.7-65.2) among infertile men (Fig.S6, See Supplementary Online Information at www.ijfs.ir).

#### **Meta-regression**

Meta-regression based on year was not significant in terms of lifetime infertility prevalence (coefficient: - 0.000, 95% CI: -0.057 to 0.055, P=0.976) and current infertility (coefficient: 0.057, 95% CI: -0.005 to 0.119, P=0.073), primary infertility (coefficient: -0.021, 95% CI: -0.084 to 0.040, P=0.496), and secondary infertility (coefficient: -0.017, 95% CI: -0.106 to 0.071, P=0.700, Fig.5).

#### Sensitivity analysis

Sensitivity analysis with individual study elimination for all meta-analyzes showed a strong overall result (Fig.S7-S9, See Supplementary Online Information at www.ijfs.ir).

### **Publication bias**

Publication bias tests were not significant for studies about the prevalence of lifetime, current, primary, and secondary infertility (Fig.S10, See Supplementary Online Information at www.ijfs.ir).

Study name		Statis	tics for ea	ch study	
	Event	Lower	Upper		
	rate	limit	limit	Z-Value	p-Value
Ahmadi Asr Badr Y, 2006	0.020	0.016	0.026	-30.885	0.000
Vahidi S, 2006 (East Azarbaijan)	0.218	0.187	0.253	-13.025	0.000
Vahidi S, 2006 (West Azarbaijan)	0.253	0.217	0.293	-10.546	0.000
Vahidi S. 2006 (Ardabil)	0.364	0.305	0.428	-4.113	0.000
Vahidi S, 2006 (Isfahan)	0.203	0.174	0.235	-14.294	0.000
Vahidi S, 2006 (Ilam)	0.439	0.351	0.531	-1.308	0.191
Vahidi S, 2006 (Bushehr)	0.201	0.145	0.273	-6.745	0.000
Vahidi S, 2006 (Tehran)	0.177	0.160	0.196	-24.371	0.000
Vahidi S, 2006 (Chaharmahal and Bakhtiari)	0.238	0.176	0.314	-6.006	0.000
Vahidi S 2006 (Khorasan)	0.239	0.216	0.264	-17.093	0.000
Vahidi S, 2006 (Khuzestan)	0.240	0.211	0.272	-13 391	0.000
Vahidi S. 2006 (Zanjan)	0.210	0.280	0.409	-4 459	0.000
Vahidi S, 2006 (Semnan)	0.105	0.055	0.190	-6.002	0.000
Vahidi S. 2006 (Sistan Baluchastan)	0.105	0.000	0.109	1 420	0.000
Vahidi S, 2006 (Fars)	0.401	0.407	0.315	-15.072	0.103
Mahlal C. 2000 (Damin)	0.201	0.174	0.231	-10.073	0.000
Vanidi S, 2006 (Qazvin)	0.300	0.250	0.355	-0.012	0.000
	0.301	0.230	0.384	-4.497	0.000
Vahidi S. 2006 (Keman)	0.382	0.324	0.443	-3.129	0.000
venue 5, 2000 (reman)	0.173	0.137	0.214	-11.411	0.000
Vahidi S, 2006(Kermanshah)	0.292	0.248	0.339	-7.903	0.000
vanur 5, 2000(Konkiuyen and Boyer Ahmad)	0.433	0.335	0.537	-1.261	0.207
Vahidi S, 2006 (Golestan)	0.211	0.165	0.264	-8.701	0.000
vanidi 5, 2006 (Gullan)	0.222	0.186	0.264	-10.754	0.000
Vahidi S, 2006 (Lorestan)	0.281	0.234	0.333	-7.526	0.000
Vahidi S, 2006 (Mazandaran)	0.224	0.191	0.261	-12.099	0.000
Vahidi S, 2006 (Markazi)	0.374	0.313	0.440	-3.676	0.000
Vahidi S, 2006(Hormozgan)	0.303	0.244	0.369	-5.524	0.000
Vahidi S, 2006(Hamedan)	0.363	0.310	0.420	-4.621	0.000
Vahidi S, 2006 (Yazd)	0.182	0.128	0.253	-7.047	0.000
Mohammad baygi R, 2002	0.144	0.123	0.169	-18.791	0.000
Moghaddam A, 2000	0.120	0.109	0.132	-35.189	0.000
Sadegh Moghadam L, 2008	0.066	0.045	0.096	-12.822	0.000
Siahkal MS, 2003	0.073	0.062	0.085	-29.470	0.000
Parsanezhad ME, 1998	0.058	0.047	0.071	-24.641	0.000
Barouti E, 1999	0.219	0.201	0.239	-22.200	0.000
Nojomi M, 2002	0.083	0.069	0.101	-22.708	0.000
Delpisheh A, 2014	0.059	0.046	0.076	-20.776	0.000
Kazemijaliseh H, 2015	0.173	0.152	0.197	-19.314	0.000
Shafi H, 2012	0.155	0.135	0.178	-20.164	0.000
Aflatoonian A. 2009	0.033	0.028	0.038	-43.438	0.000
Rostami Dovom M. 2014	0.211	0.185	0.239	-16.055	0.000
Akbondi MM 2013	0.211	0.100	0.200	-64 610	0.000
Mirzoni M 2019	0.202	0.130	0.209	20.400	0.000
Iviii Zaci Ivi, 2010	0.031	0.025	0.038	-30.490	0.000
EISHAULE, 2000	0.066	0.039	0.108	-9.580	0.000
Hotorogonoity: 12-08 2104	0.183	0.154	0.210	-14.068	0.000
acterogeneny: 1*= 98.31%, P	< 0.001				

