

Colorectal endometriosis-associated infertility: should surgery precede ART?

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Objective: To compare the impact of first-line assisted reproductive technology (ART; intracytoplasmic sperm injection [ICSI]-IVF) and first-line colorectal surgery followed by ART on fertility outcomes in women with colorectal endometriosis-associated infertility.

Design: Retrospective matched cohort study using propensity score (PS) matching (PSM) analysis.

Setting: University referral centers.

Patient(s): A total of 110 women were analyzed from January 2005 to June 2014. A PSM was generated using a logistic regression model based on the age, antimüllerian hormone (AMH) serum level, and presence of adenomyosis to compare the treatment strategy.

Intervention(s): First-line surgery group followed by ART versus exclusive ART with in situ colorectal endometriosis.

Main Outcome Measure(s): After PSM, pregnancy rates (PRs), live-birth rates (LBRs), and cumulative rates (CRs) were estimated.

Result(s): After PSM, in the whole population, the total LBR and PR were 35.4% (39/110) and 49% (54/110), respectively. The specific cumulative LBR at the first ICSI-IVF cycle in the first-line surgery group compared with the first-line ART was, respectively, 32.7% versus 13.0%; at the second cycle, 58.9% versus 24.8%; and at the third cycle, 70.6% versus 54.9%. The cumulative LBRs were significantly higher for women who underwent first-line surgery followed by ART compared with first-line ART in the subset of women with good prognosis (age \leq 35 years and AMH \geq 2 ng/mL and no adenomyosis) and women with AMH serum level $<$ 2 ng/mL.

Conclusion(s): First-line surgery may be a good option for women with colorectal endometriosis-associated infertility. (Fertil Steril® 2017; ■:■-■. ©2017 by American Society for Reproductive Medicine.)

Key Words: Colorectal endometriosis, infertility, propensity score (PS) matching (PSM), ART, surgery

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Endometriosis is a source of pelvic pain and infertility in women of reproductive age and is characterized by the presence of ectopic endometrium outside the uterus (1–3). Among the various anatomical locations of deep infiltrating endometriosis (DIE), colorectal endometriosis represents the

most severe form, affecting 5.3% to 12% of women with endometriosis (4–6) and accounting for more than 90% of all cases of bowel endometriosis (6–9).

Colorectal endometriosis is often associated with other anatomical lesions, and thus the impact of colorectal endometriosis alone on fertility remains

unclear (2, 4, 5, 10, 11). Due to the absence of a high level of evidence, and despite international guidelines, there is currently no consensus about the best infertility treatment for women with DIE, and especially for those with colorectal endometriosis (4,12–16). The European Society for Human Reproduction and Embryology (ESHRE) guidelines state that the effectiveness of surgical excision of deep nodular lesions before assisted reproductive technology (ART) in women with endometriosis-associated infertility is not well established in terms of reproductive outcome (2, 3). In a recent literature review, Cohen et al.

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(4) reported a pregnancy rate (PR) of 37.9% after ART in infertile women with in situ bowel endometriosis and of 35% after ART in infertile women after surgical removal of colorectal endometriosis. However, the latter subgroup corresponded to patients with poor prognosis because of failure of spontaneous pregnancy. Be that as it may, interpreting fertility outcomes in women with colorectal endometriosis is somewhat blurred due to the heterogeneity of the populations included in series reported to date and the lack of information on how pregnancies were achieved. Thus, one of the key challenges is to identify women who will benefit from first-intention ART and those who will benefit from first-line surgery. To date, there is no study comparing the two strategies in a homogeneous population.

Hence, the aim of the present study was to compare the impact of first-line ART (intracytoplasmic sperm injection [ICSI]-IVF) and first-line colorectal surgery followed by ART on fertility outcomes (PRs, live birth rates [LBRs], and cumulative rates [CRs]) in women with proved infertility by using propensity score (PS) matching (PSM) analysis (17).

MATERIALS AND METHODS

Patients

From January 2005 to June 2014, the data of all women with DIE with colorectal endometriosis were extracted from prospectively maintained databases including two French referral centers: Tenon University Hospital and Rouen University Hospital. Infertile women who were addressed for prior ART (ICSI-IVF) or prior surgical treatment followed by ART (ICSI-IVF) were retrospectively included in the study. In the absence of clear guidelines, the women chose between first-line surgery or IVF after receiving clear information about the benefits and risks of each strategy, given by the surgeon and the ART specialist.

Colorectal endometriosis was defined by DIE with infiltration of at least the rectal muscularis. All the women had proven infertility for at least 1 year. Fertility investigations included a hysterosalpingography, cycle day 3 serum level measurements of E₂, FSH, inhibin B, and antimüllerian hormone (AMH), transvaginal sonography, and semen analysis for the partner. Diagnosis of colorectal endometriosis was based on physical examination, transvaginal sonography, and magnetic resonance imaging using previously published imaging criteria (18). Associated adenomyosis was defined as previously published by Bazot et al. (18). Prospective recording of data was approved by the French authority, the Advisory Committee on Information Processing in Healthcare Research. All the women gave their informed consent.

