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Cervical pregnancy in assisted reproduction: an analysis of risk factors in 91,067 ongoing pregnancies

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Running Title: Cervical pregnancy in ART

Capsule: Cervical pregnancy represents 3.5/10,000 ART pregnancies and the main risk factors are a history of pregnancy/miscarriage/curettage, and smoking.

ABSTRACT

OBJECTIVE:

To assess the frequency of cervical pregnancy (CP) in women undergoing assisted reproductive techniques (ART) and to ascertain its risk factors

DESIGN:

Case-control study. Two control groups were established: tubal ectopic pregnancies and intrauterine pregnancies.

SETTING:

25 private assisted reproduction clinics run by the same group in Spain

PATIENT(S):

Women undergoing ART (artificial insemination, or IVF with own or donor oocytes).

INTERVENTION(S):

None.

MAIN OUTCOME MEASURE(S):

Frequency of CP. Ascertainment of demographic and clinical risk factors. Assessment of the influence of IVF parameters on CP risk.

RESULT(S):

There were 32 CPs out of 91,067 ongoing pregnancies, yielding a rate of 3.5/10,000. CPs represented 2.02% of all ectopic pregnancies (32/1582). The main risk factors were: ≥ 2 previous pregnancies (OR= 2.68; CI=1.18-6.07), ≥2 previous miscarriages (OR= 4.21, CI=1.7-10.43), ≥ 2 previous curettages (OR=4.71; CI= (1.19-18.66) and smoking (OR= 2.82 (1.14-6.94).

History of cesarean sections and tubal pregnancy were not associated with an elevated CP risk. Infertility conditions and endometrial thickness were similar across the three groups. The proportion of women from whom < 10 oocytes were retrieved was higher in the CP group than in either of the control groups.

CONCLUSION(S):

In ART, the main risk factors for ectopic pregnancy are a history of at least 2 pregnancies/miscarriages/curettages, and smoking. IVF parameters do not seem to influence the development of CP. CP is less common in ART than previously reported, likely attributable to improvements in ART, although a publication bias cannot be ruled out in early IVF reports.

INTRODUCTION

Ectopic pregnancy has been reported to occur in 1.4% of pregnancies (Petrides et al, 2014). About 95% of ectopic pregnancies correspond to tubal ectopic pregnancies (TEPs), while the remaining forms are much more uncommon (Farquhar, 2005; Chukus et al, 2015). Cervical pregnancy (CP) accounts for less than 1% of ectopic pregnancies (Farquhar 2005; Chukus et al, 2015; Kochi et al, 2014). In the most recent large series, 1 out 10,000 pregnancies (12/120,000) corresponded to CP (Vela and Tulandi, 2007). In much smaller or older series, the frequency has ranged from 1:1,000 to 1:95,000 (Celik et al, 2003; Shinagawa and Nagayama, 1969; Parente et al, 1983; Dees, 1966; Ushakov, 1997; Hofmann et al, 1987).

It has been suggested that use of assisted reproductive techniques (ART) could be a risk factor for CP (Gun and Mavrogiorgis, 2002; Kochi et al, 2014; Chukus et al, 2015; Shan et al, 2014; Chetty and Elson, 2009; Parker and Srinivas, 2016; Fylstra, 2014; Ginsburg et al, 1994; Karande et al, 1991). In several small case series, the authors have indicated that IVF predisposed women to CP (Ushakov et al, 1997; Bennett et al, 1993; Ginsburg et al 1994; Bayati et al, 1989).

Several reports have focused on the epidemiology of TEP and a number of risk factors for TEP have been described (Shaw et al, 2010). In contrast, much less is known about the

epidemiology and risk factors of CP, attributable to its rarity. In retrospective uncontrolled studies, the following risk factors for CP have been suggested: previous curettage, previous cesarean section, Asherman syndrome, Chlamydia infection and ART (Vela and Tulandi, 2007; Verma and Goharkhay, 2009; Chen et al, 2015). Nonetheless, as well as lacking a control group, many such previous studies were not specifically designed to analyze risk factors. In a recent systematic review of the uncontrolled reports from the literature, we identified the following risk factors: advanced age, multiparity, previous cesarean section, previous curettage, cervical surgery, previous TEP, ART (Matorras et al, submitted 2019). Since ART use itself was a risk factor that could be associated with a number of the aforementioned parameters, we have focused the present study on our ART population.

