Natural pregnancy seeking in subfertile women with endometriosis.

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Abstract

Several pathogenetic mechanisms have been postulated to explain the association between endometriosis and subfertility. However, to date, definitive conclusions cannot be drawn. In this study, we hypothesized that the reduced exploitation of the natural chances of conception could be an additional detrimental factor. Due to dyspareunia or the need for hormonal treatment to temper pelvic pain, one may expect affected women to exploit less the chances of natural pregnancy. In this cross-sectional study of 292 women undergoing IVF, we investigated the severity of pelvic pain symptoms, the sexual function (using the Female Sexual Function Index [FSFI]) and the reproductive strategies of women with (n=62) and without (n=230) endometriosis. Basal clinical and demographic characteristics did not differ between the two groups. Conversely, all pelvic pain symptoms scores were increased in women with endometriosis. Endometriosis patients also showed greater pain at the FSFI, but no other significant differences were detected as regards sexual function. The use of hormonal contraceptive agents did not differ between the study groups. Moreover, questions aimed at disentangle whether affected women exploited less the natural chances of pregnancy did not reveal any significant difference. In conclusion, this study does not support the hypothesis that women with endometriosis exploit less the chances of natural pregnancy, despite the presence of pelvic pain.

Key words: endometriosis / natural pregnancy / dyspareunia / sexual function

Introduction

Endometriosis is associated with subfertility.[1,2] However, the pathogenetic mechanisms interfering with natural conception have yet to be fully clarified.[1,3] The most plausible ones include the detrimental effects of local inflammation on gametes and embryos, the adhesions-mediated interference with the tubal retrieval of the complex oocyte-cumulus and embryo transport, and the reduced receptivity consequent to perturbed uterine motility or altered endometrium.[1,3] The associations of endometriosis with other gynecological conditions that interfere with fertility such as adenomyosis and endometrial polyps could also play a role.[3] In the vast majority of affected women, a definitive diagnosis of sterility, i.e. an absolute impediment to conception, cannot be drawn and natural pregnancies may occur even in most severe cases.[4,5]

In the present study, we aimed at investigating a neglected but plausible additional factor of subfertility in women with endometriosis, i.e. the reduced exploitation of the chances of natural conception. Indeed, dyspareunia is a typical symptom of women with endometriosis,[6] and one could speculate that affected women seeking pregnancy may have less intercourses compared to other causes of infertility, which could reduce the chances of natural conception. In addition, because of severe pain symptoms, a significant proportion of women with endometriosis may have to assume hormonal treatments such as progestins or estroprogestins. These women can be scheduled for *in vitro* Fertilization (IVF) anyway by transiently discontinuing these treatments for the time needed to undergo the procedure, but cannot conceive on their own.

To investigate whether or not patients with endometriosis exploit less their chances of natural conception, we set up a cross-sectional study of infertile women scheduled for IVF and investigated sexual function and reproductive strategies, as well as the use of hormonal medications in those with and without the disease.

Materials and methods

The data analyzed in this study were derived from a larger research project focused on infertility related distress and female sexual function conducted at the Infertility Unit of the Fondazione Ca' Granda Ospedale Maggiore Policlinico between April 2017 and March 2018, after approval of the local Institutional Review Board. Women referring to our center to undergo IVF or Intracytoplasmatic Sperm Injection (ICSI) were prospectively considered for study entry. Only Italian native speakers could be included. Women with diagnosed physical or psychological conditions commonly associated with sexual dysfunction were excluded. In particular, we excluded women whose cause of infertility was sexual inactivity (such as male impotence or chronic anejaculation). Recruited women who returned signed informed consent were requested to fill a questionnaire during the hospital stay for oocytes' retrieval. Participants could be included in the study only once.

Clinical information was retrieved from patients' charts. Women were labeled with a diagnosis of endometriosis if they previously underwent surgery for the disease and/or had sonographic evidence of ovarian endometriomas or deep invasive lesions at the time of IVF initiation. The sonographic diagnosis of endometriosis was done according to recently reported instructions.[7]

