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MATERNAL-FETAL MEDICINE

Should we consider integrated approach for endometriosis-associated infertility as gold standard management? Rationale and results from a large cohort analysis

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Abstract
Purpose To evaluate reproductive and maternal–fetal outcomes after integrated approach for endometriosis-associated infertility (EAI).
Methods We retrospectively analyzed reproductive and maternal–fetal outcomes of 277 women affected by EAI, subdividing patients in two groups: in the first one (surgery group), we included all women who underwent laparoscopic surgery for EAI; in the second one (integrated group), we included women who failed to conceive spontaneously after surgery within 6–12 months and underwent in vitro fertilization and embryo transfer (IVF). We evaluated delivery rate (DR), maternal and neonatal outcomes of the first pregnancies, and, finally, the type (spontaneous or IVF) of subsequent pregnancies.
Results We did not find significant difference regarding DR between surgery and integrated groups. We found significantly lower birth weight ($p < 0.001$) and gestational age at delivery ($p < 0.001$) in integrated group respect to surgery group; conversely, we found higher rate of preterm birth ($p < 0.001$), small for gestational age ($p = 0.003$), and admission to the neonatal intensive care unit ($p < 0.001$) respect to surgery group. Finally, 92 women became pregnant for the second time: 8% were spontaneous and 20% were IVF pregnancies.
Conclusions We suggest the integrated approach as gold standard treatment for carefully selected patients (young, good ovarian reserve, partner with normal semen parameters) affected by EAI. As consequence, IVF should be reserved as the secondary treatment for women who fail to conceive spontaneously after surgery within 6–12 months, since it is able to increase DR significantly.

Keywords Endometriosis · Infertility treatment · Laparoscopy · In vitro fertilization · Delivery rate · Obstetric outcomes

Introduction

Endometriosis is defined as the presence of endometrial-like endometrial cells, glands, and stroma outside the uterus, causing a strong inflammatory-like microenvironment in the affected tissue [1, 2]. Although the exact prevalence of endometriosis is still unknown, according to accurate epidemiological studies, it affects approximately in 2–10% of women in reproductive age, and up to 50% of infertile women [3]. The etiology of endometriosis still remains controversial: immune, hormonal, genetic, and epigenetic factors may be all involved, and several theories have been proposed to explain it [4–6]. In this regard, accumulating evidence suggests that once the endometriotic foci are established, a breakdown in the peritoneal homeostasis occurs: on one hand, peripheral mononuclear cells secrete inflammatory cytokines in the early phases as well as angiogenic and fibrogenic cytokines in the late stages of the disease [7, 8]; on the other hand, immune-mediated scavenging systems fail to attack and remove endometriotic cells which, consequently, escape from the immune surveillance, implant, and proliferate [9–11]. Among the several symptoms of endometriotic patients, infertility plays a detrimental role on quality of life and its management represents a challenge. Although

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clear and definitive data about the exact cause(s) of endometriosis-associated infertility (EAI) are not so robust to draw firm conclusion, accumulating evidence suggests that endometriotic patients have slightly fewer children than age-matched women without endometriosis and, furthermore, have increased risk for miscarriages and ectopic pregnancies [12]. Among the possible causes of EAI, several authors proposed that this could be due, at least in part, to the distortion of pelvic anatomy with consequently impaired oocyte release and utero-tubal transport [13–15]. In addition, the typical pro-inflammatory microenvironment in both ectopic and eutopic endometrium may disturb ovulation, play detrimental effect(s) on embryo quality, and, last but not least, alter endometrial receptivity [16–19].

EAI management relies on surgery, assisted reproductive technology, or both: the so-called “integrated approach”. On one hand, it was showed that coagulation or excision of endometriotic lesions, tubal and ovarian adhesiolysis, and enucleation of endometriomas may improve fertility [20, 21]. On the other hand, in vitro fertilization (IVF) is able to improve the fertility rate in these patients, overcoming the possible altered pelvic anatomy due to the disease itself or (sometimes inevitable) too radical surgery [22, 23]. Despite some studies found no significant improvement of fertility in endometriotic patients undergoing IVF respect to other indications [24–26], recent evidence suggests that fertility will improve within 1 year after surgical treatment [27] and in subsequent years due to assisted reproductive techniques [12]. Considering all these elements, the integrated approach combines the therapeutic advantages of both surgery and IVF and may be the most appropriate and feasible option for EAI [27, 28]. After the surgery, the patient may have spontaneous pregnancy, avoiding the possibility of IVF-related complications, if there is no associated male-dependent infertility; conversely, if the patient fails to conceive within 6–12 months, the surgery should be followed by IVF [27].

