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Short Communication

Comparison of success rates in early stages of in vitro fertilization (IVF) in women with and without endometriosis

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Abstract

Endometriosis remains a significant challenge for reproductive-aged women and is frequently associated with infertility. Although in vitro fertilization (IVF) is used to address infertility in women with endometriosis, its effectiveness in this context is still debated, particularly in developing countries such as Indonesia, where IVF remains a major challenge. The aim of this study was to investigate the success rates of early stages of IVF in women with and without endometriosis. A retrospective cohort study was conducted at the Graha Amerta Fertility Clinic, located within Dr. Soetomo Academic General Hospital in Surabaya, Indonesia. The quantity and quality of oocytes (the number of oocytes obtained by ovum pick-up (OPU) and the number of metaphase II (MII) oocytes), fertilization quality (the number of two-pronuclei oocytes and fertilization rate), embryo development quality (cleavage rate and blastocyst rate), biochemical pregnancy, clinical pregnancy, and live birth rate were collected from IVF patients between 2017–2022. Independent Student's t-test or Mann-Whitney test was used accordingly for comparison analysis. A total of 410 IVF patients were included in the study; 93 had endometriosis, while 317 had no endometriosis. Oocyte quantity obtained by OPU (p=0.016) and oocyte quality (p=0.045), as measured by the number of MII oocytes, were significantly lower in the endometriosis group compared to the non-endometriosis group. However, there were no significant differences between the two groups in terms of the number of two-pronuclei oocytes (p=0.105), fertilization rate (p=0.987), cleavage rate (p=0.467), blastocyst rate (p=0.128), biological pregnancy rates (OR: 0.98; 95%CI: 0.60–1.60; p=0.940), clinical pregnancy rate (OR: 0.69; 95%CI: 0.39–1.24, p=0.219), or live birth rate (p=0.609). These findings suggest that while endometriosis may reduce oocyte quantity and quality, it does not significantly impact the success rates of IVF.

Keywords: Endometriosis, in vitro fertilization, oocyte, pregnancy, live birth rate

Introduction

Endometriosis remains a significant concern for women of reproductive age and is frequently associated with infertility [1,2]. While the exact mechanisms through which endometriosis leads to infertility are not fully understood, it is believed to adversely affect ovarian reserves, oocyte quality, and embryo quality [3]. In vitro fertilization (IVF), a series of treatments that includes the extracorporeal fertilization of gametes, is a commonly used assisted reproductive technology for managing endometriosis-related infertility in women [4]. However, IVF presents considerable challenges in Indonesia, as a developing nation [5].

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The impact of endometriosis on IVF outcomes has been a subject of ongoing debate, with some studies presenting conflicting results [3,6,7]. Some studies suggest that endometriosis may negatively impact IVF success rates by reducing pregnancy and live birth rates [8-10]. It can affect various aspects of reproductive functions, including ovarian responsiveness to stimulation, oocyte quality, and endometrial receptivity [11]. Conversely, other studies found no statistically significant difference in IVF outcomes between women with and without endometriosis, indicating that endometriosis may not necessarily impair fertility in every case [12-14]. The aim of this study was to investigate the success rates of early stages of IVF in women with and without endometriosis in Indonesia.

Methods

Study design and settings

A retrospective cohort study was conducted at the Graha Amerta Fertility Clinic, located within Dr. Soetomo Academic General Hospital in Surabaya, Indonesia, between 2017 and 2022. This study determined the difference between patients with and without endometriosis in the quantity of oocytes obtained by ovum pick-up (OPU), the quantity of metaphase II (MII) oocytes, the quantity of two-pronuclei oocytes, the fertilization rate, the cleavage rate, the blastocyst rate, the biochemical pregnancy rate, the clinical pregnancy rate, and the live birth rate. Total sampling was employed in this study.

Patients

The endometriosis group included infertile women diagnosed with endometriosis undergoing IVF. The diagnosis was based on clinical symptoms, physical examination, transvaginal ultrasonography (TVUS) examination, a history of cystectomy with pathological findings of endometrioma, or diagnostic laparoscopy. In addition, the non-endometriosis group included infertile women undergoing IVF with benign gynecological disorders other than endometriosis, as well as those with infertility solely attributed to male sperm factors. Patients with irregular menstrual cycles or polycystic ovarian syndrome (PCOS) were excluded from the study.

Data collection

Data were collected from medical records of patients at the Graha Amerta Fertility Clinic who underwent IVF treatment between 2017 and 2022. All patients who met the inclusion and exclusion criteria were also contacted for telephone interviews to complete and verify the information in their medical records.

