

1 **Infertility related distress and female sexual function during assisted reproduction**

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4 Running head: INFERTILITY RELATED DISTRESS AND FEMALE SEXUAL FUNCTION

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7 FACCHIN Federica, PhD ^{a*}; SOMIGLIANA Edgardo, MD-PhD ^b; BUSNELLI Andrea, MD ^b;
8 CATAVORELLO Anita, MD ^c; BARBARA Giusy, MD ^b; VERCELLINI Paolo, MD ^b

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11 ^a Department of Psychology, Catholic University of Milan, Milan, Italy.

12 ^b Department of Clinical Sciences and Community Health, Università degli Studi di Milano, and
13 Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

14 ^c Department of General Surgery and Medical Surgical specialities, University of Catania, Catania, Italy

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17 * Corresponding author at: Department of Psychology, Catholic University of Milan, Largo A. Gemelli 1,
18 Milan, MI 20123 Italy. Tel.: +39 02 7234 5942; fax: +39 02 7234 5962.

19 *E-mail address:* federica.facchin@unicatt.it
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21 **Abstract**

22

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

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

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

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

35 **Participants/materials, setting, methods:** We included 269 consecutive patients with infertility aged 24-
36 45 (37.8 ± 4.0 years). Sexual function outcomes were sexual dysfunction (assessed with the Female
37 Sexual Function Inventory – FSFI), sexual distress (evaluated with the Female Sexual Distress Scale-
38 Revised – FSDS-R), dyspareunia, and number of intercours in the month preceding ovarian stimulation.
39 Infertility related distress was measured with the Fertility Problem Inventory (FPI). The effects of
40 potential confounders such as demographic variables (women's and partners' age, level of education) and
41 infertility related factors (type and cause of infertility, number of previous IVF cycles, duration of
42 infertility) were also examined.

43 **Main results and the role of chance:** Women with higher infertility related distress were more likely to
44 report sexual dysfunction (OR = 1.02 per point of score, 95%CI: 1.01–1.03, $P = .001$). Three FPI
45 domains (i.e., social, relational, and sexual concerns) were correlated with almost all sexual function
46 outcomes ($P_s < .05$).

47 **Limitations, reasons for caution:** Women who were not sexually active were not included, thus reasons
48 for sexual inactivity should be further explored in future studies. Data regarding men (e.g., sexual
49 function, infertility related distress) were lacking, thus cross-partner effects were not examined. Recall
50 bias (also due to the fact that questionnaires were administered on the day of oocytes retrieval) and social
51 desirability bias may have also affected women's responses to the questionnaires.

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

54 **Study funding/competing interest(s):** None.

55 **Trial registration number:** Not applicable.

56 **Date of first patient's enrolment:** 5 May 2017

57

58 **Keywords:** infertility / assisted reproduction / sexual dysfunction / sexual function / infertility related
59 distress

60 **Introduction**

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

69 The quality of sexual function in women can be affected by a variety of stressors, including
70 infertility. Even if not fully concordant, the available literature reported a higher proportion of female
71 sexual dysfunction in infertile women compared to women without infertility (Gabr *et al.*, 2017; Khademi
72 *et al.*, 2008; Millheiser *et al.*, 2010; Mirblouk *et al.*, 2016; Turan *et al.*, 2014). This body of literature
73 identified a number of risk factors that may lead to impaired sexual function in women with infertility.
74 Keskin *et al.* (2011) found a higher prevalence of sexual dysfunction in women with secondary infertility.
75 Women's and partners' age, level of education, duration of infertility, prior history of infertility treatment
76 and a female cause of infertility can also be associated with sexual dysfunction (Davari Tahna *et al.*,
77 2014; Iris *et al.*, 2013; Keskin *et al.*, 2011; Oskay *et al.*, 2010; Winkelman *et al.*, 2016). Moreover,
78 women undergoing assisted reproduction often report sexual problems, especially in terms of decreased
79 interest and desire for sex, poorer arousal and lubrication, and orgasm difficulties (Nelson *et al.*, 2008;
80 Purcell-Lévesque *et al.*, 2018; Smith *et al.*, 2015).

