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Review Article

The Impact of Infertility on Female Sexual Function: A Systematic Review and Meta-analysis

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Abstract

Introduction: Infertility is a complex disease experienced by 13-17% of couples that can involve different dimensions of women's health, not only from an underlying organic and biological point of view, but also from their sexual health. Objectives: The aim of this systematic review and meta-analysis was to evaluate infertility's impact on female sexuality. **Methods:** A systematic review and meta-analysis were conducted. A literature search was done for publications from 1 January 2012 to 31 December 2022 via the databases PubMed, EBSCO (MEDLINE and Health Policy Reference Center) and Websci, databases, which assess female sexual function based on the Female Sexual Function Index (FSFI) in adult women between 18 and 49 years old. Heterogeneity was estimated using I 2. The risk of bias in the selected studies was assessed using the Newcastle-Otawa Quality Assessment Scale (NOS) adapted for case-control and cross-sectional studies. **Results:** A total of 8 studies were included. The results indicated an association between greater sexual dysfunction and infertility in women (WMD = 2.22, 95% CI = 3.57 to 0.87, p<0.001), and high heterogeneity was observed between studies (I2=97%, p<0.00001). The study was complemented with a meta-analysis of the individual FSFI domains, and it was observed that infertile women had significantly lower scores in all domains. **Conclusion**: Our review showed that infertility has a negative impact on female sexual health. These findings may help professionals in the field to deal with female sexual and reproductive health, from diagnosis to therapy, thus benefiting the couple's sexual function.

Keywords: infertility; sexual function; FSFI; female: metaanalysis

Introduction

Infertility is a current, global problem, which affects both men and women [1]. Globally, the World Health Organization (WHO) considers it a public health problem affecting approximately one in six adults at least once in their lifetime [2], meaning 48 million couples and 186 million people all over the world, being the global prevalence around 17% [3]. Infertility is defined by WHO as the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse [4]. The Centers for Disease Control and Prevention (CDC) adds that for women over the age of 35, infertility can be considered the inability of establishing a clinical pregnancy after six months of adequate unprotected sexual intercourse [5]. It may be classified as primary (inability to conceive) or secondary (previous pregnancy), and its rate has reported to be ranged from 0.6% to 3.4% for the primary infertility, and 8.7% to 32.6% for the secondary infertility [6]. There are multiple different causes of female infertility, of which the main ones are ovulation failure, tubal disease, endometriosis, uterine anomalies and psychosexual disorders. However, there is often a combination of the above, along with male factors, or indeed it may be unexplained. Quality of life, emotional health, and sexual relationship of the couples may be negatively affected by infertility. Sexual intercourse may lose its spontaneity and erotic value because the main aim be- comes conception. This may affect the ability for intimate sexuality and can provoke certain sexual dysfunctions [7]. Many couples describe the period of diagnosis and treatment as the most stressful of their life [8]. Female sexual dysfunction (FSD) is a multicausal and multidimensional disorder combining biological, psychological and interpersonal determinants, it occurs during the sexual response cycle and prevents the individual from experiencing satisfaction from sexual activity [9] being defined by the WHO as "the various ways in which a woman is unable to participate in a sexual relationship as she would wish" According to the [10] DSM-V-TR FSD could be divided in three major categories: Female Orgasmic Disorder; Female Sexual Interest/Arousal disorder (FSIAD); and Genito Pelvic Pain/Penetration disorder. The diagnosis implies that the symptoms must be experienced on almost all or all occasions (approx. 75–100%), must have been present for at least 6 months, and cause clinically significant distress in the individual [11]. The International Society for the Study of Women's Sexual Health (ISSWSH) divided female sexual disorders in: hypoactive sexual desire disorder, female genital arousal disorder, persistent genital arousal disorder, female orgasmic disorder, pleasure dissociative orgasm disorder, and female orgasmic illness syndrome. Prevalence data diverse, varying according to the authors and the geographic region, but Europe and North America typically

