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ARTICLE

Impaired implantation in endometriosis compared with couples with male subfertility after transfer of equal quality embryos: a matched cohort study

BIOGRAPHY

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KEY MESSAGE

This study suggests that, in women with endometriosis, an impaired implantation factor contributes to reduced pregnancy outcomes after fertility treatment as well as impairing ovarian function. This relationship should be researched in future prospective studies, including the role of uterine receptivity in pregnancy outcomes.

ABSTRACT

Research question: Is implantation impaired in patients with endometriosis undergoing IVF and intracytoplasmatic sperm injection (ICSI) cycles?

Design: A retrospective matched cohort study was carried out on IVF/ICSI cycles with fresh single embryo transfer at the Department of Assisted Reproductive Medicine, Ghent University Hospital, Belgium, between July 2015 and August 2017 (n = 1053). A total of 118 endometriosis cases were matched 1:1 to 118 couples diagnosed with male subfertility and stratified by embryo quality (identical ALPHA grading categories), female age (±1 year) and parity (±1 delivery). Transvaginal ultrasound, magnetic resonance imaging or laparoscopy was used to diagnosed endometriosis, and the revised American Society for Reproductive Medicine score was used to classify the endometriosis into grade I/II versus grade III/IV. Male subfertility was defined in accordance with World Health Organization criteria (fifth edition).

Results: Compared with endometriosis cases, control couples with male subfertility had significantly higher rates of positive HCG test on day 16 (P = 0.047, OR 2.077, CI 1.009 to 4.276), ongoing implantation (defined as a positive fetal heart rate on transvaginal ultrasound at a gestational age of at least 6.5–7 weeks) (P = 0.038, OR 2.265, CI 1.048 to 4.893), ongoing pregnancy (defined by a vital pregnancy at 11 weeks) (P = 0.046, OR 2.292, CI 1.016 to 5.173) and live birth (P = 0.043, OR 2.502, CI 1.029 to 6.087).

Conclusions: After matching for embryo quality, woman's age and parity, rates of positive HCG tests, ongoing implantation, ongoing pregnancy and live birth were more than twice as high in the control group compared with the endometriosis group.

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KEYWORDS

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INTRODUCTION

Endometriosis is a benign, gynaecological pathology defined by the presence of endometrial-like glands and stroma outside the uterus. It affects about 10% of the female population, with a prevalence peaking during reproductive life (*Eskenazi and Warner, 1997*; *Viganò et al., 2004*; *Kennedy et al., 2005*; *Vercellini et al., 2013*; *Nisenblat et al., 2016*). Three main phenotypes can be distinguished: endometriomas, superficial endometriosis and deep infiltrating endometriosis; a broad spectrum of symptoms can also be present, of which dysmenorrhoea is the most common (*Vercellini et al., 2006*; *Nisenblat et al., 2016*; *Chapron et al., 2017*).

Endometriosis remains an important study domain because of its association with subfertility. Lower pregnancy outcomes in IVF and intracytoplasmatic sperm injection (ICSI) cycles have been described, although the mechanism causing this subfertility remains ambiguous (*Barnhart et al., 2002*; *Muteshi et al., 2018*). For successful embryo implantation, a good-quality embryo and optimal endometrial receptivity are needed. Most studies on endometriosis have focused on ovarian function and described a lower number of retrieved oocytes and lower oocyte quality, although embryo quality does not seem to be impaired (*Simon et al., 1994*; *Kuivasaari et al., 2005*; *Al-Fadhli et al., 2006*; *Matalliotakis et al., 2007*; *Barcelos et al., 2009*; *Opoien et al., 2012*; *Shebl et al., 2017*).

The effect of endometriosis on uterine receptivity is still under debate (*Barnhart et al., 2002*; *Kuivasaari et al., 2005*; *Omland et al., 2006*; *Matalliotakis et al., 2011*; *Opoien et al., 2012*; *Dong et al., 2013*; *Harb et al., 2013*; *Senapati et al., 2016*; *Muteshi et al., 2018*). The focus of research has recently shifted to this uterine factor, partly because of the growing interest in adenomyosis, a uterine pathology defined by the presence of basal endometrial glands and stroma in the myometrium. Adenomyosis is associated with implantation failure, and is closely related to endometriosis (*Kunz et al., 2005*; *Cakmak and Taylor, 2011*; *Brosens et al., 2012*; *Maheshwari et al., 2012*; *Leyendecker et al., 2015*; *Younes and Tulandi, 2017*).

It remains unclear whether the ovarian or the uterine factor is the main cause for endometriosis-associated subfertility. In contrast to most studies focusing on oocyte and embryo impairment, the aim of the present study was to analyse implantation after transfer of equal quality embryos, compared with women who have endometriosis, and couples diagnosed with male subfertility without any known female subfertility cause and thus treatments, where the uterine factor was presumed to be normal.

MATERIALS AND METHODS

Study design

A single-centre, retrospective, matched cohort study was developed at the Department for Reproductive Medicine at Ghent University Hospital, Belgium. This study was approved in May 2017 by the hospital's Ethics Committee (EC/2017/0757). All first, fresh IVF and intracytoplasmic sperm injection (ICSI) cycles carried out between 1 July 2015 and 31 August 2017 resulting in a single embryo transfer (SET) on day 5 were assessed for eligibility for inclusion (n =1053). The start of the study period was determined by creating a new electronic health record (IDEAS version 6.0, Mellowood Medical, Canada) to obtain more complete data. Follow-up and data collection took place up to August 2018.