Although women completed the questionnaires on the day of oocytes' retrieval, they were asked to respond considering the months preceding the initiation of hormonal stimulation. The submitted questionnaires included general demographic information, specific items aimed at collecting information on reproductive strategies and pelvic pain symptoms, and the Female Sexual Function Index (FSFI). Women could ask for clarifications to medical personnel if needed. They filled the questionnaires in a silent room, in the absence of relatives and without time pressures. Questions regarding reproductive strategies mainly aimed at disentangle whether or not women properly exploited their chances of natural pregnancy. These questions focused on the awareness of the residual chances of natural pregnancy, on the frequency of sexual intercourses and on whether or not women made efforts to time intercourse in the fertile period. These questions were developed

and tested in a preliminary group of 20 volunteers to ensure that participants could properly understand the questions (preliminary investigation). Dysmenorrhea, dyspareunia and non-menstrual chronic pelvic pain was measured using a 0 (no pain at all)-10 (the worst imaginable pain) Numerical Rating Scale (NRS) and the Biberoglu-Behrman classification.[8] Dyschezia and disuria were measured only with the NRS. The FSFI is a 19-item, validated, multidimensional, self-report instrument for assessing six major categories of female sexual function, i.e. desire, arousal, lubrication, orgasm, satisfaction, and pain.[9,10] Each question is answered using a 1-5 or a 0-5 Likert scale (with zero indicating no sexual activity), and scores are transformed by multiplying domain scores by a factor of 0.3-0.6 to equally weigh each domain depending on the number of questions per domain. The maximal score per domain is 6, the total score ranges from 2 to 36. Sexual dysfunction is diagnosed for a total score below 26.55.[11]

Data were analyzed using the Statistical Package for Social Science (SPSS, IL), version 23.0. Women with and without endometriosis were compared using Student *t*-test, non parametric Mann-Whitney test, Fisher Exact test or Chi-square test, as appropriate. The sample size (about 300 women) was based on the following assumptions: i) expected rate of women with endometriosis in our unit 20%, ii) type I and II error set at 0.05 and 0.10, iii) expected rate of women properly exploiting their natural chances (≥5 fertile periods exploited during the last 6 months) of 50% (information obtained from the preliminary investigation), iv) halving of this rate (thus <25%) was postulated to be a clinically relevant difference.

Results

Three-hundred forty women were eligible, of whom 300 accepted to participate. Of these 300 women, 8 (3%) were not included in this study because they provided remarkably incomplete information of the FSFI, so that final participants were 292 infertile women. Sixty-two women (22%) were diagnosed with endometriosis; of these, 46 (74%) had a history of surgery for the disease (four were operated twice) and 41 (66%) were staged III-IV according to the ASRM

classification. In the remaining 21 cases, the disease was exclusively diagnosed based on US findings. Overall, endometriosis could be demonstrated at US at the time of the study in 35 (56%) women (17 non-operated and 18 previously operated women).

The 62 women with endometriosis were compared to the remaining 230 women without evidence of the disease. Baseline characteristics of the two study groups are shown in Table 1. No main differences emerged. Only the indication to IVF differed but this was expected because of the study design (we compared women with and with endometriosis). Table 2 shows chronic pelvic pain symptoms and the FSFI results in the two groups. As expected, all pelvic pain symptoms were more common in women with endometriosis. Of relevance here is the remarkable difference in dyspareunia frequency and severity. As regards the FSFI, there was a significant between-group difference only for the pain domain, with endometriosis participants displaying greater levels of pain. However, the two groups did not differ on the other five domains, as well as on the FSFI global score. Women with endometriosis assumed more commonly estroprogestins or progestins (5% versus 1% in controls) but this difference was not statistically significant.

Considering reproductive strategies, none of the investigated items was found to differ between the study groups. The awareness of the subfertility status, sexual activity and the exploitation of the fertile periods did not differ (Table 3). The rate of women properly exploiting their natural chances (i.e. being confident that they had a proper number of timely intercourses in 5 or more ovarian cycles during the last 6 months) was 45% and 39% in women with and without endometriosis (Table 3).

Discussion

Results of this study do not support our initial hypothesis. Subfertile women with endometriosis appear to exploit their chances of natural pregnancy similarly to those who were diagnosed with other causes of subfertility. A reduction in the number of sexual intercourses cannot be advocated as

an additional mechanism to explain endometriosis-related subfertility. To note, this similarity emerged despite the significant increase in pelvic pain symptoms, including dyspareunia. In addition, it has to be underlined that only a small minority of affected women had to assume hormonal treatments (estroprogestins or progestins) to cope with the endometriosis-related pain symptoms. The impact of this potential detrimental indirect effect of endometriosis is thus marginal.

