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Early Embryo Development in Women with Endometriosis: A Retrospective Study

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ABSTRACT

Background: Endometriosis (EN) is known to be detrimental to fertility in many ways. Evidence drawn from oocyte recipient cycles suggests compromised oocyte quality in endometriosis. This retrospective case-control study aimed to evaluate embryo quality in women with endometriosis compared to those with tubal factor (TF) or unexplained infertility.

Methods: IVF cycles from two fertility centres were retrospectively analysed for oocyte yield, fertilisation, early embryo arrest and blastocyst formation. Multicentre retrospective studies were performed. Treatment cycles and embryology records of women with and without endometriosis undergoing IVF were reviewed via the IDEAS™ database. The number of oocytes collected per mature follicle, fertilisation rate, pregnancy rate, morphology and morphometric assessment of the embryo at all stages were evaluated.

Results: Women with endometriosis had fewer oocytes per mature follicle and a higher proportion of embryos that failed to reach the 8-cell stage. However, fertilisation rate, blastocyst formation and clinical pregnancy rate were not significantly different. A total of 678 women who had IVF treatment were analysed (EN, $n = 89$; TF, $n = 214$; unexplained subfertility [UE], $n = 375$). The mean age for each group were EN, 34.4 ± 3.3; TF, 33.5 ± 3.7 and UE, 34.6 ± 3.2, respectively. The number of mature follicles (>14 mm) on the day of trigger injection was similar ($P = 0.75$) between all groups. The percentage of oocytes collected per mature follicle was lower in endometriosis compared to other groups ($P = 0.01$; EN, 65 ± 23; TF, 76 ± 20; UE, 71 ± 24). Higher percentages of embryos fail to achieve the 8-cell stage in EN compared to control groups ($P = 0.02$; EN, 4.0 ± 1.6 TF, 1.2 ± 0.4; UE, 1.5 ± 0.4). Percentages of embryos at all grades (Grade 1–4) per woman were similar between the comparison groups ($P > 0.05$). EN did not impair ($P > 0.05$) blastocyst development or the development of fully expanded hatching blastocysts (FEHB).

Conclusions: EN may impair early embryo development through compromised oocyte quality, but not later embryo development or pregnancy rate. This study finds women with endometriosis have a lower number of oocytes per total number of follicles. The presence of endometriosis is associated with a higher rate of early embryo arrest, which implicates poor oocyte quality. However, endometriosis has no effect on the embryo quality beyond the 8-cell stage of embryo development.

***Keywords*:** Endometriosis; Endometrioma; In-vitro Fertilization.

INTRODUCTION

A significant number of subfertile women with endometriosis may eventually require assisted reproductive techniques (ART) with in vitro fertilisation (IVF) and/or intra-cytoplasmic sperm injection (ICSI) to conceive. Up to 15% of women undergoing ART have endometriosis.[1] Endometriosis (EN) is known to be associated with subfertility, although its pathophysiology is still unclear. EN can be detrimental to fertility at the level of the endometrium, oocyte and/or embryo.[2,3]

Research from our group and others showed that women with endometriosis have a lower number of oocytes retrieved per cycle of ART,[4–8] and those with endometrioma require a higher dose of follicle-stimulating hormone (FSH) stimulation and have a higher cancellation rate during their IVF cycles.[6] Animal studies suggest that oocyte and embryo development were poorer when exposed to follicular and peritoneal fluid of women with endometriosis.[9–11] Studies on oocyte recipient cycles showed poorer reproductive outcomes in recipients who receive oocytes from women with endometriosis, thus strongly suggesting that the oocyte quality of women with endometriosis is compromised,[12,13] although the vast majority of previous studies directly examining the impacts of endometriosis on oocyte and embryo quality fail to conclude

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that endometriosis detrimentally impacts oocyte and/or embryo quality as observed in ART cycles.[2,3,8,14–17] The oocytes from women with endometriosis have structurally and functionally abnormal mitochondria[18] and a higher rate of aneuploidy[19] compared to controls, although reports on the aberrant morphology of oocyte meiotic spindle are controversial.[20,21]

The current available studies examining the oocyte/embryo quality in women with and without endometriosis have the following limitations. Embryo morphological assessment[22] is traditionally subjected to a high intra- and inter-observer variability when considering factors associated with morphological dysmorphisms such as fragmentation, asymmetry and multinucleation despite the recent consensus on standardising.[23] Only one study utilised a standardised objective embryo morphological assessment.[2,23] Most studies made their assessments on day 3 rather than day 5, and none of the studies utilised data obtained from time-lapse technology. The majority of the studies assessed the embryo quality as a secondary outcome rather than as their primary outcome.

