




Endometriosis does not affect live birth rates of patients submitted to assisted reproduction techniques: analysis of the Latin American Network Registry database from 1995 to 2011

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Abstract

Purpose The purpose of this study is to compare the results of ART treatment in patients with and without endometriosis in a large cohort of patients from different centers over an extended period of time.

Methods This retrospective study is using data from patients undergoing 27,294 cycles of IVF/ICSI treatment between 1995 and 2011 that were registered in the database of the Latin American Registry maintained by the Latin America Network of Assisted Reproduction.

Results The mean number of retrieved oocytes was higher in the control group, but the mean number of metaphase II oocytes was similar. Fertilization rate and transfer rate were higher in the control group. We observed higher pregnancy rates, per cycle initiated and per embryo transfer and higher live birth rate in the endometriosis group. In the group of patients with 25–35 years old, the number of oocytes, fertilization rate, and number of transferred embryos were significantly higher in the control group. However, pregnancy rate and live birth rate were higher in the endometriosis group. In the group of patients with 36–40 years old, the number of transferred embryos was higher in the control group, but the pregnancy rate and live birth rate were higher in the endometriosis group. In the group of patients with 41 to 42 years old, the number of transferred embryos and the transfer rate were higher in the control group, but the pregnancy rate was higher in the endometriosis group.

Conclusion Our results demonstrate that endometriosis does not affect the outcome of patients subjected to IVF/ICSI and although patients with endometriosis present lower number of oocytes and higher cancellation rate, these shortcomings do not reduce pregnancy and live birth rates.

Keywords Endometriosis · Assisted reproduction · Pregnancy · Take home baby

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Introduction

Endometriosis is a disorder characterized by the presence of endometrial tissue outside the uterine cavity, associated with pelvic pain and infertility [1, 2]. The prevalence of endometriosis has been estimated as 176 million women worldwide [3] with an incidence of 10 to 15% in the general population, and from 30 to 50% among infertile patients [4].

Among the several therapeutic options suggested for the treatment of infertility associated with endometriosis, assisted reproductive technology (ART) is considered the most effective [5, 6]. However, it is still unknown whether endometriosis affects the success rates of ART and evidence presented so far is contradictory. Indeed, some studies suggest that patients

with endometriosis subjected to in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) treatment have lower pregnancy rates than women with tubal factor or other causes of infertility [7–11]. On the other hand, a prospective cohort study showed similar fecundity rates in infertile patients with endometriosis (18.2%) and with unexplained infertility (23.7%), suggesting that endometriosis does not reduce pregnancy rates in natural cycles [12]. Other studies show that patients with endometriosis subjected to IVF/ICSI have pregnancy rates comparable to those of patients with infertility due to tubal factor, male factor, and unexplained infertility [13–19]. Recent studies suggested that improvement of controlled ovarian stimulation (COS) with gonadotropin-releasing hormone (GnRH) agonists and the use of ICSI technology may suppress the negative influence of endometriosis on pregnancy [16, 20].

Therefore, we performed the present study to compare the results of ART treatment in patients with and without endometriosis in a large cohort of patients from different centers over an extent period of time.

Materials and methods

We performed a retrospective study using data from patients undergoing 27,294 cycles of IVF/ICSI treatment between 1995 and 2011 that were registered in the database of the Latin American Registry maintained by the Latin America Network of Assisted Reproduction (REDLARA). The registry started in 1995 with less than 50 reporting centers and nowadays has 145 reporting centers. All reporting centers have informed consent form, signed by patients authorizing the data to be published in scientific studies. A total of 7496 patients with endometriosis only, tubal factor, and unexplained infertility were included in the study. Patients were divided into two groups: endometriosis group, comprising 1749 patients who underwent IVF/ICSI due to endometriosis only and control group, with 5747 patients subjected to IVF/ICSI due to tubal factor or unexplained infertility. Patients with missing data or other associated pathologies were not included. Definition of endometriosis, tubal factor, and unexplained infertility was based on the standards by the REDLARA [21]. Endometriosis was considered after surgery with or without histological confirmation.

The main outcome measure was live birth rate (number of live births per pregnancy). The secondary outcomes were implantation and clinical pregnancy (gestational sac with heartbeat) rates. Data collected were grouped according to the maternal age, length of infertility, and cause of infertility. Number of oocytes, number of metaphase II, fertilization rate, embryo quality, and transfer rate were also analyzed.

Statistical analysis

Data was presented as percentages and as mean (\pm standard deviation). The chi-square and Student's *t* tests were used to compare the results of both groups. A logistic regression model was employed to identify the variables influencing pregnancy rate. Statistical differences were considered significant at a 95% confidence interval ($p < 0.05$).