To date, most of the available studies evaluated the efficacy of EAI treatments as pregnancy rates (PRs) or ongoing PRs, without to provide accurate and detailed information about obstetric outcomes. Nevertheless, we truly think that live birth rate and obstetrical outcomes should be considered as parameters of paramount importance. In this regard, it was already demonstrated that endometriosis is associated with increased risk for preterm birth (PB), preeclampsia, and the delivery of small for gestational age (SGA) newborns [29, 30]. Furthermore, women affected by endometriosis seem to have increased risk of antepartum hemorrhage, placental complications, and cesarean section [29]. Last but not least, IVF procedures themselves increase the risk of twin pregnancies and adverse maternal–fetal outcomes [31–33].

Based on these strong pieces of evidence, the primary aim of our study was to evaluate delivery rates (DRs) after surgery and integrated approach; secondary aims were to evaluate maternal and neonatal outcomes for the first pregnancies after surgery and integrated approach, and to analyze the type (spontaneous or IVF) of subsequent pregnancies.

Patients and methods

We performed an observational, single-centre, retrospective study at the Department of Human Reproduction, Division of Obstetrics and Gynecology, University Medical Centre, Ljubljana (Slovenia) between January 2004 and December 2007. We consecutively enrolled 277 women that underwent laparoscopic surgery for infertility. We included women aged less than 35 years, infertile from 1 year or more, with normal ovarian reserve and whose partner was not affected by male infertility. Patients did not undergo any infertility treatment, including the previous surgery or IVF, before enrolling to the study. Endometriosis was confirmed by histology on the surgical specimen. Ovarian reserve was tested using follicle stimulating hormone (FSH) cutpoint 10–20 IU/L and antral follicle count (AFC) cutpoint 3–10, following the recommendation of the American Society for Reproductive Medicine [34]. Sperm parameters were defined as normal following Kruger strict criteria [35]. We excluded women affected by any other kind of endocrine, metabolic, cardiovascular, autoimmune, oncological, or other gynecological disorder (including adenomyosis) and consequent therapies that may affect the investigated outcomes. In addition, since recent data found Deep Infiltrating Endometriosis (DIE) as an independent risk factor for pregnancy and delivery complications [36], we excluded it from the current analysis to avoid possible biases.

The study design is in accordance with the Helsinki Declaration, conforms the Committee on Publication Ethics (COPE) guidelines (http://publicationethics.org/), and was approved by the Institutional Review Boards (IRB) of the hospital in which it was performed. All the patients enrolled in this study were well informed regarding the procedures that they would undergo and signed a consent form allowing data collection for research purposes. All the design, analysis, interpretation of data, drafting, and revisions followed the Reporting of studies Conducted using Observational Routinely collected health Data (RECORD) Statement [37], available through the Enhancing the Quality and Transparency of Health Research (EQUATOR) network (http://www.equatornetwork.org/).

Laparoscopies were performed by six skilled senior surgeons, each one with more than 200 performed laparoscopic procedures for major gynecological surgery. The retrospective observation period ranged from 66 to 113 months (average = 90 months). Laparoscopic procedures included electrocoagulation or excision of all visible endometriotic implants, adhesiolysis, and endometriomas enucleation by stripping (as gold standard treatment in case of ovarian endometriomas [38]). Endometriosis was classified according to the revised American Fertility Society (rAFS) classification system [39]. We recorded additional information about fixation of the ovary, adhesions, and location of the endometriomas.

The IVF and embryo transfer procedure was offered to the women who failed to conceive spontaneously from 6 to 12 months after laparoscopic surgery. Short antagonist cetrorelix protocol or long desensitization buserelin protocol were used for ovarian stimulation, as previously described [32]. We used the blastocyst grading system proposed by Gardner et al. [40]. One or two embryos were transferred on day 3 or 5 after oocyte retrieval.

