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Infertility related distress and female sexual function during assisted reproduction

Running head: INFERTILITY RELATED DISTRESS AND FEMALE SEXUAL FUNCTION

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Abstract

Study question: Is infertility related distress a risk factor for impaired female sexual function in women undergoing assisted reproduction?

Summary answer: Infertility related distress, and especially social, sexual, and relationship concerns, are associated with female sexual dysfunction.

What is known already: Women with infertility are more likely to present sexual dysfunction relative to those without infertility. Moreover, assisted reproduction is associated with increased risk for female sexual problems. To date, this higher proportion of sexual impairment in infertile women has been simplistically linked to the stress associated with the condition and investigated risk factors included mainly demographic and clinical variables. Quantitative studies aimed at identifying risk factors for sexual dysfunction that also included the evaluation of infertility related distress are conversely lacking.

Study design, size, duration: This observational study was conducted at the Infertility Unit of the Fondazione Ca’ Granda, Ospedale Maggiore Policlinico of Milan between 2017 and 2018.

Participants/materials, setting, methods: We included 269 consecutive patients with infertility aged 24-45 (37.8 ± 4.0 years). Sexual function outcomes were sexual dysfunction (assessed with the Female Sexual Function Inventory – FSFI), sexual distress (evaluated with the Female Sexual Distress Scale-Revised – FSDS-R), dyspareunia, and number of intercourses in the month preceding ovarian stimulation. Infertility related distress was measured with the Fertility Problem Inventory (FPI). The effects of potential confounders such as demographic variables (women’s and partners’ age, level of education) and infertility related factors (type and cause of infertility, number of previous IVF cycles, duration of infertility) were also examined.

Main results and the role of chance: Women with higher infertility related distress were more likely to report sexual dysfunction (OR = 1.02 per point of score, 95%CI: 1.01–1.03, \( P = .001 \)). Three FPI domains (i.e., social, relational, and sexual concerns) were correlated with almost all sexual function outcomes (\( Ps < .05 \)).
Limitations, reasons for caution: Women who were not sexually active were not included, thus reasons for sexual inactivity should be further explored in future studies. Data regarding men (e.g., sexual function, infertility related distress) were lacking, thus cross-partner effects were not examined. Recall bias (also due to the fact that questionnaires were administered on the day of oocytes retrieval) and social desirability bias may have also affected women’s responses to the questionnaires.

Wider implications of the findings: Social, relational, and sexual concerns should be assessed and addressed in psychological counselling with the infertile couple.

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Introduction

Sexuality is a fundamental component of women’s health, with a remarkable impact on general wellbeing, quality of life, and self-concept (Furukawa et al., 2012). Female sexual function is complex and multidimensional – one may say ‘kaleidoscopic’ (Barbara et al., 2016) – since it results from the interaction of multiple physical, psychological, relational, and sociocultural factors. Overall, women are more likely to present sexual dysfunction as compared with men (Lewis et al., 2004). Research demonstrated that the prevalence of sexual concerns (e.g., lack of interest in sex, orgasm difficulties, poor lubrication, pain, low satisfaction), which often remain unreported to physicians, is high among women seeking routine gynaecological care (Nusbaum et al., 2000).

The quality of sexual function in women can be affected by a variety of stressors, including infertility. Even if not fully concordant, the available literature reported a higher proportion of female sexual dysfunction in infertile women compared to women without infertility (Gabr et al., 2017; Khademi et al., 2008; Millheiser et al., 2010; Mirblouk et al., 2016; Turan et al., 2014). This body of literature identified a number of risk factors that may lead to impaired sexual function in women with infertility. Keskin et al. (2011) found a higher prevalence of sexual dysfunction in women with secondary infertility. Women’s and partners’ age, level of education, duration of infertility, prior history of infertility treatment and a female cause of infertility can also be associated with sexual dysfunction (Davari Tahna et al., 2014; Iris et al., 2013; Keskin et al., 2011; Oskay et al., 2010; Winkelman et al., 2016). Moreover, women undergoing assisted reproduction often report sexual problems, especially in terms of decreased interest and desire for sex, poorer arousal and lubrication, and orgasm difficulties (Nelson et al., 2008; Purcell-Lévesque et al., 2018; Smith et al., 2015).

The negative impact of infertility and its treatment on sexual function is generally attributed to the stress caused by the inability to conceive, especially due to forced timing of intercourse, negative effects of treatment (both on physical and psychological wellbeing), and pressure from family members and people around the couple (see the systematic review by Luk and Loke, 2015). Compared to men, women appear more stressed about infertility (Donarelli et al., 2015) and more likely to develop sexual
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dysfunction (Wischmann, 2010), with great variability in their subjective experiences, as well as in the
difficulties encountered during treatment (Benyamini et al., 2005; Dhaliwal et al., 2004). However, to our
knowledge, there are no quantitative studies exploring the association between infertility related distress
and female sexual function in a systematic fashion.