On the other hand, the influence of the specific aspects of ART in CP has not previously been analyzed.

MATERIAL AND METHODS

We performed a retrospective review of all the pregnancies achieved at the 25 clinics of the IVI group in Spain between 2007 and 2015. Similar ovarian stimulation protocols and laboratory procedures were used in all clinics. All women with a diagnosis of CP constituted the study population (n= 32). Two control groups were established: cases of TEP and cases of intrauterine pregnancy (IUP). In both control groups, for each case of CP, 5 control cases were randomly selected (by taking the 5 pregnancies obtained immediately after each CP), yielding a total of 164 TEPs and 164 IUPs. During the study period, there were 91,067 ongoing pregnancies and 1,582 ectopic pregnancies. In the study population (CP) 41.9% of pregnancies were obtained by oocyte donation, 22.58% by cryotransfer, 32.26% by ICSI and 3.23% by IVF. There were no cases of CP obtained by artificial insemination.

Institutional board approval was obtained (PI2017021; 1612-BIO-086-FQ)

Inclusion criteria in the CP group were: pregnancy obtained by ART and CP diagnosis established by pathology or by ultrasound (Kirk et al, 2006). Exclusion criteria were heterotopic pregnancy and cesarean-scar pregnancy.

Inclusion criteria for the TEP control group were: pregnancy obtained by ART and CP diagnosis established by pathology or by ultrasound (Kirk et al, 2006) or laparoscopic visualization.

Exclusion criteria were heterotopic pregnancy, pregnancy of unknown localization (PUL), multiple TEP and non-tubal ectopic pregnancy.

Inclusion criteria in the IUP control group were: pregnancy obtained by ART and normal single gestational ultrasound at 6 weeks.

Cases and controls were obtained from our central database, searching for the pregnancy code. The charts were manually reviewed by a single researcher (AZ), and the clinical and reproductive data at the time of the pregnancy under study were retrieved. Data were retrospectively retrieved without knowing whether they corresponded to a case of CP, TEP or IUP. Data were extracted from the records as they were registered during the infertility work-up, following the standard clinical management. Specifically, vaginal ultrasound was performed in every patient, and if the cavity was abnormal, hysteronosography was performed. The following diagnostic tests were performed depending on the findings and the clinical setting: hysteroscopy, hysterosalpingography, magnetic resonance imaging and laparoscopy. If abnormalities were found which might reduce the chances of pregnancy and these were potentially correctable, surgery was performed, at the discretion of the gynecologist in charge.

Statistical analysis was performed with Student's t test and the χ^2 test as appropriate, and the strength of associations was assessed with odds ratios (ORs) and their 95% confidence intervals (CIs). In order to obtain adjusted odds ratios (AORs), we attempted to build a multivariate logistic regression model using the study variables. Unfortunately, due the relatively small number of cases of ectopic pregnancy and the significance levels of the tests comparing the variables between groups, we did not obtain a model with both high sensitivity and high specificity (the best model having a sensitivity of 0.223 and a specificity of 0.987). Consequently, the AORs were unrepresentative, and have not been reported.

RESULTS

1. Incidence

There were 32 CPs out of 91,067 ongoing pregnancies, yielding a CP rate of 3.5/10,000 (CI= 2.5/10,000 – 4.5/10,000). During the same period, there were 1,582 ectopic pregnancies, and hence, CP represented 2.02% of ectopic pregnancies (32/1582) (CI= 1.33- 2.71)

2. Demographic and reproductive parameters (Table 1 and 2)

Women's mean age was significantly higher in CPs than in TEPs, and tended to be higher than in IUPs, though this difference did not reach significance. The other continuous parameters analyzed were very similar across the three populations. (Table 1). When data were studied as discontinuous parameters, the proportion of women aged > 46 was higher in CPs (18.75%) than in IUPs (4.88%; OR= 4.5; CI=1.44-14.03) and also tended to be higher, though not significantly, in IUPs (9.15%; OR= 2.38; CI=0.845-6.726).

