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ORIGINAL ARTICLE *Infertility*

Endometriosis fertility index predicts live births following surgical resection of moderate and severe endometriosis

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STUDY QUESTION: Can live birth be accurately predicted following surgical resection of moderate-severe (Stage III–IV) endometriosis?

SUMMARY ANSWER: Live births can accurately be predicted with the endometriosis fertility index (EFI), with adnexal function being the most important factor to predict non-assisted reproductive technology (non-ART) fertility or the requirement for ART (www.endometriosi-sefi.com).

WHAT IS KNOWN ALREADY: Fertility prognosis is important to many women with severe endometriosis. Controversy persists regarding optimal post-operative management to achieve pregnancy and the counselling of patients regarding duration of conventional treatments before undergoing ART. The EFI is reported to correlate with expectant management pregnancy rate, although external validation has been performed without specifically addressing fertility in women with moderate and severe endometriosis.

STUDY DESIGN, SIZE, DURATION: Retrospective cohort study of 279 women from September 2001 to June 2016.

PARTICIPANTS/MATERIALS, SETTINGS, METHODS: We included women undergoing laparoscopic resection of Stage III–IV endometriosis who attempted pregnancy post-operatively. The EFI was calculated based on detailed operative reports and surgical images. Fertility outcomes were obtained by direct patient contact. Kaplan–Meier model, log rank test and Cox regression were used for analyses.

MAIN RESULTS AND THE ROLE OF CHANCE: The follow-up rate was 84% with a mean duration of 4.1 years. A total of 147 women (63%) had a live birth following surgery, 94 of them (64%) without ART. The EFI was highly associated with live births ($P < 0.001$): for women with an EFI of 0–2 the estimated cumulative non-ART live birth rate at five years was 0% and steadily increased up to 91% with an EFI of 9–10, while the proportion of women who attempted ART and had a live birth, steadily increased from 38 to 71% among the same EFI strata ($P = 0.1$). A low least function score was the most significant predictor of failure ($P = 0.003$), followed by having had a previous resection ($P = 0.019$) or incomplete resection ($P = 0.028$), being older than 40 compared to <35 years of age ($P = 0.027$), and having leiomyomas ($P = 0.037$).

LIMITATIONS REASONS FOR CAUTION: The main limitation of this study is its retrospective design. Imprecision was higher with low EFI due to smaller sample size in this subgroup. Finally, the EFI is somewhat subjective and could be prone to intra- and inter-observer variations.

WIDER IMPLICATIONS OF THE FINDINGS: Women with a high EFI score have excellent fertility prognosis and may be advised to try to become pregnant with timed intercourse compared to women with a low score, for which prompt referral to ART seems more reasonable. Other prognostic factors can be used to guide the management of women with an intermediate EFI score. These data follow women over many years post-resection and represent longitudinal fertility data rarely demonstrated in such a cohort. The location and impact of lesions on the ability of the adnexa to function seems crucial for the fertility prognosis and should be further investigated.

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Key words: Severe endometriosis / infertility / predict / pregnancy outcomes / live birth / prognosis / surgical management / laparoscopy / endometriosis fertility index / staging

Introduction

Endometriosis negatively impacts fertility (Schwartz and Mayaux, 1982) and surgical removal of minimal to mild disease improves the chances of pregnancy, based on two RCTs (Marcoux *et al.*, 1997; Parazzini, 1999) and a subsequent systematic review (Jacobson *et al.*, 2002). Other non-randomized studies suggest that removal of deeply infiltrating endometriosis (DIE) also improves fertility (Adamson and Pasta, 1994; Abbott *et al.*, 2003; Darai *et al.*, 2005; Lyons *et al.*, 2006; Stepniewska *et al.*, 2009; Meuleman *et al.*, 2014), although pregnancy rates with expectant fertility management in such women are difficult to predict and contribute to the controversy regarding optimal postoperative management. In fact, the reasonable time to attempt expectant fertility management before referring for ART remains unknown when endometriosis severely affects the pelvis. Guidelines mainly rely on expert opinion (Leyland *et al.*, 2010; Practice Committee of the American Society for Reproductive Medicine, 2012; Johnson and Hummelshoj, 2013).