Results

The mean age was higher in the control group (35.4 ± 3.8 , range 25–42 years) than that in the endometriosis group (34.9 ± 3.6 , range 25–42 years) ($p < 0.001$). The percentage of women using GnRH agonist protocol (long and short protocol) was higher among the patients with endometriosis (41%) than that in the control group (35.8%) ($p < 0.001$). The remaining used antagonist protocol. Classic IVF and ICSI were similar in both groups (ICSI was performed in 78.4 and 79.9%, respectively for endometriosis and control groups).

The mean number of retrieved oocytes was higher in the control group, but the mean number of metaphase II (MII) oocytes was similar in both groups. The mean number of fertilized oocytes was similar in both groups, and the fertilization rate was significantly higher in the control group. The mean number of transferred embryos and the transfer rate were higher in the control group, and the percentage of embryos transferred in cleavage stage was similar in both groups. We observed higher pregnancy rates, per cycle initiated and per embryo transfer, in the endometriosis group. The live birth rate and twin pregnancy rate were also higher in the endometriosis group. Miscarriage rate was higher in the control group. The incidence of triplets and ectopic pregnancy was similar in both groups (Table 1). When we used the logistic regression analysis, we observed that patients with endometriosis had a higher pregnancy rate, considering the effects of the associated factors of age, embryo development stage at transfer, and type of insemination (OR = 1.78, $p = 0.003$).

As we observed a significant difference in the mean age of the groups, we also analyzed the treatment outcomes separately according to the patient's age group. Patients of both groups were subdivided into three age groups: 25 to 35; 36 to 40; and 41 to 42 years old. In the group of patients with 25–35 years old, the number of oocytes, fertilization rate, number of transferred embryos, and transfer rate were significantly higher in the control group. However, pregnancy rate and live birth rate were higher in the endometriosis group. Other results were similar in both groups (Table 2). In the group of patients with 36–40 years old, the number of transferred embryos and the transfer rate were higher in the control group, but the

Table 1 Results from patients with and without endometriosis submitted to treatment with ART

	Endometriosis (n = 1749)	Control (n = 5747)	p
Oocytes	8.7 ± 6.0 (0–39)	9.0 ± 5.9 (0–50)	0.03
MII oocytes	7.1 ± 5.1 (0–33)	7.2 ± 4.6 (0–40)	0.71
Fertilized oocytes	5.2 ± 3.8 (0–23)	5.4 ± 3.6 (0–29)	0.23
Fertilization rate	72.8%	74%	0.010
Transferred embryos	2.1 ± 0.8 (0–6)	2.2 ± 0.8 (0–6)	< 0.001
Transfer rate	84.6%	89%	< 0.001
Cleavage stage embryo transfer	87.2%	85.2%	0.06
Pregnancy rate/initiated cycle	41.6%	30.5%	< 0.001
Pregnancy rate/embryo transfer	49.1%	34.3%	< 0.001
Live birth rate/pregnancy	85.4%	79.2%	< 0.001
Twin pregnancy rate	20.5%	16%	0.008
Triplet pregnancy rate	0.5%	1%	0.198
Miscarriage rate	13.6%	20.2%	< 0.001
Ectopic pregnancy rate	1%	0.6%	0.37

Mean ± SD (range)

pregnancy rate and the live birth rate were significantly higher in the endometriosis group. Other results were similar in both groups (Table 3). In the group of patients with 41 to 42 years old, the number of transferred embryos and the transfer rate were higher in the control group, but the pregnancy rate was significantly higher in the endometriosis group. Other results were similar in both groups (Table 4).

Discussion

Our study demonstrated that endometriosis does not affect the live birth rates and pregnancy rates in infertile patients submitted to IVF/ICSI. A limitation of the study is the fact that not all patients in the control group were submitted to laparoscopy; therefore, we cannot confirm the absence of endometriosis.

The mean number of retrieved oocytes in the endometriosis group was lower than that in the control group. This result is in

agreement with other previous studies showing that patients with endometriosis have lower number of retrieved oocytes [17–19]. Opoien et al. (2012) also observed that the number of oocytes was lower among the patients with stage III/IV endometriosis in comparison with that of patients with tubal factor. However, they showed similar rates of retrieved oocytes in patients with stage I/II endometriosis and the control group. As we did not differentiate the stage of endometriosis, we cannot state whether it has an impact in the number of oocytes. Moreover, as it was not informed whether the patients had previous ovarian surgery, we cannot confirm if the reduction was caused by the endometriosis or previous ovarian surgery. However, this finding did not interfere with the outcome of the treatment as the number of MII oocytes was similar in both groups. This was observed even when considering the different age groups. Therefore, we can assume that endometriosis does not affect oocyte maturity.

