CEOG Clinical and Experimental Obstetrics & Gynecology

Effect of cervical conization on pregnancy outcome of in-vitro fertilization/intracytoplasmic sperm injection treatment: a retrospective cohort study

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Summary

Aims: To investigate the effect of cervical conization on the outcome of in-vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment. *Materials and Methods:* The authors performed a retrospective, database-searched cohort study based on patients undergoing controlled ovarian hyperstimulation and IVF/ICSI between 2009 and 2013 in the present hospital. Cervical intraepithelial neoplasia (CIN) or cervical cancer was carefully confirmed by transvaginal ultrasound, hysteroscopy, and biopsy. High-quality case-control study with strict inclusion criteria was conducted. The authors analyzed basic characters and main IVF/ICSI outcomes between both groups. *Results:* The authors included 48 patients with a history of cervical conization who underwent IVF/ICSI and control group without cervical conization. No significant differences were found in IVF/ICSI outcomes between both groups. No obvious evidence was found indicating that cervical stenosis could impact IVF operation. *Conclusions:* The present results suggest that cervical conization does not affect IVF/ICSI outcomes. Patients can receive cervical conization before undertaking assisted reproductive technology.

Key words: Cervical conization; In vitro fertilization; Pregnancy; Cohort study.

Introduction

Cervical screening for early identification and treatment of cervical intraepithelial neoplasia (CIN) has reduced incidence and mortality from cervical cancer [1-3]. Cervical conization including cold knife conization and loop electrosurgical excision procedure (LEEP) is an efficient and low-morbidity treatment for CIN [4, 5]. Loss of normal functional cervical structure and healing process in regenerated crater after excision may inhibit sperm penetration and conception [6, 7]. Previous studies have shown conflicting results on the outcome of pregnancy following cervical conization and those studies are limited in certain countries. One meta-analysis by Kyrgiou *et al.* [8] showed that both cold knife conization and LEEP were significantly associated with preterm delivery and low birth weight. However, Kalliala *et al.* [9] conducted a cohort study on CIN treatment and pregnancy outcomes of 3,530 women and the results indicated that CIN treatment did not reduce pregnancy incidence and women had more live births after compared to before CIN treatment. Demeter *et al.* [10] discovered that pregnant patients with CIN who underwent cold knife conization during pregnancy were not at increased risk of adverse pregnancy outcomes, however they were at increased risk of cesarean delivery. Recently, Kyrgiou *et al.* [11] conducted a systematic review and meta-analysis of cohort studies on fertility and early pregnancy outcomes after treatment for CIN. They found that treatment for CIN had no adverse impact on fertility, although treatment was associated with a significantly increased risk of miscarriages in the second trimester.

Although the impact of treatment for cervical precancer on obstetric sequelae has been extensively described [12, 13], its effect on the subsequent in-vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) procedure and outcomes for infertile patients has been relatively under-reported. Then the question whether cervical conization could affect IVF/ICSI outcomes appeared. Many investigations focused on just pregnancy outcomes but not on IVF outcomes. It has not been fully illustrated whether this surgical treatment is adverse to pregnancy after IVF/ICSI. There are only few studies about this topic until now.

To this aim, the present authors conducted a retrospective case-controlled study to explore the effect of cervical conization on IVF/ICSI. Additionally they observed whether some side-effects of this surgery, like cervical stenosis, could influence embryo transfer (ET) operation.

Revised manuscript accepted for publication March 26, 2015

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLIII, n. 4, 2016
doi: 10.12891/ceog3028.2016

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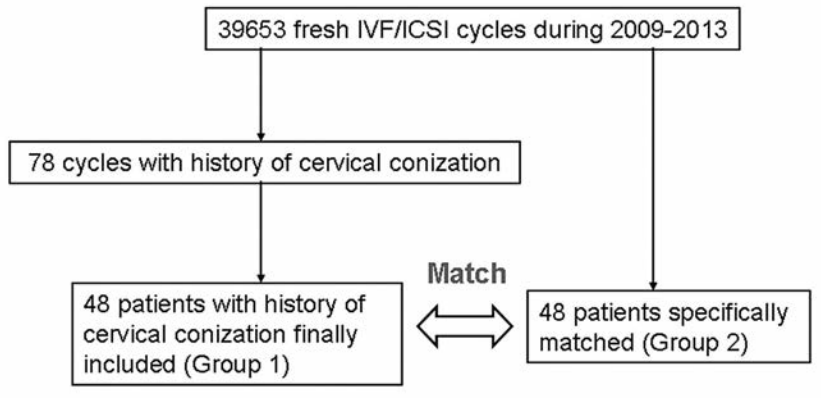

Figure 1. — Database searching pathway and group division. Forty-eight patients with a history of cervical conization undergoing the same number of fresh embryo transfer (ET) cycles, along with 48 related matched controls were included in the final analysis.