Management decisions usually consider prognostic factors such as age, duration of infertility, prior pregnancy (Collins *et al.*, 1995) and extent of endometriosis, although evidence shows that endometriosis classified by the revised American Society for Reproductive Medicine (r-ASRM) (American Society for Reproductive Medicine, 1997) fails to predict chances of pregnancy (Guzick *et al.*, 1997). Previous work (Adamson and Pasta, 2010) suggests considering the impact of endometriosis on the function of the adnexa to better predict fertility outcomes. The proposed endometriosis fertility index (EFI) has been externally validated for prediction of non-ART as well as ART outcomes (Wei *et al.*, 2011; Tomassetti *et al.*, 2013; Wang *et al.*, 2013; Zeng *et al.*, 2014; Boujenah *et al.*, 2015; Garavaglia *et al.*, 2015; Ibrjam *et al.*, 2016), with none specifically addressing the case of severe endometriosis, where the greatest controversy exists. The objective of this study is to determine fertility outcomes and predictors, including clinical characteristics and EFI scoring system, of non-ART live births and live births resulting from ART following resection of Stage III–IV endometriosis.

Materials and Methods

Study design

This retrospective cohort study was conducted in two hospitals (Prince of Wales Private Hospital and Royal Hospital for Women, Sydney, Australia)—tertiary referral units for women with severe endometriosis. Women were included who underwent a fertility-sparing surgery between September 2001 and June 2016 for Stage III–IV endometriosis (r-ASRM score ≥16) confirmed at histopathology and who attempted pregnancy post-operatively. Women with <6 months of follow-up after their index surgery were excluded.

Surgical procedure

Surgeries were undertaken by consultant gynaecological surgeons and advanced trainees in laparoscopic gynaecologic surgery under direct supervision of a consultant. Procedures were performed under general anaesthesia using a four-port approach after establishment of pneumoperitoneum via a Veress needle. A visual inspection of the abdomen and pelvis was undertaken, adhesions were divided as required to normalize anatomy as much as possible, and endometriosis was resected with monopolar scissors using a retroperitoneal approach (Garry *et al.*, 2000). Endometriomas were excised using a stripping technique (Busacca *et al.*, 1999). Deeply invasive endometriosis in the cul-de-sac was removed by sharp dissection and laparoscopic segmental or disc bowel resection was undertaken, as appropriate, for symptomatic lesions. Complete surgical treatment of all recognizable endometriotic lesions was performed whenever achievable without fertility impairment or alteration of consent.

Data sources and variables

From May 2010, potentially eligible participants were identified using a coded electronic database of surgical procedures and then contacted by telephone for further assessment of eligibility and data collection. If women could not be contacted twice by phone, they were sent two emails to notify them of the study. Participants were asked to report pregnancy attempts pre- and post-operatively, live births and whether they were delivered following expectant management, conventional treatment with ovulation induction/ovarian stimulation and/or intrauterine stimulation (non-ART live births), or with the addition of ART using either conventional oocyte insemination (IVF) or ICSI (overall live births).

Electronic medical records were reviewed and the r-ASRM score was confirmed from the detailed operative report and pictures. When not recorded at the time of surgery, records were also used to calculate the EFI as previously described in the literature (Adamson and Pasta, 2010) (www.endometriosisefi.com), combining historical (the age, duration of infertility and prior pregnancy of the woman) and surgical factors (least function score at conclusion of surgery, r-ASRM endometriosis score and ASRM total score) to achieve a total score from 0 to 10 (Fig. 1). The least function score was obtained by addition of the lowest function score at the conclusion of surgery on each side from the fallopian tube, fimbria, and ovary (Fig. 1). If an ovary was absent on one side, the least function score was obtained by doubling the lowest score on the side with the ovary (Adamson and Pasta, 2010). The EFI was calculated independently and without knowledge of subsequent fertility outcomes.