## B

Study name		Statistics for each study				Eve	ent rate and 959	% CI		
	Event rate	Lower limit	Upper limit	Z-Value	p-Value				Relative weight	
Ahmadi Asr Badr Y, 2006	0.012	0.009	0.017	-27.245	0.000				7.75	
Mohammad baygi R, 2002	0.040	0.029	0.055	-18.698	0.000				7.72	
Moghaddam A, 2000	0.012	0.009	0.016	-26.013	0.000				7.72	
Sadegh Moghadam L, 2008	0.053	0.034	0.080	-12.581	0.000				7.49	
Siahkal MS, 2003	0.014	0.010	0.020	-22.319	0.000				7.65	
Parsanezhad ME, 1998	0.053	0.043	0.066	-24.432	0.000				7.87	
Nojomi M, 2002	0.037	0.027	0.049	-21.044	0.000				7.77	
Delpisheh A, 2014	0.037	0.027	0.050	-19.539	0.000				7.73	
Aflatoonian A, 2009	0.021	0.017	0.025	-39.544	0.000				7.92	
Rostami Dovom M. 2014	0.078	0.062	0.097	-19.736	0.000				7.85	
Akhondi MM, 2013	0.003	0.002	0.004	-35.609	0.000				7.73	
Mirzaei M, 2018	0.029	0.023	0.036	-30.050	0.000				7.87	
Ershadi F, 2006	0.042	0.022	0.080	-9.147	0.000				6.94	
	0.025	0.016	0.040	-14.935	0.000	•				
Heterogeneity: I <sup>2</sup> = 97.05%, P	< 0.001					0.00	0.50	1.00		

Fig.2: Prevalence of infertility. A. Primary infertility and B. Secondary infertility. Red rhombus; Overall estimate.

