Factors affecting pregnancy outcomes following the surgical removal of intrauterine adhesions and subsequent in vitro fertilization and embryo transfer

XUECHUN WANG¹, JINGSONG YI¹, XI XIE¹, SHENGRONG DU², LIYING LI¹ and XIUQIONG ZHENG¹

¹Department of Obstetrics and Gynecology, and ²Assisted Reproductive Technologies Research Institute, Fujian Provincial Maternity and Children's Hospital, Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian 350001, P.R. China

Received June 27, 2019; Accepted August 14, 2019

Abstract. This study aimed to investigate the clinical factors affecting pregnancy rates following the surgical removal of intrauterine adhesions (IUAs) and subsequent in vitro fertilization and embryo transfer (IVF-ET). We retrospectively evaluated case data from patients who had undergone hysteroscopic surgery to remove varying degrees of IUAs and who had subsequently received assisted reproductive treatments with IVF-ET (in all 140 cycles) at our hospital between January, 2011 and January, 2015. The patient data were divided into either the pregnancy or non-pregnancy groups based on the pregnancy outcomes, and a number of clinicopathological variables were compared between these two groups, such as age, infertility (type and duration), the number of prior surgical treatments for and severity of IUAs, the baseline follicle-stimulating hormone/luteinizing hormone (FSH/LH) ratio and estradiol level, endometrial thickness on the day of human chorionic gonadotropin (hCG) administration, etc. We selected the variables with statistically significant differences to generate multivariate logistic regression and linear correlation analyses. We found that i) the mean endometrial thickness on the day of hCG administration was greater in the pregnancy group, and that the average gestational age was younger than that in the non-pregnancy group. The different age groups had significantly different pregnancy rates. The mean baseline FSH/LH ratio of the women in the pregnancy group was lower than that in the women in the non-pregnancy group. The number of embryos transferred in the pregnancy group was higher than that in the non-pregnancy group. However, the other variables exhibited similar values between these two groups. ii) Our multivariate logistic regression analyses revealed that age and endometrial thickness on the day of hCG administration had significant effects on the pregnancy outcome. The baseline FSH/LH ratio and the number of embryos transferred were similar between the groups. On the whole, age and endometrial thickness on the day of hCG administration are the most important predictors of pregnancy outcome in the patients undergoing IVF-ET following the surgical removal of IUAs. Importantly however, the identification of effective methods with which to improve the endometrial thickness and the ovarian response in patients with diminished ovarian reserves warrants further investigation in future research.

Introduction

Intrauterine adhesions (IUAs) or Asherman syndrome (1) refers to the presence of fibrous bands in the endometrium of the uterus that result from damage due to physical or chemical factors, such as surgery or inflammatory diseases that destroy the lining of the intima and its normal self-repair capacity, causing the exudation and deposition of large amounts of fibrinogen. Adhesions between the inner walls of the uterus form where the walls abnormally adhere or stick to each other. IUAs lead to alterations in the uterine cavity size and shape, reductions in the normal endometrial area and changes in the uterine microenvironment (2). In addition, the endometrial receptivity is reduced, leading to infertility and to adverse effects on women's physical and mental health (3). Since the birth of a baby resulting from in vitro fertilization (IVF) in 1978, the rapid development of assisted reproductive technologies has brought joy to numerous otherwise infertile couples. Hysteroscopic surgery for the dissection of IUAs followed by reproductive assistance technology to aid conception is the most effective treatment for good pregnancy outcomes (4).

In this study, we examined cases of patients with IUAs from January, 2011 to January, 2015 at the Fujian Province Maternal and Child Health Hospital. These patients had been treated with hysteroscopic operations followed by assisted reproductive treatment for a total of 140 cycles, and the clinical factors affecting their pregnancy outcomes were identified.
Materials and methods

Patients. This Institutional Review Board approved study, analyzed cases from 140 cycles of assisted reproductive IVF-ET treatment from patients with varying degrees of IUAs who had undergone hysteroscopic surgery for the removal of IUAs at the Fujian Maternal and Child Health Hospital from January, 2011 to January, 2015. Informed written consent was obtained from all patients for the surgical procedures. For the present study, patient consent was waived as it was a retrospective analysis, with no direct contact between the authors and the patients, and personal privacy was protected through anonymization.

