Use of the EFI score in endometriosis-associated infertility: A cost-effectiveness study

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\textbf{A B S T R A C T}

\textbf{Background:} The management of endometriosis-related infertility is still under debate. The Endometriosis Fertility Index (EFI) score is performant to predict the occurrence of a spontaneous pregnancy following surgery, but was not evaluated in a cost-effectiveness perspective. Our objective was to quantify fertility outcomes, and costs of different care pathways for endometriosis-associated infertility after primary surgery, with a stratification on the EFI score.

\textbf{Study design:} We conducted a cost-effectiveness analysis based on a decision-tree model in a Tertiary-care university hospital. Extracted form a prospectively maintained database, 608 patients with endometriosis-associated infertility, who underwent laparoscopic treatment with an evaluation of the EFI score, were discriminated between different strategies: natural conception, immediate IVF-ICSI, delayed IVF-ICSI. The pregnancy rate and the live birth rate were the effectiveness outcomes. We considered direct and indirect costs in each strategies. The analysis was stratified according to the EFI score.

\textbf{Results:} After surgery, 163 women with immediate IVF-ICSI (strategy I) were compared with 445 women who had natural conception attempts during a year (strategy II). After a year failure of natural conception attempts, 133 women continuing natural conception attempts (strategy III) were compared with 168 women who had delayed IVF-ICSI (strategy IV). The respective PR and LBR were 62.6 \% and 52.1 \% for strategy I, and 32.4 \% and 23.8 \% for strategy II. Compared to strategy II, strategy I was more costly and more effective [Incremental Cost Effectiveness Ratio (ICER): 31,469 €/pregnancy and 33,568 €/live birth]). No added benefit was observed for patients in strategy I with an EFI score [0–3] after two IVF-ICSI cycles. Strategy III was strongly dominant versus strategy IV for patients with an EFI score [9–10]. Compared to strategy III, strategy VI was more costly and more effective [ICER: 79,674 €/pregnancy, 53,188 €/pregnancy and 27,748 €/pregnancy respectively for patients with an EFI score [7–8], [4–6] and [0–3]).

\textbf{Conclusion:} Immediate IVF-ICSI after surgery is effective but associated with substantial costs for the healthcare system. Taking into account healthcare costs, the EFI is a useful score for helping a couple decide between different care pathways – natural conception, immediate or delayed IVF-ICSI – after surgery for endometriosis-associated infertility.

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https://doi.org/10.1016/j.ejogrb.2020.08.031
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Introduction

Endometriosis, a chronic gynecologic condition, is estimated to affect from 6 to 10% of women of reproductive age, which is close to 200 million women worldwide [1, 2]. Between a third and a half of women with endometriosis have some degree of infertility [3, 4].

Direct healthcare costs for managing endometriosis, as well as indirect costs to patients, employers and society, are substantial [5]. The current therapeutic options for managing endometriosis-associated infertility include medical and/or surgical treatments and/or Assisted Reproductive Techniques (ART) [6, 7].

However, the best treatment strategy (surgery or ART) remains a matter of debate. Furthermore, the economic burden of treatment strategies is particularly obscure due to (i) the complexity and heterogeneity of the disease, (ii) the disparity of care pathways throughout the world, and the lack of high-level evidence-based guidelines. This issue is especially relevant when deciding on a care pathway option for patients requiring surgical management as no consensus exists between ‘immediate IVF-ICSI’ versus ‘delayed IVF-ICSI’ versus ‘natural conception’ management. For patients who undergo initial surgery to enhance natural fertility, Adamson et al. created and recommend the use of the Endometriosis Fertility Index (EFI) score for predicting the occurrence of a spontaneous pregnancy following surgery [5]. In this study, the cumulative spontaneous pregnancy rate at three years after surgery progressively increased from 9.9% for patients with a score of 0–3 to 74.9% for patients with a score of 9–10. This score includes several historical and surgical factors (not all independent) [8] but fails to address the cost burden for the society. Therefore, there is a need for additional objective criteria to better determine a global strategy taking into account the cost for healthcare systems.