had rates of FSD below 40%, whereas regions such as the Middle East and Africa had rates as high as 62% [12,13] Several factors have been associated to FSD. According to the results of a metaanalysis that includes 94 studies, and despite the heterogeneity of the population evaluated, the following factors showed to have a significant, protective effect: older age at marriage, exercise, good overall health, daily intimacy and relationship satisfaction, positive body image, sex education and finding sex to be "important" [13] Some studies have evaluated the relationship between FSD and infertility but the results remain controversial [14-16]. Thus, the aim of this systematic review was to provide a meta-analytical estimate of the relation between infertility and FSD.

Methods

The methods for this systematic review and meta-analysis were developed according to the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements [17] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [18].

Search strategy

Data for this review were identified by searches of PubMed and Web of Science, as well as a multiple database search platform, EBSCO, which provided access to MEDLINE and Health Policy Reference Center databases, to identify studies assessing sexual dysfunction in infertile women, based on the FSFI, published between January 2012 and December 2022.

The following strategy was used: (infertility OR female infertility OR fertility OR female fertility) AND (sexual function OR sexual dysfunction OR sexual disorder) AND (female sexual function index OR FSFI OR Female Sexual Function Index) AND (female OR women OR woman).

Eligibility criteria

The inclusion criteria defined were as follows: a) comparative observational studies (cross-sectional, case-control, and cohort) that compare sexual dysfunction in infertile women vs. fertile women; b) diagnosis of infertility according to the WHO definition; c) women aged between 18 and 49 years; d) outcomes reported through Female Sexual Function Index (FSFI); e) studies published between January 2012 and December 2022.

As exclusion criteria were considered: a) studies with samples smaller than 20; b) studies in which the participants were paid.

Screening process

We compiled all records identified from searches in Zotero, a reference management tool, and removed all duplicates. After removing duplicate records four reviewers independently screened the retrieved studies, first the title and abstract, and then the full

article text. Any discrepancies were referred to another reviewer and resolved by consensus.

Data extraction and outcomes

A standardized data extraction form in Excel format was designed to retrieve important information from the included studies. The extracted data included: first author's name, year of publication, country, study design and setting, study population, FSFI score with mean, standard deviation, and p value; and prevalence of sexual dysfunction. FSFI is a brief multidimensional scale for assessing sexual function in women [19]. The FSFI is a 19-item self-report scale that assesses female sexual function over the past four weeks, considering six domains Sexual Desire (questions 1 and 2), Subjective Arousal (questions 3 to 6), Lubrication (questions 7 to 10), Orgasm (questions 11 to 13), Sexual satisfaction (questions 14 to 16), Sexual Pain (questions 17 to 19). Each question has five or six answer options graded on a scale of 0 to 5 or 1 to 5, and only one must be chosen. The measure allows the calculation of specific indices for each dimension, as well as a sexual function index (calculated through the sum of specific dimensional indices), with higher scores indicating higher levels of sexual functioning, with a score being less than or equal to 26.55 corresponding to risk of sexual dysfunction [19].

Risk of bias assessment

Quality assessment of the included studies was performed by Newcastle-Ottawa Scale (NOS) scale [42]. A study which the NOS score is greater than or equal to seven will be considered as high quality.

Statistical analysis

RevMan 5.4.1 (The Cochrane Collaboration) software was used. The meta-analysis was performed based on the Mantel– Haenszel random-effects model. This model was used given the considerable variability across the included studies.

The standard mean difference (SMD) with 95% confidence intervals (CI) was applied for the overall effect of group comparisons for continuous outcomes. The pooled odds ratio (OR) with 95% confidence interval (95% CI) was calculated to evaluate the percentage of students who met the intervention learning objectives. The statistical heterogeneity was calculated using the I2 statistic. The statistical heterogeneity among the selected studies was measured by using I² in each analysis [20]. We set the significance level at 0.05 for pooled estimation results and built forest plots for each outcome.