This study aims to assess the oocyte and embryo development based on recently performed ART cycles, using standardised criteria for the assessment of embryo development, to evaluate the quality of oocytes and embryos in women with endometriosis compared to those with no endometriosis.

Defined Research Question (PICO):

Population: Infertile women undergoing IVF

Intervention: Endometriosis

Comparator: Tubal factor (TF) and unexplained infertility

Outcome: Early embryo development (oocyte yield, arrest before 8-cell stage, blastocyst development)

METHODS

Data extraction

Ethical approval was obtained from the institutional review boards at both participating centres. Due to the retrospective nature, informed consent was not required. Data were anonymised and used in accordance with local governance policies.

This study was a retrospective case-control study, performed in two tertiary referral fertility centres in the United Kingdom. Anonymised data from IDEAS V.6™ (Electronic IVF database, Mellowood Medical, USA) from January 2011 to December 2014 in both fertility centres were extracted, analysed and reviewed. Data obtained from the database were exported to Excel (Microsoft, USA) before data analysis was performed using statistical analysis package.

Study group and inclusion/exclusion criteria

This study included women under 40 years old who underwent IVF treatment using their own gametes. Oocyte donor cycles (altruistic or sharer) or couples with co-existing male factor subfertility that required ICSI were excluded.

The study group (EN) consisted of women who were subfertile for at least 1 year with endometriosis, diagnosed laparoscopically and/or sonographically, irrespective of the disease severity and duration. All women with laparoscopically diagnosed and treated endometriosis were included in the study group, regardless of the type of surgical treatment performed.

Our control groups included women with TF subfertility or unexplained subfertility (UE) defined as being subfertile for at least 1 year with no identified reasons for subfertility (normal hormonal profile, patent tube(s) and normozoospermia). Women were considered to be in the TF group if they were subfertile for at least 1 year with evidence of tubal disease in either one or both tubes. If the tubes were blocked, resulting in hydrosalphinges, the normal practice in the United Kingdom would be to remove or clip the tube(s). They do not have a history of endometriosis, with the absence of any current signs or symptoms of endometriosis, and have no ultrasound evidence of endometriosis.

Ovarian stimulation protocols were limited to the antagonist cycle and long agonist cycle. Short flare agonist cycles were excluded. There were no restrictions on the type of stimulation drugs used; however, recombinant FSH was the predominant drug of choice, with a starting dose based on the age and AMH level, in accordance with local dosing protocol. The day of trigger (hCG) was determined by the presence of three or more follicles over 17 mm. The number of oocytes on the folliculogram >14 mm was an arbitrary level of cut-off taken to compare the oocyte retrieval rates between the two groups from follicles that were most likely mature at the time of oocyte collection. This is of particular interest because work from our group and others has shown a possibility of oocyte DNA damage as a sequela of endometriosis which impacts follicular maturation and development.[4,10]

Oocytes and embryos assessment

Qualified and trained embryologists from each centre performed the oocyte and embryo assessment. Following the oocyte retrieval procedure, oocytes were incubated in the culture media until the IVF procedure. Where possible, the collected oocytes were scored according to the appearance of cumulus cells, zona pellucida, and cytoplasm.[23]

Irrespective of the oocyte score, insemination was performed at approximately 1400H in the afternoon of the same day of egg collection. Fertilisation checks were done 17 ± 1 hours post-insemination (HPI). Normal fertilisation was defined as the presence of two polar bodies with two centrally located pronuclei that are evenly sized.