Statistical analyses

Statistical analyses and preparation of figures were undertaken using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA). Survival curves and estimated cumulative live birth rates were calculated according to the Kaplan–Meier model and subgroups were compared using the log rank test. Women were censored from the survival analyses when they were lost to follow-up or became pregnant with or without ART. We processed a Cox proportional hazards regression model with all variables in a backward fashion

	Points
Historical factors	
Age	
≤35 years	2
36-39 years	1
≥40 years	0
Years infertile	
≤3 years	2
>3 years	0
Prior pregnancy	
Yes	1
No	0
Surgical factors	
Least function score	
7–8	3
4–6	2
1–3	0
r-ASRM endometriosis score	
<16	1
≥16	0
r-ASRM total score	
<71	1
≥71	0
Total	**EFI score**

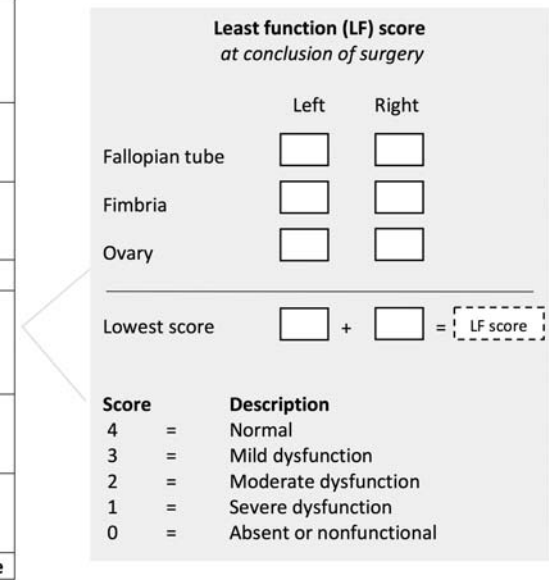

Figure 1 EFI and least function score calculation. As described in Adamson *et al.* (2010). r-ASRM, revised American Society for Reproductive Medicine, EFI, endometriosis fertility index.

to identify predictors of success. Adjusted hazard ratios (HR) and 95% CI were calculated. The Cochrane-Armitage exact test was used to test trend among ordinal categories of scoring. Missing data were infrequent (<5%) and were therefore ignored. Two-tailed *P*-values < 0.05 were considered statistically significant.

Ethical approval

The protocol was approved by the local Human Research Ethics committee (ref.:09/120) and written informed consent was obtained from all participants.

Results

Of the 279 eligible women who underwent a fertility-sparing resection of moderate-severe endometriosis and attempted pregnancy in the post-operative period, 235 (84%) were contacted and agreed to participate in the study (Supplementary Figure S1) with a mean follow-up of 4.1 years. Calculation of the EFI was not possible in seven participants due to missing data. Demographic data for the participants are reported in Table I. Residual disease was present in 18% of women at the end of the surgery and reasons reported were: 'not compatible with conservative removal' (mainly serosal uterine endometriosis, adenomyosis or DIE of uterine or ovarian vessels) and 'beyond the scope of the consent' (mainly DIE requiring bowel resection). Leiomyomas were observed in 26 participants (12%) at the time of surgery and laparoscopic and hysteroscopic myomectomy were performed in six (3%) and two (1%) of them, respectively.

Overall, 147 (63%) women had a live birth following surgery, 94 of them (64%) without ART. Life-table analyses are presented in Table II and Fig. 2. Stratifying the EFI into five classes, we observed a significant relationship between EFI and time to achieve non-ART and overall live births ($P < 0.001$ for both). The cumulative non-ART live birth rate at 5 years was 0% for women with an EFI of 0–2 and steadily increased up to 91% for women with an EFI of 9 or 10. Similarly, the cumulative overall live birth rate (including ART) steadily increased from 39 to 95% in women with an EFI of 0–2 and 9 or 10, respectively. Cumulative non-ART live birth rate continued to increase after 2 years for women with a high EFI score with an increase from 58% at 2 years to 91% at 5 years for women with an EFI of 9 or 10.