Results

Characteristics of Studies

Of the 652 citations retrieved through electronic searches, 272 duplicates were excluded, leaving 380 titles and abstracts to be screened. Based on the title and/ or abstract, 345 citations were excluded. The full texts of 35 publications were evaluated. In the end, 23 studies fulfilled all the selection criteria.

Figure 1 presents a PRISMA flowchart with reasons for exclusion:



Figure 1: Study selection flowchart – PRISMA

The tables 1 and 2 describe the characteristic and results of the included studies. Of the 23 studies, 12 [5, 21-23] were comparative studies and included 2,303 women with infertility and 2,149 controls (table 1) and 11 were non comparative studies, evaluating 3,315 women with infertility (table 2). The studies included women aged between 18 and 49 years, from different ethnic and geographical areas.

Author (Year)	Country	Tipo de estudo	NOS	Infertility diagnosis	Sample size			Age (mean ± SD)		Mean Score FSFI (mean ± SD)		p value FSFI between	FSD prevalence		p value between
					WI	С	WI		С	WI	С	groups	WI	С	groups
Kulaksiz et al. (2022) ²³	Turkey	Crosssectional	****	WHO	246	242	31.8 ±2.8		32.2 ±2.9	20.4 ±2.2	24.8 ±2.3	<0.001			NA
Ashrafi et al. (2022) ²⁴	Iran	Crosssectional	****	POS Endometriosis Male factors (MF)	POS: 80 E: 80 MF: 80	160	POS: 31.9 ± E: 28.3 ±4.3 MF: 32.4 ±5.	4.4 .7	31.6 ±1.9	POS: 21.6 ±2.9 E: 22.4 ±1.8 MF: 26.1 ±1.8	29.0 ± 2.5	0.001	POS: 99% E: 100% MF: 80%	36%	<0.001
Wang et al. (2022) ²⁵	China	Casecontrol	****	Authors' definition	324	326	30.9 ±5.1		31.4 ±5.3	24.3 ±6.2	25.6 ±5.7	0.008	59%	50%	0.033
Oindi et al. (2019) ²⁶	Pakistan	Crosssectional	****	WHO	93	93	32.4 ±5.8			27.8 ±5.1	29.1 ±3.8	0.056	31%	23%	0.187
Potur et al. (2019) ²⁷ p	Turkey	Casecontrol	****	WHO	316	316	30.9 ± 4.8		30.5 ± 5.0	30.5 ± 0.4	33.4 ± 0.4	0.001	32%	15%	< 0.001
Ozturk et al. (2019)	Turkey	Crosssectional	****	WHO	96	96	31.1 ± 5.1		32.5 ± 5.2	31.8 ± 7.8	35.7 ± 6.3	<0.001	88%	70%	0.003
Salomão et al. (2018)	Brazil	Casecontrol	****	Women undergoing infertility treatment	140	140	36.0		34.0				34%	35%	0.9
Shahraki et al. (2018)	Iran	Crosssectional	****	WHO	78	115	31.3 ± 6.2		32.9 ± 7.2	24.7 ± 5.1	25.7 ± 7.2	0.5	65%	44%	0.01
Gabr et al. (2017)	Egypt	Crosssectional	**** **** *	Authors' definition	200	200	30.0 ±6.0		32.0 ±6.0	26.8 ±3.8	27.9 ±3.5	0.003	47%	30%	<0.001
Turan et al. (2014)	Turkey	Crosssectional	**** *	WHO	352	301	29.2 ±4.3		28.7 ±4.0	26.2 ±2.5	28.2 ±1.7	<0.001	33%	17%	<0.001
Mendonça et al. (2014)	Brazil	Crosssectional	****	Authors' definition	168	110	33.3±4.6		31.2±6.7	27.7 ±4.5	28.1 ±4.2	0.2	36%	28%	0.3
Khodarahimi et al. (2014)	Iran	Crosssectional	**** **	WHO	50	50	29.7 ±4.0			55.8±17.2	64.0 ±13.9	0.01	17%		