Smoking was significantly more common in women with a CP (28.13%) than those with a TEP (10.37%; OR= 3.38; CI= 1.35-8.49) or IUP (12.2%; OR= 2.82; CI= 1.14-6.94). There were no differences concerning body mass index.

The percentage of women who had had ≥ 2 previous pregnancies was significantly higher in the CP group (37.5%) than the IUP control group (18.29%) (OR= 2.68; CI= 1.18-6.07). Nonetheless, there were no significant differences concerning history of vaginal deliveries or cesarean sections.

Further, the percentage of women who had had ≥ 2 miscarriages was significantly higher in the CP group (31.25%) than the TEP (9.76%) or IUP (9.76%; OR= 4.21, CI=1.7-10.43) groups. There were no significant differences regarding history of induced abortions. The percentage of women who had a history of TEP was similar across the three groups.

3. History of surgery and gynecological conditions (Table 3)

A significantly higher percentage of women with CPs had a history of curettage. Specifically, 34.38% of women with CPs had had ≥ 1 previous curettage compared to 12.2% of those with TEPs (OR= 3.77, CI = 1.59-8.97) and 11.59% of those with IUPs (OR=3.99; CI= 1.67-9.56). Furthermore, 12.5% of women with CPs had had ≥ 2 previous curettages compared to just 1.83% of those with TEPs (OR= 7.67; CI=1.63-36.12) and 3.05% of those with IUPs (OR=4.71; CI=1.19-18.66).

Concerning myoma, the rates were similar across the groups. Regarding previous submucosal myoma, the rate was 6.67% in the CP group vs 0.64% and 1.9% in the TEP and IUP groups, respectively, but the differences did not reach significance (OR= 11.07; 95% CI= 0.97- 126.3

and OR= 3.69; 95%CI= 0.59- 23.09). Rates of other gynecological conditions/infertility factors also did not differ significantly between the three groups.

4. Assisted reproduction techniques (ART) and related parameters (Table 4)

There were no differences regarding the ART employed. Endometrial thickness was very similar in the three groups. Regarding estradiol levels, they were significantly lower in CPs (724.95 ±1009.01) than in TEPs (1033.83 ±1038.28; p= 0.03), and tended to be lower in IUPs, though the difference was not significant (1017.05 ±1063.76; p= 0.057). The percentage of women from whom < 10 oocytes were retrieved was 38.71% in the CP group vs 21.71% in the IUP group (OR = 2.28; CI= 1.04-5.17).

All the other variables studied were very similar across the three groups.

DISCUSSION

The rate of CP in our ART population is 3.5/10,000, somewhat higher than the 1/10,000 usually reported in the literature in unselected populations (Vela and Tulandi, 2007; Ushakov et al, 1997). On the other hand, our rate is somewhat lower than the 10/10,000 previously reported in an ART population, though this figure came from a small series (1 out 825 pregnancies) (Karande et al, 1991).

On the other, although it is classically accepted that CP represents <1 % of ectopic pregnancies, in our ART population, it represented 2% (32/ 1582). Previous classical reports have stated that CP represented 3.7% of ectopic pregnancies in ART (Karande et al, 1991) or even 16.6% (Ginsburg et al, 1994), but these figures correspond to very short case reports (1 CP out of 27 ectopic pregnancies and 3 of 17) (Ginsburg et al, 1994).

The rareness of CP also hampers the analysis of associated risk factors. While a number of risk factors for TEP are well known, such as tubal factor, a history of pelvic inflammatory disease or ectopic pregnancy, smoking, endometriosis and use of ART (Shaw et al, 2010), the risk factors for CP are not so evident. Since the place of abnormal implantation is different in CP and TEP, the risk factors could also differ between them.