Surgery

All the women in the surgery group underwent complete laparoscopically assisted removal of colorectal endometriosis performed by three experienced surgeons (M.B., E.D., and H.R.). The surgeon-specific procedure volume per year is 50–60 cases. The procedures were performed with the same extent of resection including either ovarian endometriomas

cystectomy or ablation using plasma energy (19), salpingectomy, uterosacral ligament resection, partial colectomy, partial bladder resection, ureterolysis, and ureteral reimplantation when required (20). Rectal shaving was considered for endometriotic lesions with serosal or limited infiltration of the rectal muscularis (6, 20, 21). In case of deep muscularis infiltration, a full-thickness disc excision or segmental colorectal resection was performed depending on multifocality and lesion size.

ART Procedures

Women were monitored and managed according to institutional clinical protocols. Various controlled ovarian stimulation (COS) protocols were used, with 150–450 IU/day of recombinant FSH or hMG in a GnRH antagonist protocol, a long agonist protocol, or a short agonist protocol. The gonadotropin starting dose and type of COS protocol were determined according to each patient's characteristics (age, body mass index [BMI], antral follicle count [AFC], and AMH). Transvaginal oocyte retrieval was scheduled 35–36 hours after hCG injection, and ICSI or classic IVF was performed per standard operating procedure of the hospital. Fertilization was assessed by the appearance of two pronuclei. Cleavage-stage embryos were graded as per the Istanbul consensus (22). Fresh ET was performed 2–3 or 5 days later. Embryos were vitrified or slow frozen on day 2, 3, or 5. Top-quality embryos were frozen and all others discarded. The luteal phase was supported by vaginal administration of micronized P (400 mg/day) started on the day of ovarian puncture. Pregnancies were diagnosed by an increasing concentration of serum β -hCG 14 days after ET. Clinical pregnancies were defined as ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy (23).

Statistical Analysis

PS and PSM procedures. Before PSM, the population was divided into two groups according to the treatment strategy adopted (i.e., first-line ART or first-line surgery followed by ART). All demographics and treatment characteristics were analyzed at this step. Afterward, a PS was generated using a logistic regression model as described by Rosenbaum and Rubin based on the patient's demographics and biological and magnetic resonance imaging findings (24–26). To reduce any bias related to parameters negatively impacting fertility outcomes based on previous studies, the following covariates were included in the PS model to adjust and optimize the matching procedure (27): serum AMH level (≤ 2 ng/mL or ≥ 2 ng/mL), age ($>$ or ≤ 35 years), and adenomyosis (yes/no).

A PS was then assigned to each patient to determine the conditional probability of receiving first-line ART or first-line surgery followed by ART. The area under the receiver operating characteristic curve (28) for this model was 0.76 (0.71–0.81). Each woman who underwent first-line ART was matched (a 1:1 match) to a corresponding woman who underwent first-line surgery followed by

ART using an optimal matching algorithm by randomly selecting for each pair with the closest PS. To find matched women from the two groups, we adopted a caliper matching approach that has the ability to avoid bad matches (too large differences in PS).

Outcomes. After PSM, fertility outcomes (PRs, LBRs, and CRs) were estimated and compared according to each treatment strategy in the whole population and to determine the treatment impact in the following subsets: [1] good prognosis (age ≤ 35 years and AMH ≥ 2 ng/mL and no adenomyosis); [2] low level of serum AMH (<2 ng/mL); [3] age (>35 years); and [4] in the presence of adenomyosis (27). Live birth was defined as the number of women with a delivery that resulted in a live neonate divided by the number of women who started a first, second, or third cycle (23). Clinical PR referred to the total number of pregnancies obtained, divided by the number of women in the studied population after one, two, or three cycles, considering both fresh and thawing cycles. The cumulative LBR is the number of women who achieve a live birth after one, two, or three added cycles divided by the number of women who started treatment.

Other analyses. Clinical pregnancies were defined as the presence of a gestational sac on vaginal ultrasound examination from the fifth week. Statistical analysis was based on Student's *t*-test or analysis of variance test, as appropriate for continuous variables, and the χ^2 test or Fisher's exact

test, as appropriate for categorical variables. $P < .05$ was considered statistically significant.

The Kaplan-Meier method was used to estimate the CRs, and comparisons of CRs were made using the log-rank test. Data were analyzed using R 3.0.1 software, available online.

RESULTS

Characteristics of the Population

A total of 137 women were extracted from the multicenter database from Tenon University Hospital and Rouen University Hospital. Patient assignment before and after PSM is reported in Supplemental Figure 1. After matching, the analysis focused on 110 women (55 women in each group). The median age of the study population was 32 years (range, 24–39), and the BMI was 21.4 kg/m² (range, 17.1–35.3). The median duration of infertility was 3 years (range, 1–9). Sixty-four women 58.2% (64/110) had undergone prior surgery for endometriosis, including diagnostic laparoscopy and cystectomy for endometriomas, but none for DIE or colorectal surgery. Hence none of them had rectal shaving, full-thickness nodule resection, or segmental resection.