The primary objective of the current study was thus to quantify incremental direct and indirect healthcare costs and fertility outcomes of three care pathways for endometriosis-associated infertility after primary surgery followed by: natural conception, immediate IVF-ICSI and delayed IVF-ICSI. The second objective was to stratify the analysis according to the EFI to validate its relevance in terms of cost-effectiveness.

Material and methods

We conducted a retrospective analysis of data from a prospectively maintained database of patients with endometriosis-associated infertility undergoing primary surgical treatment from September 2004 to December 2015 in the Department of Gynecology-Obstetrics of Jean Verdier University Hospital. In this hospital, all patients with endometriosis managed by surgery or ART are prospectively recorded in the database. Then, patients cares (ART, subsequent surgery) and fertility are regularly evaluated.

Patients

The inclusion criteria were: (i) patients with endometriosis, (ii) with more than 12 months of documented infertility, (iii) normo-ovulating, (iv) wishing to conceive and, (v) who underwent surgery for endometriosis.

Patients with a cause of infertility requiring first-intention IVF-ICSI (e.g., priori bilateral salpingectomy), over 43 years or with severe sperm abnormalities in the spouse were excluded from the analysis.

Patient characteristics, surgical findings and treatments, postoperative follow-up, IVF-ICSI procedures and subsequent fertility were collected from the database [9]. Surgical procedures were performed by laparoscopy with the intention of complete resection of endometriotic lesions. Details of surgical and IVF-ICSI procedures have been previously published [10]. The EFI score was retrospectively calculated for all patients as described by Adamson et al. [11]. This scoring system combines historical factors at the time of surgery (age, duration of infertility and pregnancy history), extensiveness of endometriosis (revised American Fertility Society (rAFS) endometriosis lesion score and total rAFS score), and adnexal function at conclusion of surgery (Least Function score). Evaluation of the Least Function score was retrospectively performed with a double-blind calculation performed by the operative surgeon and another surgeon specialized in endometriosis with the use of the operative report.

Ethics approval

Data regarding history of infertility, previous symptoms and surgery, extent of endometriosis, postoperative management of infertility, and fertility outcomes (pregnancy rate (PR), live-birth rate (LBR)) were collected. Informed consent was obtained from each patient before beginning the surgery. This study was approved by the National Data Protection Authority (Commission Nationale de l’Informatique et des Libertés no. 1755849). The Ethics Committee of Jean Verdier University Hospital approved the study protocol (JVR893140-09-2012).

Cost-effectiveness analysis

Model

We generated a decision-tree model. Patients were divided into two pathway strategies after surgery: immediate IVF-ICSI (strategy I) versus natural conception for 1 year (strategy II). Strategy I was sequenced by the number of IVF-ICSI cycles performed. Patients following strategy II who failed to become pregnant after 1 year, were then divided into two groups, i.e., those who continued to attempt natural conception (strategy III) or those who underwent delayed IVF–ICSI cycles (strategy IV) (Fig. 1). The follow up was 4 years for all patients.

Endpoints and cost measurement

Fertility outcomes (i.e., the effectiveness measure) were compared between strategies I (immediate IVF-ICSI) vs. II (natural conception attempts only) and III (pursuing natural conception attempts) vs. IV (delayed IVF-ICSI). The clinical PR (defined by the presence of intra-uterine pregnancy with an embryo with cardiac activity) referred to the number of patient who obtained at least one pregnancy, divided by the number of patient in the strategy group. The LBR referred to the number of patients who gave birth to a live child.

Two economic evaluations were performed taking into account the PR and the LBR. According to the French guidelines [12], we considered direct and indirect costs for each strategy from a societal perspective. Costs included the medical costs of IVF-ICSI cycles, costs related to complications (severe ovarian hyperstimulation syndrome (OHSS)), and costs related to productivity loss due to the time needed to carry out an IVF-ICSI cycle (1 day for oocyte retrieval). The costs related to the IVF-ICSI cycles were extracted from specific codes of the French Common Classification of Procedures (CCAM) [13] and included physician visits, ultrasound and laboratory evaluation, medication and, for complete cycles, oocyte retrieval, intracytoplasmic sperm injection (ICSI) if needed, embryo transfer (ET), and embryology fees for cryopreservation. Due to the nature of our database, we used a gross-costing technique. As IVF-ICSI costs may vary depending on different factors (type of anesthesia, embryo freezing, ICSI techniques), we used the average cost of the technique. We also added the amount corresponding to French public funding for ART departments.
(MIGAC) [14], proportional to their annual number of IVF-ICSI cycles [15]. As the procedures are fully covered by the public health insurance in France, we considered out-of-pocket costs to be zero. All other parameters needed for cost measurement and estimations are summarized in the supporting information (Table S1).