The pregnancy outcome data were collected between January and July 2013 from the hospital informational program of surgical procedures (Hipokrat d.o.o., Obalno-Kraška, Slovenia) and birth information system (BIS). In addition, we sent a questionnaire to the women who did not return to our hospital for delivery, to get data about pregnancy (both spontaneous pregnancy after surgery or after IVF, date of delivery, and maternity hospital). Subsequently, we retrieved data about maternal–fetal outcomes from all the 14 Slovenian maternity hospitals through the National Institute of Public Health of the Republic of Slovenia.

We analyzed data including the patients in two groups: in the first one (surgery group), we included all women who underwent laparoscopic surgery for EAI; in the second one (integrated group), we included women who failed to conceive spontaneously after surgery (6–12 months) and underwent IVF.

Forty out of two hundred and seventy-seven (14%) women in the surgery group were lost to follow up. IVF results are presented as DR per cycle and cumulatively after consecutive cycles, including also frozen-thawed cycles.

In the second part of the analysis, we compared the following neonatal outcomes between surgery and integrated group: birth weight, mean gestational age at delivery, PB rate, low (0–6) 5 min Apgar score, rate of fetal distress, admittance to neonatal intensive care unit, and of SGA neonates. In detail, gestational age in the group of spontaneous pregnancy after surgery was determined in weeks since the last menstrual period and confirmed or corrected by early (first trimester) ultrasonography; in the integrated group, gestational age was determined as the number of weeks between the oocyte retrieval and the delivery plus 2 weeks. PB was defined as spontaneous or induced vaginal delivery or elective cesarean section before completed 37 weeks of gestation. Slovene reference standard curves for weight, length, and head circumference at birth for given gestational age were used for fetal and neonatal growth estimation [41]. SGA was defined as growth below the fifth percentile according to the aforementioned growth curves.

Furthermore, we evaluated rate of cesarean section, placenta praevia, antepartum and postpartum hemorrhage, and twin pregnancy rate in both groups. Placenta praevia was diagnosed in cases of placental edge lying closer than 2 cm to the internal cervical os or over it. Antepartum bleeding was defined as occurring during first (until 12 weeks of pregnancy), second (from 13 to 24 weeks of pregnancy), or third (after 35 weeks of pregnancy) trimester. Postpartum hemorrhage was defined as a blood loss of 500 mL or more after vaginal delivery, and 1000 mL or more after cesarean section.

Finally, we analyzed the type of subsequent second pregnancy (spontaneous or IVF) in the surgery and integrated groups.

All data analyses were performed using SPSS ver. 22.0 (SPSS Inc., Chicago, IL, USA). Student's t test and Mann–Whitney test were used for quantitative variables, and Chi-square test was used to compare qualitative variables. The significance level for all analyses was p value < 0.05.

Results

During the study period (January 2004–December 2007), 277 women affected by EAI underwent laparoscopy, 93 additionally underwent IVF program, and 5 declined IVF treatment (Fig. 1). As shown in Table 1, we did not found significant differences between surgery and integrated group regarding patients' age ($p = 0.66$), rAFS stage ($p = 0.34$), percentages of unilateral ($p = 0.32$) or bilateral ($p = 0.43$) endometriomas, adhesions ($p = 0.43$), and ovarian fixation ($p = 0.96$): this element allows all the subsequent data analysis that we performed, since the investigated outcomes would not be affected by the baseline characteristics of the two groups. As corollary result, the implantation rate in integrated group was 17.66% (83/470).

Delivery rates in surgery and integrated groups

In the surgery group, the DR was 52.3% (Table 2). Ninety-three women who did not conceive spontaneously within 6–12 months after surgery were referred to IVF (271 total cycles, 72 with single and 199 with double embryo transfer). Regarding integrated group, we analyzed DR ratio per cycle and cDR ratio, including repeated IVF cycles and frozen-thawed cycles together. As shown in Table 3, DR per cycle was 20.6%; in the same group, cDR was 60.2%. DR per cycle was significantly higher ($p = 0.03$) in rAFS stage I–II respect to stage III–IV.