In a recent systematic review of uncontrolled studies in the literature, we identified the following potential risk factors: advanced age, multiparity, a history of cesarean section, curettage, cervical surgery and/or TEP, as well as the use of ART (Matorras et al, submitted 2019). Nonetheless, as well as lacking a control group, these previous original studies included relatively small numbers of cases and many were not specifically designed to analyze risk

factors. Since ART itself was a risk factor that could be associated with a number of the aforementioned parameters, we decided to investigate risk factors for CP in our ART population.

In our study, the proportion of women > 46 years was significantly higher in CPs than TEPs, whereas the difference did not reach significance compared with IUPs. Regarding reproductive parameters, having had ≥ 2 previous pregnancies was associated with higher odds of a CP risk compared with IUP (OR= 2.68; CI= 1.18- 6.07), but previous vaginal deliveries and cesarean sections had no impact. On the other hand, having had ≥ 2 previous miscarriages was significantly associated with CP (OR= 4.21; CI= 1.7 - 10.43). It could be speculated that some preexisting endometrial problem would both increase the risk of miscarriage and preclude eutopic implantation, or that women with recurrent miscarriage would be more prone to produce abnormal embryos and, in turn, impaired eutopic implantation. Alternatively, as we will discuss further below, the difference could be a consequence of miscarriage treatment, which was surgical in many cases.

Concerning history of surgery, the only significant risk factor was a previous curettage: ≥1 with an OR of 3.99 (CI= 1.67- 9.56) and ≥2 with an OR of 4.71 (1.19- 18.66). In our opinion, as well as the two hypotheses set out above regarding miscarriage, it could be that in some cases curettage damages the endometrial cavity, precluding eutopic implantation, or even damages the cervical canal, inducing vascular or histological changes that could favor cervical implantation. Other types of surgery, including myomectomy and tubal surgery, did not influence CP risk.

We found a much higher rate of CP among women with a history of submucosal myoma (OR of 11.07 compared to TEP and 3.69 compared to IUP). Although significance was not reached, further studies are needed to analyze this association. It is well known that the standard management of submucosal myoma is hysteroscopic myomectomy (Donnez and Dolmans, 2018). It could be speculated that the contractility of the uterine cavity is increased as a consequence of scarring after hysteroscopic myomectomy, or of some remnant myoma tissue, producing contractions able to expel the embryo out of the uterine cavity.

Smoking is a risk factor for a number of gynecological conditions, including ectopic pregnancy. In our CP series, the rate of smoking was significantly higher than in the TEP (OR= 3.38; 95% CI= 1.35-8.49) or IUP (OR= 2.82; CI= 1.14-6.94) groups. Although the reason that smoking causes EP remains unknown (Shaw et al, 2010), animal and human studies have shown that

cigarette smoke may impair fallopian tube function by affecting ciliary beat frequency and smooth muscle contraction (Shaw et al, 2010; Riveles et al, 2004; Talbot and Riveles, 2005).

Our study provides evidence that, among the factors considered, the most important risk factors for CP in ART are previous pregnancies, in particular, the number of previous miscarriages and uterine curettages, and smoking, in agreement with previously published in uncontrolled non-ART publications (Matorras et al, submitted 2019; Vela and Tulandi, 2007; Verma and Goharkhay. 2009; Chen et al, 2015). Other parameters suggested as risk factors in the uncontrolled non-ART literature such as history of cesarean section and TEP (Matorras et al, submitted 2019; Vela and Tulandi, 2007; Verma and Goharkhay. 2009; Chen et al, 2015) were not confirmed in our study.

Regarding infertility conditions and ART technique, they were similarly distributed across our groups: CP, TEP and IUP. Interestingly, the CP rate did not differ by endometrial thickness, ruling out the hypothesis that a poor endometrial development increases the risk of this type of pregnancy. On the other hand, the proportion of women from whom < 10 oocytes were retrieved was significantly lower in CPs than in IUPs, and a trend to lower estradiol levels was observed. Nevertheless, embryo characteristics were very similar across the three groups.