As all the patient underwent laparoscopic surgery, surgery costs weren’t retained. We assumed a zero cost for natural conception attempts, and mild and moderate OHSS. We also assumed non-medical direct costs (i.e., costs of medical transportation, formal care, and daily allowance for sick leave) to be zero. Indeed, according to previous data, the number of sick leave days usually prescribe during IVF-ICSI procedures is lower than the period of days of deficiency in France (i.e. 3 days) [16].

An annual actualization rate of 4% was applied to all costs and pregnancies occurring after the year of the surgery [12].

**Statistical and medico-economic analysis**

The patient characteristics for each strategy group were compared using ANOVA and χ² tests. Cumulative PR (CPR) and cumulative LBR (CLBR) curves were estimated with the Kaplan Meier method and compared with log-rank tests. We applied univariate logistic regression to search for correlation between the EFI score and the postoperative PR and LBR. We also performed univariate and multivariate logistic regression in specific EFI subgroups to search for a correlation between other individual characteristics and the PR.

Comparison between strategies was made by computing the Incremental Cost Effectiveness Ratio (ICER), defined by the difference in cost between two possible interventions, divided by the difference in their effect. We considered strongly dominant strategies to be more effective and cheaper above another. Subsequently, the analysis was stratified, and patients were analyzed according to four subgroups of EFI: 0–3, 4–6, 7–8, and 9–10, according to the previous stratification by Adamson et al. [11].

All analyses were performed using Stata/IC 14.0 and Excel 2013 software.

**Results**

A total of 608 patients were included in the present analysis, with a mean age of 32 years (range: 24–39) and a mean infertility duration of 3 years (range: 1–9). After surgery, 163 (26.8%) patients underwent immediate IVF-ICSI cycles (strategy I), and 445 (73.2%) attempted to conceive naturally for 1 year (strategy II). One hundred fifty-four (34.6%) patient in strategy I became pregnant. Of those in strategy II who failed to conceive naturally within 1 year, 133 (29.9%) continued to attempt natural conception (strategy III) and 168 (37.5%) underwent delayed IVF-ICSI cycles (strategy IV) (Fig. 1).

The patient characteristics for strategy I and II are presented in Table 1. Patients in strategy I had a lower EFI score, lower stages of endometriosis considering the rASRM classification and were more often affected by adenomyosis.

**Fertility outcomes in the population**

The Overall PR and LBR for strategy I and II are presented in Tables 2a and 2b.

The EFI subgroup was correlated with the probability of pregnancy and live birth for patients in strategy I (after four IVF-ICSI cycles), according to univariate logistic regression. Figs. 2a and 2b presents the CPR curves and the CLBR curves stratified by the EFI subgroups for patients in strategy I. There was a statistical difference between each curve for both the PR and the LBR, according to the log-rank test (p < 0.05). In strategy II, the PR and the LBR were not statistically different between patients with an EFI score [4–6] and [7–8]. However, patients with an EFI score [0–3] had a lower PR and LBR (p < 0.001 and p = 0.04, respectively), and patients with an EFI score [9–10] had a higher PR and LBR (p = 0.002 and p = 0.09, respectively).

**Medico-economic analysis between strategies I and II stratified by EFI subgroup**

The results of the medico-economic analysis are presented in Tables 3a and 3b. Overall, strategy I cost 9,509 €/patient, 15,196 €/
pregnancy and 18,235 €/live birth. No costs were retained for strategy II. For the PR, the ICER of strategy I (with four IVF-ICSI cycles) vs strategy II was 31,469 €/pregnancy. Strategy I restrained to one, two and three cycles were weakly dominated. For the LBR, the ICER of strategy I (with two IVF-ICSI cycles) vs strategy II was 30,740 €/live birth. Consecutive ICERs for three and four IVF-ICSI cycles were 34,686 €/live birth and 55,497 €/live birth.