Following index surgery, 46% ($n = 107$) of women underwent ART. The proportion of live births obtained by ART steadily increased with the EFI score stratified into five classes from 38% (EFI = 0–2) to 71% (EFI = 9–10) although this increase did not reach statistical significance ($P = 0.1$; Table III).

Cox proportional hazards analysis of all participant characteristics revealed that having a least function score of 1 to 3 compared to 7–8 (HR = 0.2; CI = 0.1–0.5; $P = 0.003$), having had a previous (HR = 0.6; CI = 0.4–0.9; $P = 0.019$) or incomplete resection of endometriosis (HR = 0.5; CI = 0.2–0.9; $P = 0.028$), being age 40 years or more compared to less than 35 years (HR = 0.6; CI = 0.4–0.9; $P = 0.027$), and having uterine leiomyomas (HR = 0.3; CI = 0.1–0.9; $P = 0.037$) were all negatively correlated with the probability to obtain a non-ART live birth.

Discussion

In our study of 235 women attempting pregnancy after resection of moderate-severe (Stage III–IV) endometriosis, we found that chances of live births are variable and highly correlated with the EFI—a higher EFI being associated with better fertility prognosis. The least function

Table I Characteristics of participants.

Variable	*N* = 235
Age (years)	34 ± 5 (20–47)
≤35	150 (64)
36–39	59 (25)
≥40	26 (11)
Partner's age (years)	34 ± 5 (21–54)
Previous pregnancy	66 (28)
BMI (kg/m^2)	24 ± 5 (17–41)
Ever smoked	83 (35)
Previous resection of endometriosis	80 (34)
Indication of surgery	
Subfertility and pelvic pain	125 (53)
Pelvic pain	62 (26)
Subfertility	43 (18)
Ovarian cyst(s)	5 (2)
Infertility duration (months)	23 ± 29(0–156)
≤36	195 (83)
>36	40 (17)
r-ASRM staging	
Stage III	88 (37)
Stage IV	147 (63)
Complete cul-de-sac obliteration	87 (38)
Resection of endometrioma(s)	118 (50)
Bowel resection	7 (3)
Uterine leiomyomas	26 (12)
Complete resection of disease	193 (82)
Least function score	
7–8	71 (31)
4–6	119 (52)
1–3	38 (17)
r-ASRM endometriosis score	
<16	59 (26)
≥16	169 (74)
r-ASRM total score	
<71	155 (68)
≥71	73 (32)
Attempted ART post-operatively	102 (43)
Follow-up (months)	49 ± 25 (6–120)

Data are presented as mean ± SD (range) or *n* (%).
r-ASRM, revised American Society for Reproductive Medicine.

Table II Life-table estimated cumulative non-ART and overall live birth rate at 1, 2, 3 and 5 years according to the EFI.

EFI	No. of women	Cumulative incidence (percentage ± SD) 1 year	2 years	3 years	5 years
Non-ART live births*					
9–10	39	46 ± 9	58 ± 9	64 ± 10	91 ± 10
7–8	72	40 ± 6	56 ± 6	59 ± 7	63 ± 7
5–6	83	27 ± 5	32 ± 6	34 ± 6	34 ± 6
3–4	25	9 ± 6	21 ± 10	21 ± 10	21 ± 10
0–2	9	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Overall live births*					
9–10	39	62 ± 8	72 ± 7	78 ± 7	95 ± 6
7–8	72	43 ± 6	63 ± 6	70 ± 6	81 ± 6
5–6	83	41 ± 6	50 ± 6	58 ± 6	60 ± 6
3–4	25	28 ± 9	49 ± 10	49 ± 10	49 ± 10
0–2	9	11 ± 11	39 ± 20	39 ± 20	39 ± 20

EFI, endometriosis fertility index.
*Log rank test, $P < 0.001$.

score, accounting for the impact of endometriosis on the function of the adnexa, was the strongest predictor of poor outcome, followed by an incomplete or previous resection of endometriosis, older age and uterine leiomyomas.