At 68 ± 1 HPI, all embryos were reassessed and scored using a standardised scoring system[23] according to the cell number, fragmentation rate and multinucleation. The scoring was documented in the embryology record electronically. At this stage, fertilised oocytes that had not cleaved were categorised as arrested at day 1 (D1) and were discarded.

On day 3, selected women underwent an embryo transfer procedure, which was decided according to the respective unit's embryo transfer criteria and protocol. Embryos that were not transferred at day 3 were cultured to the blastocyst stage. On day 5 of culture, embryos were rescored. Suitable good-quality blastocysts were usually frozen on the same day or the day after (D6) if the criteria were met.

Time-lapse

As an alternative to a conventional daily time-specific embryo morphological check, Eeva™ was used for embryo monitoring following the fertilisation check. Eeva™ uses non-invasive, time-lapse imaging of embryos during undisturbed incubation, which detects critical and subtle differences in cell division. The time-lapse data were available only in one of the two centres.

Outcome measure definitions

The number of oocytes retrieved is defined as the total number of oocytes collected per oocyte collection procedure. Percentage of oocytes per mature follicles is defined as the total number of oocytes collected over the total number of follicles (measuring >14 mm on the day of trigger). The number of fertilised oocytes is defined as the number of normally fertilised oocytes per number of patients. Fertilisation rate is defined as the number of normally fertilised

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oocytes per number of inseminated oocytes. Day one (D1) arrested embryo is defined as fertilised oocytes in which development has arrested and has not reached cleavage stage. On day 3, individual embryos were scored into four Grades (1, 2, 3, and 4). Grade 1 and Grade 2 embryos at day three were grouped and deemed as good-quality oocytes, whereas Grade 3 and Grade 4 were grouped and deemed as poor-quality oocytes. The number of embryos transferred and cryopreserved are defined as the number of embryos transferred into the uterus and frozen, respectively, over the number of patients. Utilisation rate is defined as the percentage of embryos transferred or cryopreserved over the number of oocytes retrieved. Blastulation rate is defined as the percentage of blastocysts over the number of fertilised oocytes. Fully expanded and hatching blastocyst (FEHB) is defined as good-quality blastocysts at Grade 4 and above. Clinical pregnancy is defined as the presence of at least one foetal heart. For time-lapse data, the time taken for the fertilised embryos to develop from the 2-pronuclei stage to 2 cell (P2) and 3 cell (P3) were recorded.

Statistical analysis and data representation

Statistical analyses were performed using unpaired *t*-tests for parametric data. The Fischer exact test or chi-square test was used for categorical data. A *P*-value <0.05 were considered to be significant. One-way ANOVA was used for comparison of more than two groups with the normally distributed data. If the ANOVA showed a statistically significant difference, post-hoc analysis was done using Tukey's post-hoc test. Kruskal–Wallis test was used for comparison of more than two groups with non-parametric data. All statistical analyses were performed using the Statistical Package for Social Sciences software, version 18 (SPSS Inc., Chicago, IL, USA) or Prism 6 (GraphPad, USA), except effect size, which was calculated using the Cohen's *d* Test (G*Power, USA). Data is expressed as mean ± standard deviation (SD) or standard error (SE) or as percentage ± SD or SE.

RESULTS

Demographic characteristics of the patients between groups

A total of 678 women who had IVF treatment were analysed, and they comprised three groups (EN, *n* = 89; TF, *n* = 214; UE, *n* = 375, Table 1). The mean age (years ± SD) for each group was EN, 34.4 ± 3.3, TF, 33.5 ± 3.7 and UE, 34.6 ± 3.2 (Table 1). Data for age were normally distributed, and there were no differences found between EN and the other groups (TF, *P* = 0.17; UE, *P* = 0.78, Table 1). Women in the TF group were, however, younger than UE groups (*P* = 0.002), with a small effect size, *d* = 0.3214 (Cohen *d* Test).

On the other hand, AMH levels were not normally distributed, and therefore non-parametric tests were performed which showed no significant difference between the three groups (*P* = 0.432; Median: EN, 11.7 [6.16–20.15]; TF, 15.7 [7.27–24.3]; UE, 12.28 [6.70–22.93], [Table 1]). There were significantly more women in the endometriosis group (*n* = 37, 42%) who had a long protocol compared to the control groups (TF, *n* = 17, 8%, *P* = 0.0001; UE, *n* = 15, 4%, *P* = 0.0001).