The IVF process involved ovarian stimulation using a combination of fertility drugs, oocyte retrieval (OPU) from ovarian follicles, and fertilization of oocytes in vitro with sperm. Approximately 18 hours after intracytoplasmic sperm injection (ICSI), two pronuclei (2PN) within the zygote would confirm successful fertilization. The resulting embryos were then transferred into the uterus. Embryo transfer could occur at either of the two developmental stages: cleavage stage embryos, transferred to the uterus 4–8 hours after fertilization, or blastocyst stage embryos, transferred on day five, which were considered superior in quality. The luteal phase was supported by progesterone supplementation to enhance endometrial receptivity. A beta-human chorionic gonadotropin (β-hCG) blood test was performed following embryo transfer to determine the success of the IVF cycle and confirm pregnancy. The IVF process was documented in the patient's medical records at each stage.

Study outcomes

All oocyte evaluations were conducted using a microscope. The quantity of oocytes obtained during OPU was determined by counting the total number of oocytes retrieved, irrespective of their maturity stage. Oocyte quality by OPU was assessed by counting the number of MII oocytes, which are mature oocytes that have completed the first polar body division, indicating readiness for fertilization [7].

Fertilization quality was evaluated based on the number of fertilized oocytes and the fertilization rate. The number of fertilized oocytes was defined by the number of 2PN oocytes, which contain two distinct nucleus [14]. This evaluation was performed 18 to 20 hours post-

intracytoplasmic sperm injection (ICSI). The fertilization rate was calculated by dividing the number of 2PN oocytes by the total number of oocytes injected with sperm and was expressed as a percentage [8].

Embryo development quality was assessed through cleavage and blastocyst rates. The cleavage rate was determined by counting the number of embryos reaching the four-cell stage by day 3 (D-3) post-fertilization and dividing this by the total number of fertilized oocytes, with the result expressed as a percentage [4]. The blastocyst rate was calculated by counting the number of embryos that developed into the blastocyst stage by day 5 (D-5) and dividing this by the total number of fertilized oocytes, also expressed as a percentage [4].

Biochemical pregnancy was defined as a positive beta-human chorionic gonadotropin (β-hCG) test result exceeding 20 IU/mL on day 12 post-embryo transfer. Clinical pregnancy was confirmed through the detection of a fetal heartbeat via ultrasound. The live birth rate was calculated by dividing the number of live births by the total number of embryo transfers [15].

Statistical analysis

To compare the outcomes between the two groups, independent t-test was employed for normally distributed data, while the Mann-Whitney test was used for non-normally distributed data. Meanwhile, nominal variables were analyzed using the Chi-squared test. Statistical significance was considered at $p<0.05$ and analyses were conducted using SPSS software (SPSS Inc., Chicago, USA).

Results

Characteristics of the patients

Out of 920 initial IVF patients, 445 were excluded due to irregular menstrual cycles, PCOS, or incomplete records. After further exclusions due to loss of follow-up, 93 patients were confirmed and included within the endometriosis group, and 317 patients were classified as non-endometriosis (**Figure 1**). A total of 410 IVF patients were included in this study, as presented in **Table 1**. The mean age of the patients was 32 years and the average duration of infertility was 6 to 7 years. There were no significant differences in age and duration of infertility between the groups, indicating that the two groups were comparable.