Epidemiological, clinical, and biological characteristics of the population before and after PSM are summarized in Table 1. After PSM, no differences in age, BMI, duration of infertility, associated male factor infertility, associated adenomyosis, or AMH serum level were found between the

TABLE 1

Patient characteristics before and after PSM.

| Variable | Before PSM, % (n) | | | After PSM, % (n) | | |
|--|-------------------|--------------------------|---------|------------------|--------------------------|---------|
| | ART (n = 82) | Surgery and ART (n = 55) | P value | ART (n = 55) | Surgery and ART (n = 55) | P value |
| Age (y) | | | | | | |
| Median (range) | 32 (24–42) | 31 (26–38) | | 32 (24–39) | 31.3 (26–38) | |
| <35 | 68.3 (56) | 81.8 (45) | | 82 (45) | 82 (45) | |
| ≥ 35 | 31.7 (26) | 18.2 (10) | .0778 | 18 (10) | 18 (10) | 1 |
| BMI (kg/m ²), median (range) | | | | | | |
| <25 | 74.4 (61) | 80.0 (44) | | 74.6 (41) | 80.0 (44) | |
| ≤ 25 and <30 | 20.7 (17) | 14.5 (8) | | 21.8 (12) | 14.5 (8) | |
| ≥ 30 | 4.9 (4) | 5.5 (3) | .6548 | 3.6 (2) | 5.5 (3) | .5753 |
| Duration (y) of infertility-median (range) | | | | | | |
| 1–3 | 60.0 (49) | 47.0 (26) | | 63.6 (35) | 47.3 (26) | |
| >3 | 40.0 (33) | 53.0 (29) | .1502 | 36.4 (20) | 52.7 (29) | .0842 |
| Infertility, n (%) | | | | | | |
| Primary | 81.7 (67) | 89.1 (49) | | 76.4 (42) | 89.1 (49) | |
| Secondary | 18.3 (15) | 10.9 (9) | .2396 | 23.6 (13) | 10.9 (6) | .077 |
| Associated endometrioma, n (%) | | | | | | |
| No | 32.9 (27) | 61.8 (34) | | 32.7 (18) | 61.8 (34) | |
| Yes | 67.1 (55) | 38.2 (21) | .0008 | 67.3 (37) | 38.2 (21) | .0022 |
| Male factor, n (%) | | | | | | |
| No | 57.3 (47) | 70.9 (39) | | 58.2 (32) | 70.9 (39) | |
| Yes | 42.7 (35) | 29.1 (16) | .1067 | 41.8 (23) | 29.1 (16) | .163 |
| Serum AMH level (ng/mL), median (range) | | | | | | |
| ≤ 2 | 3.2 (0.12–14.30) | 3.0 (0.2–12.1) | | 3.3 (0.12–12.40) | 3.01 (0.2–12.1) | |
| >2 | 40.2 (33) | 30.9 (17) | .2659 | 34.5 (19) | 30.9 (17) | .6844 |
| Adenomyosis | | | | | | |
| No | 69.5 (57) | 54.5 (30) | | 65.5 (36) | 54.5 (30) | |
| Yes | 30.5 (25) | 45.5 (25) | .0744 | 34.5 (19) | 45.5 (25) | .2429 |

Note: AMH = antimüllerian hormone; ART = assisted reproductive technology; BMI = body mass index; PSM = propensity score matching.

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two compared strategies. Significant differences between the two comparative strategies are observed for associated endometrioma.

Outcomes

The total number of ICSI-IVF cycles was 162. The median number of ICSI-IVF cycles per patient was 1 (range, 1–3). The mean number of embryos routinely transferred is 2. The mean number of embryos transferred per cycle were 1.59, 2.1, and 2.16 embryos in cycles 1, 2, and 3, respectively.

In the whole population, the total PR was 49% (54/110). PRs per treatment were, after the first, the second, and the third ICSI-IVF cycles, 52.9% (37/70), 46.4% (13/28), and 33.3 (4/12), respectively. According to the treatment strategies and the cycle, PRs per treatment were 42.4% (14/33), 35.3% (6/17), 20% (1/5), and 62.2% (23/37), 63.6% (7/11), 42.9% (3/7) for women who underwent first-line ART versus first-line surgery followed by ART, respectively.

In the whole population, the total LBR was 35.4% (39/110). LBRs per treatment were, after the first, the second, and the third ICSI-IVF cycles, 35.7% (25/70), 35.7% (10/28), and 33.3 (4/12), respectively. According to the treatment strategies and the cycle, PRs per treatment were 21.2% (7/33), 17.6% (3/17), 40% (2/5), and 48.6% (18/37), 63.6% (7/11), 28.5% (2/7) for women who underwent first-line ART versus first-line surgery followed by ART, respectively.

CRs

LBR. In the whole population, the overall cumulative LBR (CLBR) was 22.9% after one ICSI-IVF cycle, 42.2% after two, and 61.5% after three. The specific CLBR at the first ICSI-IVF cycle in the first-line surgery group compared with first-line ART was, respectively, 32.7% versus 13.0%; at the second cycle, 58.9% versus 24.8%; and at the third cycle, 70.6% versus 54.9%, ($P=.0078$; Fig. 1A).