Among patients with an EFI score [0–3], strategy I was weakly dominated if a single IVF-ICSI cycle was performed. After two IVF-ICSI cycles, the ICER of strategy I vs II was 26,346 €/pregnancy and 54,476 €/live birth. Strategies I with three and four IVF-ICSI cycles were strongly dominated.

Among patients with an EFI score [4–6], strategy I was dominated if one or two IVF-ICSI cycles were performed. The ICER of strategy I (with three IVF-ICSI cycles) vs strategy II was 41,913 €/pregnancy and 47,428 €/live birth. The ICER of the fourth IVF-ICSI cycle was 51,533 €/pregnancy and 103,066 €/live birth.

For PR, strategy I was dominated among patients with an EFI score [7–8] if one, two or three IVF-ICSI cycles were performed. The ICER of strategy I (with four IVF-ICSI cycles) vs strategy II was 22,734 €/pregnancy. For the LBR, the consecutive ICERs of strategy I with two, three and four IVF-ICSI cycles were 23,227 €/live birth, 29,070 €/live birth and 67,389 €/live birth.

Among patients with an EFI score [9–10], strategy I was dominated if either one, two or three IVF-ICSI cycles were performed. The ICER of strategy I (with four IVF-ICSI cycles) vs strategy II was 20,387 €/pregnancy and 17,474 €/live birth.

Logistic regression for patients in strategy II with an EFI score [4–8]

According to univariate logistic regression, in the subgroup of strategy II patients with an EFI score [4–8], prior ovarian cystectomy (OR = 0.23 [0.05;0.99]; p = 0.049), incomplete resection during surgery (OR = 2.97 [1.28;6.86]; p = 0.043 (for a complete resection)), a low antral follicular count (<12) (OR = 0.52 [0.26;1.03]; p = 0.06) significantly decreased the probability of pregnancy. In multivariate logistic regression, incomplete resection during surgery (OR = 3.57 [1.41;9.05]; p = 0.007 (for a complete pregnancy)), and a low antral follicular count (OR = 0.47 [0.22;0.99]; p < 0.05) had a significant impact on the probability of conceiving naturally.

Statistically, the endometriosis phenotype, and especially the presence of deep endometriosis or colorectal endometriosis had no impact on the likelihood of conceiving.

Comparison of strategy III versus IV

The PR and LBR for strategies III and IV, and the associated medico-economic analysis, are presented in Table 4.


Among patients with an EFI score [9–10], strategy III was strongly dominant over strategy IV for both the PR and the LBR.

Among patients with an EFI score [7–8], the ICER of strategy IV vs strategy III was 79,674 €/pregnancy and 58,985 €/live birth. Among patients with an EFI score [4–6], the ICER of strategy IV vs strategy III was 53,188 €/pregnancy and 39,916 €/live birth.

Among patients with an EFI score [0–3], the ICER of strategy IV vs strategy III was 27,748 €/pregnancy. However, strategy IV was strongly dominated by strategy III for LBR.

Discussion

Main findings

To the best of our knowledge, this is the first report of a study estimating the direct and indirect incremental healthcare costs and fertility outcomes of alternative pathways of care – natural conception, immediate and delayed IVF-ICSI– after surgery for endometriosis.

We demonstrated that immediate IVF-ICSI is effective but associated with substantial costs for the healthcare system. Natural conception attempts after surgery remains a relevant strategy especially for patients with an EFI score [9–10] (i.e. with a

Table 1
Patients’ characteristics for strategies I (immediate IVF-ICSI) and II (natural conception attempts for 1 year).