As shown in Table 2, we did not find significant differences regarding DR between surgery (52.3%) group and integrated group (60.2%). Since we addressed to IVF patients who did not conceive after surgery within 6–12 months, the

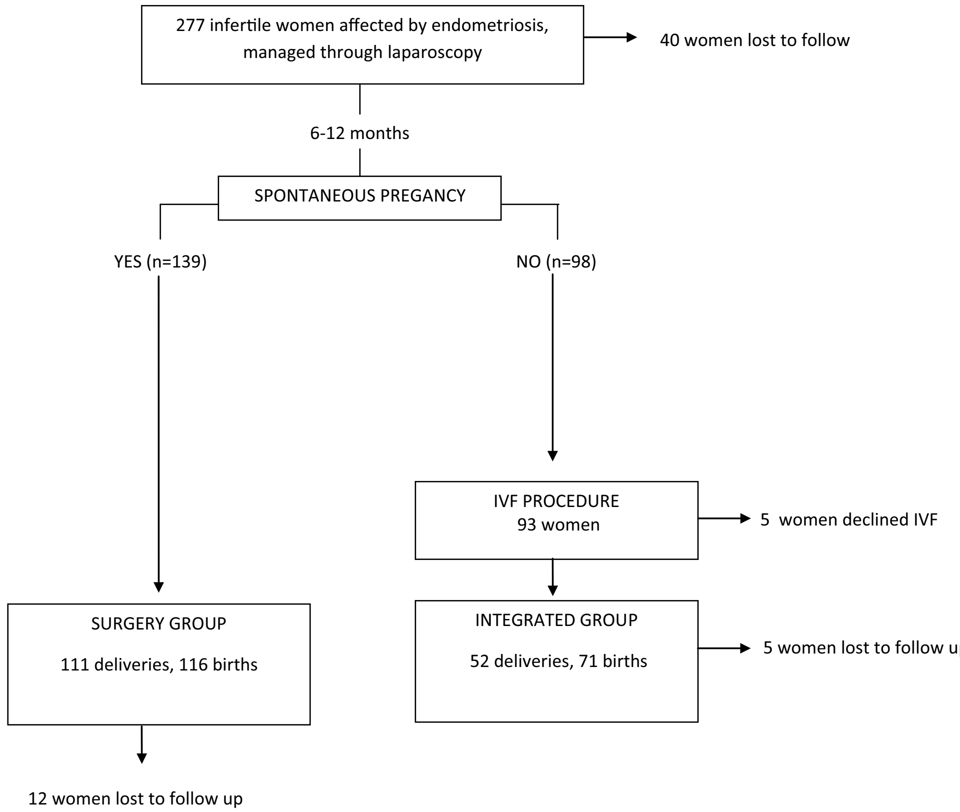

Fig. 1 Flowchart of the study

Table 1 Demographic and surgical characteristics in the surgery and integrated groups

	Surgery group ($n = 277$)	Integrated group ($n = 93$)	p
Mean age	30.23 ± 3.18	30.00 ± 2.78	0.66
rAFS stage			
I + II	207 (74.7)	74 (79.6)	0.34
III + IV	70 (25.3)	19 (20.4)	
Unilateral endometrioma	77 (27.8)	21 (22.6)	0.32
Bilateral endometriomas	25 (9.0)	11 (11.8)	0.43
Adhesions	111 (40.1)	33 (35.5)	0.43
Ovarian fixation	93 (33.6)	31 (33.3)	0.96

Data are expressed as means and standard deviations or as *n* (%)

rAFS revised American Fertility Society classification of endometriosis

cumulative DR statistically increased from 52.3% (124/237) to 75.9% (180/237).

Table 2 Comparison of delivery rate according to the rAFS stage between the surgery and integrated groups

	Surgery group	Integrated group	p
rAFS stage I + II			
DR	52.5 (94/179)	62.1 (46/74)	NS
rAFS stage III + IV			
DR	51.7 (30/58)	52.6 (10/19)	NS
Total			
DR	52.3 (124/237)	60.2 (56/93)	NS

DR delivery rate, *rAFS* revised American Fertility Society classification of endometriosis, *NS* non-significant

Maternal–fetal outcomes in surgery and integrated groups

Obstetric outcomes for surgery and integrated groups are reported in Table 4, although data about 17 patients were lost to follow up. In full agreement with the previous published data [42], we did not find any significant difference between these two groups regarding obstetric outcomes, apart from the well-known significantly higher ($p < 0.001$) rate of twin pregnancies due to IVF procedure.