For this reason, we conducted the current study, whose primary aim was to examine the
association between infertility related distress and female sexual dysfunction in the context of assisted
reproduction. The secondary aim of our study was to investigate the relation between infertility related
distress and three other sexual function dimensions: dyspareunia (i.e., genital pain before, during, and/or
after intercourse), women’s sexually related personal distress, and frequency of intercourses in the month
preceding the initiation of ovarian stimulation. Our main hypothesis was that infertility related distress
may negatively affect female sexual function, to the point of being associated with sexual dysfunction.

Materials and Methods

Women attending the Infertility Unit of the Fondazione Ca’ Granda, Ospedale Maggiore Policlinico of
Milan were consecutively recruited between 2017 and 2018 after approval of the local Institutional
Review Board. Patients were included if they were aged between 18-45 years and had not been able to
conceive after 12 months of unprotected sexual intercourse in a heterosexual relationship. Women who
had never been able to conceive were diagnosed with primary infertility, while secondary infertility was
diagnosed in women who previously had been able to conceive (either in case of live birth or miscarriage;
Keskin et al., 2011). Women were excluded if they were non-Italian speaking, not sexually active in the
past four weeks (because women with this condition could not complete all sexual function measures),
had diagnosed psychiatric disorders such as anxiety, depression, and substance abuse, and/or medical
conditions other than endometriosis that are frequently associated with sexual dysfunction (e.g., genital
tract abnormalities, diabetes, heart disease, kidney failure, autoimmune and rheumatic diseases). All
participants received complete information regarding the research. Data were collected on the day of
oocytes retrieval from women who accepted to participate in the study and provided written informed
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consent. However, participants were asked to respond to the questionnaires focusing on the 30 days before the initiation of ovarian stimulation.

Women’s demographic data (such as age and level of education) and age of partner were collected using a structured interview. Clinical information, including type and aetiology of infertility, and number of previous IVF cycles, was retrieved from medical records. Duration of infertility was determined as time from couples’ first attempt to conceive to study entry. As regards infertility aetiology, participants were divided into four categories: female factors (endometriosis, tubal factor, ovulatory dysfunction), male factors (abnormal sperm production), male and female factors, and unexplained infertility. All these variables were entered in our statistical analyses as potential confounders.

Sexual dysfunction was assessed using the Female Sexual Function Index (FSFI), a 19-item multidimensional questionnaire assessing six key dimensions of sexual function (desire, arousal, lubrication, orgasm, pain, satisfaction), with a total score ≤ 26.55 indicating the presence of sexual dysfunction (Rosen et al., 2000). Of these 19 items, 4 assess the quality of sexual life in general (e.g., “Over the past four weeks, how would you rate your degree of sexual desire or interest”), with responses scored from 1 (very low) to 5 (very high). The other 15 items are related to specific aspects of sexual activity (e.g., “Over the past four weeks, how often did you become lubricated during sexual activity or intercourse”), with responses scored from 0 (no sexual activity in the past four weeks) to 5 (very often).

Dyspareunia was evaluated using a 0-10 numerical rating scale (NRS) from 0 = “no pain at all” to 10 = “the worst imaginable pain”. The Female Sexual Distress Scale-Revised (FSDS-R), a 13-item validated scale, measured sexually related distress (e.g., in the past 30 days, “How often did you feel distressed about your sex life”; “How often did you feel sexually inadequate”); responses were scored on a 0-4 scale (0 = “Never”; 4 = “Always”), with higher total score indicating greater stress (Derogatis et al., 2008). Women also reported the number of sexual intercourses during the 30 days before the initiation of ovarian stimulation.

Fertility related distress was evaluated using the Fertility Problem Inventory (FPI), a multidimensional 46-item validated questionnaire assessing five domains of infertility related distress
(plus a full scale score): social concern (e.g., “It doesn’t bother me when I’m asked questions about children”), sexual concern (e.g., “During sex, all I can think about is wanting a child”), relationship concern (e.g., “My partner doesn’t understand the way the fertility problem affects me”), rejection of childfree lifestyle (e.g., “At times, I seriously wonder if I want a child”), and need for parenthood (e.g., “Pregnancy and childbirth are the two most important events in a couple’s relationship”). Responses range from 1 (“Strongly agree”) to 6 (“Strongly disagree”) and higher scores indicate greater distress (Newton et al., 1999; Donarelli et al., 2015). Cronbach’s $\alpha$ ranged from .90 for the FPI to .93 for both the FSFI and the FSDS-R.