81 The negative impact of infertility and its treatment on sexual function is generally attributed to the
82 stress caused by the inability to conceive, especially due to forced timing of intercourse, negative effects
83 of treatment (both on physical and psychological wellbeing), and pressure from family members and
84 people around the couple (see the systematic review by Luk and Loke, 2015). Compared to men, women
85 appear more stressed about infertility (Donarelli *et al.*, 2015) and more likely to develop sexual

86 dysfunction (Wischmann, 2010), with great variability in their subjective experiences, as well as in the
87 difficulties encountered during treatment (Benyamini *et al.*, 2005; Dhaliwal *et al.*, 2004). However, to our
88 knowledge, there are no quantitative studies exploring the association between infertility related distress
89 and female sexual function in a systematic fashion.

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

97

98 **Materials and Methods**

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

112 consent. However, participants were asked to respond to the questionnaires focusing on the 30 days
113 before the initiation of ovarian stimulation.

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

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

129 Dyspareunia was evaluated using a 0-10 numerical rating scale (NRS) from 0 = "no pain at all" to
130 10 = "the worst imaginable pain". The *Female Sexual Distress Scale-Revised* (FSDS-R), a 13-item
131 validated scale, measured sexually related distress (e.g., in the past 30 days, "How often did you feel
132 distressed about your sex life"; "How often did you feel sexually inadequate"); responses were scored on
133 a 0-4 scale (0 = "Never"; 4 = "Always"), with higher total score indicating greater stress (Derogatis *et al.*,
134 2008). Women also reported the number of sexual intercours during the 30 days before the initiation of
135 ovarian stimulation.

136 Fertility related distress was evaluated using the *Fertility Problem Inventory* (FPI), a
137 multidimensional 46-item validated questionnaire assessing five domains of infertility related distress

138 (plus a full scale score): social concern (e.g., “It doesn’t bother me when I’m asked questions about
139 children”), sexual concern (e.g., “During sex, all I can think about is wanting a child”), relationship
140 concern (e.g., “My partner doesn’t understand the way the fertility problem affects me”), rejection of
141 childfree lifestyle (e.g., “At times, I seriously wonder if I want a child”), and need for parenthood (e.g.,
142 “Pregnancy and childbirth are the two most important events in a couple’s relationship”). Responses
143 range from 1 (“Strongly agree”) to 6 (“Strongly disagree”) and higher scores indicate greater distress
144 (Newton *et al.*, 1999; Donarelli *et al.*, 2015). Cronbach’s α ranged from .90 for the FPI to .93 for both the
145 FSFI and the FSDS-R.

147 **Statistical analysis**

148 Statistical analyses were conducted with SPSS (Statistical Package for Social Sciences, SPSS Inc.,
149 Chicago, IL, USA) software version 17. We report mean \pm standard deviation for continuous variables
150 and frequencies for qualitative variables. Participants who reported zero to ≥ 8 FSFI items were not
151 included in the analyses, because data from these women were not considered as valid measures of sexual
152 function due to insufficient sexual activity, as suggested by the literature (Baser *et al.*, 2012; Hevesi *et al.*,
153 2017). We also excluded women who did not complete all sections of the questionnaires. To generally
154 determine the impact of infertility related distress on the likelihood of having sexual dysfunction (FSFI
155 total score ≤ 26.55), controlling for the effects of our putative confounders, we developed a hierarchical
156 binary logistic regression model: demographic factors (women’s and partners’ age, and level of
157 education) were included in the first block (Model 1); infertility related factors (type and cause of
158 infertility, number of previous IVF cycles, and infertility duration) were added in the second block
159 (Model 2), and infertility related distress (the FPI total score) was included in the third block (Model 3).
160 Secondly, one-way and multivariate ANOVA were used to compare the means of the FPI total score, as
161 well as the five FPI domains in women with vs. without sexual dysfunction, with η^2_p values of .01, .06,
162 and .14 indicating small, medium, and large effect sizes respectively. More specific analyses (i.e., Pearson
163 or Spearman correlation, as appropriate) were then conducted to further explore the association between