WI – Women with infertility; C – Control; SD – Standard deviation; NOS - Newcastle-Ottawa Scale; POS - polycystic ovarian syndrome; MF – Male factors

Table 1: Controlled studies

Author (Year)	Country	Tipo de estudo	NOS	Infertility diagnosis	Sample size	Age (mean ± SD)	Mean Score FSFI (mean ± SD)	FSD prevalence
Amraei et al. (2022)	Iran	Cross- sectional	****	Authors' defi- nition	150	29.6±5.5	22.1 ± 7.8	55%
Dong et al. (2021)	China	Case- control	****	who	715	32.6 ± 4.3	27.0 ± 2.8	
Riazi et al. (2020)	Iran	Cross- sectional	*****	Authors' definition	250	29.7 ±5.2	NA	61%
Facchin et al. (2019)	Italy	Cross- sectional	****	WHO	269	37.8 ± 4.0	28.4 ± 4.7	30%
Maroufiza- deh et al. (2019)	Iran	Cross- sectional	****	Inability to conceive after 1 year of regular unprotected inter- course	250	29.7 ±5.2	20.71±5.0	
Shahraki et al. (2019)	Iran	Cross- sectional	*****	***** WHO		28±5.9	9.9±0.1	
Alirezaei et al. (2018)	Iran	Cross- sectional	****	Inability to conceive after 1 year of regular unprotected inter- course	85	31.1 ±5.5	NA	72%
Lo & Kok (2016)	China	Cross- sectional	****	Authors' defi- nition	159	32.8±3.8	24.9 ±4.2	33%
Suna et al. (2015)	Turkey	Cross- sectional	****	Inability to conceive after 1 year of regular unprotected inter- course	142	20-40 (range)	25.6	
Jamali et al. (2014)	Iran	Cross- sectional	*****	WHO	502	30.9 ±6.8	16.3 ±4.7	87%
Pakpour et al. (2012)	Iran	Cross- sectional	*****	Inability to conceive after 1 year of regular unprotected intercourse	604	30.0 ±7.8	22.5 ±3.6	56%
SD – Standard d	eviation; NO	S - Newcastle	-Ottawa Scale					

 Table 2: Non comparative studies

Comparative studies

In the 12 comparative studies analysed, the samples ranged from a minimum of 50 women per group to a maximum of 352. FSFI values were significantly higher in women with infertility in 8 of the 12 analysed studies. As for the prevalence of FSD, the values are disparate among the studies ranging from 100% in women with endometriosis-related infertility to 15% in one of the control groups.

Non comparative studies

In Iran, seven of the 11 non-comparative studies evaluated were conducted. The studies evaluate samples ranging from 85 to 715 women with infertility, with FSD prevalence ranging from 30% to 87%.

Risk of Bias

All studies included were assessed for their methodologic

quality. According to NOS, the risk of bias for these studies is presented as low (Tables 1 and 2).

Meta-analysis

The meta-analysis evaluated 8 studies comparing FSFI in women with infertility versus a control group. The results point to significantly lower FSFI scores in infertile women (mean difference -2.22, [95% CI -3.57 to -0.87], p<0.0001).

Figure 2 - FSFI Total Score: Meta-analysis

In addition, meta-analysis was carried out for each subdomain of the scale, and it was observed that infertile women presented significantly lower scores in all domains: mean differences - desire -0. 31, [95% CI -0.55 to -0.07, p = 0.01]; in arousal -0.50, [95% CI -0.81 to -0.18, p = 0.002]; lubrication -0.30, [95% CI --0.53 to -0.07, p = 0.01]; orgasm -0.37, [95% CI -0.59 to -0.16], p = 0.0006 (figure 3); satisfaction -0.46, [95% CI -0.71 to -0.20], p = 0.0004 (figure 4); and pain -0.40, [95% CI -0.65 to -0.15], p = 0.002.