For women with Stage III–IV endometriosis and an EFI score of >7, the chance of non-ART live birth after surgery is ~60% at 3 years, rising to 75% at 5 years. Women may be appropriately counselled in this regard, since expectant management allows avoidance of costly and invasive fertility treatments, particularly in low resource areas, where access to ART is poor or simply when women choose not to have ART. These data are consistent with previous validations of the EFI scoring system for all stages of disease (Adamson and Pasta, 2010; Boujenah *et al.*, 2015). We also observed that live births continue to increase even after 3 years, suggesting that ART may not be required in appropriately selected and counselled patients who still have additional chance of pregnancy with expectant management. However, for women with a poor EFI score (≤2) the chance of pregnancy with expectant management is very low (0–10%) and it is most appropriate to refer these women for ART early in the post-operative course to optimize their chance of pregnancy (Adamson and Pasta, 2010; Boujenah *et al.*, 2015). Despite ART in these women, live birth rates remain low, at <40%, and women should be counselled regarding this fact when undergoing treatment. In fact, the success of ART linearly increased with the EFI score although this increase was not statistically significant, most likely due to insufficient power. In contrast to mild endometriosis, Stage III–IV endometriosis was found to negatively impact ART outcomes in a systematic review of 36 studies (Hamdan *et al.*, 2015). Data from a retrospective comparative study of 661 women suggest that resection of DIE also improves success of ART (Opoien *et al.*, 2011) compared to no resection. Surgery could therefore have both a therapeutic and predictive role to play in these women attempting ART.

Data from this and previous studies (Adamson and Pasta, 2010; Tomassetti *et al.*, 2013) suggest that it is not the severity of endometriosis based on r-ASRM stage that is of primary importance in predicting pregnancy, but rather adnexal involvement, including ovarian disease, and extensive endometriosis. It is also clear that all three criteria for surgical findings, i.e. least function score, high r-ASRM lesion score and high r-ASRM total score, are highly correlated and interdependent. For example, the presence of an endometrioma increases the r-ASRM