Selection of the study populations

Within the 1053 eligible cycles, couples with endometriosis and sole male subfertility were selected according to the inclusion criteria described below. A total of 571 couples was excluded because of other fertility issues or the combination of male subfertility with other fertility diagnoses. One patient with endometriosis was excluded because of previous chemotherapy (FIGURE 1). To define the endometriosis group, a previous confirmed diagnosis by laparoscopy, magnetic resonance imaging (MRI) or transvaginal ultrasound (TVUS) was required. One diagnostic method was linked to every patient (laparoscopy preferred over MRI, and MRI over TVUS). This resulted in an endometriosis population of 121 patients. Only seven (5.8%) of the 121 endometriosis cases were diagnosed by TVUS. Six out of the seven patients diagnosed by TVUS had endometrioma-like cysts on ultrasound, resulting in a diagnosis of endometriosis, and one patient had a description of 'endometriosis signs' in the patient file. The stage of endometriosis was classified according to the revised American Society for Reproductive Medicine criteria (*American Society for Reproductive Medicine, 1997*).

Patients who had undergone previous surgery or pharmacological treatment were included.

Couples diagnosed with sole male subfertility, defined by World Health Organization criteria *(2010)*, and with the exclusion of co-existing female pathologies, were assigned to a control group, resulting in 361 patients (FIGURE 1).

Female age, male age, anti-Müllerian hormone (AMH) and number of IVF/ICSI cycles were not significantly different between the endometriosis patients, couples with male subfertility and the total population, demonstrating the representativeness of the samples (Supplementary Table 1). Endometriosis was present in 11.5% of the total study population (121/1053).

Matching

Patients with endometriosis were automatically matched 1:1 to couples diagnosed with male subfertility in SPSS (Statistics Package for Social Sciences; version 25) (Chicago, IL, USA), based on embryo quality (exact matching to four categories), female age (±1 year) and parity (previous live birth or stillbirth; ±1 delivery). On the basis of these criteria, only 118 of the 121 endometriosis patients could be matched, resulting in 118 cases and 118 controls. Matching on the basis of embryo quality was applied to observe implantation outcomes after equal quality embryo transfer, reducing the influence of possible ovarian alterations, followed by matching on the basis of age and parity to correct for age-related subfertility and reproductive history (*Zondervan et al., 2002*).

Assisted reproductive technology protocol

At Ghent University Hospital, three different ovarian stimulation protocols were applied: the short agonist, long agonist and short antagonist protocol, as previously described by *Blank et al. (2019)*. The short agonist protocol (standard protocol), starts with at least 2 weeks of oral contraceptives (Microgynon® 50), followed by gonadotrophin releasing hormone (GnRH) analogues (day 3–9) (Decapeptyl®, Ferring Co., Germany subcutaneous 0.1 mg/day) and FSH (from