<table>
<thead>
<tr>
<th></th>
<th>Strategy I (N = 163)</th>
<th>Strategy II (N = 445)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean ± SD)</td>
<td>32 ± 4.5</td>
<td>32.6 ± 4.8</td>
<td>0.169 [1]</td>
</tr>
<tr>
<td>Infertility duration (months) (mean ± SD)</td>
<td>39.5 ± 20.2</td>
<td>37.2 ± 22.8</td>
<td>0.249 [1]</td>
</tr>
<tr>
<td>Adenomyosis</td>
<td>24 (14.7 %)</td>
<td>34 (7.6 %)</td>
<td>0.008 [2]</td>
</tr>
<tr>
<td>Prior ovarian surgery</td>
<td>15 (9.2 %)</td>
<td>24 (5.4 %)</td>
<td>0.009 [2]</td>
</tr>
<tr>
<td>Prior tubal surgery</td>
<td>9 (5.5 %)</td>
<td>11 (2.5 %)</td>
<td>0.062 [2]</td>
</tr>
<tr>
<td>Endometriosis phenotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Superficial</td>
<td>96 (58.9 %)</td>
<td>284 (63.8 %)</td>
<td>0.393 [2]</td>
</tr>
<tr>
<td>-Ovarian</td>
<td>10 (6.1 %)</td>
<td>31 (7.0 %)</td>
<td></td>
</tr>
<tr>
<td>-Deep endometriosis</td>
<td>38 (23.3 %)</td>
<td>69 (15.5 %)</td>
<td></td>
</tr>
<tr>
<td>-Mixed endometriosis</td>
<td>19 (11.7 %)</td>
<td>61 (13.7 %)</td>
<td></td>
</tr>
<tr>
<td>Complete resection</td>
<td>134 (82.2 %)</td>
<td>380 (85.4 %)</td>
<td>0.336 [2]</td>
</tr>
<tr>
<td>Tubal surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Adhesiolyis</td>
<td>77 (47.2 %)</td>
<td>197 (44.3 %)</td>
<td>0.327 [2]</td>
</tr>
<tr>
<td>-Tubal plasty</td>
<td>13 (8.0 %)</td>
<td>38 (8.5 %)</td>
<td>0.210 [2]</td>
</tr>
<tr>
<td>-Salpingectomy</td>
<td>13 (8.0 %)</td>
<td>13 (2.9 %)</td>
<td>0.055 [2]</td>
</tr>
<tr>
<td>rASRM stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-I</td>
<td>58 (35.6 %)</td>
<td>194 (43.6 %)</td>
<td></td>
</tr>
<tr>
<td>-II</td>
<td>34 (20.9 %)</td>
<td>106 (23.8 %)</td>
<td></td>
</tr>
<tr>
<td>-III</td>
<td>26 (16.0 %)</td>
<td>64 (14.4 %)</td>
<td></td>
</tr>
<tr>
<td>-IV</td>
<td>45 (27.6 %)</td>
<td>81 (18.2 %)</td>
<td></td>
</tr>
<tr>
<td>EFI score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-9 – 10</td>
<td>28 (17.2 %)</td>
<td>112 (25.2 %)</td>
<td>0.001 [2]</td>
</tr>
<tr>
<td>-7 – 8</td>
<td>59 (36.2 %)</td>
<td>194 (43.6 %)</td>
<td></td>
</tr>
<tr>
<td>-4 – 6</td>
<td>61 (37.4 %)</td>
<td>123 (27.6 %)</td>
<td></td>
</tr>
<tr>
<td>-0 – 3</td>
<td>15 (9.2 %)</td>
<td>16 (3.6 %)</td>
<td></td>
</tr>
</tbody>
</table>

p-value for statistical tests searching difference across groups. 1: Student test; 2: chi2 test.
good prognosis) for whom attempted natural conception for more than 1 year may be suggested.

Despite the publication of national and international guidelines, the management of endometriosis-related infertility is still under debate due to the lack of evidence supporting the effectiveness of surgery. Marcoux et al. [17] reported that surgery enhanced fertility for early American Society of Reproductive Medicine (rASRM) stages with a spontaneous PR at 9 months of 17.2% whereas Parazzini et al. [18] found no positive impact of surgery with a PR of 22.2% at one-year. Overall, randomized trials report very low PR [19] suggesting that other infertility factors have been underestimated postoperatively. Adamson et al. meta-analysis of the effects of surgery on the PR reported a higher benefit for advanced rASRM stages [20]. Finally, Vercellini et al. underlined the lack of relation between rASRM classification and fertility outcomes probably because patient characteristics such as age correlated to ovarian reserve and the duration of infertility were not taken into account [21]. In the current study of a large and homogeneous cohort of patients who underwent surgery for endometriosis-associated infertility, we demonstrated that the PR was 32.4% after surgery followed by a year of attempted natural conception and 62.6% for patients who underwent surgery followed by immediate IVF-ICSI (four cycles). Patients continuing to attempt natural conception beyond 1 year reached a PR of 64% after 3.5 years of follow-up. We thus confirm that natural conception should be considered following surgery even though immediate IVF-ICSI remains a good option.