PRs. In the whole population, the overall cumulative PR (CPR) was 33.6% after one ICSI-IVF cycle, 55.2% after two, and 70.1% after three. The specific CPR at the first ICSI-IVF cycle in the first-line surgery group compared with first-line ART was, respectively, 41.8% versus 25.5%; at the second cycle, 64.4% versus 45.8%; and at the third cycle, 79.7% versus 56.6%, ($P=.037$; Fig. 1B).

LBR, PR, and CRs according to fertility parameters (Table 2). In the subgroup of women with good prognosis (age ≤ 35 years, AMH ≥ 2 ng/mL, and no adenomyosis), we found no difference in PRs between the two strategies ($P=.0759$). In the subgroup of women with at least one negative factor, we found a significantly higher PR for women who underwent first-line surgery ($P=.0122$; Supplemental Fig. 2).

The CLBRs were significantly higher for women who underwent first-line surgery followed by ART compared with first-line ART in the subset of women with good prognosis factors ($P=.0384$) and women with AMH serum level <2 ng/mL ($P=.0456$). No significant differences between the two strategies are reported in the subsets of women with age > 35 years ($P=.1210$) or with adenomyosis ($P=.0853$; Supplemental Figs. 3A, 3B, 3C, 3D). Results corresponding to CPR are reported in Supplemental Figures 4A, 4B, 4C, and 4D.

DISCUSSION

To our knowledge, this is the first report of a study comparing the effect of first-line ART and first-line surgery followed by ART on fertility outcomes in women with colorectal endometriosis using a PSM technique. We demonstrate that first-line surgery is correlated with higher PRs, LBRs, and CLBRs than first-line ART in the whole population, for women with good prognosis and with AMH level < 2 ng/mL. In addition, a significant benefit of first-line surgery was found for women with at least one poor prognostic factor, suggesting

FIGURE 1

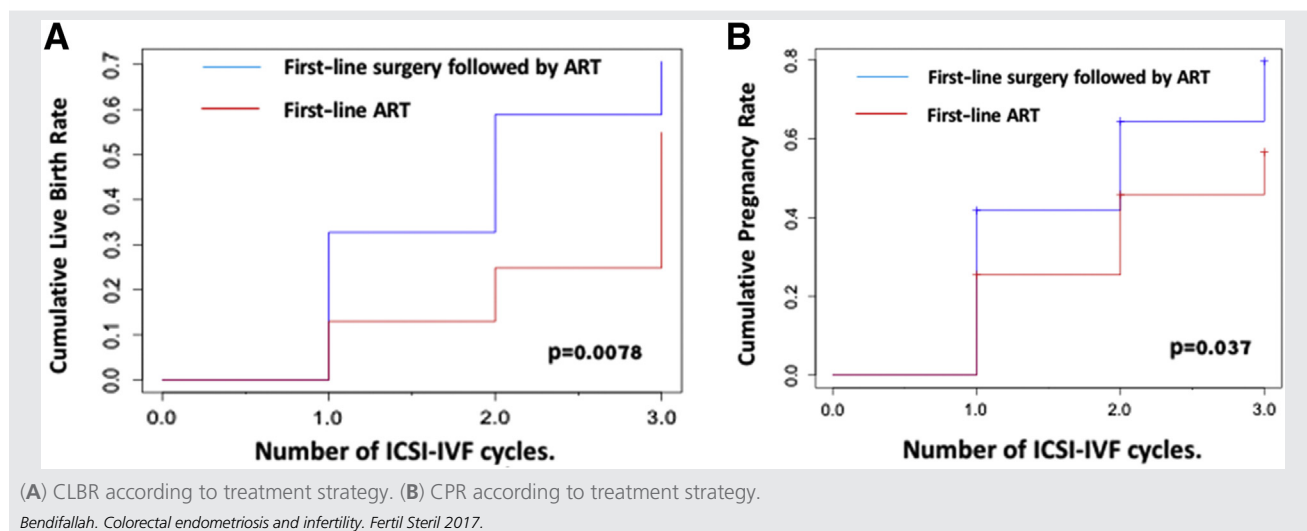


TABLE 2

PR and CPR according to fertility parameter subgroups.