### Statistical analysis

Statistical analyses were conducted with SPSS (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA) software version 17. We report mean $\pm$ standard deviation for continuous variables and frequencies for qualitative variables. Participants who reported zero to $\geq$ 8 FSFI items were not included in the analyses, because data from these women were not considered as valid measures of sexual function due to insufficient sexual activity, as suggested by the literature (Baser et al., 2012; Hevesi et al., 2017). We also excluded women who did not complete all sections of the questionnaires. To generally determine the impact of infertility related distress on the likelihood of having sexual dysfunction (FSFI total score $\leq$ 26.55), controlling for the effects of our putative confounders, we developed a hierarchical binary logistic regression model: demographic factors (women’s and partners’ age, and level of education) were included in the first block (Model 1); infertility related factors (type and cause of infertility, number of previous IVF cycles, and infertility duration) were added in the second block (Model 2), and infertility related distress (the FPI total score) was included in the third block (Model 3). Secondly, one-way and multivariate ANOVA were used to compare the means of the FPI total score, as well as the five FPI domains in women with vs. without sexual dysfunction, with $\eta^2_p$ values of .01, .06, and .14 indicating small, medium, and large effect sizes respectively. More specific analyses (i.e., Pearson or Spearman correlation, as appropriate) were then conducted to further explore the association between
infertility related distress and all sexual function outcomes (the six FSFI dimensions, dyspareunia, sexual distress, and frequency of intercourses). Significance tests were performed at $P < .05$. Based on Cohen’s guidelines for power analysis (Cohen, 1992), our sample was large enough to detect a medium-sized difference ($f = .25$) between the means of two independent groups (women with vs. without sexual dysfunction) at Power = .80 for $\alpha = .05$.

**Results**

A total of 340 women were invited to participate in the study. Because 40 patients (12%) declined our invitation, eligible participants were 300 women who returned signed consent form. Of the 300 women originally recruited, 31 (10%) were excluded because they responded zero to $\geq 8$ FSFI items (18 women [6%]) or provided incomplete information (13 women [4%]). Of the 18 women who responded zero to $\geq 8$ FSFI items, 7 (39%) also provided remarkably incomplete information (on the FSFI as well). Final participants were 269 women aged 24-45 (37.8 ± 4.0 years), 179 (67%) with primary infertility vs. 90 (33%) with secondary infertility. Of these participants, 124 (46%) underwent IVF, while the remaining 145 (54%) underwent ICSI. All participant characteristics are reported in Table 1. None of the included couples had a sexual disorder, such as for instance vaginismus and/or erectile dysfunction, as an indication for IVF.

**Infertility related distress and sexual dysfunction**

Female sexual dysfunction, evaluated on the basis of the FSFI cut-off score, was reported by 81 participants (30%). The hierarchical binary logistic regression conducted showed that the likelihood of having sexual dysfunction was significantly associated only with infertility related distress (Table 2). Only the likelihood ratio $\chi^2$ of Model 3 was statistically significant ($\chi^2 = 12.89, df = 1, P < .001$), revealing that the inclusion of the FPI total score significantly improved the regression model. For infertility related distress, the odds ratio (OR) for sexual dysfunction was 1.02 per unit of score (95% CI
1.01–1.03; \( P = .001 \)), indicating that women with greater global infertility related distress were more likely to report sexual dysfunction.

As revealed by the analyses of variance conducted, women with sexual dysfunction had significantly greater overall infertility related distress (\( F = 15.36; \ P < .001; \eta^2_p = .064 \)), as well as social (\( F = 9.86; \ P = .002; \eta^2_p = .042 \)), sexual (\( F = 35.76; \ P < .001; \eta^2_p = .14 \)), and relationship concerns (\( F = 10.64; \ P = .001; \eta^2_p = .05 \)) relative to participants without sexual dysfunction. Characteristics of women with vs. without sexual dysfunction are reported in Table 3.

**Infertility related distress and sexual function**

Pearson and Spearman correlations between infertility related distress and all sexual function outcomes (see Table 4) revealed that infertility related distress was significantly associated with sexual function, and specifically: greater social, sexual, and relationship concerns, as well as the FPI full scale score, were associated with poorer sexual function on almost all the FSFI domains, as well as with greater sexual distress (\( Ps < .05 \)). Social and sexual concerns, and the FPI global score were also associated with increased dyspareunia, but no significant correlations were found with self-reported number of sexual intercourses in the 30 days before ovarian stimulation.