The EFI score was developed as a reproductive tool to ( imperfectly) predict the likelihood of spontaneous conception after surgery for infertile patients with endometriosis [10,11,22–24]. Our data underlined a high variability in PR and LBR for patients attempting natural conception according to the EFI score: the PR varied between 44.6% for the EFI subgroup 9–10 and 6.3% for the EFI subgroup 0–3 (with an LBR of 31.3 and 6.3, respectively) during the year following surgery. Correlation between the EFI score and the PR/LBR was observed in patients continuing natural conception attempts after 1 year. Little evidence has been reported to date on the correlation between the EFI score and PR [25]. In our analysis, the EFI score was effective to predict the PR and the LBR after IVF-ICSI cycles, either performed immediately after surgery or delayed.

Strengths and limitations

Some limits of the current study deserve to be underlined. First, the retrospective nature of the study cannot rule out all biases. The patients’ selection in the strategies was not random and was influenced by several factors that couldn’t be fully captured. Second, patients in the strategy II and III groups (natural conception) who benefit from ovarian stimulation and/or intra-uterine insemination were not excluded from the study. We couldn’t provide the proportion of patients who had those procedures, especially after 1 year of failure. However, in the princeps study of EFI score development [8] and in the external validation studies of the score [9,26,27], patients who had ovarian stimulation and/or intra-uterine insemination were included, and the subsequent pregnancies were categorized as “spontaneous pregnancies”. Moreover, a recent study reported that further studies are required to establish the threshold at which ovarian stimulation or intra-uterine insemination is cost-effective compared to expectant management [28]. Third, although one-third of our population had deep endometriosis, no cost-effective strategy specific to these patients was evaluable in spite of a recent literature review showing that natural conception resulted in a higher PR than both intra-uterine insemination and IVF-ICSI [29]. Fourth, the time frame of 4 years after surgery for our population could be considered relatively short. However, in the current study, no increase in PR was noted beyond 3 years whatever the strategy. Finally, the Least Function score was retrospectively evaluated for all patients using the operative record. However, the evaluation was performed by two surgeons, double-blind, with less than 1% of discrepancy [8]. Moreover, the retrospective evaluation of the Least Function score was validated through multiples external validation cohort of the EFI score [9,26,27,30–35].

Interpretation

A crucial issue for infertile patients after surgery is to determine what benefit to expect from IVF-ICSI as opposed to natural conception attempts, and to know when to embark on an IVF-ICSI program. In our population of patients who did not conceive after surgery, the data suggests that IVF-ICSI could be superior to natural conception attempts for all the EFI subgroups. However, the inclusion of cost parameters and the relatively high PR and LBR for a subgroup of patients continuing to attempt natural conception beyond 1 year, put these findings in perspective. Moreover, the choice of a strategy after surgery depends heavily on a couple’s preference.

For patients with an EFI score [0–3], (i.e., with a poor prognosis of spontaneous pregnancy) IVF-ICSI emerges as the most relevant strategy even if supplementary live births cost around €26,000. However, performing more than two IVF-ICSI cycles in this subgroup of patients was ineffective, inducing more costs for no added benefit. In this setting, oocyte donation could be an option to consider.

Patients with an EFI score [9–10] had a good PR and LBR after undertaking a strategy of immediate IVF-ICSI although at least four cycles had to be performed in case of failure. Compared with 1 year

<table>
<thead>
<tr>
<th>Table 2a</th>
<th>Pregnancy rates for strategies I (immediate IVF-ICSI) and II (natural conception attempts for 1 year) for the whole population and stratified by EFI score.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n)</td>
</tr>
<tr>
<td>Strategy II</td>
<td>32.2% (53/163)</td>
</tr>
<tr>
<td>Whole population</td>
<td>23.8% (106/445)</td>
</tr>
<tr>
<td>Strata</td>
<td>52.3% (55/106)</td>
</tr>
<tr>
<td>EFI 0–3</td>
<td>6.3% (4/16)</td>
</tr>
<tr>
<td>EFI 4–6</td>
<td>23.6% (29/123)</td>
</tr>
<tr>
<td>EFI 7–8</td>
<td>21.1% (41/194)</td>
</tr>
<tr>
<td>EFI 9–10</td>
<td>31.3% (35/112)</td>
</tr>
</tbody>
</table>