| | PR, % (n/N) | | | LBR, % (n/N) | | | CPR at 3 cycles, % | | | |
|---|--------------|--------------|-----------------|--------------|-------------|-----------------|--------------------|---------|-----------------|------|
| | Overall | ART | Surgery and ART | Overall | ART | Surgery and ART | Overall | ART | Surgery and ART | |
| | P value | P value | P value | P value | P value | P value | P value | P value | P value | |
| Good prognosis (Supplemental Fig. 4A) | 52.7 (19/36) | 48.0 (10/21) | 60.0 (9/15) | 41.6 (15/36) | 28.5 (6/21) | 60.0 (9/15) | 86.4 | 100 | 77.7 | .28 |
| Adenomyosis (Supplemental Fig. 4B) | 45.4 (20/44) | 32.0 (6/19) | 56.0 (14/25) | 27.2 (12/44) | 10.5 (2/19) | 40.0 (10/25) | 63.6 | 41.1 | 71.2 | .31 |
| Age > 35 y (Supplemental Fig. 4C) | 40.0 (8/20) | 20.0 (2/10) | 60 (6/10) | 30.0 (6/20) | 20.0 (2/10) | 40.0 (4/10) | 55.6 | 28 | 82.5 | .085 |
| AMH level <2 ng/mL (Supplemental Fig. 4D) | 50.0 (18/36) | 36.8 (7/19) | 64.7 (11/17) | 38.8 (14/36) | 21.0 (4/19) | 58.8 (10/17) | 70.5 | 44.7 | 84.1 | .14 |

Note: AMH = antimüllerian hormone; ART = assisted reproductive technology; CPR = cumulative pregnancy rate; LBR = live-birth rate; PR = pregnancy rate; Bendifallah. Colorectal endometriosis and infertility. *Fertil Steril* 2017.

the relevance of surgical management in this selected subgroup of women. In contrast, similar fertility outcomes were found between both strategies in the subset of women >35 years old and with associated adenomyosis.

The Added Value of the PSM Technique

The randomized controlled trial (RCT) remains the study design of choice for evaluating and comparing treatments. However, RCTs are in some cases “inappropriate, impossible or inadequate” (29). Currently, the lack of published RCTs comparing first-line ART to first-line surgery represents a major limit in the management of colorectal endometriosis-associated infertility (2). In addition, the evidence of the benefit of either strategy to improve fertility is limited by [1] heterogeneous practices between centers, [2] the great heterogeneity between published series, and [3] methodological limitations to adjust the comparison. We adopted the PSM method to overcome these limitations and provide updated comparative data of the two strategies. PSM presents a range of advantages over conventional regression models and some methodological similarities with RCTs (24, 25, 29). Efforts have been made to ensure that the two treatment groups are similar in terms of patient characteristics (corresponding to randomization in RCTs and matching in PS studies) (24). We specifically focused on this point by matching women with identified factors of fertility outcomes, which is often the source of bias in studies (27). Second, we estimated the treatment effects in a balanced sample of women who underwent first-line ART or first-line surgery correctly adjusted and matched (17). While we lack solid data comparing the two strategies, the ongoing ENDO-FERT trial (ClinicalTrials.gov Identifier: NCT02948972) is the sole RCT designed to answer this specific question.

First-Line ART versus First-Line Surgery

Although PSM cannot replace randomization, we hypothesized its interest to improve patient management and guide treatment decisions. We demonstrated that the PR was 21.8% (12/55) in the first-line ART group and 49% (27/55) in the surgery group ($P=.00343$). Furthermore, the specific CLBR at first (32.7% vs. 13.0%), second (58.9% vs. 24.8%), and third ICSI-IVF cycle (70.6% vs. 54.9%) was significantly improved after first-line surgery compared with first-line ART ($P=.0078$). Although first-line ART remains a good option, our results suggest that first-line surgery should be systematically considered. In this specific setting, a recent French retrospective study (30) reported no difference in PR and birth rate after IVF-ICSI between women with no surgery or incomplete or complete removal of endometriotic lesions. However, this study did not specifically assess the outcomes among women with colorectal involvement. Our results are rather in accordance with those of Stepniewska et al. who reported a higher overall PR (both spontaneous and after ART) in women undergoing complete removal of DIE including colorectal resection (31). Meuleman et al. reported a similar impact of colorectal surgery on fertility (32). Among 48

women undergoing colorectal surgery with at least one patent fallopian tube, 38% became pregnant spontaneously. However, it was not possible to distinguish between women with proven infertility from those wishing to conceive without proven infertility. Finally, Cohen et al. recently published a review on fertility outcomes (spontaneous and after ART) after colorectal surgery including 24 series published between 1990 and 2015 involving a total of 854 women (5). The overall PR was 50.2% (spontaneous pregnancies in 32.2% and ART pregnancies in 18.4%). All these results seem to confirm the negative impact of colorectal endometriosis on reproductive outcomes as well as a potential benefit of its removal to enhance fertility (5). However, such a benefit should be interpreted with caution due to the small sample size of our study. It should be underlined, nevertheless, that the expected benefit must be weighed against surgery-associated morbidity. Indeed, this option exposes women to major postoperative complications including neurogenic bladder, rectovaginal fistulae and anastomotic dehiscence, or pelvic abscesses causing women to further delay their fertility project.