Women with endometriosis have lower number of oocytes retrieved per follicle >14 mm

The mean number of follicles (>14 mm) on the day of trigger injection was similar between all groups (*P* = 0.75; EN, 12 ± 5; TF, 13 ± 6; UE, 13 ± 6; Table 1). The mean number of oocytes (mean ± SE) collected at oocyte retrieval was similar (*P* = 0.31; EN, 8.6 ± 0.5; TF, 9.5 ± 0.4; UE, 9.2 ± 0.2; Table 1). The mean percentage of oocytes (mean ± SE) collected per follicle >14 mm was significantly lower in endometriosis compared to TF groups (*P* = 0.01; EN, 65 ± 3.4 and TF, 76 ± 1.7; Table 2) but similar between endometriosis and the unexplained group (*P* = 0.34; EN, 65 ± 3.4 and UE, 70 ± 1.5; Table 1).

Women with endometriosis have a similar fertilisation rate compared to controls

All the collected oocytes were inseminated irrespective of their maturity, and the mean number of fertilised oocytes (mean ± SE) per woman was found to be similar between groups (*P* = 0.31, EN, 5.7 ± 0.4; TF, 6.4 ± 0.3; UE, 6.3 ± 0.2; Table 2). The percentages of fertilised oocytes were calculated over the number of oocytes inseminated to represent the actual fertilisation rate. There were no differences in the mean percentage (mean ± SE) of oocytes fertilised per number of oocytes inseminated across the three groups (*P* = 0.76, EN, 66 ± 3.3; TF, 76 ± 1.7; UE, 71 ± 1.5; Table 1).

At this stage, unfertilised oocytes were discarded, and fertilised oocytes were incubated and cultured until another routine at day 3. The number and the rate of fertilised embryo that have successfully cleaved were examined.

Table 1. AMH result, number of oocytes retrieved, fertilisation rate and early embryo development amongst different comparison groups.

	Endometriosis (*n* = 89)	Tubal factor (*n* = 214)	Unexplained (*n* = 375)	*P*-value
AMH (pmol/L)	11.7 (6.2–20.2)	15.7 (7.3–24.2)	12.3 (6.7–22.9)	0.43
Number of long protocol cycles (%)	37 (42)	17 (8)	15 (4)	0.001
Number of follicles at trigger*	12 ± 5	13 ± 6	13 ± 6	0.75
Oocyte retrieval rate per follicle	65 ± 3.4	76 ± 1.7	71 ± 1.5	0.01
Number of fertilised oocytes	5.7 ± 0.4	6.4 ± 0.3	6.3 ± 0.2	0.31
Fertilisation rate (%)**	66 ± 3.3	70 ± 1.7	69 ± 1.5	0.76
Number of embryos arrested at D1	0.14 ± 0.4	0.08 ± 0.3	0.11 ± 0.7	0.69
Rate of embryo arrested at D1 (%)***	4.0 ± 1.6	1.2 ± 0.4	1.5 ± 0.4	0.02

*Number per patient ± SE; **Percentage of fertilised oocyte per collected oocyte ± SE; ***Percentages of arrested embryo per fertilised oocyte.
AMH = Anti Mullerian Hormone, D1 = day 1.

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Women with endometriosis have a higher early embryo arrest and poorer progression to the 8-cell cleavage rate

Following the fertilisation check, fertilised oocytes were cultured and incubated before reassessment at 68 ± 1 hours post insemination. During the assessment, fertilised oocytes were expected to cleave and progress to the 8-cell stage. At this stage of the assessment, the majority of the oocytes were found to have developed further, but some were arrested and had failed to cleave. The mean number (mean ± SE) of arrested embryos per woman was similar amongst the three groups ($P = 0.688$; EN, 0.14 ± 0.4; TF, 0.08 ± 0.3; UE, 0.11 ± 0.7; Table 1). The rate of embryo arrest per fertilised oocyte (percentage mean ± SE) was significantly lower in women with endometriosis compared to controls ($P = 0.02$; EN, 4.0 ± 1.6 TF, 1.2 ± 0.4; UE, 1.5 ± 0.4; Table 1). Post-hoc analysis showed a higher percentage of arrested embryos in the EN compared to the TF groups ($P = 0.02$; MD 2.77, 95% CI [0.33, 5.21]; Table 1) and UE groups [$P = 0.03$, MD 2.51, 95% CI [0.22, 4.79]; Table 1].