Columns for strategy I present pregnancy rates after a single, two, three and four IVF-ICSI cycles, respectively.
of attempted natural conception, supplementary live births cost around €17,500. However, continuing natural conception attempts beyond 1 year, resulted in high PR and LBR. Consequently, this strategy would appear to be highly relevant and save resources which could be used for patients with a poorer prognosis.

Patients with an intermediate EFI score (4–8) may benefit from ART, whether immediately after surgery of after a year of attempted natural conception. In our logistic regression, we identified prognostic factors, other than the EFI score, which could orient patients towards immediate IVF-ICSI: incomplete resection during surgery, or a low antral follicular count. According to the computed ICERS, performing more than three IVF-ICSI cycles immediately after surgery would appear to be ineffective, especially for patients with an EFI score [4–6]. Delayed IVF-ICSI was more effective than continuing natural conception attempts, for incremental costs of €40,000 and €59,000 per live birth.

The European Society of Human Reproduction and Embryology (ESHRE) guidelines recommend ART after surgery for endometriosis-associated infertility (grade C) without any stratification based on fertility prognostic factors [6]. In France, guidelines from the Haute Autorité de Santé (HAS) and the Collège National des Gynécologues et Obstétriciens Français (CNGOF) stipulate that ART (grade C) should be considered 6–12 months after complete surgery in the absence of poor prognostic factors for natural conception (tubal pathology or severe male infertility) (7). Despite these guidelines, in daily practice, the treatment strategy undertaken for most patients with endometriosis-associated infertility depends on the physician's preference based on his/her own experience. The EFI score appears as a reproducible tool, relevant to advise couples in their wish of conception. Then, taking into account healthcare costs will raise many issues including: 1/
Table 3a
Cost-effectiveness analysis based on pregnancy rates, comparing strategy I (immediate IVF-ICSI) and strategy II (natural conception attempts only for 1 year) considering one cycle only, two cycles only, three cycles only and 4 cycles.

<table>
<thead>
<tr>
<th>Strategy II</th>
<th>Strategy I 1 cycle</th>
<th>Strategy I 2 cycle</th>
<th>Strategy I 3 cycle</th>
<th>Strategy I 4 cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>Cost (£)</td>
<td>PR</td>
<td>Cost (£)</td>
<td>ICER</td>
</tr>
<tr>
<td>Whole population</td>
<td>32.6 % 0</td>
<td>35.6 % 3,964</td>
<td>50.9 % 6,445</td>
<td>33.3 % 7,135</td>
</tr>
<tr>
<td>EFI 0–3</td>
<td>6.1 % 0</td>
<td>30.6 % 3,964</td>
<td>33.3 % 7,135</td>
<td>26,246</td>
</tr>
<tr>
<td>EFI 4–6</td>
<td>29.3 % 0</td>
<td>26.2 % 3,964</td>
<td>41.0 % 6,888</td>
<td>41,013</td>
</tr>
<tr>
<td>EFI 7–8</td>
<td>29.4 % 0</td>
<td>42.4 % 3,964</td>
<td>55.9 % 6,114</td>
<td>41,013</td>
</tr>
<tr>
<td>EFI 9–10</td>
<td>44.6 % 0</td>
<td>50.0 % 3,964</td>
<td>71.4 % 5,904</td>
<td>41,013</td>
</tr>
</tbody>
</table>

PR: Pregnancy rate; ICER: Incremental Cost Effectiveness ratio; †: weakly dominated; ‡: strongly dominated. Columns for strategy I present pregnancy rates, cost and ICERs after a single, two, three and four IVF-ICSI cycles, respectively.

Table 3b
Cost-effectiveness analysis based on live-birth rate rates, comparing strategy I (immediate IVF-ICSI) and strategy II (natural conception attempts only for 1 year) considering one cycle only, two cycles only, three cycles only and 4 cycles.