	Infertile women			Control group				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Ashrafi et al., 2022	23.17	3.23	162	29.07	2.5	160	13.0%	-5.90 [-6.53, -5.27]	+
Gabr et al., 2017	26.8	3.8	200	27.9	3.5	200	12.9%	-1.10 [-1.82, -0.38]	-
Kulaksik et al., 2022	20.4	2.2	246	24.8	2.3	242	13.2%	-4.40 [-4.80, -4.00]	-
Mendonça et al., 2014	27.7	4.5	168	28.1	4.2	110	12.4%	-0.40 [-1.44, 0.64]	
Oindi et al., 2019	27.86	5.14	93	29.14	3.82	93	11.9%	-1.28 [-2.58, 0.02]	
Shahraki et al., 2018	24.7	5.1	78	25.7	7.2	115	10.9%	-1.00 [-2.74, 0.74]	
Turan et al., 2014	26.2	2.5	352	28.2	1.7	301	13.2%	-2.00 [-2.32, -1.68]	
Wang et al., 2021	24.38	6.27	324	25.63	5.73	326	12.6%	-1.25 [-2.17, -0.33]	-
Total (95% CI)			1623			1547	100.0%	-2.22 [-3.57, -0.87]	•
Heterogeneity: Tau ² = 3.	.54; Chi ² =	= 239.9	6, df =	7 (P < 0	.00001	$I); I^2 = 9$	97%		
Test for overall effect: $Z = 3.23$ (P = 0.001)								Infertile women Control group	

Figure 2: FSFI Total Score: Meta-analysis

	Infertile women		Control group					Mean Difference	Mean Difference			
Study or Subgroup	Mean SD 7		Total	Mean	SD	SD Total Weight IV, Random, 95% CI		IV, Rando	om, 95% CI			
Ashrafi et al., 2022	3.36	0.82	162	4.49	0.81	160	13.2%	-1.13 [-1.31, -0.95]	+			
Gabr et al., 2017	4.2	0.7	200	4.6	0.6	200	13.8%	-0.40 [-0.53, -0.27]				
Kulaksik et al., 2022	3.9	0.6	246	4.2	0.8	242	13.8%	-0.30 [-0.43, -0.17]	-			
Mendonça et al., 2014	4.6	1	168	4.7	1.1	110	12.0%	-0.10 [-0.36, 0.16]		 		
Oindi et al., 2019	4.69	1.27	93	4.86	1.11	93	10.6%	-0.17 [-0.51, 0.17]		+		
Shahraki et al., 2018	4.1	1.3	78	4.5	1.5	115	9.7%	-0.40 [-0.80, -0.00]		1		
Turan et al., 2014	4.5	0.54	352	4.7	0.45	301	14.2%	-0.20 [-0.28, -0.12]	-			
Wang et al., 2021	4.09	1.5	324	4.33	1.31	326	12.6%	-0.24 [-0.46, -0.02]				
Total (95% CI)			1623			1547	100.0%	-0.37 [-0.59, -0.16]	•			
Heterogeneity: $Tau^2 = 0$.	.08; Chi ²	= 94.92	, df = 7	(P < 0.	00001)	; $I^2 = 9$	3%		- <u> </u>			
Test for overall effect: Z	= 3.41 (P	-2 =1	Control group									