164 infertility related distress and all sexual function outcomes (the six FSFI dimensions, dyspareunia, sexual
165 distress, and frequency of intercourses). Significance tests were performed at $P < .05$. Based on Cohen's
166 guidelines for power analysis (Cohen, 1992), our sample was large enough to detect a medium-sized
167 difference ($f = .25$) between the means of two independent groups (women with vs. without sexual
168 dysfunction) at Power = .80 for $\alpha = .05$.

170 **Results**

171 A total of 340 women were invited to participate in the study. Because 40 patients (12%) declined our
172 invitation, eligible participants were 300 women who returned signed consent form. Of the 300 women
173 originally recruited, 31 (10%) were excluded because they responded zero to ≥ 8 FSFI items (18 women
174 [6%]) or provided incomplete information (13 women [4%]). Of the 18 women who responded zero to \geq
175 8 FSFI items, 7 (39%) also provided remarkably incomplete information (on the FSFI as well). Final
176 participants were 269 women aged 24-45 (37.8 ± 4.0 years), 179 (67%) with primary infertility vs. 90
177 (33%) with secondary infertility. Of these participants, 124 (46%) underwent IVF, while the remaining
178 145 (54%) underwent ICSI. All participant characteristics are reported in Table 1. None of the included
179 couples had a sexual disorder, such as for instance vaginismus and/or erectile dysfunction, as an
180 indication for IVF.

182 ***Infertility related distress and sexual dysfunction***

183 Female sexual dysfunction, evaluated on the basis of the FSFI cut-off score, was reported by 81
184 participants (30%). The hierarchical binary logistic regression conducted showed that the likelihood of
185 having sexual dysfunction was significantly associated only with infertility related distress (Table 2).
186 Only the likelihood ratio χ^2 of Model 3 was statistically significant ($\chi^2 = 12.89$, $df = 1$, $P < .001$),
187 revealing that the inclusion of the FPI total score significantly improved the regression model. For
188 infertility related distress, the odds ratio (OR) for sexual dysfunction was 1.02 per unit of score (95% CI

189 1.01–1.03; $P = .001$), indicating that women with greater global infertility related distress were more
190 likely to report sexual dysfunction.

191 As revealed by the analyses of variance conducted, women with sexual dysfunction had
192 significantly greater overall **infertility** related distress ($F = 15.36$; $P < .001$; $\eta^2_p = .064$), as well as social
193 ($F = 9.86$; $P = .002$; $\eta^2_p = .042$), sexual ($F = 35.76$; $P < .001$; $\eta^2_p = .14$), and relationship concerns ($F =$
194 10.64 ; $P = .001$; $\eta^2_p = .05$) relative to participants without sexual dysfunction. Characteristics of women
195 with vs. without sexual dysfunction are reported in Table 3.

197 ***Infertility related distress and sexual function***

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

206 **Discussion**

207 The primary aim of this study was to examine whether infertility related distress, assessed using a
208 multidimensional validated questionnaire (the FPI; Donarelli *et al.*, 2015), was associated with female
209 sexual dysfunction in women undergoing assisted reproduction. It is worth underlining that the 1.02 OR
210 for sexual dysfunction per unit of score emerged from our analyses is clinically significant if one
211 considers that: (1) the FPI is a 46-item questionnaire, with responses scored on a 6-point Likert scale
212 (from 1 to 6); (2) in our sample the FPI total scores ranged from 70 to 227. Although the sexual impact of
213 demographic and infertility related factors such as type and cause of infertility (whose effects were
214 controlled in our analyses) was investigated in most studies on this topic (Davari Tahna *et al.*, 2014; Iris

215 *et al.*, 2013; Keskin *et al.*, 2011; Oskay *et al.*, 2010; Winkelman *et al.*, 2016), to our knowledge this is the
216 first study that directly examined the association between women's distress about their condition and
217 sexual function. Although most research interpreted the higher percentage of sexual dysfunction reported
218 by women with infertility as caused by the psychological consequences of this condition (Luk and Loke,
219 2015), this interpretation was based on general literature on the psychological impact of infertility (i.e.,
220 not directly focused on the relation between infertility related distress and sexual dysfunction), rather than
221 on clear quantitative evidence. The present study thus provides for the first time a direct scientific support
222 to this long-lasting assumption.