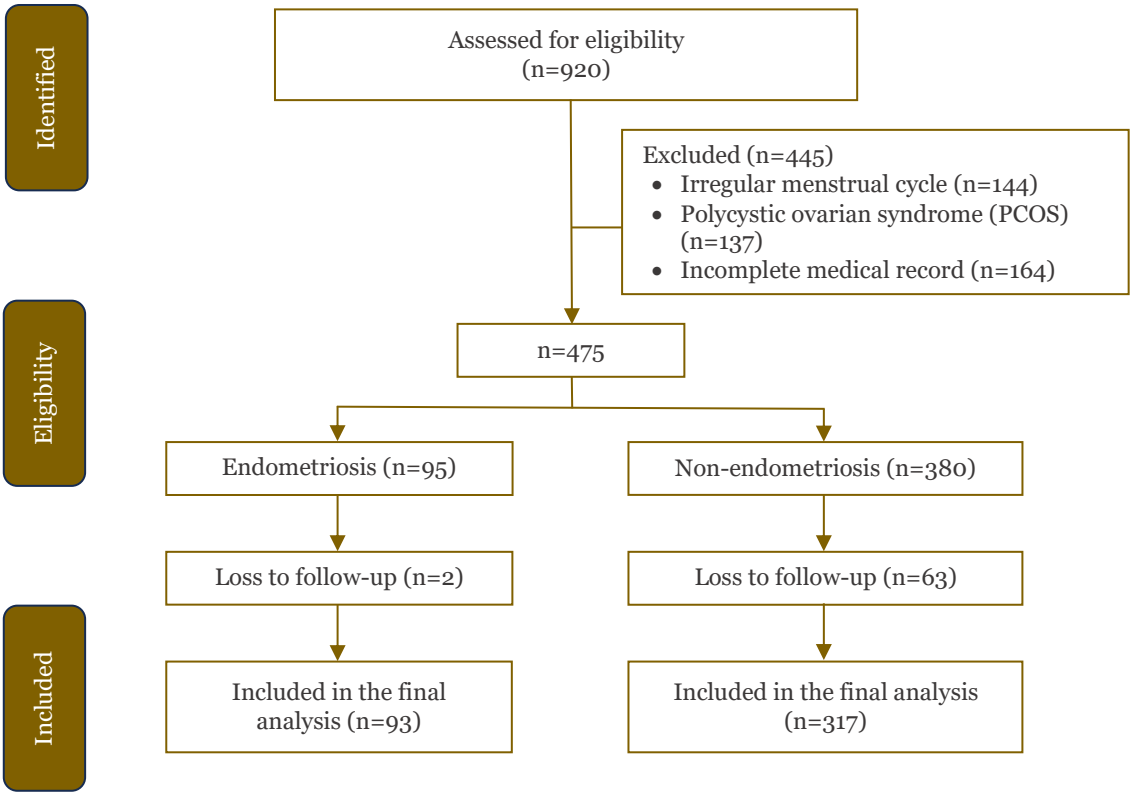

Figure 1. CONSORT flow diagram of the study.

Table 1. Characteristics of women with and without endometriosis underwent in vitro fertilization (IVF) included in this study

Characteristics	Endometriosis n=93	Non-endometriosis n=317	*p*-value
Age			
Mean±SD	32.63±4.03	32.81±3.90	0.697[a]
Median (min-max)	33 (20–42)	33 (23–42)	
Duration of infertility			
Mean±SD	6.5±3.83	6.79±3.51	0.293[a]
Median (min-max)	6 (0.5–18)	6 (0.8–18)	

[a] Analyzed using Mann-Whitney test

Comparison of quantity and quality of oocytes, quality of fertilization, and quality of embryo development

The endometriosis group received a median of seven oocytes by OPU, while the non-endometriosis group received a median of eight. In the endometriosis group, the median number of mature oocytes at the MII stage was six, compared to seven in the non-endometriosis group. Significant differences were observed between the groups in both the number of oocytes obtained by OPU and the number of MII stage oocytes, with p=0.016 and p=0.045, respectively. Conversely, the quality of fertilization and the quality of embryo development had no significant differences (**Table 2**).

Table 2. Comparison of the quantity and quality of oocytes, quality of fertilization, and quality of embryo development between women with and without endometriosis who underwent in vitro fertilization (IVF)

Outcome	Endometriosis n=93	Non-endometriosis n=317	*p*-value
The quantity and quality of oocytes			
Number of oocytes obtained by OPU (cells)			0.016[a*]
Mean±SD	7.86±4.48	9.40±5.63	
Median (min-max)	7 (1–24)	8 (1–33)	
Numbers of MII oocytes (cells)			0.045[a*]
Mean±SD	6.42±3.6	7.57±4.64	
Median (min-max)	6 (1–17)	7 (0–28)	
The quality of fertilization			
Number of two pronuclei (2PN) oocytes (cells)			0.105[a]
Mean±SD	4.99±3.14	5.73±3.67	
Median (min-max)	5 (0–15)	5 (0–24)	
Fertilization rate (%)			0.987[a]
Mean±SD	77.52±22.48	78.32±20.09	
Median (min-max)	80 (0–100)	80 (0–100)	
The quality of embryo development			
Cleavage rate (%)			0.467[a]
Mean±SD	71.58±32.26	75.21±28.79	
Median (min-max)	80 (0–100)	83 (0–100)	
Blastocyst rate (%)			0.128[a]
Mean±SD	21.56±30.25	26.79±32.20	
Median (min-max)	0 (0–100)	10 (0–100)	

MII: metaphase II; OPU: ovum pick-up
[a] Analyzed using Mann-Whitney test
[*]Statistically significant at p<0.05

Comparison of pregnancy rate and live birth rate

No significant differences were observed between the two groups in terms of biochemical pregnancy or clinical pregnancy (**Table 3**). The incidence of biochemical pregnancies was lower in the endometriosis group (33.3%) compared to the non-endometriosis group (OR: 0.98; 95%CI: 0.60–1.60). Similarly, the clinical pregnancy rate was also lower (19.4%) in the endometriosis group (OR: 0.69; 95%CI: 0.39–1.24). Live birth rates between the endometriosis group and the non-endometriosis group had no significant differences. The mean live birth rate was 7.25% in the endometriosis group and 8.29% in the non-endometriosis group (**Table 3**). Despite the lack of significant differences, **Figure 2** indicates that the non-endometriosis group had slightly better average outcomes for early-stage IVF than the endometriosis group.