Patient Selection per Treatment Option

The real challenge is to identify women who will benefit from first-intention ART and those who will benefit from first-line surgery. In the absence of clear recommendations on this specific point, no selective criteria have been reported to date to suggest one option over the other (2, 14, 33). Hence, in daily practice, the treatment strategy undertaken for most women with colorectal endometriosis-associated infertility depends on the physician's preference based on his or her own experience. Physicians often opt for ART in the context of infertility rather than select patients who may benefit from prior surgery. The present results may encourage a multidisciplinary approach with first-line surgery and ART for women with negative factors. This could be particularly relevant for women with a low AMH serum level and associated adenomyosis: higher LBRs, PRs, CLBRs, and CPRs were found in these women who underwent first-line surgery (27). Patient age is recognized as an important prognostic factor in reproductive medicine (33, 34). Garrido et al. demonstrated that women's age was a negative factor from 35 to 37 years, with a marked decrease in LBRs beyond 40 years (34). Barri et al. also demonstrated an age-dependent benefit of first-line surgery and IVF for infertile patients with endometriosis (35).

Limitations

Several limitations of the current study deserve to be underlined. First, although the results indicated that PSM is an effective and useful way of creating a matched case-control study to assess fertility outcomes, our study was a retrospective analysis of nonrandomized data of a relatively small number of patients. However, this limitation is also true of other methods used in nonrandomized studies that attempt to reduce bias due to group differences using stratification techniques or adjustments (24, 25, 29). Second, details concerning certain characteristics related to fertility outcomes such as the duration of infertility or the specific

etiology were not included in the PS model to adjust the strategies. Third, we arbitrarily defined a risk subset according to published parameters impacting fertility outcomes, which may limit the interpretation of results. Hence, our results must be analyzed with caution, due to the small sample size of the subsets, the highly selected population used to design the following study, and the inability to correctly distinguish the prognostic weight of each of these parameters. Fourth, we cannot provide specific fertility outcomes of spontaneous PRs after first-line surgery. However, as previously reported in retrospective studies, PRs vary from 35% to 39%, suggesting that ART could be avoided in many women in the first-line surgery group (5, 21, 31). Finally, although PSM allowed balancing of three prognostic (age, adenomyosis, AMH serum level) factors, we observed that endometrioma were twice as common in the first-line ART strategy. This point may explain the low rate of pregnancy in this subgroup of patients due to a deleterious effect of endometrioma on ART results. However, in the recently published ESHRE guidelines for the management of women with endometriosis, it was stated that in infertile women with endometrioma larger than 3 cm there is no evidence that cystectomy before treatment with ART improves PRs, suggesting the lack of evidence of the negative impact of endometrioma on clinical PR (2). Furthermore, as reported by a Cochrane review, it has been demonstrated that there is no evidence of a difference for clinical PR (36).

Conclusion

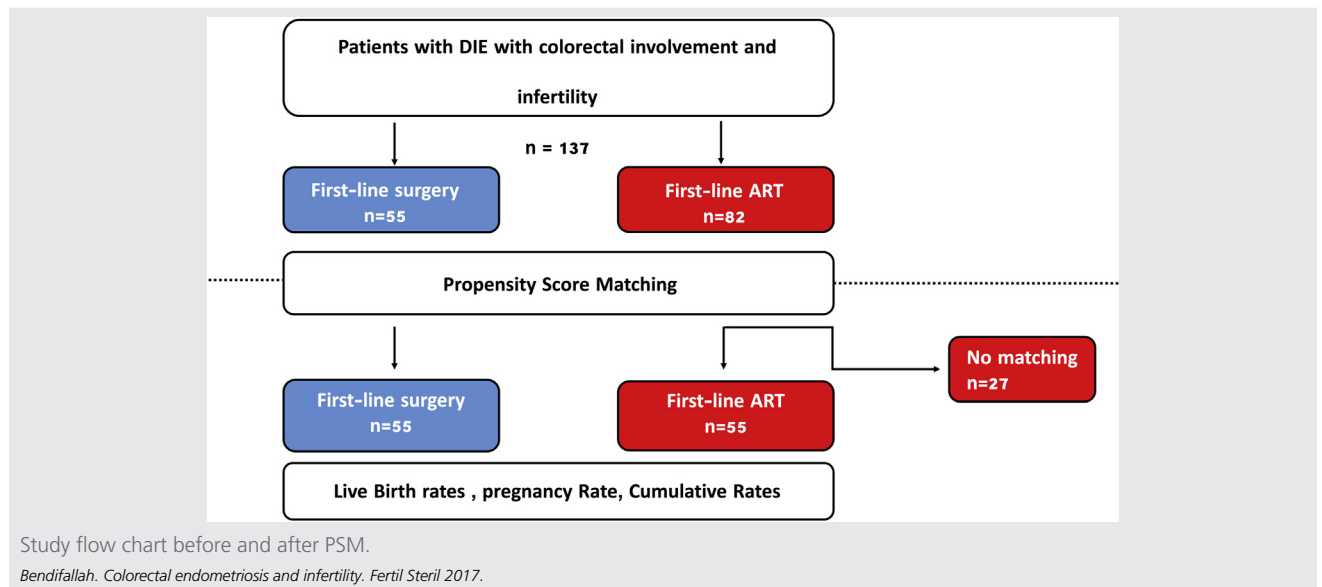
Our results strongly suggest that surgery followed by ART is a good option for women with colorectal endometriosis-associated infertility, especially those with factors negatively impacting fertility outcomes, indicating that first-line ART is not the only option. However, these results must be interpreted with caution. Indeed, future RCTs comparing first-line ART to first-line surgery followed by ART are warranted in such complex management.