Materials and Methods

Study design

The authors performed a retrospective cohort study involving the collection of data from the electronic records of a total of 39,653 IVF/ICSI cycles between January 2009 and December 2013 in the Centre for Reproductive Medicine, Shandong Provincial Hospital affiliated to Shandong University.This study was approved by the Institutional Review Board (IRB) of Shandong University. Written informed consent was obtained from the participants at the time of presentation for IVF/ICSI treatment.

Briefly, the study group (group 1) met the following inclusion criteria: (1) age 44 years or less; (2) fresh stimulated and transferred cycles; (3) with a history of cervical conization including cold knife conization and LEEP. The control group (group 2) without a history of cervical conization was matched to the study group by criteria described previously [14]. The authors attempted matching as closely as possible, and most cases were able to match at least three of these criteria. Researchers performing the matching were blinded to IVF/ICSI outcomes. If multiple patients fitted the criteria, one was selected at random. The following exclusion criteria were used: (1) oocyte donor treatment cycles; (2) presence of other comorbidities which prevented matching, e.g. chromosome abnormalities. All the data for assessment originated at Shandong Provincial Hospital affiliated to Shandong University and were comparable.

Statistical analysis

Statistical analysis was performed using SPSS17.0, taking the matching into consideration between women and controls of each case. For continuous variables (birth weight, age), the difference between the case and the mean of the control was computed and tested with a *t*-test for paired comparisons. For proportions, the Chi-square test or Fisher's exact test were applied to obtain group comparisons. Data are presented as mean ± SD (standard deviation). The two-tailed p-value < 0.05 was considered significant. Baseline characteristics that were found to differ between the groups ($p < 0.05$) were entered into two-category models to control for confounders.

Results

Ultimately, 48 patients with a history of cervical conization undergoing the same number of fresh ET cycles, along with 48 related matched controls, were included in the final analysis (Figure 1). As for study group (group 1), diagnosis was micro-invasive carcinoma in one (2.1%) case, carcinoma in situ of cervix in eight (16.7%) cases, CIN3 in 11 (22.9%) cases, CIN2 in 12 (25.0%) cases, CIN1 in one (2.1%) case, cervicitis (not the right indication for cervical conization) in one (2.1%) case, and status unknown in 14 (29.2%) cases. Pregnancy outcomes are shown in Table 1; 94.6% of patients in both groups were undergoing their first or second ET cycle and 10% of patients in study group had recurrent miscarriage history.

Table 1. — *IVF/ICSI outcomes in groups 1 and 2.*

Item	Group 1	Group 2	*p*
Term deliveries rate	9/48(18.8%)	12/48(25.0%)	NS
Preterm deliveries rate per cycle	4/48(8.3%)	1/48(2.1%)	NS
Cancellation rate	5/48(10.4%)	0/48(0.0%)	NS
Clinical miscarriage rate	5/26(19.2%)	7/20(35.0%)	NS
Vaginal delivery rate	4/48(8.3%)	5/48(10.4%)	NS
Caesarean delivery rate	9/48(18.8%)	8/48(16.7%)	NS

Note: values are given as n (%) or means ± SE unless otherwise indicated.

Cervical conization has no significant effect on pregnancy outcomes.

Baseline characteristics of Group 1 (study group) and 2 (control group) are shown in Table 2. There were no significant differences between both groups in terms of age, body mass index (BMI), duration of infertility, or ovarian reserve. Main indications included male, tubal and combination factors, and other unknown reasons.

The outcomes of ovarian stimulation and IVF/ICSI are shown in Tables 1 and 3. There was no significant difference in any of listed ovarian response parameters or embryological parameters between both groups. There was no significant difference in cycle cancellation rate, term deliveries rate, preterm deliveries rate per cycle, clinical miscarriage, non-pregnant, vaginal delivery, and caesarean delivery rate. Although preterm deliveries rate of study group is higher than the control group, there is no statisti-

Table 2. — *Baseline characteristics of study group (group 1) and control group (group 2).*

Item	Group 1	Group 2	*p*
Age [a]	33.2±4.40	33.2±4.36	NS
Body mass index (kg/m^2)	22.9±3.22	23.2±3.37	NS
History of infertility(years)	4.6±3.3	4.4±3.1	NS
Day 3 serum FSH (IU/ml)	6.5±2.22	6.9±2.00	NS
Mean day 3 E2 (pg/ml)	39.0±18.19	54.6±48.26	NS
Indication to IVF			
Male factor	3 (6.3%)	7 (14.6%)	NS
Tubo factor	34 (70.8%)	25 (52.1%)	NS
Combination	5 (10.4%)	14 (29.2%)	NS
Other	6 (12.5%)	2 (4.2%)	NS

Note: values are given as means ± SE or n (%).
FSH = follicle-stimulating hormone; NS = not significant.