А
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Study name		Statis	tics for ea	ach study		Ever	Event rate and 95% Cl		
	Event rate	Lower limit	Upper limit	Z-Value	p-Value				Relative weight
Kamali M, 2007	0.286	0.269	0.304	-20.628	0.000				6.16
Bakhtiari A, 1999	0.433	0.401	0.465	-4.076	0.000				6.09
Karimpour Malekshah AK, 2011	0.347	0.332	0.362	-18.412	0.000				6.19
Esmailzadeh S, 1999	0.312	0.293	0.331	-17.092	0.000				6.16
Parsanezhad ME, 1998	0.670	0.634	0.704	8.744	0.000				6.02
Moini A, 1999	0.459	0.444	0.474	-5.416	0.000				6.20
Karimpour A, 2005	0.604	0.566	0.641	5.305	0.000				6.03
Delpisheh A, 2014	0.556	0.465	0.643	1.199	0.230				5.27
Shagheibi Sh, 2017	0.518	0.477	0.559	0.873	0.383				6.01
Kazemijaliseh H, 2015	0.514	0.442	0.585	0.368	0.713				5.60
Vizheh M, 2015	0.390	0.308	0.479	-2.414	0.016				5.28
Aflatoonian A, 2009	0.300	0.253	0.352	-7.076	0.000				5.80
Rostami Dovom M. 2014	0.586	0.525	0.645	2.736	0.006				5.74
Sepidarkish M, 2016	0.217	0.180	0.260	-10.636	0.000				5.79
Hosseinrashidi B, 1998	0.345	0.320	0.371	-10.963	0.000				6.12
Yousefi Z, 2001	0.390	0.368	0.412	-9.371	0.000				6.15
Mirzaei M, 2018	0.541	0.456	0.623	0.946	0.344				5.39
	0.433	0.382	0.486	-2.460	0.014				
Heterogeneity: $I^2 = 97.85\%$	. P< 0.00	)1				0.00	0.50	1.00	

## B

Study name		Statis	tics for ea	ich study		Event	rate and 95% C	<u>I_</u>	
	Event rate	Lower limit	Upper limit	Z-Value	p-Value				Relative weight
Kamali M, 2007	0.505	0.485	0.524	0.481	0.631				6.26
Bakhtiari A, 1999	0.226	0.200	0.254	-15.613	0.000				6.11
Karimpour Malekshah AK, 2011	0.389	0.374	0.405	-13.436	0.000				6.27
Esmailzadeh S, 1999	0.348	0.328	0.368	-13.920	0.000				6.24
Parsanezhad ME, 1998	0.202	0.174	0.234	-14.520	0.000				6.03
Moini A, 1999	0.506	0.491	0.521	0.787	0.431				6.28
Karimpour A, 2005	0.482	0.444	0.521	-0.897	0.370				6.11
Delpisheh A, 2014	0.222	0.156	0.306	-5.634	0.000		F		5.00
Shagheibi Sh, 2017	0.302	0.266	0.341	-9.245	0.000				6.05
Kazemijaliseh H, 2015	0.292	0.231	0.361	-5.480	0.000				5.54
Vizheh M, 2015	0.260	0.190	0.345	-5.085	0.000				5.16
Aflatoonian A, 2009	0.132	0.100	0.173	-11.631	0.000				5.54
Rostami Dovom M. 2014	0.195	0.151	0.248	-8.981	0.000				5.58
Sepidarkish M, 2016	0.360	0.315	0.408	-5.539	0.000				5.97
Hosseinrashidi B, 1998	0.382	0.356	0.409	-8.401	0.000				6.20
Yousefi Z, 2001	0.350	0.329	0.372	-12.690	0.000				6.23
Mirzaei M, 2018	0.393	0.314	0.477	-2.476	0.013				5.42
	0.320	0.276	0.368	-6.902	0.000		•		
Heterogeneity: I <sup>2</sup> = 97.93%	, P< 0.00	1				0.00	0.50	1.00	