We reported neonatal outcomes in Table 5: confirming the previous data [43–45], we found significantly lower birth weight ($p < 0.001$) and gestational age at delivery

Table 3 DR per cycle and cDR according to the rAFS stage in the integrated group

	Delivery
rAFS stage I + II	
Rate per cycle	22.7 (46/203)*
Cumulative rate	62.1 (46/74)
rAFS stage III + IV	
Rate per cycle	11.6 (10/86)*
Cumulative rate	52.6 (10/19)
Total	
Rate per cycle	20.6 (56/271)
Cumulative rate	60.2 (56/93)

DR per cycle in rAFS stages I + II vs. DR per cycle in rAFS stages III + IV

rAFS revised American Fertility Society classification of endometriosis

*$p = 0.03$

($p < 0.001$) in integrated group with respect to surgery group; in the same group, we found higher rate of PB ($p < 0.001$), SGA ($p = 0.003$), and admission to the neonatal intensive care unit ($p < 0.001$) with respect to surgery group, although the incidence of low 5-min Apgar score was comparable ($p = 0.537$).

Considering that the higher rate of twin pregnancies in the integrated group could have influenced the neonatal outcomes, we performed a logistic regression analysis for the investigated parameters: in full agreement with the previous data [46], twin pregnancies are significantly associated with PB ($p < 0.001$) and admission to the neonatal intensive care unit ($p < 0.001$).

Subsequent pregnancies

During the long period of follow-up, we were able to collect data about 92 women who become pregnant for the second time (Table 6): 8% (74/92) were spontaneous and 20% (18/92) were IVF pregnancies.

Discussion

Despite the improvement of surgical and medical treatments, EAI management represents still a challenge. To the best of our knowledge, data about PR/DR after treatment of EAI are

Table 4 Obstetric outcomes in surgery and integrated groups

	Surgery group ($n = 111$)	Integrated group ($n = 52$)	p
Mean age at delivery	31.94 ± 3.38	32.56 ± 2.68	0.25
Pregnancy			
Singleton	106 (95.5)	34 (65.4)	< 0.001
Twin	5 (4.5)	18 (34.3)	
Miscarriage	16 (14.4)	13 (25)	0.12
Cesarean section	25 (22.5)	18 (34.6)	0.10
Placenta praevia	1 (0.9)	3 (5.8)	0.06
Postpartum hemorrhage	7 (6.3)	8 (15.4)	0.06
Antepartum hemorrhage			
First trimester	7 (6.3)	3 (5.8)	0.60
Second trimester	3 (2.7)	0	0.31
Third trimester	0	1 (0.6)	0.32

Data are expressed as means and standard deviations or *n* (%)

Table 5 Neonatal characteristics in the surgery and integrated groups

	Surgery group ($n = 116$)	Integrated group ($n = 71$)	p
Neonatal birth weight	3308.23 ± 663.21	2604.49 ± 975.22	< 0.001
Mean gestational age at delivery	38.70 ± 2.59	36.51 ± 4.22	< 0.001
Preterm birth	12 (10.3%)	31 (43.7%)	< 0.001
Low (0–6) 5-min Apgar score	4 (3.4%)	3 (4.2%)	0.537
Fetal distress	0	0	–
Admission to neonatal intensive care unit	5 (4.3%)	18 (25.4%)	< 0.001
Small for gestational age	4 (3.4%)	13 (18.4%)	0.003

Data are expressed as means and standard deviations or *n* (%)

Table 6 Type of subsequent pregnancies in surgery and integrated groups

	Surgery group ($n = 139$)	Integrated group ($n = 69$)	Total ($n = 208$)
Subsequent spontaneous	57 (41.0%)	17 (24.6%)	74 (35.6%)
Subsequent IVF	4 (2.9%)	14 (20.3%)	18 (8.6%)
Total	61 (43.9%)	31 (44.9%)	92 (44.23%)

Data are expressed as *n* (%)

still scarce and do not allow to draw firm conclusion. The previous data analysis [47] found that surgery alone is able to increase PR of about 50%. However, a recent study found that colorectal endometriosis, regardless of the previous surgery, is associated with high risk of complication both during cesarean section and vaginal delivery [48]; in this regard, it seems that persistence of the rectovaginal DIE is a major risk factor for severe complications during both pregnancy and delivery [36]. Similarly, a high rate of cesarean section and PB was observed after laparoscopic ureterolysis due to endometriosis [49]. Nevertheless, other authors did not find an elevated risk for perineal or vaginal laceration in women with a history of surgery for DIE, even when a resection of the rectum or of the posterior vaginal wall had been performed [50]. Probably, we did not observe a similar high rate of complication due to the selection bias of the study (we excluded patients affected by DIE). In any case, we support the potential benefit of surgery on fertility outcomes for women with DIE, as was recently demonstrated by others [51–56].