Table 3. — *Ovarian stimulation outcomes in groups 1 and 2.*

Item	Group 1	Group 2	*p*
Cycles	48	48	
Protocol of ovary stimulation, n (%)			
Short agonist	17 (23.7%)	11 (22.9%)	NS
Long agonist	30 (62.5%)	36 (75.0%)	NS
Ultra long GnRH agonists	1 (2.1%)	1 (2.1%)	NS
Other	0 (0.0%)	0 (0.0%)	NS
Starting dose of Gn	192.5±53.7	191.9±56.8	NS
Total dosage of Gn per cycle (IU)	2009±874	1959±857	NS
Duration of Gn stimulation (days)	10.6±2.0	10.4±2.0	NS
Endometrial thickness on hCG day, cm	1.06±0.2	1.06±0.1	NS
Mean number of oocytes retrieved	12.8±5.5	12.4±9.2	NS
Good quality embryo transferred	1.72±0.99	1.62±0.98	NS
Mean number of embryos transferred	0.92±1.05	0.40±0.63	NS

Note: hCG = human chorionic gonadotropin; Gn = gonadotropin; GnRH = Gn-releasing hormone.

cal significance. As for causes of preterm delivery, in the study group, one was unicornuate uterus, one underwent cesarean for pregnancy-induced hypertension, one underwent cervical conization twice, and one was without other abnormal conditions; both of the latter underwent cesarean section, while the other two were vaginal deliveries.

Discussion

The present study compared basic information and pregnancy outcomes of 48 patients with a cervical conization history and matched group. According to the strict criterion and analysis, the present authors conclude that cervical conization does not significantly impair IVF/ICSI outcomes, especially miscarriage and preterm delivery rates. Although preterm delivery birth (PTB) rate and cesarean delivery rate were higher than the control group but there was no statistical significance. Recently, Pinborg *et al.* [15] reported that in the ART singleton deliveries, the PTB rate was significantly higher in women with cervical conization than without (13.1 *vs.* 8.2%) while it nearly doubled in ART twin deliveries. Compared to Pinborg *et al.* study, the present authors did not achieve significant results perhaps due to their small sample size. Also they did not analyze the PTB on ART twin deliveries. However, Acharya *et al.* discovered that LEEP in women with CIN did not significantly increase the risk of low birth weight or preterm birth in subsequent pregnancy in comparison to their controls, which is partly consistent to the present study [16]. There has also been reported that LEEP does not affect mode of delivery in the subsequent pregnancy [17-20]. Pinborg *et al.* [15] also reported that cervical dysplasia did not increase the risk of any of the other adverse outcomes in ART singletons or twins, which is also consistent with the present study.

There were no records regarding difficulty during ET procedure related to patients' cervical conization history. The present authors perform hysteroscopy before IVF/ICSI routinely. That may also help to evaluate the cervical morphology.

The present study has the following strengths: first, the relationship of cervical conization and outcomes of IVF seems to be only recently placed on the agenda, hence researches on this issue are insufficient. Nowadays, IVF/ICSI protocols have continued to evolve with efforts to improve outcomes [21, 22]. Treatment success may be related to certain procedural factors and the present authors made efforts to prove whether cervical conization affects IVF/ICSI success. Although they collected only 48 patients' baseline information and treatment outcomes, this study provides references to clinicians for patient consultation and in choosing optional treatment strategy. Second, the matching procedures are one of the most important strengths of this study. Control groups were specifically chosen so that confounding variables were eliminated. As far as the present authors know, few previous studies were as strictly and systematically controlled for age, number of cycles, comorbidities, and other confounding factors in comparison to this study. Many other studies were uncontrolled (or historically controlled). Third, the authors observed that cervical stenosis did not influence IVF/ICSI procedure. There were no records regarding any difficulty on the ET procedure in the study group.

There are some limitations as well. This is a retrospective study, which by nature can include selection bias. For example, data were collected from one IVF center. The sample size is small, just because the present authors were only able to collect 48 patients that met the study group criterion; as a consequence the results should be interpreted with caution. Also they did not have sufficient data to study the height of the cervical cone or the severity of the CIN lesions or the time window between diagnosis of CIN and ART treatment. For further study, the authors can collect larger

number of samples to analyze. It was reported that LEEP was safer for future pregnancies when compared to cold knife conization [23]. The present authors can evaluate the advantage of LEEP on IVF outcomes in their future work.

Conclusion

With strict inclusion criteria and randomly selected paired controls, the present results suggest that cervical conization may not have a strong adverse effect on IVF/ICSI outcomes. Future studies should carefully explore associations between treatment and subsequent IVF/ICSI outcomes stratifying by size of excision, treatment technique, and number of embryos implanted.

Acknowledgments

This study was financially supported by Science Research Foundation item of no-earnings health vocation (201402004), National Natural Science Foundation of China (81202057), Family Planning Science and Technology Development Program of Shandong Province (No. 2014-19), and Independent Innovation Foundation of Reproductive Medical Hospital affiliated to Shandong University (No. 20141107).

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