Embryo development and quality at day 3 were unaffected by endometriosis

Embryo assessment at day 3 was usually performed to monitor the development of individual embryos and to choose the most suitable embryo/s for transfer or for extended culture until blastocyst stage, with the clinical circumstances taken into account. In this study, the mean percentages of embryos +/− SE amongst all grades of embryo per woman were similar between the comparison groups; Grade 1 embryos ($P = 0.651$; EN, 23 ± 3.4; TF, 20 ± 1.9; UE, 22 ± 1.5; Table 2), Grade 2 embryos ($P = 0.242$; EN, 42 ± 3.2; TF, 43 ± 2.0; UE, 39 ± 1.5; Table 2), Grade 3 embryos ($P = 0.768$; EN, 24 ± 2.8; TF, 26 ± 1.8; UE, 26 ± 1.3; Table 2), and Grade 4 embryos ($P = 0.607$; EN, 12 ± 2.4; TF, 12 ± 2.2; UE, 13 ± 2.2; Table 2).

Considering the tools were subjective and had high inter- and intra-observer variability, embryos graded as 1 and 2 were pooled as 'good quality' embryos, whilst embryos graded as 3 and 4 pooled as 'poor quality'.

There were no differences in percentages across the three comparison groups, whether the comparison was made with good-quality embryos ($P = 0.59$; EN, 64 ± 4.0; TF, 63 ± 2.3; UE, 61 ± 1.8) or the poor-quality embryos ($P = 0.59$; EN, 36 ± 4.0; TF, 37 ± 2.3; UE, 39 ± 1.8).

The development of blastocyst or fully expanded hatching blastocysts (FEHB) were similar in women with endometriosis compared with controls

Women who had a blastocyst transferred at day 5 or D6 were accounted for in the blastocyst number and blastulation rate. Those who already had an embryo transferred before day 5 were excluded from this analysis.

The number of embryos (mean ± SD) at the blastocyst stage per woman were similar amongst all three groups ($P = 0.62$; EN, 4.2 ± 2.5; TF, 3.8 ± 2.2; UE, 3.7 ± 2.2; Table 2), and the blastulation rate was also similar across all groups ($P = 0.50$; EN, 51 ± 4.3; TF, 49 ± 2.3; UE, 46 ± 1.9; Table 2).

FEHB per woman were found to be similar amongst the three groups ($P = 0.38$; EN, 2.8 ± 0.4; TF, 3.0 ± 0.2; UE, 2.6 ± 0.2; Table 2), and FEHB rate per fertilised oocyte were not statistically different across the three groups ($P = 0.34$; EN, 35 ± 3.9; TF, 38 ± 2.4; UE, 34 ± 2.2; Table 2).

Utilisation of embryos was similar between women with and without endometriosis

The utilisation rate represented the number of embryos transferred and the number of embryos frozen per cycle individually and also in combination. The utilisation rate was the percentage of total transferred and frozen embryos per woman over the total number of oocytes retrieved per woman.

The number of embryos transferred per cycle (mean ± SD) was the same among the comparison groups ($P = 0.18$; EN, 1.5 ± 0.7; TF, 1.5 ± 0.6; UE, 1.5 ± 0.6; 3). The mean number of embryos cryopreserved per cycle (mean ± SE) was also the same across all groups ($P = 0.86$; EN, 1.6 ± 2.3; TF, 1.5 ± 2.3; UE, 1.6 ± 2.3; Table 3).