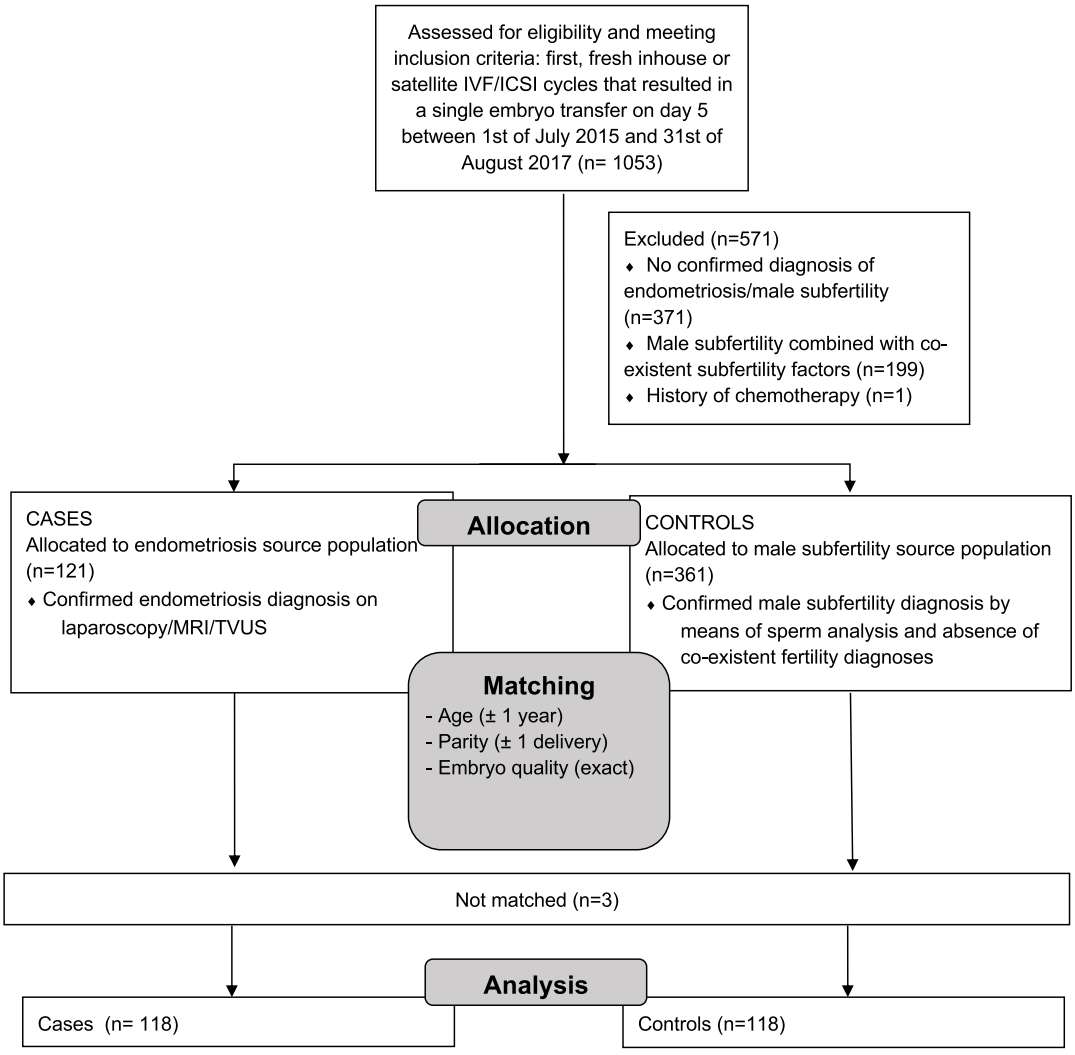

FIGURE 1 Patient enrolment.

day 5 until day of HCG administration (Microgynon®, Bayer, South Oak Way, UK; Gonal-F®, Serono Co., Aubnne, Switzerland; Menopur®, Ferring Pharmaceuticals Inc., Suffern, New York; Puregon®, Organon, Oss, the Netherlands or Fostimon®, IBSA, Lodi - Italy subcutaneous 150 IU/day). The long agonist protocol adds, after 2 weeks of oral contraceptives, a decapeptyl administration for 2 weeks (Decapeptyl Depot® or daily subcutaneous 0.1 mg/day). Thereafter, in both protocols, if a basal endometrium is observed on TVUS, oral contraceptives were interrupted and FSH was started on day 7 until HCG administration. If not, oral contraceptives were added for 2 weeks, followed by identical steps as described above. The short antagonist protocol applies no oral contraceptives and starts FSH on day 3 of the natural cycle until HCG administration. On day 6, a GnRH antagonist, Cetrotide® (subcutaneous 0.25 mg/day), was added. The initiating FSH dose was based on age, serum AMH and FSH (*La Marca et al., 2012*).

Intracytoplasmic sperm injection was indicated in the following cases: number of motile spermatozoa less than 1.106; normal morphology less than 1%; azoospermia requiring testicular sperm extraction (TESE) or microsurgical epididymal sperm aspiration (MESE); failed previous IVF cycles with less than 40–50% fertilized oocytes; failed previous intrauterine insemination (IUI); low number of oocytes; and donor oocytes. Indications, however, could be modified based on the opinion of the gynaecologist and the couple.

Embryo quality was scored on day 5, the day of transfer, according to Gardner and Schoolcraft criteria, including blastocyst expansion and stage of hatching (score 1–5), inner cell mass (A–D) and trophectoderm (A–D) (*Gardner and Schoolcraft, 1999*; *Van Den Abbeel et al., 2013*). The embryos were then divided into four categories: excellent, good, moderate and poor quality (Supplementary Table 2).

Measurement outcomes

On day 16 after embryo transfer, an HCG serum test was conducted. At 6.5–7 weeks of pregnancy, a TVUS was used to evaluate the presence of an intrauterine gestational sac and a fetal heart rate, signifying an ongoing implantation. An ongoing pregnancy was defined by a vital pregnancy at 11 weeks and, finally, live birth rate (LBR) was evaluated by a questionnaire at 40 weeks.

Statistical analyses

SPSS (Statistics Package for Social Sciences; version 25) (Chicago, IL, USA) was used for statistical analyses. A normal distribution was determined by the Q–Q

TABLE 1 OOCYTE AND EMBRYO CHARACTERISTICS IN THE GENERAL ENDOMETRIOSIS POPULATION COMPARED WITH THE GENERAL POPULATION OF COUPLES WITH MALE SUBFERTILITY (BEFORE MATCHING)

		Endometriosis (*n* = 121)		Male subfertility (*n* = 361)		*P*-value
		***n* (missing)**	**Statistical dispersion[a]**	***n* (missing)**	**Statistical dispersion[a]**	
AMH, µg /l		113 (8)	1.92 [1.04–3.15]	298 (63)	2.21 [1.26–3.70]	0.112[b]
Stimulation protocol		121 (0)		361 (0)		<0.001[c]
	Short agonist		57 (47.1%)		275 (76.2%)	
	Long agonist		47 (38.8%)		7 (1.9%)	
	Antagonist		17 (14.0%)		78 (21.6%)	
	No stimulation		0 (0.0%)		1 (0.3%)	
Stimulation days, *n*		120 (1)	14 ± 3.4	361 (0)	14 ± 2.8	0.848[d]
Follicles after stimulation, *n*		119 (2)	12 ± 5.8	349 (12)	13 ± 3.4	0.295[d]
Oocytes, *n*		121 (0)	5.5 ± 3.26	361 (0)	6.1 +_3.30	<0.001[d]
Fertilization rate (%)[g]		121 (0)	58 ± 20.7	361(0)	55 ± 20.4	0.128[d]
Embryo quality		121 (0)		361 (0)		0.020[e,f]
	Excellent		25 (20.7%)		105 (29.1%)	
	Good		55 (45.5%)		150 (41.6%)	
	Moderate		29 (24.0%)		93 (25.8%)	
	Poor		12 (9.9%)		13 (3.6%)	

[a] Normally distributed variables: mean ± SD; non-normally distributed variables: median [interquartile range]; categorical variables: frequency (%).