The mean number of fertilized oocytes was similar in both groups; however, the fertilization rate was higher in the

Table 2 Results from patients with and without endometriosis submitted to treatment with ART with age between 25 and 35 years old

	Endometriosis (n = 941)	Control (n = 2781)	p
Oocytes	9.5 ± 6.2	10.3 ± 6.2	0.002
MII oocytes	7.8 ± 5.3	8.0 ± 4.8	0.748
Fertilized oocytes	5.7 ± 3.9	5.9 ± 3.7	0.166
Fertilization rate	72.6%	73.8%	0.037
Transferred embryos	2.1 ± 0.7	2.2 ± 0.7	< 0.001
Transfer rate	88%	92.3%	0.001
Pregnancy rate/initiated cycle	47.6%	35.9%	< 0.001
Live birth rate/pregnancy	85.7%	80%	0.008

Mean ± SD (range)

Table 3 Results from patients with and without endometriosis submitted to treatment with ART with age between 36 and 40 years old

	Endometriosis (<i>n</i> = 722)	Control (<i>n</i> = 2455)	<i>p</i>
Oocytes	5222 (7.8 ± 5.6)	19,071 (8.2 ± 5.4)	0.139
MII oocytes	4238 (6.5 ± 4.8)	15,530 (6.7 ± 4.5)	0.221
Fertilized	3110 (4.8 ± 3.6)	11,516 (5.0 ± 3.5)	0.130
Fertilization rate	73.4%	74.2%	0.31
Transferred embryos	1343 (2.1 ± 0.9)	5033 (2.3 ± 0.9)	0.001
Transfer rate	81.4%	86.9%	<0.001
Pregnancy/initiated cycle	35.7%	27.6%	<0.001
Live birth rate/pregnancy	85.2%	78.2%	0.01

Mean ± SD (range)

control group. This result is similar to that described by Senapati et al. (2016) that analyzed a large database and observed lower fertilization rate in patients with endometriosis as the only infertility factor. A meta-analysis by Harb et al. (2013) also showed lower fertilization rates in patients with stage I/II endometriosis.

The present study revealed a lower number of transferred embryos ($p < 0.001$) and a greater number of cycles with no embryo transfer in the group of patients with endometriosis ($p < 0.001$). This result is in agreement with the two previous studies [17, 18], which showed that patients with endometrioses had less transferred embryos and increased cancellation.

This study revealed significantly higher rates of live birth per pregnancy in the endometriosis group. This result contrasts with the meta-analysis published by Harb et al. (2013), which concluded that stage III/IV endometriosis (but not stage I/II) is associated with lower implantation and pregnancy rates in patients subjected to IVF. On the other hand, the rates observed herein are similar to those reported previously [15–19]. The present study solely included women with infertility due to endometriosis only. Therefore, the results suggest that endometriosis, as the only factor, does not affect the pregnancy and live birth rates of patients submitted to ART.

As the mean age was lower among the patients with endometriosis, we stratified the groups by age range in order to identify any possible bias. The observed results for each age category were similar to those observed when all the patients

were compared. Indeed, patients of the endometriosis group presented lower number of retrieved oocytes, similar number of MII oocytes and number of fertilized oocytes, and higher pregnancy when compared to control group. Live birth rate was higher in the group of patients with 25–35 years old and with 36–40 years old. However, in the group of patients with 41 and 42 years old, the difference was not significant. This fact can be explained by the small number of patients in this group. These data corroborate the analyses not stratified according to age.

It is important to emphasize that analysis of multicenter database is important and demonstrates the results of several communities of different geographic locations, and therefore can be extrapolated to the general population. Also, it allows the analysis of a great number of subjects (more than 7000 patients) that usually is difficult to reach when a study is performed in one center only. Moreover, as we studied the data from a long period of time, i.e., 15 years, it also assures consistent results. In fact, our results are in accordance with those of the study published using the same database, but in a smaller period of time (2010 to 2012) [22]. On the other hand, our study does not allow the analysis of the potential impact of the different stages of endometriosis and/or previous treatment on the ART outcome, as this data was not included in the registry.

In conclusion, our results suggest that women with endometriosis may have the same pregnancy and live birth rates in

Table 4 Results from patients with and without endometriosis submitted to treatment with ART with age between 41 and 42 years old

	Endometriosis (<i>n</i> = 86)	Control (<i>n</i> = 511)	<i>p</i>
Oocytes	472 (6.4 ± 5.2)	3004 (6.4 ± 4.1)	0.966
MII oocytes	388 (5.4 ± 4.5)	2507 (5.4 ± 3.4)	0.954
Fertilized	270 (3.9 ± 3.5)	1849 (4.0 ± 2.7)	0.711
Fertilization rate	69.6%	73.8%	0.085
Transferred embryos	132 (2.1 ± 1.1)	1035 (2.4 ± 1.1)	0.047
Transfer rate	65.1%	80.6%	0.001
Pregnancy rate/initiated cycle	24.4%	15.3%	0.035
Live birth rate/pregnancy	81%	77%	0.69

Mean ± SD (range)

IVF/ICSI than women without endometriosis; therefore, we understand that ART is an excellent alternative for treatment of infertility due to endometriosis.

Compliance with ethical standards

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

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