In addition, we found that integrated approach significantly increases overall DR respect to surgical approach in women affected by EAI and partners with normal sperm parameters. Our results are fully comparable with recent published case series by Barri et al. [27] and Coccia et al. [28]. Considered altogether, these data corroborate the recommendation of an accurate management of all the visible endometriotic implants at the time of laparoscopy even in rAFS stage I–II, to allow a significantly higher DR in women undergoing IVF [57]. In full agreement with a recent meta-analysis [58], we found that rAFS stage III–IV is associated with a significantly lower DR per cycle ($p = 0.03$) with respect to rAFS stage I–II, despite a satisfying overall cDR.

In our view, integrated approach of EAI should be not considered the same as "surgery prior to IVF" approach: in this view, we strongly suggest to leave the possibility of spontaneous conception to the patient after the surgery, avoiding to refer her immediately to IVF. In this regard, the integrated approach has several advantages: on one hand, the occurrence of spontaneous conception after surgery will avoid all the risks related to IVF procedures [59], including ovarian hyperstimulation syndrome and egg-retrieval procedure complications (the latter is even more risky in endometriotic patients [60]); on the other hand, the reduction of IVF pregnancies would decrease the well-known rate of neonatal complications [43–45, 61]. Last but not least, we should consider that laparoscopic treatment should be reserved just as the first-line therapy prior to IVF, since it was recently found that the second-line surgery is associated with poor ovarian response to controlled ovarian stimulation and IVF outcomes in infertile women with ovarian endometrioma recurrence [62].

In any case, the initial laparoscopic treatment appears to be mandatory, since it allows histological confirmation of endometriosis, eliminates the pain symptoms, and prevents late consequences (progression of endometriosis, missing an occult malignancy, and spontaneous rupture of endometrioma) [63]. Nevertheless, it is crystal clear that patients should be selected for integrated approach only when they are young, and have normal ovarian reserve and no other infertility factor (including altered sperm parameters of the partner).

In the second part of our analysis, we confirmed that IVF pregnancies are more likely to be associated with adverse neonatal outcomes (PB, SGA, and admission to the neonatal intensive care unit) due, at least in part, to the higher rate of twin pregnancies. Regarding this point, the rate of twin pregnancies in the study population is higher than the average rate of our Institution (18.9%) [64]: this may depend on higher rate (73.4%) of two-embryo transfer in endometriotic patient comparable to our whole infertile population (64.7%) and, consequently, should be taken into account as possible limitation for the interpretation of our data. About this point, in future, we intend to overcome the high rate of twin pregnancy in IVF group using elective single-embryo transfer (eSET): according to large database analysis [65], it seems that eSET does not modify overall PR and thus could be helpful also for EAI patients undergoing IVF. Apart from the higher rate of twin pregnancies in IVF group with respect to surgery group, we could not find any significant difference for the rate of cesarean section, placenta praevia, antepartum, and postpartum hemorrhage, although we acknowledge that others showed different results on larger cohorts [66].

During the follow-up of our study, more than 40% of all women, who became pregnant for the first time, became pregnant again. In detail, women who became pregnant spontaneously after surgery seem to have higher chance to become pregnant spontaneously for the second time; confirming other cohort analysis [67], we showed that IVF after surgical treatment for EAI is not mandatory for the subsequent pregnancy: indeed, several women had spontaneous subsequent pregnancy even if the first one was IVF.

In conclusion, we suggest the integrated approach as gold standard treatment for carefully selected patients (young, good ovarian reserve, partner with normal semen parameters) affected by EAI. As a consequence, IVF should be reserved as secondary treatment, since it is able to increase significantly DR.

Considering that our conclusions are based on a retrospective study and that data about 14% pregnancy and 17 deliveries were lost to follow up, we take the opportunity to solicit future studies about the topic to clarify the role of integrated approach for patients affected by EAI.

Author contributions VŠ: protocol development and data collection. IV: data analysis and manuscript writing. ASL: manuscript editing. EV-B: project supervision and manuscript editing

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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