Data from 108 cycles of IVF and 32 cycles of intracytoplasmic single sperm injections (ICSI). We included data from patient with ages ranging from 23 to 47 years with infertility durations ranging from 1 to 15 years. The causes of infertility varied (121 cases had secondary infertility and 19 had primary infertility), but included tubal infertility, partners with oligo-asthenoteratozoospermia syndrome, repeated intrauterine insemination (IUI) failure, pelvic endometriosis IV, follicular rupture luteinization syndrome (LUFS), unexplained infertility and others. We included data from women with basal endocrine levels within the normal range and diagnosed as having varying degrees of IUAs; we also excluded data from patients with premature ovarian failure, space-occupying ovarian lesions, unilateral or bilateral hydrosalpinx, or endometritis prior to embryo transfers or uterine malformations.

Hysteroscopic surgery for the removal of IUAs. All patients underwent diagnostic hysteroscopy and treatment within 7 days following the clearance of their menstruation cycles. The physicians used hysteroscopy to determine the type and extent of the IUAs, and to place the micro-shear or vaporization electrode to separate the adhesions, and restore the shape and size of the uterine cavity to the greatest extent possible. Following the procedure, an intrauterine device (IUD) was placed into the uterus, followed by treatment with Bujiale® (estradiol valerate tablets) and dydrogesterone for 3 months. Finally, a hysteroscopy and IUD removal procedure were performed, and if deemed necessary, the IUA removal was repeated.

Classification of IUAs. Different classification systems for IUAs have been proposed according to the American Fertility Society (AFS) (5) as follows: i) According to the uterine area involvement: <1/3 (1 point), between 1/3 and 2/3 (2 points), >2/3 (4 points). ii) According to adhesion types: Filmy adhesion (1 point), filmy and dense (2 points), dense adhesion (4 points). iii) According to the menstrual pattern: Normal (0 points), hypomenorrhea (2 points) and amenorrhea (4 points). The summation of the scores from the three systems yields a final evaluation of the degree of IUAs (mild, 1-4 points; moderate, 5-8 points; and severe, 9-12 points).

IVF-ET method. Superovulation, egg retrieval, IVF, ICSI and embryo cultures were carried out following the routine procedures for assisted reproductive technology laboratories. On the third day of embryo culture, 1-2 embryos were selected for transfer. Following egg retrieval, the patients were injected progestosterone to support the progress of the corpus luteum. Blood tests for human chorionic gonadotropin (hCG) were carried out 14 days after the embryo transfers. Patients with positive detection underwent ultrasonic tests after 5 weeks of implantation to observe the uterine cavity, the existence of gestational sacs and the fetal heartbeat as indicators of clinical pregnancy.

Embryo quality assessment. According to the evaluation standards presented in the study by Van Royen et al (6), the best blastomeres according to their morphology reach 8 cells on the third day following egg retrieval. High-quality embryos were defined as those being regularly uniform blastomeres with <20% fragmentation.

Grouping. Blood samples were obtained from patients for hCG tests 14 days following the embryo transfers. Biochemical pregnancies were identified by hCG levels >50 mIU/ml; ultrasound monitoring of the gestational sac and fetal heartbeat were performed 5 weeks following the embryo transfers to the uterine cavity. The data from the 140 cycles in the study were divided into a pregnancy and a non-pregnancy group according to the treatment outcome. The cases with clinical pregnancy formed the pregnancy group; while those without implantation, biochemical pregnancy, or ectopic pregnancy formed part of the non-pregnancy group. The following variables were compared between the two groups: Age, infertility duration, infertility type, number of prior surgical treatments for IUAs, IUA severity, number of prior uterine cavity operations, number of spontaneous abortions, baseline follicle-stimulating hormone/luteinizing hormone (FSH/LH) ratio, baseline estradiol level, body mass index, time interval between surgical treatment for IUAs and embryo transfer, endometrial thickness on the day of human chorionic gonadotropin administration, number of embryos transferred, and number of high-quality embryos transferred.

Statistical analyses. Statistical analyses were performed using 24.0 software (IBM, Inc.). Measurement data are expressed as the means ± standard deviation, and count data as numbers and percentages. Comparisons were made between groups using independent sample t-tests, and comparisons within groups using the Chi-squared test of listed data in tabulated row and column formats. Multivariate logistic regression and Pearson’s correlation analyses were also conducted for the variables with significant differences following the t-test and the Chi-squared test. Values of P<0.05 were considered to indicate statistically significant differences.