Table 3. Comparison of biochemical pregnancy rates, clinical pregnancy rates, and live birth rates between women with and without endometriosis who underwent in vitro fertilization (IVF)

Outcome	Endometriosis (n=93)	Non-endometriosis (n=317)	OR (95%CI)	*p*-value
	Frequency (%)	Frequency (%)		
Biochemical pregnancy			0.98 (0.60–1.60)	0.940[a]
Yes	31 (33.3%)	107 (33.8%)		
No	62 (66.7%)	210 (66.2%)		
Clinical pregnancy			0.69 (0.39–1.24)	0.219[a]
Yes	18 (19.4%)	81 (25.6%)		
No	75 (80.6%)	236 (74.4%)		
Live birth rate (%)			N/A	0.609[b]
Mean±SD	7.25±17.93	8.29±18.48		
Median (min-max)	0 (0–100)	0 (0–100)		

[a] Analyzed using Chi-squared test
[b] Analyzed using Mann-Whitney test

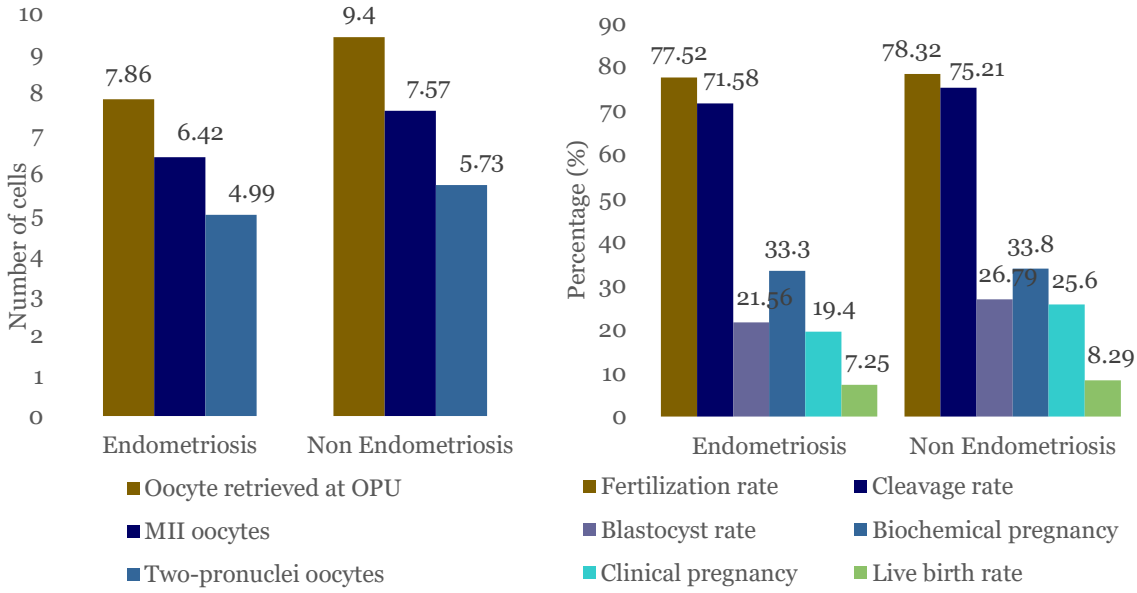

Figure 2. Comparison of several in vitro fertilization (IVF) outcomes among patients with and without endometriosis.

Discussion

Our study demonstrated that women with endometriosis retrieved a statistically significant lower number of oocytes during OPU compared to those without the disease. This finding aligns with a previous study and numerous meta-analyses, suggesting a consistent negative impact of endometriosis on oocyte quantity [11,16-18]. This decrease is likely multifactorial, with potential causes being the physical compression of ovarian tissue by endometrioma masses and the inflammatory response triggered by endometriosis. Specifically, endometriotic fluid secretes interleukin-1 (IL-1), which reduces ovarian sensitivity to gonadotropin stimulation by downregulating the expression of FSH and LH receptors [18].