223 To note, in our study we found a relatively low proportion of sexual dysfunction in infertile
224 women (30%) compared with other studies conducted with the FSFI. For example, Millheiser *et al.*
225 (2010) reported that in their research 40% of infertile participants had sexual dysfunction. Our result
226 actually suggests that infertility itself may not be necessarily associated with sexual dysfunction, and that
227 the quality of female sexual function in this population may be more associated with specific
228 psychological risk factors, such as infertility related social, relational, and sexual concerns.

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

235 Not all the FPI subscales were associated with sexual function. In our study, we found significant
236 correlations for three of the five FPI domains (as well as for the full scale score): social, relational, and
237 sexual concerns. These findings are informative and useful to clarify what type of infertility related
238 worries can compromise the quality of infertile women's sexual life. Social concerns, as assessed by the
239 FPI, are generated for instance by time spent with friends who have children, or family meetings, and
240 derive from social comparisons and feelings of isolation experienced by the person as a result of

241 infertility. Relational and sexual concerns regard the couple and specifically the impact of the stressor
242 infertility on the intimate relationship, especially in terms of dyadic coping and couple disclosure, and
243 sexuality as specifically affected by infertility. These issues should be assessed during psychological
244 counselling with infertile couples, since they represent significant risk factors for impaired sexual
245 function and actual sexual dysfunction. In our opinion, this aspect should not be neglected and may
246 deserve attention. One may also speculate that sexual dysfunction may further increase the general
247 psychological burden of infertile couples and could contribute to the high drop-out rates from treatments
248 observed in infertile couples (Gameiro *et al.*, 2012, 2013). Further evidence is however needed to support
249 this speculation.

250 Considering limitations, we should acknowledge that we did not include a control condition of
251 non-infertile women, which partially reduces the generalizability of our findings. On the other hand, it has
252 to be pointed out that the primary aim of our study was not to evaluate the prevalence of sexual
253 dysfunction in infertile vs. fertile women. Our decision of excluding women who reported no sexual
254 activity in the month preceding the initiation of ovarian stimulation may have led to a deflated estimate of
255 the prevalence of sexual dysfunction in our population, as compared with other studies (e.g., Millheiser *et*
256 *al.*, 2010). However, the inclusion of the 11 women who responded zero to ≥ 8 FSFI items, but provided
257 complete information, would have determined a very small increase in the percentage of participants with
258 sexual dysfunction (i.e., 3% increase: from 30% to 33%). Moreover, secondary analyses revealed that
259 results did not change when including these 11 participants (data not shown). An important reason for
260 excluding these women was that we did not examine the impact of other psychological and relational
261 factors, such as self- and body-esteem, level of couple intimacy (including adjustment to women's sexual
262 needs), dyadic coping, and relational satisfaction, which are key for sexual dysfunction as a multifactorial
263 condition (Iris *et al.*, 2013). As suggested by Baser *et al.* (2012), women who avoid intercourse may
264 represent a clinically distinct subgroup that requires more detailed exploration. For instance, the reasons
265 for sexual inactivity may be investigated using qualitative methods, such as in depth interviews, rather
266 than only standardized questionnaires.