Even if our study generally provides negative results, it also highlights some corollary information that deserves consideration. Of interest is the lack of difference in the frequency of sexual intercourses despite the presence of significant pain symptoms. The literature demonstrated that pelvic pain symptoms are associated with poorer mental health and quality of life in women with endometriosis.[12] The negative impact of the disease on female sexual function, especially due to dyspareunia, is also known, as well as the relation between sexuality and psychological wellbeing (see the systematic reviews by Barbara *et al.* [13,14]). However, there is poor evidence regarding psychological health and sexual function in women with endometriosis and infertility. This issue is even more relevant if one considers that not only endometriosis, but also infertility and its treatment are associated with an increased risk of sexual dysfunction.[15-22] To note, the observation that FSFI score did not differ between women with and without endometriosis should be interpreted with caution for two reasons. Firstly, women without the disease (controls) were also infertile and cannot be viewed as "healthy". In fact, previous FSFI comparisons using non-infertile women as controls showed relevant differences. [23] Secondly, in the FSFI questionnaire, dyspareunia is only one out of six domains. Even if extensively used in endometriosis research [24], the questionnaire may give insufficient relevance to this issue and may not properly capture the complexity of sexual function of these particular women.

Based on our findings, one may speculate that infertile endometriosis patients may somehow "force" themselves to have intercourse, despite the presence of pain, in order to increase their chances to conceive. The low rate of use of medical treatments further supports this concern. Unfortunately, our study was not designed to address this important issue and this hypothesis

remains speculative. Future studies should be designed to properly disentangle this point and identify the specificities of subfertile endometriosis patients. These studies should adopt a multidimensional perspective and thus control for the effects of important psychological factors (such as self-esteem and infertility-related distress) and relational variables (such as marital satisfaction). Male sexual function is also extremely important in the context of infertility, since it can affect female sexuality.[25,26]

Our study has some limitations that need to be acknowledged. Firstly, the questions on the exploitation of the fertile period were specifically developed for the present study and lack previous scientific validation. Even if a validated questionnaire would have provided more robust information, the preliminary development of the administered questions in a group of volunteers, the availability of dedicated personal for clarification during the time of questionnaire filling and the absence of non-responders tend to exclude a major detrimental effect of this limitation. Secondly, even if the investigated items were generally simple, collection of information was retrospective. Albeit more complicated, a prospective collection of the information over a 6-month period using a specific sexual diary would have provided more robust information. Finally, women were interviewed at the time of oocytes' collection. This choice consented to arrange for women a situation without time pressures (women had to stay in the hospital from 8.00 am to 2.00 p.m.), but we cannot exclude some confounding effect due the very peculiar physical and emotional status. In this regard, we cannot exclude that our findings may have been partially affected by recall bias. Thirdly, we cannot exclude that the inclusion of women with unexplained infertility in the control group may have diluted differences. Women with unexplained infertility could indeed harbor sexual dysfunctions. For this reason, we repeated all the analyses excluding these women but results did not differ substantially (data not shown). Finally, some caution is needed prior to firmly infer our findings to the whole population of infertile women with endometriosis. Some potential selection biases may have occurred. In particular, one cannot rule out that infertile women with most severe pain symptoms could be less prone to initiate an IVF program and referred less. The low rates of

women assuming hormonal therapy to temper endometriosis-related pain (5%) and reporting severe dyspareunia (16%) support this possible concern. Future studies recruiting women from endometriosis referral units rather than from an infertility unit are needed to address this limitation.

In conclusion, we failed to document an endometriosis-related indirect effect on the exploitation of the natural chances of pregnancy. This mechanism does not play an essential role in explaining endometriosis-related infertility.

Declaration of Conflicting Interests

The first author (ES) declares a conflict of interest with Merck-Serono and Ferring because he has handled grants of research from both companies. All the other authors declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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Table 1. Baseline characteristics of women with and without endometriosis

Characteristics	Endometriosis N=62	Controls N=230	p
Age (years)	37.6 ± 4.4	37.9 ± 3.9	0.58
Education			0.17
Primary and middle school	9 (14%)	17 (7%)	
High school	24 (39%)	77 (33%)	
University	29 (47%)	136 (60%)	
Marital Status			0.45
Married	40 (65%)	160 (70%)	
Unmarried	22 (35%)	70 (30%)	
Job condition			0.27
Active	55 (89%)	214 (93%)	
Non active	7 (11%)	16 (7%)	
BMI (Kg/m^2)	22.0 ± 3.0	21.9 ± 3.7	0.97
Duration of infertility (years)	5.6 (4.1)	5.9 (3.5)	0.66
Previous deliveries	7 (11%)	37 (16%)	0.43
Previous IVF-ICSI cycles	25 (40%)	104 (45%)	0.49
Serum FSH (IU/mL)	7.9 (6.2-9.5)	7.4 (6.1-9.5)	0.55
Serum AMH (ng/mL)	1.3 (0.5-3.8)	1.7 (0.9-3.0)	0.18
Indication to IVF			<0.001
Male factor	0 (0%)	94 (41%)	
Endometriosis	48 (77%)	0 (0%)	
Tubal factor (PID)	0 (0%)	37 (16%)	
Anovulation refractory to ovulation induction	0 (0%)	8 (3%)	
Unexplained	0 (0%)	75 (33%)	
Mixed	14 (23%)	16 (7%)	

Data is reported as number (%), mean ± SD or Median (interquartile range), as appropriate.