### Meta Analysis

## С

Study name		Statis	tics for ea	ich study		Event r	6 CI		
	Event rate	Lower limit	Upper limit	Z-Value	p-Value				Relative weight
Kamali M, 2007	0.116	0.104	0.129	-32.466	0.000				10.26
Bakhtiari A, 1999	0.272	0.244	0.301	-13.302	0.000				10.19
Karimpour Malekshah AK, 2011	0.146	0.135	0.158	-38.115	0.000				10.34
Esmailzadeh S, 1999	0.219	0.202	0.237	-24.491	0.000				10.31
Delpisheh A, 2014	0.043	0.018	0.099	-6.802	0.000	-			5.37
Vizheh M, 2015	0.154	0.101	0.230	-6.814	0.000				8.15
Aflatoonian A, 2009	0.042	0.025	0.070	-11.448	0.000				7.81
Sepidarkish M, 2016	0.175	0.141	0.215	-11.849	0.000				9.69
Hosseinrashidi B, 1998	0.065	0.053	0.080	-23.634	0.000				9.87
Yousefi Z, 2001	0.130	0.115	0.146	-27.467	0.000				10.22
Mirzaei M, 2018	0.111	0.068	0.176	-7.593	0.000				7.80
	0.125	0.096	0.162	-12.767	0.000	♦			
Heterogeneity: I <sup>2</sup> = 96.79%	, P< 0.00	)1				0.00	0.50	1.00	

## D

Study name		Statis	tics for ea	ch study		Ever	nt rate and 95	% CI	
	Event rate	Lower limit	Upper limit	Z-Value	p-Value				Relative weight
Kamali M, 2007	0.093	0.082	0.105	-33.019	0.000				6.10
Bakhtiari A, 1999	0.070	0.055	0.088	-20.012	0.000				5.93
Karimpour Malekshah AK, 2011	0.118	0.108	0.129	-39.649	0.000				6.13
Esmailzadeh S, 1999	0.063	0.053	0.074	-30.536	0.000				6.05
Parsanezhad ME, 1998	0.128	0.106	0.155	-16.866	0.000				5.99
Moini A, 1999	0.035	0.030	0.041	-40.267	0.000				6.07
Karimpour A, 2005	0.142	0.117	0.170	-16.105	0.000				5.99
Delpisheh A, 2014	0.179	0.120	0.260	-6.309	0.000				5.44
Shagheibi Sh, 2017	0.180	0.150	0.213	-14.030	0.000				6.00
Kazemijaliseh H, 2015	0.146	0.102	0.204	-8.484	0.000				5.61
Vizheh M, 2015	0.195	0.134	0.275	-6.228	0.000		-		5.51
Aflatoonian A, 2009	0.048	0.030	0.077	-11.655	0.000				5.36
Rostami Dovom M. 2014	0.371	0.314	0.432	-4.078	0.000				5.93
Sepidarkish M, 2016	0.247	0.207	0.291	-9.677	0.000				5.98
Hosseinrashidi B, 1998	0.208	0.187	0.231	-19.511	0.000				6.10
Yousefi Z, 2001	0.130	0.115	0.146	-27.467	0.000				6.10
Mirzaei M, 2018	0.326	0.252	0.409	-3.957	0.000		▆╴│		5.72
	0.136	0.102	0.178	-11.264	0.000	•			
Heterogeneity: I <sup>2</sup> = 97.82%	, P< 0.00	)1				0.00	0.50	1.00	

Fig.3: The prevalence of infertility. A. Female, B. Male, C. Both, and D. Unexplained causes. Red rhombus; Overall estimate.