267 The fact that we did not include data regarding male sexual function (such as erection status),
268 which can affect female sexuality (Cayan *et al.*, 2004; Yeoh *et al.*, 2014), represents another limitation,
269 especially if one considers that infertility treatment involves the couple, rather than the individual. In this
270 particular context, men frequently report erectile and ejaculatory problems (Gao *et al.*, 2013; Shindel *et*
271 *al.*, 2008), as well as decreased levels of sexual desire and satisfaction following the diagnosis of
272 infertility (Hammarberg *et al.*, 2010; Ramezanazadeh *et al.*, 2006). Men's feelings and perspectives are
273 also important. In this regard, Purcell-Lévesque *et al.* (2018) recently underlined the importance of
274 assuming a dyadic approach in the unique context of infertility treatment by demonstrating an association
275 between men's attachment insecurities (i.e., avoidance) and their partners' orgasm difficulties. Future
276 studies should examine whether men's sexual problems and infertility related distress impact on women's
277 sexual function using dyadic research designs (see also Donarelli *et al.*, 2012).

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

285 In this regard, the sexual assessment time is particularly important. Our participants completed the
286 questionnaires on the day of oocytes retrieval, although focusing on the 30 days before ovarian
287 stimulation. Although the assessment time was the same for all women and consented to standardize the
288 conditions (silent room, without relatives and without time pressure), our methodological decision may
289 have influenced our findings. For instance, the actual proportion of sexual dysfunction in our sample may
290 have been underestimated due to difficulties in remembering sexual activity in the month preceding
291 ovarian stimulation (*recall bias*), also associated with women's physical and psychological conditions
292 (related to both hormonal stimulation and the specificities of the situation) on the day of oocytes retrieval.

293 The potential impact of women's inclination to answer in line with social desirability (*social desirability*
294 *bias*) should also be taken into account. Because of the sensitivity of the topic, the potential effects of
295 social desirability bias on women's responses to sexual questionnaires should always be considered, as
296 reminded by other authors (see Wischmann, 2013).

297 Despite these limitations, our study may usefully contribute to the investigation and treatment of
298 infertility by providing support to the hypothesis that infertility related distress may disrupt sexual
299 function (see also Wischmann, 2010) and deserves consideration for clinical management of infertile
300 couples. Based on our findings, this situation does not seem to translate into a reduction of the frequency
301 of intercourses and thus may not impair the parallel chances of natural pregnancy. However, because "sex
302 on demand" has been acknowledged as an important source of stress for infertile couples (Monga *et al.*,
303 2994), even a high frequency of intercourse itself does not necessarily indicate healthy sexual function in
304 this population. This may represent an important research avenue for future studies. The nature of the
305 association between infertility related distress and sexual dysfunction also requires further investigation.
306 In our study, this psychological variable was conceptualized as risk factor for impaired sexuality.
307 However, we speculate that a multidimensional model based on a circular – rather than linear – notion of
308 causality that implies the mutual interaction of multiple factors may be more appropriate to explain this
309 complex association. We encourage a fruitful dialogue between quantitative and qualitative research to
310 develop such a model.

312 **Conclusions: implications for clinical practice**

313 The importance of assessing sexual function in couples undergoing assisted reproduction has been widely
314 acknowledged by researchers and clinicians (Smith *et al.*, 2015; Wischmann, 2010, 2013). However, the
315 studies conducted so far have not provided firm conclusions regarding the association between infertility
316 and female sexual dysfunction, not only in terms of rates, but also as regards the factors and mechanisms
317 underlying this association. Our study – although focused on women – may help clarify that couples'
318 subjective experience of infertility and its treatment does make the difference in terms of sexual outcomes.

319 Patient-centred counselling should systematically entail an accurate assessment of couples' concerns and
320 levels of stress, because these factors can compromise sexual life, to the point of being associated with
321 female sexual dysfunction, as demonstrated by our study. It is also known that dealing with patients'
322 stress, especially when it translates into impatience and unrealistic expectations or demands, is
323 challenging for fertility healthcare professionals (see Boivin *et al.*, 2017). In this regard, the presence of
324 psychologists and psychotherapists is key in the multidisciplinary fertility team to improve patient care,
325 as well as to decrease professionals' difficulties working with couples.

327 **Authors' roles**

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

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336 **Conflict of interest**

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