Figure 3: Orgasm subscore results

	Infertile women			tile women Control group				Mean Difference		Mean Difference			
Study or Subgroup	Mean SD To		Total	otal Mean SD Total		Weight	IV, Random, 95% CI		IV, Random, 95% CI				
Ashrafi et al., 2022	4.01	0.89	162	5.1	0.78	160	12.7%	-1.09 [-1.27, -0.91]	-	-			
Gabr et al., 2017	4.9	0.5	200	5.2	0.5	200	13.4%	-0.30 [-0.40, -0.20]		-			
Kulaksik et al., 2022	3.5	0.9	246	4.6	0.8	242	13.0%	-1.10 [-1.25, -0.95]	-	-			
Mendonça et al., 2014	5.1	0.8	168	5.1	1.1	110	12.2%	0.00 [-0.24, 0.24]		_			
Oindi et al., 2019	5.02	1.11	93	5.32	0.87	93	11.6%	-0.30 [-0.59, -0.01]					
Shahraki et al., 2018	4.4	1.3	78	4.7	1.2	115	10.6%	-0.30 [-0.66, 0.06]					
Turan et al., 2014	4.4	0.55	352	4.7	0.28	301	13.5%	-0.30 [-0.37, -0.23]		-			
Wang et al., 2021	4.41	0.96	324	4.61	1.04	326	13.0%	-0.20 [-0.35, -0.05]					
Total (95% CI)			1623			1547	100.0%	-0.46 [-0.71, -0.20]		•			
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 168.29$, $df = 7$ (P < 0.00001); $I^2 = 96\%$										-1	1	+	
Test for overall effect: Z	= 3.54 (F)	P = 0.00	04)						-z	tilo womon	Control group	2	

Figure 4: Satisfaction subscore results

Discussion

The World Health Organization (WHO) assumes that all human beings have the right to enjoy the highest levels of physical and mental health and considers infertility as a public health problem that affects thousands of people worldwide, significantly impacting the health of the individual, family, and community, in the relational dimension, both at intra and interpersonal levels [1]. Concurrently, there is a growing body of research that suggests a link between infertility and female sexual dysfunction. In this review we intend to assess whether the levels of female sexual dysfunction are higher in women with infertility [24, 25, 1, 7]. Our meta-analysis results, which compare 1623 women with infertility with 1547 controls, confirmed that women with infertility have a significantly lower mean FSFI score observed in all domains of the scale when compared to that of fertile women, with satisfaction and orgasm being the most affected. We came up with a few hypotheses: Could low satisfaction have something to do with sex being too mechanical and focused on conception? In the same way: Could orgasm also have something to do with it? Is penetrative sex the focus of sexual intercourse in infertile couples, and therefore the woman's stimulation is neglected and, consequently, there are fewer experiences of orgasm and satisfaction? We did not perform a meta-analysis to compare the results of FSD prevalence between women with infertility and control groups, given the enormous variability of the prevalence results. Looking at the data recorded in the systematic review, more than half of the studies presented significant differences, showing a higher prevalence of FSD in the groups of women with infertility. The reasons that might account for the association between infertility and FSD are varied and are beyond the scope of this study. However, we must always consider that there are comorbidities that constitute risk factors for both infertility and FSD, such as endometriosis, polycystic ovary syndrome (PCOS), and pelvic inflammatory disease (PID). At the same time, the emotional stress associated with infertility can itself be a cause of FSD and, on the other hand, FSD can make it difficult or impossible for women to conceive, so it seems to exist a potential bi-directional relationship between infertility and sexual function [15].

Study limitations

The major limitation of this review is the relative heterogeneity of the populations considered. Although many of the studies included considered the WHO definition as a criterion for infertility, in many others the criteria were different. Another aspect that deserves attention is the country of origin of the studies, which does not include any studies conducted in North America and includes only one study conducted in Europe.

Because nearly all studies were cross-sectional studies, it is not possible to draw conclusions as to the causal associations. Another limitation was related with the search strategy, which was focused on sexual function/dysfunction, and did not specify sexual difficulties (e.g., sexual desire, sexual arousal, orgasm, pain).

Conclusion

Our study revealed that infertility causes a negative impact on female sexual function, however it is still difficult to establish for sure a bidirectionality, as the populations involved in the studies have a great heterogeneity.

Further studies are necessary for a better understanding of the role of infertility influencing factors, both personal and relational, that impact on sexual function and couples' satisfaction.

Reflecting on the findings of this systematic review, it is essential to promote strategies that prevent and minimize a couple's dysfunction, improve the sexual and affective relationship, and, consequently, increase quality of life.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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