### A

A									
Study name		Statistics for each study				Event ra	Event rate and 95% CI		
	Event rate	Lower limit	Upper limit	Z-Value	p-Value				Relative weight
Kamali M, 2007	0.204	0.180	0.230	-17.386	0.000				9.32
Bakhtiari A, 1999	0.648	0.611	0.684	7.426	0.000				9.30
Karimpour Malekshah AK, 2011	0.584	0.561	0.606	7.146	0.000				9.43
Esmailzadeh S, 1999	0.460	0.432	0.489	-2.679	0.007				9.40
Karimpour A, 2005	0.610	0.561	0.656	4.331	0.000				9.19
Shagheibi Sh, 2017	0.647	0.591	0.699	5.004	0.000				9.07
Kazemijaliseh H, 2015	0.702	0.607	0.782	3.995	0.000		-		8.27
Aflatoonian A, 2009	0.588	0.495	0.674	1.863	0.062				8.51
Rostami Dovom M. 2014	0.460	0.382	0.540	-0.979	0.328				8.74
Masoumi SZ, 2015	0.566	0.536	0.596	4.312	0.000				9.39
Yousefi Z, 2001	0.519	0.487	0.550	1.162	0.245				9.38
	0.540	0.456	0.622	0.942	0.346		٠		
Heterogeneity: I <sup>2</sup> = 97.93%	, P< 0.00	01				0.00	0.50	1.00	

Meta Analysis

### B

Study name		Statis	tics for ea	ch study		Event rate and 95% Cl			
	Event rate	Lower limit	Upper limit	Z-Value	p-Value				Relativ weigh
Kamali M, 2007	0.127	0.108	0.149	-20.325	0.000				9.6
Bakhtiari A, 1999	0.048	0.034	0.067	-16.249	0.000				9.05
Karimpour Malekshah AK, 2011	0.301	0.280	0.322	-16.613	0.000				9.84
Esmailzadeh S, 1999	0.105	0.089	0.124	-22.284	0.000				9.66
Karimpour A, 2005	0.244	0.205	0.289	-9.667	0.000				9.54
Shagheibi Sh, 2017	0.247	0.201	0.299	-8.336	0.000				9.44
Kazemijaliseh H, 2015	0.067	0.032	0.135	-6.717	0.000	<b>-</b>	-		6.94
Aflatoonian A, 2009	0.246	0.175	0.333	-5.157	0.000		-		8.75
Rostami Dovom M. 2014	0.067	0.036	0.119	-8.062	0.000				7.63
Masoumi SZ, 2015	0.173	0.152	0.197	-19.290	0.000				9.73
Yousefi Z, 2001	0.264	0.237	0.292	-14.027	0.000				9.76
	0.155	0.113	0.210	-8.998	0.000	•			
Heterogeneity: I <sup>2</sup> = 97.07%	b, P< 0.0	01				0.00	0.50	1.00	

Meta Analysis

## С

Study name		Statis	tics for ea	ch study		Even	t rate and 95%	% CI	
	Event rate	Lower limit	Upper limit	Z-Value	p-Value				Relative weight
Kamali M, 2007	0.041	0.030	0.055	-19.780	0.000				10.17
Bakhtiari A, 1999	0.065	0.048	0.087	-16.728	0.000				10.17
Karimpour Malekshah AK, 2011	0.039	0.031	0.048	-26.566	0.000				10.29
Esmailzadeh S, 1999	0.022	0.015	0.032	-18.830	0.000				9.99
Karimpour A, 2005	0.058	0.039	0.086	-12.981	0.000				9.94
Shagheibi Sh, 2017	0.107	0.076	0.147	-11.363	0.000				10.06
Aflatoonian A, 2009	0.079	0.042	0.145	-7.073	0.000				9.18
Rostami Dovom M. 2014	0.140	0.093	0.205	-7.714	0.000				9.84
Masoumi SZ, 2015	0.187	0.165	0.212	-18.673	0.000				10.39
Yousefi Z, 2001	0.025	0.017	0.037	-17.722	0.000				9.97
	0.062	0.035	0.106	-9.054	0.000	•			
Heterogeneity: I <sup>2</sup> = 97.08%	P< 0.0	01				0.00	0.50	1.00	