In our study, the relatively small number of cases precluded multivariate analysis. That is, we were not able to assess the relative impact of a number of parameters that are usually related (such as age, low estradiol levels and low ovarian response).

Our rate of CP in ART is much lower than rates previously reported, and we propose two explanations. First, previous studies may have overestimated the CP rate since they usually correspond to relatively reduced series of both cases and controls, and this may have resulted in a publication bias. Second, most epidemiological reports on CP are relatively old, and in recent decades, a number of changes have been introduced that could reduce CP rates such as the implementation of ultrasound-guided embryo transfer (Matorras et al, 2002), improvements in embryology laboratory management (Grifo et al, 2014) and the huge increase in single embryo transfers (Adamson et al, 2018). Concerning physiopathology, it can be speculated that adverse endometrial conditions, resulting from endometrial trauma (specifically that associated with curettage), preexisting conditions (e.g., age, the adverse effects of smoking, and conditions resulting in miscarriage) could hamper eutopic implantation, rejecting the embryo from the endometrial cavity and favoring cervical implantation. Regarding uterine curettage, it is also possible that some kind of cervical damage or even seeding of endometrial tissue into the cervix might promote cervical implantation.

Finally, it can be concluded that the increase in the prevalence of CP in ART, if any, do not seem to be attributable to the causes of infertility or any condition related to management of the current cycle, since IVF parameters in women with CPs were very similar to those in women with IUPs, except for a higher rate of retrieval of < 10 oocytes.

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KEY MESSAGE

In ART, main risk factors for ectopic pregnancy are previous pregnancies/miscarriages/curettages, and smoking.

IVF parameters do not seem to influence CP occurrence.CP in ART is less common than previously reported, which probably is related with improvements in ART, although a publication bias cannot be ruled out in early IVF reports.

	Cervical pregnancy (CP)	Tubal ectopic pregnancy (TEP)	Intrauterine pregnancy (IUP)	p-value
Woman's age	40.06 (±5.11)	37.9 (±4.9)	38.38 (±5.25)	0.02 vs TEP;
				0.08 vs IUP
Man's age	41.9 (±7.89)	39.71 (±6.8)	40.04 (±6.64)	> 0.10
Previous no. of pregnancies	1.34 (±1.62)	0.88 (±1.12)	0.77 (±1.18)	>0.10
Previous no. of vaginal deliveries	0.16 (±0.37)	0.1 (±0.36)	0.13 (±0.45)	> 0.10
Previous no. of cesarean sections	0.06 (±0.26)	0.1 (±0.36)	0.05 (±0.24)	> 0.10

Table 1. Demographic characteristics in cervical pregnancy compared with tubal ectopic pregnancy and intrauterine pregnancy. Mean comparison

	Cervical Pregnancy (CP)	Tubal ectopic pregnancy (TEP)	Intrauterine pregnancy (IUP)	CP vs TEP	CP vs IUP
				OR (95% CI)	OR (95% CI)