[b] Mann–Whitney U test.

[c] Fisher's exact test.

[d] Unpaired Student's t-test.

[e] Chi-squared test.

[f] Bonferroni correction in post-hoc tests.

[g] The rate of fertilized oocytes/total number of oocytes retrieved. Post-hoc chi-squared tests: the long agonist versus the short agonist protocol ($P < 0.001$) and the antagonist protocol ($P < 0.001$ and poor versus excellent ($P = 0.002$), good ($P = 0.028$) and moderate quality embryos ($P = 0.014$).

AMH, anti-Müllerian hormone.

plots, skewness and kurtosis values, and the distribution of the histograms. All statistical analyses were tested two-sided and $P < 0.05$ was considered statistically significant. Wilson score confidence intervals were applied to determine if significant differences in proportions were present between subcategories within a variable; if 0.5 is part of the calculated interval, no significant difference between the subcategories is present. To compare continuous variables between more than two samples, the following unpaired tests were applied: the one-way analysis of variance was applied if variables were considered normally distributed in all groups, and equal variances could be assumed after Levene's test ($P \geq 0.05$). If equal variances could not be assumed, the Welch's F-test was interpreted. The Kruskal–Wallis test was applied for non-normally distributed variables. To compare continuous variables between both source populations or the cases versus controls, unpaired tests involving two samples were applied. The unpaired Student's t-test was applied for normally distributed variables if equal variances could be assumed after Levene's test ($P \geq 0.05$). If no equal variances were present, the Welch's F-test was interpreted. The Mann–Whitney U test was applied for non-normally distributed variables. To compare categorical variables between two samples, chi-squared tests were applied. The chi-squared test was interpreted if the following requirements were fulfilled: 20% or less of the contingency cells had expected values less than 5; and no cells had an expected value less than 1. If the requirements were not fulfilled, Fisher's exact test was applied. Post-hoc chi-squared and Fisher's exact tests were conducted if needed, by applying a Bonferroni correction, with pi ≤ ∝k (k = number of paired tests). To analyse the effect of endometriosis on assisted reproductive technology (ART) outcomes, univariate tests were applied. Next, a multiple logistic regression (MLR) model was designed to evaluate the presence of possible confounders. The enter method was applied to include the following variables: the matching variables (embryo quality, female age and parity as matching does not exclude confounding); and the independent variables that reached significance in the univariate descriptive analyses, if clinically relevant. The largest subcategories were selected as reference category.

RESULTS

Ovarian and embryo characteristics before matching

Before matching, oocyte and embryo characteristics were compared between the general endometriosis population ($n = 121$) and the population diagnosed with male subfertility ($n = 361$) (TABLE 1). No significant differences were detected in AMH ($P = 0.112$), number of stimulation days ($P = 0.848$), number of follicles after stimulation ($P = 0.295$) and fertilization rate ($P = 0.128$). A statistically significant difference, however, was found in the stimulation protocol ($P < 0.001$), post-hoc chi-squared tests (the long agonist versus the short agonist protocol [$P < 0.001$] and the antagonist protocol [$P < 0.001$]), with a more frequent application of the long agonist protocol and less frequent use of the short agonist and antagonist protocols

TABLE 2 PATIENT CHARACTERISTICS IN CASES AND CONTROLS

		Endometriosis (cases, *n* = 118)		Male subfertility (controls, *n* = 118)		*P*-value
		***n* (missing)**	**Statistical dispersion[a]**	***n* (missing)**	**Statistical dispersion[a]**	
BMI, kg/m^2		104 (14)	23 ± 3.8	102 (16)	24 ± 3.3	0.335[b]
Smoking		91 (27)	8 (8.8%)	53 (65)	7 (13.2%)	0.403[c]
Duration of subfertility, years[d]		93 (25)	4 ± 2.8	84 (34)	4 ± 2.5	0.297[b]
Primary subfertility[e]		118 (0)	113 (95.8%)	116 (2)	110 (94.8%)	0.735[c]
Cycle duration		109 (9)		102 (16)		0.926[f]
	Regular (25–35 days)		95 (87.2%)		89 (87.3%)	
	Oligomenorrhoea (>34 days)		7 (6.4%)		6 (5.9%)	
	Polymenorrhoea (<25days)		1 (0.9%)		2 (2.0 %)	
	Irregular not specified		6 (5.5%)		5 (4.9%)	
Parity, *n*		118 (0)	0 [0–1]	118 (0)	0 [0–1]	-
Dysmenorrhoea[g]		92 (26)		89 (29)		<0.001[f,h]
	Grade 0		13 (18.6%)		21 (32.3%)	
	Grade 1		13 (18.6%)		29 (44.6%)	
	Grade 2		19 (27.1%)		15 (23.1%)	
	Grade 3		21 (30.0%)		0 (0.0%)	
	Grade 4		4 (5.7%)		0 (0.0%)	

[a] Normally distributed variables: mean ± SD; non-normally distributed variables: median [IQR]; categorical variables: frequency (%).

[b] Unpaired Student's t-test.

[c] Chi-squared test.

[d] The period between the start of the wish to conceive and the date of oocyte retrieval.

[e] No previous spontaneous pregnancies resulting in a live birth.

[f] Fisher's exact test.