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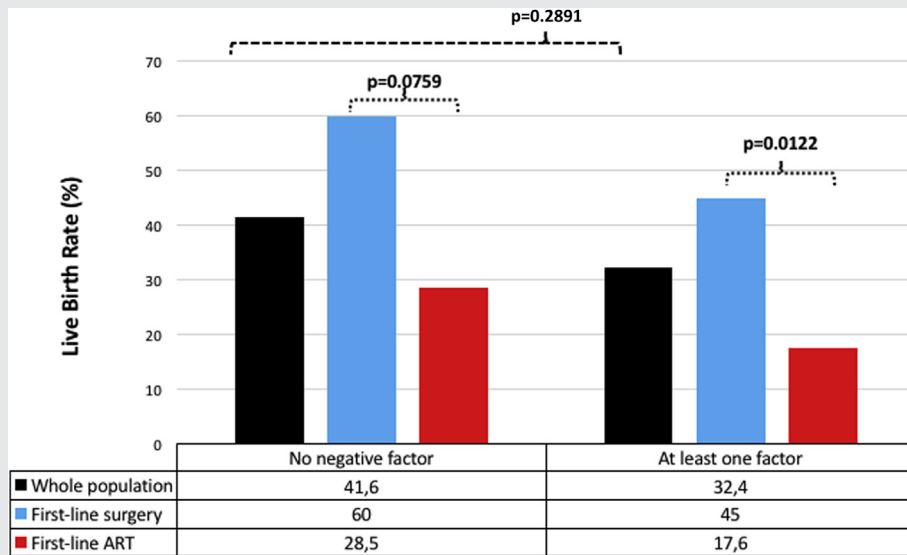
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SUPPLEMENTAL FIGURE 1



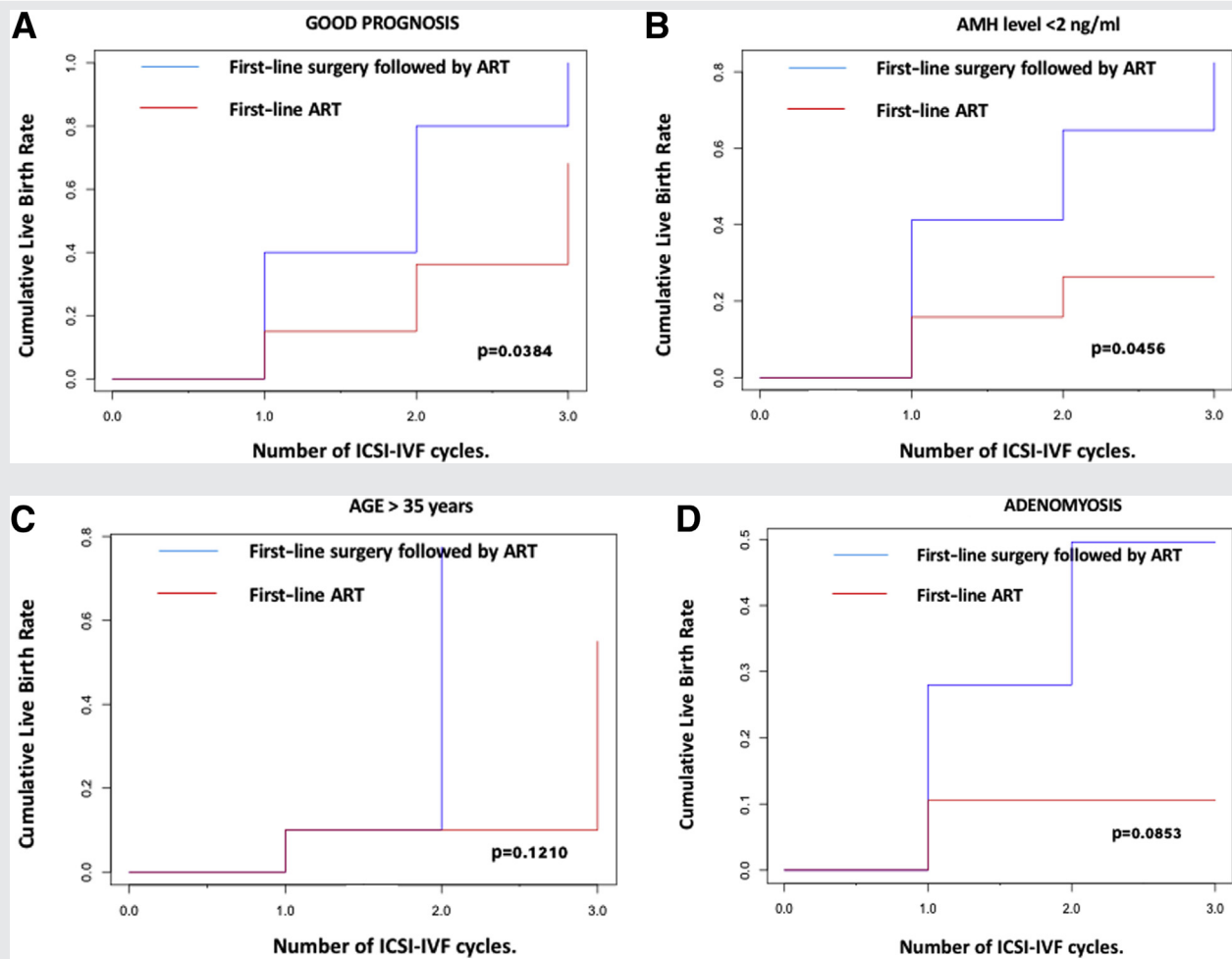
SUPPLEMENTAL FIGURE 2



LBRs according to fertility factors.