Woman's age ≥ 46 years	18.75 (6/32)	4.88 (8/164)	9.15 (15/164)	4.5 (1.44-14.03)	2.38 (0.845-6.726)
Man's age ≥ 46 years	23.33 (7/30)	15.58 (24/154)	16.56 (27/163)	1.65 (0.64-4.27)	2.38 (0.85-6.73)
Smoking	28.13 (9/32)	10.37 (17/164)	12.2 (20/164)	3.38 (1.35-8.49)	2.82 (1.14-6.94)
Obesity	9.68 (3/31)	6.92 (11/159)	5.26 (8/152)	1.44 (0.38-5.5)	1.93 (0.48-7.72)
≥ 1 previous pregnancy	53.13 (17/32)	50.61 (83/164)	43.9 (72/164)	1.11 (0.52-2.36)	1.45 (0.68-3.1)
≥ 2 previous pregnancies	37.5 (12/32)	23.17 (38/164)	18.29 (30/164)	1.9 (0.89-4.44)	2.68 (1.18-6.07)
≥ 1 previous vaginal delivery	16.13 (5/31)	9.15 (15/164)	10.37 (17/164)	1.85 (0.62-5.52)	1.63 (0.56-4.9)
≥ 2 previous vaginal deliveries	0 (0/31)	0.61 (1/164)	1.83 (3/164)	1.73 (0.07-43.44)	0.73 (0.04-14.53)
≥ 1 previous cesarean section	3.23 (1/31)	5.49 (9/164)	4.27 (7/164)	0.57 (0.07-4.7)	0.75 (0.09-6.3)
≥ 2 previous cesarean sections	0 (0/31)	0.61 (1/164)	0.61 (1/164)	1.73 (0.07-43.44)	1.73 (0.07-43.44)
≥ 1 previous miscarriage	40.63 (13/32)	35.37 (58/164)	29.88 (49/164)	1.25 (0.58-2.71)	1.61 (0.74-3.51)
≥ 2 previous miscarriages	31.25 (10/32)	9.76 (16/164)	9.76 (16/164)	4.21 (1.7-10.43)	4.21 (1.7-10.43)
≥ 1 elective abortion	12.5 (4/32)	9.76 (16/164)	4.88 (8/164)	1.32 (0.41-4.25)	2.82 (0.79-9.88)

Table 2. Demographic characteristics in cervical pregnancy compared with tubal ectopic pregnancy and intrauterine pregnancy. Odds ratio (OR) analysis

	Cervical pregnancy (CP) % (n/N)	Tubal ectopic pregnancy (TEP) % n/N	Intrauterine pregnancy (IUP) % n/N	CP vs TEP OR (95% CI)	CP vs IUP OR (95% CI)
≥ 1 previous curettage (a)	34.38 (11/32)	12.2(20/164)	11.59 (19/164)	3.77 (1.59-8.97)	3.99 (1.67-9.56)
≥ 2 previous curettages (a)	12.5 (4/32)	1.83 (3/164)	3.05 (5/164)	7.67 (1.63-36.12)	4.71 (1.19-18.66)
History of gynecological surgery (b)	43.75 (14/32)	52.44 (86/164	32.32 (53/164)	0.71 (0.33-1.51)	1.63 (0.75-3.52)

History of cervical surgery (c)	3.13 (1/32)	5.79 (9/164)	3.05 (5/164)	0.56 (0.07 - 4.55)	1.03 (0.12-9.09)
History of myomectomy	6.25 (2/32)	3.66 (6/164)	6.71 (11/164)	1.76 (0.34-9.12)	0.93 (0.2-4.4)
History of tubal surgery	9.38 (3/32)	10.37 (17/164	4.88 (8/164)	0.9 (0.25-3.25)	2.02 (0.51-8.06)
History of tubal ligation	0 (0/32)	0 (0/164)	0.61 (1/164)	5.06 (0.1-259.7)	1.68 (0.07-42.1)
Uterine abnormalities (d)	31.25 (10/32)	28.66 (47/164	25 (41/164)	1.13 (0.5-2.57)	1.36 (0.6-3.12)
History of myomas	25 (8/32)	15.24 (25/164)	14.63 (24/164)	1.85 (0.75-4.59)	1.94 (0.78-4.83)
History of submucosal myomas (e)	6.67 (2/30)	0.64 (1/156)	1.9 (3/158)	11.07 (0.97-126.3)	3.69 (0.59-23.09)
Tubal reproductive factor (f)	6.25 (2/32)	14.02 (23/164	13.42 (22/164)	0.61 (0.13-2.8)	0.43 (0.1-1.93)
Male reproductive factor (g)	34.38 (11/32)	34.76 (57/164	38.42 (63/164)	1.03 (0.46-2.3)	0.84 (0.38-1.86)
Endometriosis (h)	15.63 (5/32)	15.85 (26/164)	10.37 (17/164)	0.98 (0.35-2.79)	1.6 (0.55-4.71)
History of pelvic inflammatory disease	0 (0/32)	1.83 (3/164)	0 (0/164)	0.71 (0.04-14.08)	5.06 (0.1-259.74)
Asherman syndrome (i)	0 (0/32)	0 (0/164)	1.22 (2/164)	5.06 (0.1-259.74)	1 (0.05-21.32)
Intrauterine device	0 (0/32)	0 (0/164)	0 (0/164)	5.06 (0.1-259.74)	5.06 (0.1-259.74)