[g] Grade 0: no menstrual pain and no effect on daily activity; grade 2: mild menstrual pain and seldom affects daily activity, grade 2: moderate menstrual pain and regular effect on daily activity; grade 3: severe menstrual pain, headache and severe effect on daily activity; grade 4: symptoms of grade 3 associated with nausea and vomiting.

[h] Bonferroni correction in post-hoc tests: in endometriosis patients, more grade 3 dysmenorrhoea versus grade 0 ($P < 0.001$), grade 1 ($P < 0.001$) and grade 2 ($P < 0.001$), more grade 0 and grade 1 versus grade 4 was present ($P = 0.019$ and $P = 0.006$, respectively), and significantly more grade 2 versus grade 1 ($P = 0.029$).

BMI, body mass index.

in the endometriosis group. The number of oocytes retrieved was significantly lower ($P < 0.001$), 5.5 ± 3.26 in the endometriosis group compared with 6.1 ± 3.30 in the couples diagnosed with male subfertility. Embryo quality also differed significantly between the two groups: ($P = 0.020$), post-hoc chi-squared tests poor versus excellent- ($P = 0.002$), good- ($P = 0.028$) and moderate-quality embryos ($P = 0.014$), with a higher proportion of poorer quality embryos and a lower proportion of excellent-, good- and moderate-quality embryos in total in the endometriosis group.

Patient characteristics

A significant difference in severity of dysmenorrhoea ($P < 0.001$) was observed, with more Severe forms in the endometriosis group. In 22 of the endometriosis patients and 24 male subfertility patients, dysmenorrhoea was present; however, the grade was not mentioned in the patient file. Therefore, it was not included in the analysis of dysmenorrhoea. Significantly more grade-3 dysmenorrhoea was present compared with grade 0 ($P < 0.001$), grade 1 ($P < 0.001$) and grade 2 ($P < 0.001$) in endometriosis patients (the reported *P*-values are for the post-hoc pairwise comparisons). Also, significantly more grade 0 and grade 1 was present compared with grade 4 ($P = 0.019$ and $P = 0.006$, respectively). Finally, significantly more grade 2 was present than grade 1 ($P = 0.029$) (the reported *P*-values are for the post hoc pairwise comparisons). A post hoc test for grade 3 compared with grade 4 was not conducted, as none of the women in the couples with male subfertility had grade 3 or 4 dysmenorrhoea. Other patient characteristics (body mass index, smoking, duration of subfertility, primary subfertility, cycle duration, parity) of the case and control samples after matching were not different (TABLE 2).

The subfertility characteristics of the endometriosis cases are presented in TABLE 3. A significantly higher proportion of stage III-IV endometriosis (65.3%) compared with stage I-II (34.7%) ($P < 0.001$) was found.

Ovarian and embryo characteristics after matching

The IVF/ICSI cycle characteristics after matching are presented in TABLE 4. Similar to matching in TABLE 1, significant differences were found in the distribution of stimulation protocols used ($P < 0.001$), and a lower number of oocytes were retrieved ($P = 0.003$) in the endometriosis cases compared with male subfertility controls. Embryo quality distribution in both the case and control group was as follows: 21.2% of the embryos had excellent quality; 46.6% good; 24.6% moderate; and 7.6% poor quality. One variable was added to this analysis, i.e. IVF or ICSI application, and a less frequent use of ICSI in

TABLE 3 FEMALE SUBFERTILITY CHARACTERISTICS OF ENDOMETRIOSIS CASES

		Endometriosis (cases)	
		***n* (missing)**	***n* (%)**
Diagnosis	Laparoscopy	118 (0)	109 (92.4)
	MRI		2 (1.7)
	TVUS		7 (5.9)
Endometriosis specification	Endometrioma	112 (6)	
	Unilateral		56 (50.0)
	Bilateral		9 (8.0)
	Adhesions	113 (5)	48 (42,5)
	Spots	113 (5)	64 (56.6)
	Nodules	113 (5)	15 (13.3)
	Hydrosalpinx	113 (5)	12 (10.6)
Adenomyosis		118 (0)	4 (3.4)
Classification of endometriosis	rASRM stage I-II	118 (0)	41 (34.7)
	rASRMstage III-IV		77 (65.3)
Medical pretreatment (GnRH analogue Decapeptyl)		118 (0)	12 (10.2)
Surgical pretreatment	Cystectomy	118 (0)	46 (39.0)
	Puncture of endometrioma		8 (6.8)
	Coagulation of spots		35 (29.7)
	Adhesiolysis		31 (26.3)
	Resection of foci		8 (6.8)
	Total		85 (72.0)
Tubal factor[a]	Unilateral obstruction	95 (23)	22 (23.2)
	Bilateral obstruction		6 (6.3)
Other diagnosis	Polyp	118 (0)	2 (1.7)
	Fundal band of fibrous tissue		2 (1.7)
	Myoma		7 (5.9)
	Uterine septum		1 (0.8)
	Fibroadenoma		2 (1.7)
	PCOS		7 (5.9)
	Male subfertility		59 (50.0)
Family history endometriosis (first, second degree, or both)		69 (49)	17 (24.6)

[a] Tubal patency was examined by hysterosalpingography, hysterosalpingo-foam-sonography or methylene blue during laparoscopic investigation.
GnRH, gonadotrophin releasing hormone; MRI, magnetic resonance imaging; PCOS, polycystic ovary syndrome; rASRM, revised American Society for Reproductive Medicine; TVUS, transvaginal ultrasound.

endometriosis patients was seen ($P < 0.001$; ICSI: 72.9% in cases versus 98.3% in controls).