Meta Analvsis

#### D

<u>Study name</u>		Statis	tics for ea	ch study		Ever			
	Event rate	Lower limit	Upper limit	Z-Value	p-Value				Relative weight
Kamali M, 2007	0.013	0.008	0.022	-15.517	0.000				23.95
Karimpour Malekshah AK, 2011	0.046	0.037	0.057	-27.260	0.000				26.43
Karimpour A, 2005	0.088	0.064	0.120	-13.198	0.000				25.66
Kazemijaliseh H, 2015	0.144	0.089	0.226	-6.380	0.000				23.96
	0.054	0.025	0.113	-6.992	0.000	•			
Heterogeneity: I <sup>2</sup> = 94.41%	6. P< 0.0	01				0.00	0.50	1.00	

Fig.4: The prevalence of causes related to infertility. A. Ovulation, B. Uterine tubes, and C. Endometriosis in infertile women. Red rhombus; Overall estimate.



Fig.5: Meta-regression based on year for the prevalence of infertility. A. Lifetime, B. Current infertility, C. Primary infertility, and D. Secondary infertility.

## Discussion

Infertility is a common situation with complex socioeconomic and health outcomes for the individuals and the whole society. In spite of the important outcomes of infertility, estimating its prevalence is faced with limitations. In this systematic meta-analysis, the lifetime infertility prevalence was estimated at 11.1%, while 3.7% had current infertility. The estimated incidence of infertility is between 3.5 and 30% in various countries, and this variety is probably due to the population under study, the definitions of infertility and the estimation method (4). Therefore, the major challenges in evaluating

the true infertility burden include the lack of populationbased researches and the variety of definitions. In addition, advancements in diagnosing, treating and preventing infertility in recent decades have caused great changes in infertility prevalence worldwide. In least developed countries, the prevalence of 12-month infertility varies from 6.9 to 9.3%. Significant geographic diversities have been noted in its prevalence, and the diversities are mostly explained by the difference in cultural, environmental, and socioeconomic effects and having evaluate to the health-care system (54). The prevalence varies widely from 9% in Gambia to 11.8% in Ghana compared to 21.2% in northwest Ethiopia and between 20 and 30% in Nigeria (3, 8, 55-57). We do not have much information about Asian countries and Latin America. Based on the statistics provided by WHO, infertility prevalence in these areas varies from 8 to 12% in women of childbearing ages (2). Universally, the age-standardized female infertility prevalence has elevated by 14.96% (from 1366.85 per 100,000 in 1990 to 1571.35 per 100,000 in 2017) (58). Based on a previous meta-analysis in 2013, lifetime infertility and current infertility prevalence in Iran was reported to be 10.9 and 3.3%, respectively (59), and our estimate shows a slight increase compared to the previous estimate.

Searching for assistive behaviors related to infertility services is common in Iranians. In one study, more than 75% of people with fertility problems sought medical help. An international survey reported that 56% of women in more advanced countries seek help from infertility treatment systems (54), and a Trävä study (60) found that 57% of all infertile women did so. The popularity of seeking help for infertility treatment in Iran may be owing to the present perception that in Iran, having a child is the only way to improve one's position in the family and society (61). There have been several explanations for not seeking (or following up) infertility assistance, including lack of understanding or acknowledgment of the problem (62), fear of being labeled infertile, worrying about the cost of treatment, having no intention to provoke, and the physical and psychological burden of treatment.

Decrease in fertility rates does not imply that infertility has elevated. Despite the reports of increased infertility rates in some parts of the world, the evidence suggests the total prevalence of infertility has not changed significantly over the past thirty years. In this study, no significant change was found in the prevalence of infertility in Iran based on the meta-regression models over time (between 1990-2016). The important point is the noteworthy reduction in total fertility rate (TFR) in Iran; TFR in Iran was 7 children per woman in 1960, 6.5 in 1980, 2.06 in 2000, 1.83 in 2010, and 2.11 in 2017 (1). TFR is decreasing in the world. Europe has the lowest level of fertility rate among all regions of the world. Partnership instability, better cooperation of women in education and occupations, postponement of parenthood, changes in values and economic burdens impose significant effects on fertility rates (63). On the other hand, infertility

#### Prevalence and Etiology of Infertility in Iran

is more commonly experienced by married people, reflecting the fact that people in stable relationships are more likely to become pregnant and are hence aware of fertility problems (62). Much lower prevalence among young people somewhat indicates that they may never attempt to become pregnant. Previous studies have shown prolonged transition to adulthood and increase in the interval between important reproductive events such as first sexual relationship, marriage, and birth of first child (64). On the other hand, much of the literature describes the tendency of women in developed countries to delay having children (65) and it is suggested that this tendency is rapidly becoming a global phenomenon (66).