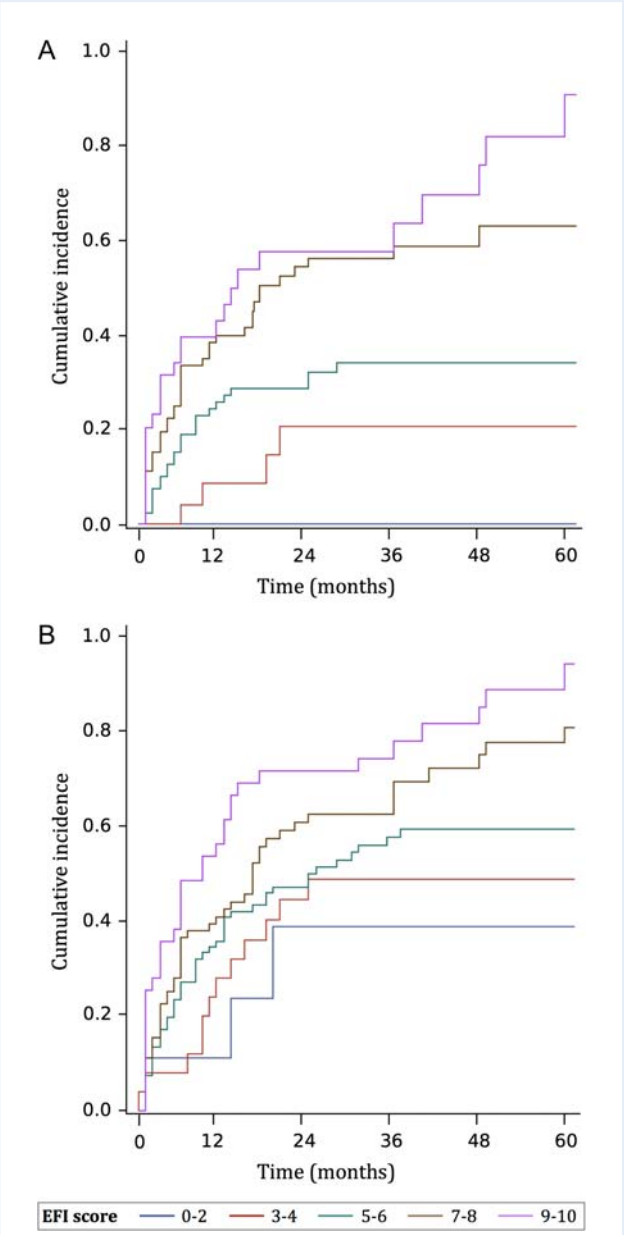

Figure 2 Cumulative 5-year incidence following resection of severe endometriosis of (**A**) non-ART live births and (**B**) overall live births.

Table III EFI and percentage of live births obtained by ART among women who attempted ART following the surgery (*N* = 107).

EFI	No. of patients	ART live birth*
9–10	14	10 (71)
7–8	27	16 (59)
5–6	43	21 (49)
3–4	15	8 (53)
0–2	8	3 (38)

Data are presented as *n* (%).
*Cochrane-Armitage exact test, $P = 0.1$

endometriosis lesion score and total score, while decreasing least function score; with all three decreasing the EFI and subsequent pregnancy rate.

The EFI takes into account surgical findings both pre- surgery (ASRM scores, essentially amount of disease) and post-surgery (least function score, essentially functional capacity post-resection), and also well-known historical factors including age, duration of infertility, and pregnancy history (Collins *et al.*, 1995). However, as we can expect, it does not explain all variations among women (Tomassetti *et al.*, 2013). Other significant prognostic factors are not included in the EFI scoring system and could be used to help choose optimal post-operative management for women with intermediate EFI score (from 3 to 6). In fact, ovarian reserve, although highly correlated with age, is by itself an important factor to take into consideration because poor ovarian reserve is associated with failure to achieve pregnancy (Boujenah *et al.*, 2017), even with ART (Broekmans *et al.*, 2006). We also found that residual disease at the end of the surgery negatively affects chances of non-ART live births. The finding of adenomyosis at surgery has been reported to decrease fertility (Ferrero *et al.*, 2009; Stepniewska *et al.*, 2009; Darai *et al.*, 2011; Abbott, 2017) and, similarly to leiomyomas, uterotubal disturbance was described as a likely contributor (Kunz *et al.*, 2005). However, fertility-sparing procedures to remove adenomyosis require a high degree of surgical skills (Gordts *et al.*, 2014) and benefits on fertility are only reported in case series (Osada *et al.*, 2011; Grimbizis *et al.*, 2014) such an approach will therefore need to be better studied before being recommended to increase fertility. Leiomyomas were also identified as poor prognostic factors in women with endometriosis (Ferrero *et al.*, 2009; Adamson and Pasta, 2010) but it remains unclear if their removal would improve the fertility prognosis and could depend on their localization (Casini *et al.*, 2006; Carranza-Mamane *et al.*, 2015). Finally, when the location of the residual disease is unlikely to affect the function of the adnexa and uterus, which is the case in bowel disease, the impact on fertility may be lessened. In fact, a recent prospective study of 203 women with DIE of the bowel reported no difference in pregnancy rates between bowel resection and conservative management (Meuleman *et al.*, 2014).