Outcomes

Univariate tests

In the univariate tests, no significant differences were present for a positive HCG test on day 16 ($P = 0.695$), ongoing implantation ($P = 0.076$) and ongoing pregnancy ($P = 0.076$) between the matched endometriosis and control group. Contrarily, LBR ($P = 0.015$) showed a significant difference between cases and controls (FIGURE 2).

Multiple logistic regression

Multiple logistic regression included the matching variables and the variables dysmenorrhoea, stimulation protocol and IVF or ICSI application, based on the univariate tests and clinical relevance. Although the number of oocytes showed a significant difference, it was not included in the MLR, as only the outcomes starting from the SET were evaluated in this study.

Subcategories were merged if clinically relevant to achieve higher subcategory numbers. For dysmenorrhoea, grade 1 and 2, and on the other side grade 3 and 4, were merged (chi-squared test remained significant, $P < 0.001$). One ICSI cycle without stimulation was excluded, as no analysis could be conducted.

No correlation was found between the potential confounding variables, evaluated by a combination of clinical knowledge and the Pearson correlation coefficient. Thereby, all variables could be included in the MLR. The condition to build a multiple regression model was fulfilled, i.e. that the continuous variables age and parity were considered linear, as *P*-values of the Hosmer and Lemeshow test were not significant. One regression model per outcome was generated. Odds ratios for cases versus controls were significant for HCG day 16 ($n = 235$) (OR 2.077, CI 1.009 to 4.276; $P = 0.047$), ongoing implantation ($n = 233$) (OR 2.265, CI 1.048 to 4.893; $P = 0.038$), ongoing pregnancy ($n = 235$) (OR 2.292, CI 1.016 to 5.173, $P = 0.046$) and LBR ($n = 219$) (OR 2.502, CI 1.029 to 6.087; $P = 0.043$) (FIGURE 2 and Supplementary Table 3). The odds of positive ART outcomes in patients with the same age, parity, embryo quality, stimulation protocol, grade of dysmenorrhoea and IVF/ICSI application were more than twice as large for the control group compared with the endometriosis group.

Sub-analysis in the endometriosis group on male subfertility

A sub-analysis was conducted to determine if the prevalence of male subfertility in the endometriosis group could have an influence on the outcomes. Therefore, an additional MLR analysis, including identical confounding variables, was conducted solely in the endometriosis group. This model showed no significant influence of this male subfertility factor on the outcomes ($P \geq 0.05$) (Supplementary Table 4).

DISCUSSION

Endometriosis is a prevalent gynaecological condition associated with reduced pregnancy chances (*Gupta et al., 2008*; *Nisenblat et al., 2016*). In this matched cohort study, significantly lower implantation, ongoing pregnancy and live birth rates after transfer of equal quality embryos were present in women with endometriosis, compared

TABLE 4 CHARACTERISTICS OF IVF AND INTRACYTOPLASMIC SPERM INJECTION CYCLES IN MATCHED CASES AND CONTROLS

			Endometriosis (cases)		Male subfertility (controls)		*P*-value
			n **(missing)**	**Statistical dispersion[a]**	***n*** **(missing)**	**Statistical dispersion[a]**	
Stimulation protocol			118 (0)		118 (0)		<0.001[b,c]
	Short agonist			55 (46.6%)		89 (75.4%)	
	Long agonist			46 (39.0%)		1 (0.8%)	
	Antagonist			17 (14.4%)		27 (22.9%)	
	No stimulation			0 (0.0%)		1 (0.8%)	
Stimulation days, *n*			117 (1)	14 ± 3.3	118 (0)	14 ± 2.9	0.712[d]
Follicles after stimulation, *n*			116 (2)	12 ± 5.8	113 (5)	13 ± 5.4	0.389[d]
Oocytes, *n*			118 (0)	9.5 ± 4.67	118 (0)	11.4 ± 5.26	0.003[d]
Fertilization rate, %			118 (0)	58 ± 20.3	118 (0)	54 ± 23.1	0.215[d]
IVF/ICSI application		IVF	118 (0)	32 (27.1%)	118 (0)	2 (1.7%)	<0.001[b]
		ICSI		86 (72.9%)		116 (98.3%)	

Cases and controls matched by embryo quality, female age and parity.

[a] Normally distributed variables: mean ± SD; non-normally distributed variables: median [IQR]; categorical variables: frequency (%).

[b] Chi-squared test.

[c] $p_i \leq \frac{0.056}{} = 0.0083$.

[d] Unpaired Student's t-test.ICSI, intracytoplasmic sperm injection.

with women undergoing IVF/ICSI because of subfertility of the partner. The present study enabled implantation to be investigated independently of oocyte and embryo characteristics, by matching embryo quality, in addition to matching woman's age and parity. By only including SETs, direct observation of implantation per embryo was possible.