Table 3. Gynecological and reproductive conditions **in cervical pregnancy compared with tubal ectopic pregnancy and intrauterine pregnancy**. Odds ratio (OR) analysis.

a) including curettage for miscarriage or abortion; b) including diagnostic laparoscopies and hysteroscopies but not curettage or cesarean section; c) not including curettage; d) including myomas, e) all of them removed ; f) diagnosed by hysterosalpingography, laparoscopy and/or ultrasound; g) diagnosed by abnormal sperm count; h) diagnosed by laparoscopy or ultrasound; and i) diagnosed by hysteroscopy

	Cervical pregnancy (CP)	Tubal ectopic pregnancy (TEP)	Intrauterine pregnancy (IUP)	CP vs TEP	CP vs IUP
				OR (95% CI)	OR(95% CI)
Oocyte donation (%)	41.94 (13/32)	37.81 (62/164)	28.66 (47/164)	1.13 (0.52-2.44)	1.7 (0.78-3.72)
Cryotransfer (%)	22.58 (7/32)	18.29 (30/164)	32.32 (53/164)	1.25 (0.5-3.16)	0.59 (0.24-1.44)
ICSI (%)	32.26 (10/32)	31.1 (51/164)	29.3 (48/164)	1.01 (0.44-2.28)	1.1 (0.48-2.49)
IVF (%)	3.23 (1/32)	2.44 (4/164)	3.05	1.29 (0.14-	1.03 (0.12-

			(5/164)	11.94)	9.09)
Artificial insemination (%)	0 (0/32)	9.76 (16/164)	7.32 (12/164)	0.14 (0.01-2.37)	0.19 (0.01-3.25)
Endometrial thickness ≤ 6 mm (%) (a)	3.33 (1/30)	8 (12/150)	3.47 (5/144)	0.4 (0.05-3.17)	0.96 (0.11-8.51)
Endometrial thickness (mm) (a)	7.52 (±2.94)	8.54 (±2.13)	9.24 (±2.1)	P > 0.10	P > 0.10
Estradiol level ≤ 500 pg/mL (%) (a)	60 (12/20)	42.22 (57/135)	50 (66/132)	2.05 (0.79-5.35)	1.5 (0.58-3.91)
Estradiol level (a)	724.95 (±1009.01)	1033.83 (±1038.28)	1017.05 (±1063.76)	P = 0.03	P= 0.057
Retrieved oocytes < 10 (%)	38.71 (12/31)	25 (37/148)	21.71 (33/152)	1.9 (0.84-4.27)	2.28 (1.04-5.17)
Retrieved oocytes	11.84 (±5.12)	12.92 (±5.48)	13.24 (±6.38)	P > 0.10	P > 0.10
Single embryo transfer (%)	32.26 (10/31)	20.27 (30/148)	25 (38/152)	1.87 (0.8-4.4)	1.43 (0.62-3.3)
No. of embryos transferred	1.74 (±0.58)	1.83 (±0.46)	1.78 (±0.49)	P > 0.10	P > 0.10
Day 3 transfer (%)	15 (3/20)	20.21 (19/94)	22.12 (23/104)	0.7 (0.19-2.63)	0.62 (0.17-2.31)

Table 4. ART parameters in cervical pregnancy compared with tubal ectopic pregnancy and intrauterine pregnancy.

Data are reported as the mean and the standard deviation, with a p value, or as a percentage, with an odds ratio and the corresponding 95% confidence interval.

a) Measured on the day of hCG administration