**Discussion**

The primary aim of this study was to examine whether infertility related distress, assessed using a multidimensional validated questionnaire (the FPI; Donarelli et al., 2015), was associated with female sexual dysfunction in women undergoing assisted reproduction. It is worth underlining that the 1.02 OR for sexual dysfunction per unit of score emerged from our analyses is clinically significant if one considers that: (1) the FPI is a 46-item questionnaire, with responses scored on a 6-point Likert scale (from 1 to 6); (2) in our sample the FPI total scores ranged from 70 to 227. Although the sexual impact of demographic and infertility related factors such as type and cause of infertility (whose effects were controlled in our analyses) was investigated in most studies on this topic (Davari Tahna et al., 2014; Iris...
et al., 2013; Keskin et al., 2011; Oskay et al., 2010; Winkelman et al., 2016), to our knowledge this is the first study that directly examined the association between women’s distress about their condition and sexual function. Although most research interpreted the higher percentage of sexual dysfunction reported by women with infertility as caused by the psychological consequences of this condition (Luk and Loke, 2015), this interpretation was based on general literature on the psychological impact of infertility (i.e., not directly focused on the relation between infertility related distress and sexual dysfunction), rather than on clear quantitative evidence. The present study thus provides for the first time a direct scientific support to this long-lasting assumption.

To note, in our study we found a relatively low proportion of sexual dysfunction in infertile women (30%) compared with other studies conducted with the FSFI. For example, Millheiser et al. (2010) reported that in their research 40% of infertile participants had sexual dysfunction. Our result actually suggests that infertility itself may not be necessarily associated with sexual dysfunction, and that the quality of female sexual function in this population may be more associated with specific psychological risk factors, such as infertility related social, relational, and sexual concerns.

In our study, infertility related distress was linked not only to a dichotomic view of sexual dysfunction (the trenchant threshold of 26.55 used for the primary analysis) but also to the six specific FSFI domains, sexual distress, and even the severity of dyspareunia. Conversely, no significant correlations were found with the number of sexual intercourse in the 30 days before the initiation of ovarian stimulation. Overall, these findings suggest that infertility related distress is more likely to negatively affect the quality rather than the frequency of sexual function.

Not all the FPI subscales were associated with sexual function. In our study, we found significant correlations for three of the five FPI domains (as well as for the full scale score): social, relational, and sexual concerns. These findings are informative and useful to clarify what type of infertility related worries can compromise the quality of infertile women’s sexual life. Social concerns, as assessed by the FPI, are generated for instance by time spent with friends who have children, or family meetings, and derive from social comparisons and feelings of isolation experienced by the person as a result of
infertility. Relational and sexual concerns regard the couple and specifically the impact of the stressor infertility on the intimate relationship, especially in terms of dyadic coping and couple disclosure, and sexuality as specifically affected by infertility. These issues should be assessed during psychological counselling with infertile couples, since they represent significant risk factors for impaired sexual function and actual sexual dysfunction. In our opinion, this aspect should not be neglected and may deserve attention. One may also speculate that sexual dysfunction may further increase the general psychological burden of infertile couples and could contribute to the high drop-out rates from treatments observed in infertile couples (Gameiro et al., 2012, 2013). Further evidence is however needed to support this speculation.

Considering limitations, we should acknowledge that we did not include a control condition of non-infertile women, which partially reduces the generalizability of our findings. On the other hand, it has to be pointed out that the primary aim of our study was not to evaluate the prevalence of sexual dysfunction in infertile vs. fertile women. Our decision of excluding women who reported no sexual activity in the month preceding the initiation of ovarian stimulation may have led to a deflated estimate of the prevalence of sexual dysfunction in our population, as compared with other studies (e.g., Millheiser et al., 2010). However, the inclusion of the 11 women who responded zero to ≥ 8 FSFI items, but provided complete information, would have determined a very small increase in the percentage of participants with sexual dysfunction (i.e., 3% increase: from 30% to 33%). Moreover, secondary analyses revealed that results did not change when including these 11 participants (data not shown). An important reason for excluding these women was that we did not examine the impact of other psychological and relational factors, such as self- and body-esteem, level of couple intimacy (including adjustment to women’s sexual needs), dyadic coping, and relational satisfaction, which are key for sexual dysfunction as a multifactorial condition (Iris et al., 2013). As suggested by Baser et al. (2012), women who avoid intercourse may represent a clinically distinct subgroup that requires more detailed exploration. For instance, the reasons for sexual inactivity may be investigated using qualitative methods, such as in depth interviews, rather than only standardized questionnaires.
The fact that we did not include data regarding male sexual function (such as erection status), which can affect female sexuality (Cayan et al., 2004; Yeoh et al., 2014), represents another limitation, especially if one considers that infertility treatment involves the couple, rather than the individual. In this particular context, men frequently report erectile and ejaculatory problems (Gao et al., 2013; Shindel et al., 2008), as well as decreased levels of sexual desire and satisfaction following the diagnosis of infertility (Hammarberg et al., 2010; Ramezanazadeh et al., 2006). Men’s feelings and perspectives are also important. In this regard, Purcell-Lévesque et al. (2018) recently underlined the importance of assuming a dyadic approach in the unique context of infertility treatment by demonstrating an association between men’s attachment insecurities (i.e., avoidance) and their partners’ orgasm difficulties. Future studies should examine whether men’s sexual problems and infertility related distress impact on women’s sexual function using dyadic research designs (see also Donarelli et al., 2012).