Our results confirmed the impaired oocyte and embryo characteristics in women with endometriosis described in most existing studies (*Simon et al., 1994*; *Kuivasaari et al., 2005*; *Al Fadhli et al., 2006*; *Matalliotakis et al., 2007*; *Barcelos et al., 2009*; *Opoien et al., 2012*; *Shebl et al., 2017*). A lower number of oocytes and more poor-quality embryos were yielded in the endometriosis group, compared with couples diagnosed with male subfertility. Subsequently, univariate analyses only detected a significant difference in LBR, but not a positive HCG test on day 16, ongoing implantation and ongoing pregnancy between the cases and controls. It must be questioned, however, if any confounding variables are interfering with these outcomes. Therefore, a MLR

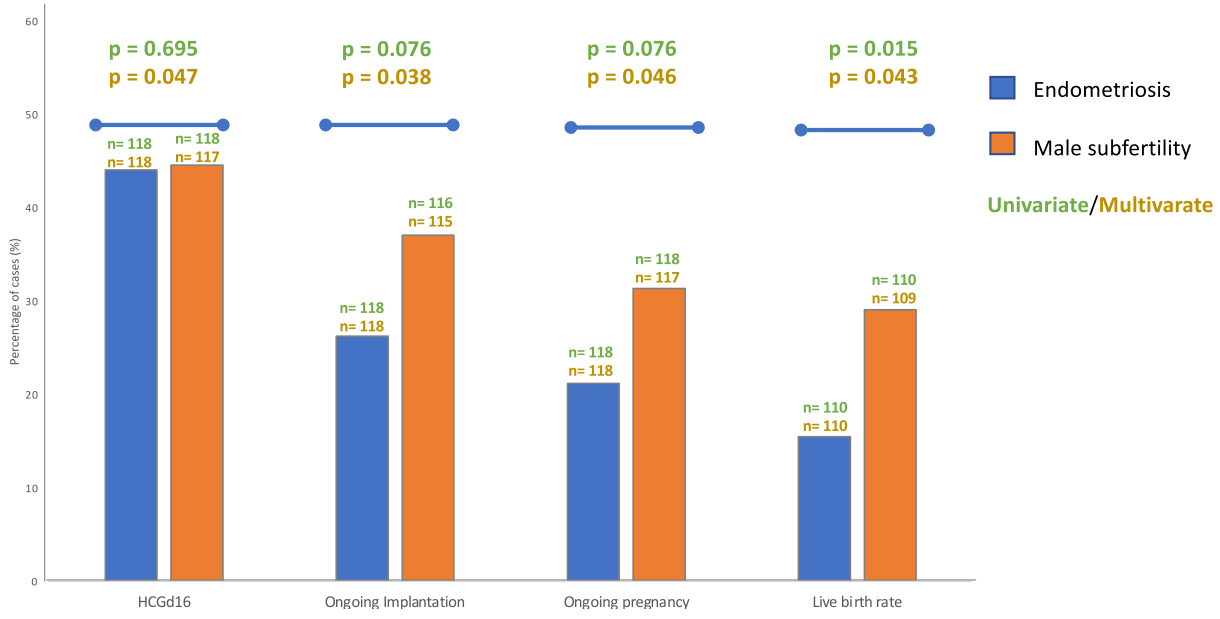

FIGURE 2 Outcome of beta-HCG test on day 16, ongoing implantation and pregnancy and live birth rate in endometriosis cases and male subfertility controls, compared using univariate tests and multiple logistic regression, which included the matching variables (embryo quality, woman's age and parity) and dysmenorrhoea, stimulation protocol and IVF or intracytoplasmic sperm injection use.

model was created adjusting for the matching variables (age, parity, embryo quality) and variables that reached significance during univariate tests: the grade of dysmenorrhoea, IVF or ICSI application and stimulation protocol. The described differences followed expectations as dysmenorrhoea is one of the major symptoms of endometriosis and the long agonist protocol is the experience-based preference for women with endometriosis in Ghent University Hospital. Furthermore, ICSI is preferred in cases of male subfertility, resulting in a more frequent application of ICSI in the control group. In this adjusted analysis, odds on positive ART outcomes in couples diagnosed with male subfertility were more than twice as large as in endometriosis patients, suggesting a significant alteration of implantation in patients with endometriosis, questioning the involvement of the uterine factor in pregnancy development in women with endometriosis. Finally, because of the high prevalence of male subfertility in the endometriosis group, a sub-analysis was conducted, which showed that the presence of co-existent male subfertility did not influence the outcomes ($P \geq 0.05$).

Comparison with other published studies is difficult because of differences in study design and populations. To the best of our knowledge, the present study is the first to use matching based on embryo quality, and thereby observing pregnancy outcomes. Therefore, a limited number of studies on implantation in women with endometriosis applying a male subfertility control group equally were compared. The following results were described and compared with our results: *Rubio et al. (1997)* and *Bukulmez et al. (2001)* described no significant difference in ongoing implantation, and *Bukulmez et al. (2001)* detected no significant effect on LBR. Both studies, however, only evaluated ICSI cycles and they suggest a reduction of the negative effect of endometriosis with the ICSI protocol (*Rubio et al., 1997*; *Bukulmez et al., 2001*). In the present study, however, after adjusting for IVF or ICSI application, results remained impaired, bringing the influence of ICSI effects into question. In contrast, *Kawwass et al. (2015)* reported a significant, but small, negative effect of endometriosis on ongoing implantation and LBR, but concluded that this is probably clinically irrelevant because of the large number of cycles. In addition, *Kawwass et al. (2015)* did not collect data on embryo quality. In conclusion, none of the available studies on equal embryo quality found a relevant significant negative influence of endometriosis on implantation in IVF/ICSI outcomes (*Rubio et al., 1997*; *Bukulmez et al., 2001*; *Kawwass et al., 2015*).