Our assessment of oocyte quality revealed that the endometriosis group had a significantly reduced number of mature (MII) oocytes. This finding is consistent with a study showing that the endometriosis group had a significantly lower MII oocyte count (0.6±0.3) compared to the control group (1.4±0.2) [19]. Another study demonstrated similar results, indicating that women with endometriosis had significantly fewer MII oocytes than the control group (6.99±5.41 vs. 8.33±5.97, p=0.04) [11]. Several factors likely contribute to the decline in both the quantity and quality of oocytes in endometriosis, including the production of cytokines that promote inflammation (IL-1, IL-6, IL-8, and tumor necrosis factor-alpha (TNF-α)) in the peritoneal fluid, excessive generation of reactive oxygen species (ROS), and disrupted folliculogenesis [5,11,20].

On the other side, our study found that the number of 2PN oocytes and fertilization rates did not significantly differ between women with and without endometriosis. This finding is consistent

with several studies reporting no substantial impact of endometriosis on fertilization rates and the number of 2PN oocytes [21-24]. However, it is important to acknowledge that other studies have reported contrasting findings [11,25]. This discrepancy underscores the need for further research to clarify the relationship between endometriosis and fertilization outcomes. For instance, sperm attributes may also contribute towards fertilization rates; the formation of 2PN oocytes, which results from the fertilization of selected oocytes by spermatozoa, is influenced by sperm motility. Previous studies have shown a strong correlation between reduced sperm count and decreased fertilization success [26,27]. Additionally, there is a significant negative correlation between high levels of DNA fragmentation in low-quality sperm and fertilization rates [26,27]. Notably, the omission of sperm analysis was identified as a limitation in this study.

In line with several other studies [7,28,29], no significant differences in cleavage or blastocyst rates were found between patients with and without endometriosis. However, it is important to note that solely relying on morphological assessments may not fully capture the impact of endometriosis on embryo quality. Factors such as altered morphokinetics or intrinsic changes like multinucleation—found to be more prevalent in embryos from women with endometriosis—could be missed. Additionally, disruptions in the cell cycle of embryos from endometriosis patients might affect embryo quality [30]. Furthermore, sperm quality is crucial for embryo development, as issues such as DNA damage and centrosome defects can impede cell division and reduce embryo quality [31]. Therefore, while our results do not show a substantial difference in blastocyst and cleavage rates, further investigation is needed to thoroughly assess the effect of endometriosis on embryo quality, considering both morphological and molecular factors.

Similarly, we found no statistically significant difference in biological and clinical pregnancy rates between women with and without endometriosis. This result is in accordance with previous studies, which also reported no notable differences in fertilization rates, embryo quality, or pregnancy rates between these two groups [16,21]. Additionally, a previous study using the endometrial receptivity analysis (ERA) tool found no significant difference in the expression of 238 genes related to endometrial receptivity between women with and without endometriosis [32]. This is noteworthy, considering successful pregnancy relies on embryo implantation, a process that requires a receptive endometrium. Such findings suggest that endometrial receptivity is similar regardless of the presence or severity of endometriosis, further supporting our conclusion that endometriosis does not significantly impact pregnancy rates [32].

Consistent with previous studies and numerous meta-analyses, our analysis did not reach statistical significance in comparing live birth rates between women with endometriosis and those without it [3,6,7,22]. These results imply that although endometriosis-affected women may have lower oocyte counts and quality compared to women with other infertility diagnoses, this does not always translate into decreased rates of pregnancy or live births.

Our study had several limitations to acknowledge. Our sample mainly consisted of patients from outside Surabaya and included medical records from 2017 to 2022, a period that covered the COVID-19 pandemic. The pandemic may have affected healthcare access and potentially led to treatment delays, which could have influenced our results. Therefore, further research in a more controlled setting, free from such external factors, is necessary to definitively assess the relationship between endometriosis and live birth rates following IVF.

Conclusion

Endometriosis may reduce the quantity and quality of oocytes, but it does not significantly affect the overall success rates of IVF in achieving pregnancy. This suggests that despite potential challenges in oocyte retrieval and fertilization, women with endometriosis can still achieve similar pregnancy rates through IVF as women without the condition.

Ethics approval

The Health Research Ethics Committee of Dr. Soetomo Hospital Surabaya has granted ethical approval for this study, with certificate number 1494/LOE/301.4.2/X/2023. The confidentiality of the study subjects was preserved by the practice of anonymizing their identities and ensuring that their data was solely utilized for research objectives.

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None to declare.

Competing interests

No conflict of interest was declared by the authors.

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Underlying data

All data underlying the results are available as part of the article and no additional source data is required.

How to cite

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