However, many studies investigating the association between female sexual function and infertility recruited women only and assessed sexual dysfunction using the FSFI (see for example Iris et al., 2013; Keskin et al., 2011; Millheiser et al., 2010; Mirblouk et al., 2016; Turan et al., 2014), which allows comparison between our findings and those from the published literature. Effort should be made by researchers to identify a common methodology to evaluate sexual function in the infertile population, given that the variability in the prevalence rates of sexual complaints may be due to the specific research methods adopted (Wischmann, 2013).

In this regard, the sexual assessment time is particularly important. Our participants completed the questionnaires on the day of oocytes retrieval, although focusing on the 30 days before ovarian stimulation. Although the assessment time was the same for all women and consented to standardize the conditions (silent room, without relatives and without time pressure), our methodological decision may have influenced our findings. For instance, the actual proportion of sexual dysfunction in our sample may have been underestimated due to difficulties in remembering sexual activity in the month preceding ovarian stimulation (recall bias), also associated with women’s physical and psychological conditions (related to both hormonal stimulation and the specificities of the situation) on the day of oocytes retrieval.
The potential impact of women’s inclination to answer in line with social desirability (social desirability bias) should also be taken into account. Because of the sensitivity of the topic, the potential effects of social desirability bias on women’s responses to sexual questionnaires should always be considered, as reminded by other authors (see Wischmann, 2013).

Despite these limitations, our study may usefully contribute to the investigation and treatment of infertility by providing support to the hypothesis that infertility related distress may disrupt sexual function (see also Wischmann, 2010) and deserves consideration for clinical management of infertile couples. Based on our findings, this situation does not seem to translate into a reduction of the frequency of intercourses and thus may not impair the parallel chances of natural pregnancy. However, because “sex on demand” has been acknowledged as an important source of stress for infertile couples (Monga et al., 2994), even a high frequency of intercourse itself does not necessarily indicate healthy sexual function in this population. This may represent an important research avenue for future studies. The nature of the association between infertility related distress and sexual dysfunction also requires further investigation. In our study, this psychological variable was conceptualized as risk factor for impaired sexuality.

However, we speculate that a multidimensional model based on a circular – rather than linear – notion of causality that implies the mutual interaction of multiple factors may be more appropriate to explain this complex association. We encourage a fruitful dialogue between quantitative and qualitative research to develop such a model.

Conclusions: implications for clinical practice

The importance of assessing sexual function in couples undergoing assisted reproduction has been widely acknowledged by researchers and clinicians (Smith et al., 2015; Wischmann, 2010, 2013). However, the studies conducted so far have not provided firm conclusions regarding the association between infertility and female sexual dysfunction, not only in terms of rates, but also as regards the factors and mechanisms underlying this association. Our study – although focused on women – may help clarify that couples’ subjective experience of infertility and its treatment does make the difference in terms of sexual outcomes.
Patient-centred counselling should systematically entail an accurate assessment of couples’ concerns and levels of stress, because these factors can compromise sexual life, to the point of being associated with female sexual dysfunction, as demonstrated by our study. It is also known that dealing with patients’ stress, especially when it translates into impatience and unrealistic expectations or demands, is challenging for fertility healthcare professionals (see Boivin et al., 2017). In this regard, the presence of psychologists and psychotherapists is key in the multidisciplinary fertility team to improve patient care, as well as to decrease professionals’ difficulties working with couples.

Authors’ roles

F.F., E.S., G.B., and P.V. conceptualized, designed, and supervised the study. Data collection and statistical analyses were conducted by F.F., A.B., and A.C. F.F. wrote a first draft of the manuscript, which was entirely revised by all authors, until full consensus was reached regarding the final version of the article.

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Conflict of interest

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