Studies selecting their control group on the basis of other subfertility issues, e.g. tubal factor, unexplained subfertility, pelvic adhesions and polycystic ovary syndrome, produced controversial results. First, most studies reported no overall effect of endometriosis on HCG tests or ongoing implantation (*Kuivasaari et al., 2005*; *Al-Fadhli et al., 2006*; *Matalliotakis et al., 2007*; *Coccia et al., 2011*). In a study by *Senapati et al. (2016)*, and a meta-analysis by *Barnhart et al. (2002)*, a significant negative effect of endometriosis was found on ongoing implantation and HCG tests and ongoing implantation, respectively. Second, *Senapati et al. (2016)* found a lower LBR in women with endometriosis, in line with the results of our study, whereas two other studies found no negative influence (*Kuivasaari et al., 2005*; *Matalliotakis et al., 2007*; *Senapati et al., 2016*). Limitations of these studies are the low sample numbers and the choice of control group. Most frequently, a tubal factor control group was applied, but as tubal disturbances could equally have lower implantation rates, the difference with endometriosis patients is lost. Furthermore, distinguishing endometriosis and tubal disease can be difficult (*Lessey, 2000*; *Al-Fadhli et al., 2006*).

The strength of our study design was the matching of embryo quality, whereby implantation and pregnancy outcomes could be observed from the start of a transfer of an equal quality embryo. The only studies striving for this discrimination and investigation of ovarian and uterine factor separately are oocyte donation studies. These studies involving endometriosis donors and fertile recipients reported a significant impairment of implantation, suggesting a lower quality of oocytes and embryos of endometriosis patients (*Simon et al., 1994*; *Shulman et al., 1999*; *Garrido et al., 2002*). On the other hand, studies of healthy donors and endometriosis recipients demonstrate no impaired implantation compared with our outcomes (*Simon et al., 1994*; *Sung et al., 1997*; *Moomjy et al., 1999*; *Navarro et al., 2000*; *Garrido et al., 2002*). These studies, however, do not specifically take embryo quality into account; moreover, low sample numbers and confounding factors were present (*Cakmak and Taylor, 2011*).

It is impossible to discuss the pathogenesis of endometriosis-associated subfertility without acknowledging the possible effect of adenomyosis. Adenomyosis was described in up to 91.1% of the women with endometriosis, and a common pathophysiologic process has been suggested, demonstrating the close relationship between the two pathologies (*Leyendecker et al., 2015*). As adenomyosis is a primarily uterine disease and is therefore associated with implantation failure, this might interfere with implantation in endometriosis patients (*Kunz et al., 2005*; *Tremellen et al., 2010*; *Cakmak and Taylor, 2011*; *Brosens et al., 2012*; *Maheshwari et al., 2012*; *Leyendecker et al., 2015*; *Younes and Tulandi, 2017*). Adenomyosis has been underreported because clinically useful diagnostic criteria and a classification system are lacking. This is evident in our study, in which only 3.4% had a confirmed adenomyosis diagnosis.

A retrospective matched cohort design was applied, as an observational study was the most appropriate approach because of the limited population numbers. The well-known risk of confounding associated with observational studies was reduced, e.g. by applying a single-centre study design and matching; however, several possible biases remain. In the first place, as only electronically recorded cycles were included, a selection bias could be present. As the number of previous IVF/ICSI cycles, duration of subfertility and percentage primary infertility, however, were similar between the cases and controls, next to the application of matching on parity, the risk of bias seems minimal. A second population bias could be caused by the lack of a complete, up-to-date gynaecological investigation before ART, including uncertainty about the extent of the endometriosis at the time of ART, a potential co-existence of adenomyosis and the impossibility of excluding mild endometriosis in the control group, as 76.9% of the control group had mild forms of dysmenorrhoea. Furthermore, 72.0% of the patients had undergone

previous surgery, which could improve outcomes by reducing the disease and impair outcomes by causing ovarian damage (*Mahutte and Arici, 2002*; *Harb et al., 2013*). In addition, 10.2% of women with endometriosis received medical pre-treatment with a GnRH agonist, potentially increasing rates of ongoing implantation, ongoing pregnancy and live birth rate (*Sallam et al., 2006*). In conclusion, several biases could have altered the outcomes in endometriosis, and future studies should take these considerations into account.

Extrapolations of the results of the present study to the general population should be made carefully, as ART protocols might have both a positive and negative effect on outcomes. First, ovarian stimulation might aggravate the development of endometriosis, as this is an oestrogen-dependent disease, although the study by *Mathiasen et al. (2018)* disproved this suggestion (*Dunselman et al., 2014*; *Mathiasen et al., 2018*). Conversely, *Bourdon et al. (2018)* detected a 50% reduction in cumulative live birth rate between fresh and frozen embryo transfers in women with endometriosis, possibly caused by the ovarian stimulation in fresh cycles. Second, in IVF/ICSI, gametes are not exposed to the potentially toxic peritoneal environment caused by endometriosis as they would be in natural conception. Third, oestrogen stimulation and luteal support could optimize the endometrial receptivity in women with endometriosis (*Yanushpolsky et al., 1998*; *Daya, 2009*). The internal validation of the results is not impaired by these arguments; however, because of the single-centre study design, case and control group were exposed to identical procedures, i.e. oocyte retrieval, oestradiol stimulation and luteal support.

In conclusion, the present study of implantation and pregnancy outcomes analysed after a transfer of equal quality embryos, by matching embryo quality, showed the odds of a positive HCG day 16, ongoing implantation, ongoing pregnancy and LBR were more than twice as low in the endometriosis group compared with couples undergoing ART because of a male subfertility diagnosis. This bring into question the alteration of the endometrial function in women with endometriosis, complementary to the already known impairment of ovarian function.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rbmo.2020.08.034.

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