In the previous meta-analysis, the primary infertility prevalence was 10.6% and secondary infertility prevalence was 2.7% (59), which was higher in our study. A global study in 2010 among one hundred and ninety countries, among pregnant women aged 20-44, primary infertility was 1.9% and secondary one was 10.5%. Some regions have a high incidence of primary infertility, but secondary infertility is low, like North Africa and the Middle East, especially Adetoro and Ebomoyi (3). However, some areas have a high incidence of secondary infertility, but the incidence of primary infertility is low, such as in Central and Eastern Europe and Central Asia. In addition, several previous studies provided information on the prevalence of gender-related infertility. For instance, the prevalence of infertility in England was 12.5% in women, but it was 10.1% in men (62). It is worth noting that in these published studies, some only examined women (42). Others only evaluated the records of men in infertility clinics (67). Likewise, these articles are performed on fairly small groups which do not represent the majority of the infertile population (36).

Results of the causes of infertility in Iran showed that the causes of infertility were as follows: 32.0% male cause, 43.3% female cause, 12.5% both genders and 13.6% unknown. This calculated percentage is consistent with reported estimates of major causes of infertility in other studies (6).

Research shows that different studies provide different definitions of infertility, which may lead to misunderstanding of the actual situation (68). Some sources define infertility as lack of pregnancy after two years of unprotected intercourse , while others consider the couple infertility if pregnancy does not occur after unprotected intercourse for 12 months (69). We only provided studies with a 12-month definition. Therefore, we even excluded good-quality studies with more than 12 months of measurement (such as the study of Safarinejad) (70).

There was a high heterogeneity among articles across all of meta-analyses, and by considering the present data, we were able to ascribe this difference to the geographical area and year based on subgroup analysis. Other differences, including the partnership instability, increased cooperation of women in better education and occupations, postponement of parenthood, changes in values and economic burdens could not be investigated by using available data.

The strengths of the present study included the use of a comprehensive search strategy, selection of studies, extracting data and even analyzing the data by two independent researchers based on MOOSE guidelines, while the diversities were sorted out via group discussion. In case of any doubt of duplicate publications or more information that was required, we contacted the first or corresponding authors. We performed a conservative estimate using the random effects model, adopted a subgroup analysis and a meta-regression model to discover the heterogeneity causes. In the present study, in addition to updating previous meta-analyses to estimate the prevalence of lifetime and current infertility with a much higher sample size, we meta-analyzed the etiological details of infertility for the first time. The weaknesses of our study included the restricted search in internal databases and exclusion of studies with different infertility definitions.

## Conclusion

In summary, the estimate of infertility burden in Iran did not change between 1990 and 2017 and its prevalence remains high. This study provides a comprehensive and upto-date understanding of the that we need prevention and management interventions to alleviate infertility in Iran. Further research is required to evaluate the risk factors of infertility for developing effective prevention and management strategies to decrease the burden of this issue.

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## Authors' Contributions

M.A., T.R., Gh.A., M.P.N.; Contributed to conception and design. M.A., Gh.A., M.P.N.; Contributed to all experimental work, data and statistical analysis, and interpretation of data. M.A., M.P.N.; Were responsible for overall supervision. M.A.; Drafted the manuscript, which was revised by M.A., T.R., Gh.A., M.P.N. All authors read and approved the final manuscript.

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#### Prevalence and Etiology of Infertility in Iran

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