Bendifallah. Colorectal endometriosis and infertility. *Fertil Steril* 2017.

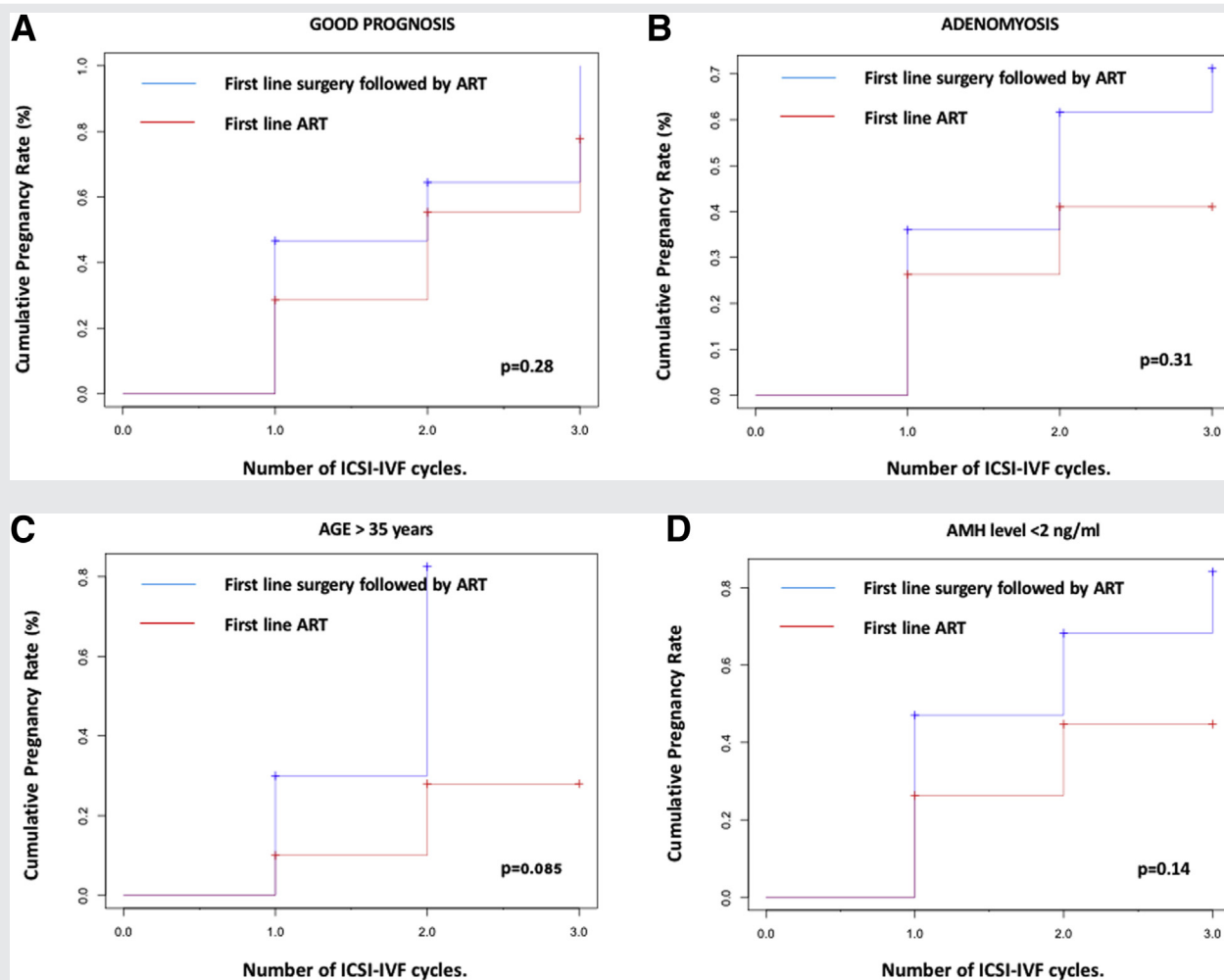
SUPPLEMENTAL FIGURE 3



CLBRs in the subset of women without negative fertility factors.

Bendifallah. Colorectal endometriosis and infertility. *Fertil Steril* 2017.

SUPPLEMENTAL FIGURE 4



CPRs in the subset of women without negative fertility factors.

Bendifallah. Colorectal endometriosis and infertility. *Fertil Steril* 2017.