<table>
<thead>
<tr>
<th>Strategy II</th>
<th>Strategy I 1 cycle</th>
<th>Strategy I 2 cycle</th>
<th>Strategy I 3 cycle</th>
<th>Strategy I 4 cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBR</td>
<td>Cost (£)</td>
<td>LBR</td>
<td>Cost (£)</td>
<td>ICER</td>
</tr>
<tr>
<td>Whole population</td>
<td>23.5 % 0</td>
<td>22.5 % 3,964</td>
<td>44.8 % 6,445</td>
<td>30,740</td>
</tr>
<tr>
<td>EFI 0–3</td>
<td>6.3 % 0</td>
<td>20.6 % 3,964</td>
<td>33.3 % 7,135</td>
<td>26,246</td>
</tr>
<tr>
<td>EFI 4–6</td>
<td>23.6 % 0</td>
<td>23.0 % 3,964</td>
<td>36.1 % 6,888</td>
<td>42.6 % 9,033</td>
</tr>
<tr>
<td>EFI 7–8</td>
<td>21.1 % 0</td>
<td>37.3 % 3,964</td>
<td>47.5 % 6,114</td>
<td>23,227</td>
</tr>
<tr>
<td>EFI 9–10</td>
<td>31.2 % 0</td>
<td>50.0 % 3,964</td>
<td>64.2 % 5,804</td>
<td>23,227</td>
</tr>
</tbody>
</table>

LBR: Live Birth Rate; ICER: Incremental Cost Effectiveness ratio; †: weakly dominated; ‡: strongly dominated. Columns for strategy I present live birth rates, cost and ICERs after a single, two, three and four IVF-ICSI cycles, respectively.

Table 4
Pregnancy rates for strategies III (pursuing natural conception attempts) and IV (delayed IVF) stratified by EFI score.

<table>
<thead>
<tr>
<th>Strategy III PR</th>
<th>Strategy IV PR</th>
<th>ICER</th>
<th>Strategy III LBR</th>
<th>Strategy IV LBR</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole population</td>
<td>64 %</td>
<td>75 %</td>
<td>85,859</td>
<td>48 %</td>
<td>58 %</td>
</tr>
<tr>
<td>EFI 0–3</td>
<td>14 %</td>
<td>38 %</td>
<td>27,748</td>
<td>14 %</td>
<td>0 %</td>
</tr>
<tr>
<td>EFI 4–6</td>
<td>50 %</td>
<td>69 %</td>
<td>53,188</td>
<td>28 %</td>
<td>53 %</td>
</tr>
<tr>
<td>EFI 7–8</td>
<td>62 %</td>
<td>73 %</td>
<td>79,674</td>
<td>51 %</td>
<td>67 %</td>
</tr>
<tr>
<td>EFI 9–10</td>
<td>91 %</td>
<td>78 %</td>
<td></td>
<td>70 %</td>
<td>62 %</td>
</tr>
</tbody>
</table>

PR: Pregnancy rate; LBR: Live Birth Rate; ICER: Incremental Cost Effectiveness ratio; †: weakly dominated; ‡: strongly dominated.

the individual and societal willingness to pay for live births, 2/ in which extent these costs should be bearded by the society.

Conclusion

The present study describes a specific care pathway—natural conception, immediate and delayed IVF-ICSI— for fertility management after surgery for endometriosis taking healthcare costs into account. Our results encourage a multidisciplinary approach based on the EFI score which appears to be relevant not only to select patients at good/poor prognosis of pregnancy but also to define care pathways in terms of cost-effectiveness.

**Contribution to authorship**

CF, JB, CP, N C-B, E MA, LC, MG, ED and SB met the criterion for authorship, substantially contributing to conception and design, or acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content.

All authors accept responsibility for the paper as published.

**Details of ethics approval**

This study was approved by the National Data Protection Authority (Commission Nationale de l’Informatique et des Libertés
no. 1755849). The Ethics Committee of Jean Verdier University Hospital approved the study protocol (JVR03140-09- 2012).

Funding source

None.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

Authors would like to acknowledge the medical and paramedical team of the department of Gynecology-Obstetrics of Jean Verdier University Hospital.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2020.08.031.

References