The number of embryos utilised was similar among the comparison groups ($P = 0.53$; EN, 2.8 ± 0.2; TF, 2.9 ± 0.1; UE, 3.0 ± 0.1; Table 3). The percentages of utilisation rate were also similar among the comparison groups ($P = 0.91$; EN, 36 ± 2.3; TF, 35 ± 1.5; UE, 37 ± 1.1; Table 3).

Pregnancy outcomes were not affected by endometriosis

The clinical pregnancy rate in women with endometriosis (39.7%) was similar ($P = 0.254$) when compared to those with no

Table 2. Quality of embryos from D3 onwards for different comparison groups.

	Endometriosis ($n = 89$)	Tubal factor ($n = 214$)	Unexplained ($n = 375$)	*P*-value
Number of D3 embryos	4.9 ± 4	5.8 ± 4	5.8 ± 4	0.14
Quality of embryo at D3 (%)*				
Grade 1	23 ± 3.4	20 ± 1.9	22 ± 1.5	0.65
Grade 2	42 ± 3.2	43 ± 2.0	39 ± 1.5	0.24
Grade 3	24 ± 2.8	26 ± 1.8	26 ± 1.3	0.77
Grade 4	12 ± 2.4	12 ± 1.4	13 ± 1.2	0.61
Number of blastocysts**	4.2 ± 2.5	3.8 ± 2.2	3.7 ± 2.2	0.62
Blastulation rate (%)	51 ± 4.3	49 ± 2.3	46 ± 1.9	0.50
FEHB**	2.8 ± 2.1	3.0 ± 2.0	2.6 ± 1.9	0.38
FEHB rate (%)	35 ± 3.9	38 ± 2.4	34 ± 2.2	0.34

*Percentages per total D3 embryos ± SE; **Number of embryos per patient ± SE.

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Table 3. Utilisation of embryos per patient amongst different comparison groups.

	Endometriosis (n = 89)	Tubal factor (n = 214)	Unexplained (n = 375)	P-value
Number of embryos transferred*	1 ± 0.5	1 ± 0.5	1 ± 0.6	0.79
Number of embryos cryopreserved*	1.6 ± 2.3	1.5 ± 2.3	1.6 ± 2.3	0.43
Cryopreservation rate (%)**	18 ± 3.1	24 ± 1.7	19 ± 1.0	0.11
Number of utilised embryos*	2.8 ± 0.2	2.9 ± 0.1	3.0 ± 0.1	0.30
Utilisation rate (%)**	36 ± 2.3	35 ± 1.5	37 ± 1.1	0.91

*Percentages per total D3 embryos ± SE; **Number of embryos per patient ± SE.

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endometriosis (TF, 43.6; UE, 38.7%). We were not able to obtain, however, the number of live birth rates.

DISCUSSION

This study confirms a lower number of oocytes retrieved per mature follicle in women with endometriosis. Despite similar follicular development, this may reflect impaired oocyte maturation. Early embryo arrest was more frequent in the endometriosis group, suggesting compromised oocyte quality. However, embryos that developed beyond the 8-cell stage showed similar developmental competence and pregnancy outcomes. Limitations include retrospective design, inter-observer variability in embryo grading, and incomplete data on surgical treatment, confounders, and live birth outcomes. Future prospective studies with time-lapse imaging and live-birth data are warranted.

The follicular response to ovarian stimulation appeared to be unaffected by the presence or absence of endometriosis, as there were similar numbers of antral follicles and mature follicles in all the groups prior to oocyte collection. However, the lower number of oocytes collected suggests the possible impacts of the endometriotic disease on oocyte development.[11] There are several factors affecting the physiological oocyte-maturation process, for example, intrinsically by high levels of oxidative stress, and extrinsically by cigarette smoking, ultraviolet (UV) radiation, or toxic drugs. Despite these effects, a more direct effect on the developing oocyte can be related to an aberrant follicular microenvironment in women with endometriosis. The content of a follicle is physiologically important for oocyte development and in endometriosis, the cellular and molecular milieu from the disease is known to mediate the damage to the ovary and the developing oocytes.[24]