Data is compared using Chi square test, Fisher Exact test, Student *t*-test and Mann-Whitney test as appropriate.

Table 2. Chronic pelvic pain and sexual function in women with and without endometriosis

Characteristics	Endometriosis N=62	Controls N=230	p
Dyspareunia			
Biberoglu-Behrman scale			<0.001
0	28 (45%)	140 (61%)	
1	24 (39%)	85 (37%)	
2-3	10 (16%)	5 (2%)	
NRS	2.1 (2.4)	1.1 (1.6)	<0.001
Dysmenorrhea			
Biberoglu-Behrman scale			<0.001
0	13 (21%)	65 (28%)	
1	19 (31%)	115 (50%)	
2-3	30 (48%)	50 (22%)	
NRS	5.2 (3.3)	3.5 (2.6)	<0.001
Non menstrual pelvic pain			
Biberoglu-Behrman scale			<0.001
0	26 (42%)	168 (73%)	
1	22 (35%)	54 (23%)	
2-3	14 (33%)	8 (4%)	
NRS	2.6 (2.9)	0.7 (1.4)	<0.001
Dyschezia (NRS > 0)	14 (23%)	6 (3%)	<0.001
Dysuria (NRS > 0)	5 (8%)	5 (2%)	0.04
FSFI			
Desire	3.8 (1.1)	3.8 (1.1)	0.75
Arousal	4.3 (1.5)	4.4 (1.4)	0.96
Lubrication	4.6 (1.6)	4.9 (1.4)	0.28
Pain	4.6 (1.6)	5.1 (1.5)	0.04
Orgasm	4.2 (1.6)	4.5 (1.5)	0.9
Satisfaction	4.6 (1.4)	4.8 (1.2)	0.34
Total score	26.2 (7.5)	27.4 (6.8)	0.24
Total score ≤26.55	25 (40%)	74 (32%)	0.23
Hormonal therapies (EP or progestins)	3 (5%)	2 (1%) [a]	0.07

NRS: Numerical Rating Scale. FSFI: Female Sexual Function Index. EP: estroprogestins.

Data is reported as mean (SD) or number (%) and compared using Chi square test, Student t-test and Mann-Whitney test as appropriate.

[a] Both women had absolute sterility (azoospermia in one case and bilateral salpingectomy in the second case).

Table 3. Sexual and reproductive habits in women with and without endometriosis

Characteristics	Endometriosis N=62	Controls N=230	p
Based on the information you received, what are your personal chances to conceive per cycle?			0.51
None	14 (22%)	71 (31%)	
1-5%	29 (47%)	91 (40%)	
> 5%	18 (29%)	68 (29%)	
In general, how many sexual intercourses do you have per week?			0.78
≤ 1	30 (48%)	108 (47%)	
2	24 (39%)	84 (37%)	
≥ 3	8 (13%)	38 (16%)	
Do you actively attempt to regularly exploit the fertile period? [a]			0.65
Yes	44 (71%)	154 (67%)	
No [b]	18 (29%)	76 (33%)	
Do you increase the frequency of sexual intercourses during the fertile period?			0.42
Yes	48 (77%)	164 (71%)	
No [b]	14 (23%)	66 (29%)	
Does your partner always reach orgasm (i.e. has ejaculation) during sexual intercourses?			0.69
Yes, always	52 (84%)	184 (80%)	
Rarely fails (< 1 out of 10)	7 (11%)	36 (16%)	
Fails sometimes (≥ 1 out of 10)	3 (5%)	10 (4%)	
During the last 6 months, how many times do you think you have properly exploited the fertile period?			0.53
5-6	28 (45%)	89 (39%)	
3-4	14 (23%)	67 (28%)	
≤ 2 or unaware [b]	20 (32%)	74 (32%)	

[a] Include women performing urinary LH assessments or calculation of the fertile period or checking of body signs suggestive of imminent ovulation (increase in cervical mucus)

[b] Include women who are unaware of the fertile period or assume hormonal therapies