Previous non-randomized studies suggest that resection of DIE improves fertility (Abbott *et al.*, 2003; Darai *et al.*, 2005; Lyons *et al.*, 2006; Stepniewska *et al.*, 2009; Meuleman *et al.*, 2014) our study results support those findings. Pain management is another essential aspect to consider, with most women in this study (80%) having pelvic pain. Resection of DIE has been associated with significant improvement of dyspareunia and quality of sex life (Garry *et al.*, 2000; Abbott *et al.*, 2003; Ferrero *et al.*, 2007; Fritzer *et al.*, 2016). The role of surgery for pain is especially important, as hormonal therapy is not an option for women who wish to become pregnant. Our findings suggest that, to optimize chances of pregnancy, surgeons should focus on the restoration or preservation of the function of the adnexa, as supported by the importance of the least function score at the conclusion of surgery, and complete resection of the disease. They should also keep in mind the potential risks of surgery, including complications, scar tissue and adhesions formation and reduction of ovarian reserve (Kwon *et al.*, 2014; Ergun *et al.*, 2015), that may negatively impact the prognosis. These risks increase with

repeated procedures (Practice Committee of the American Society for Reproductive Medicine, 2006) and could explain why first surgery was associated with better chances of success in our study, emphasizing the importance to avoid repeated procedures (Practice Committee of the American Society for Reproductive Medicine, 2006).

A limitation of our study is its retrospective design. However, the primary outcome, live birth, is objective and unlikely affected by recall bias. Women were followed over a long period of time, with a follow-up rate of 84% among eligible women, allowing us to present valid and representative estimates beyond the first 1–3 years reported in previous studies (Adamson and Pasta, 2010; Tomassetti *et al.*, 2013; Boujenah *et al.*, 2015). Imprecision in estimated cumulative live birth rates was higher with low EFI due to smaller sample size in this subgroup. Decision to attempt ART and duration of expectant management were highly dependent on women' preferences and ability to afford ART; clinician's advice was based on women's choices and clinical presentation but did not directly rely on the EFI during the study period. Also, subgroup analysis of women who attempted ART was limited by the small sample size and lack of details on ART therapy (indication, number of cycles, etc.). A criticism is that the least function score is prone to intra- and inter-observer variability; this should be assessed further in a future study. However, sensitivity analysis has already shown that variation in the least function score does not necessarily change the EFI score substantially (being reported as a range of more than 1 index point only 5% of the time) and the least function score only represents 30% of the final EFI (Adamson and Pasta, 2010). Finally, compared to previous external validation of the EFI (Tomassetti *et al.*, 2013; Boujenah *et al.*, 2015), a further strength of this study relies in the specific examination of women with moderate-severe (Stage III–IV) endometriosis for which there is a paucity of sound evidence in the literature.

In conclusion, chances of pregnancy with expectant management following resection of moderate-severe (Stage III–IV) endometriosis are highly variable among women but may be predicted with the EFI scoring system. Women with a high score have an excellent prognosis of pregnancy from expectant fertility management compared to women with a low score, and for women with a low EFI, prompt referral for ART seems prudent and appropriate. Women for whom complete resection of endometriosis could not be achieved; with clinically-significant uterine pathology including leiomyomas, adenomyosis, intrauterine adhesions or congenital anomalies; or those having repeat surgery, have poorer prognosis. These factors can be used to further guide management decisions, especially those with intermediate EFI, for individualization of care. Ovarian function and the impact of location and extent of adhesions and lesions on the function of the adnexa appear crucial for fertility prognosis and should be documented with each surgical procedure for endometriosis so that the EFI may be calculated.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Authors' roles

S.M.-L., E.N.-H. and J.A.A. designed the study. S.M.-L. and E.N.-H. were involved in the data collection and S.M.-L. performed the statistical analyses. D.A. is the primary author of the Endometriosis Fertility Index. All authors were involved in interpreting the data, as well as writing and revising the manuscript.

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Conflict of interest

None declared.

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