Whilst the fertilisation rates were not statistically different across the groups, the fertilised oocytes in the endometriosis group were more likely to arrest and fail to cleave from fertilisation to the 8-cell stage. The higher number of early embryo arrests at day 1 (D1) suggests the presence of poor oocyte quality.[25]

Despite a higher rate of D1 arrest, embryos of women from the endometriosis group that successfully cleaved were shown in this study to have similar developmental potential. At the day 3 assessment, the majority of the embryos achieved comparable quality compared to the control groups. The results were unaffected when the graded embryos were re-categorised into two groups of good and poor-quality embryos. This finding is not unexpected, as the poorer-quality oocytes that failed to develop beyond the 8-cell stage were already excluded. The latter may represent a natural biological triaging mechanism for quality control so as to prevent poor-quality oocytes from developing further, and it therefore follows that the pregnancy rate is not dissimilar when compared to the control groups.

Embryos that were not transferred at day 3 had an extended culture up to day 5, when they were further assessed. At this stage, suitable blastocysts were transferred or cryopreserved for future use. In this study, the blastulation rate and FEHB rate were similar in the endometriosis group compared to the control groups, which suggests that the increased aneuploidy rate reported by previous studies may not be apparent at embryological assessment.[19,26] This study also found similar utilisation rates of embryos between the groups, indicated by an equal number of embryos transferred and frozen per collected oocytes. This is counter-intuitive, as one expects a higher rate of arrest prior to the 8-cell stage in the endometriosis group, which in turn leads to a lower number of embryos available for freezing. This study may not be sufficiently large in sample size to delineate the difference, or the difference may become more apparent in older women or in women with low ovarian reserve, which are two groups of women not specifically examined in this study.

Although, with careful selection of the comparison groups, this study suffers from potential false positives and false negatives in relation to the diagnosis of endometriosis. Participants included in this study were grouped into those with endometriosis and those without. In the endometriosis group, women who had diagnostic laparoscopy did not necessarily receive the same surgical treatment (endometriotic spot ablation, excision, or endometrioma cystectomy); it was also not known whether these women had a complete resolution, still had residual disease, or had developed disease recurrence. The progress of the disease following surgical treatment is unpredictable and may impact IVF treatment outcomes. The presence of heterogeneity in surgical treatment and its stages may influence the success rate of IVF treatment.[27] However, these data were not available. Our inclusion criteria for the control group are likely to have excluded most women with significant endometriosis. The only group of women we were not able to exclude confidently are those with superficial peritoneal endometriosis. However, including or excluding those with superficial peritoneal endometriosis warrants performing a laparoscopy on every subfertile patient undergoing IVF. The latter is not the current practice and is also not recommended.[28] We therefore do not feel that this is justifiable, especially in the context of a retrospective study.

Additionally, potential confounders such as BMI, smoking, parity, number of prior ART cycles and undiagnosed adenomyosis were not controlled for. This should be considered a significant limitation of the study.

The mean numbers of oocytes retrieved and mature oocytes would generally be higher in agonist cycles[29–31] than in antagonist cycles, and hence, whilst the comparison groups were not balanced in terms of the stimulation regimen, with the endometriosis group having a higher number of participants who had long agonist

treatment, we believe that this would likely underestimate rather than exaggerate the difference between the two groups.

Embryology data gathered from this study were retrospective and were based on time-specific, standardised morphological assessment, which is still subject to inter- and intra-observer variability. As an alternative, it is now possible to use non-invasive, time-lapse imaging of embryos within an undisturbed incubator. By using this technology, critical and subtle differences in cell division can be recorded and analysed in greater detail. This will provide more reliable data compared to the former, although a larger study on this aspect of the data will need to be conducted in future.

CONCLUSIONS

Our study demonstrated that women with endometriosis have a lower number of oocytes collected per follicle >14 mm. The fertilisation rates were not dissimilar amongst the comparison groups, but the presence of endometriosis was associated with a higher rate of early embryo arrest, implicating poor oocyte quality. Accepting the limitations discussed, endometriosis did not impact embryo quality beyond the 8-cell stage or the overall clinical pregnancy rate.

DISCLOSURE

Nothing to disclose for all the authors.

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