Results

Association between clinical indicators and pregnancy outcomes in the two groups. Among the 140 cycles studied, we found 60 cases of clinical pregnancy (for a clinical pregnancy rate of 42.9%), and 80 cases of no implantation, biochemical pregnancy, or ectopic pregnancy. No significant differences were found in terms of infertility years, infertility type, the numbers of IUA procedures, the degree of the IUAs, the numbers of intrauterine surgeries, the number of spontaneous abortions, baseline estradiol values, body mass indexes, the
interval between the IUA procedure and embryo transfer, and the numbers of transferred high-quality embryos (all \(P>0.05\)). The average endometrial thickness of the pregnancy group was higher than that of the non-pregnancy group, and the difference was statistically significant (\(t=2.771; P=0.006\)). In addition, the age difference (\(t=-2.397, P=0.018\)), the difference in basal FSH/LH levels (\(t=1.996; P=0.048\)), and the difference in the number of transferred embryos (\(t=2.093, P=0.040\)) between the two groups were all statistically significant (Table I).

**Multivariate logistic regression analysis of age, transformation endometrial thickness, basal FSH/LH levels and the number of transferred embryos.** We performed multivariate logistic regression analyses for age, transformation day endometrial thickness, basal FSH/LH levels, and the number of transferred embryos.
of transferred embryos. The results indicated that the age (OR, 0.637; 95% CI, 0.418-0.971; P=0.05) and endometrial thickness on the day of endometrial secretory transformation (OR, 2.125; 95% CI, 1.222-3.697; P=0.01) significantly affected the pregnancy outcomes. We found that the basal FSH/LH level and the number of transferred embryos did not differ significantly (P>0.05) affect pregnancy outcomes according to our multivariate logistic regression analysis (Table II).

Correlation analysis of age and endometrial thickness on the day of triple layer appearance. We assessed the correlation between age and endometrial thickness on the day of triple layer appearance using Pearson's correlation analysis. Our analysis indicated no correlation between age and endometrial thickness (r=-0.185, P=0.029) (Fig. 1).

**Discussion**

Occurrence, prevention and treatment of IUAs. IUAs can be caused by trauma, infection, or low estrogen levels (7). A history of dilation and curettage (D&C) is an important risk factor for IUAs. Intrauterine infections are also an important cause of IUAs (8). IUAs can also occur in patients with non-tuberculous endometritis and lacking a history of intrauterine surgery; in fact, Lim et al demonstrated that postpartum or post-surgical low estrogen levels affected the repair of the endometrium, leading to IUAs (9). Thus, the endometrium post-pregnancy is more vulnerable, accounting for approximately 90% of all IUAs, most often following natural childbirth, cesarean section, or abortion. In this study, we examined 121 cases of secondary infertility (86.4%), and only 19 cases of primary infertility (13.6%), suggesting that secondary infertility causes IUAs more often, in agreement with the findings of the previous study mentioned (9).

The treatment of IUAs involves the accurate and thorough separation of adhesions, the prevention of post-operative re-adhesions and the promotion of endometrial hyperplasia (10,11). The current comprehensive treatment is mainly based on surgical adhesion removal. Surgical treatment not only restores the normal shape of the uterine cavity, but also improves the blood supply to its tissues, preventing re-adhesions. In addition, the comprehensive treatment utilizes estradiol valerate and dydrogesterone to promote endometrial repair and restore its normal function. Experts at home and abroad have recognized that hysteroscopic separation of adhesions is the ‘golden’ method for the treatment of IUAs (3). An advantage of the treatment is that the remodeling of the uterine cavity shape relieves the binding to the sub-endothelium muscle layer, restores the normal peristaltic function, increases the blood supply of the endometrial tissue, and facilitates the regeneration of endometrial epithelial cells that accelerates damage repairs. The formation of physical barriers helps prevent re-adhesion, and drug-promoted endometrial hyperplasia promotes the repair into a fully functional uterus. In this study, through hysteroscopic surgery, the patients in all 140 cycles recovered with a normal intrauterine morphology, and endometrial growth was promoted by supplying the patients with post-operative estrogen supplementation. Overall, we observed marked improvements in all the patients.

Preventing unintended pregnancies to avoid abortions, and if necessary, improving the D&C technique to make it safer will be key to reducing the incidence of complications, such as IUAs, and to improve successful pregnancy rates. The accurate and complete treatment of IUAs is important in order to re-establish normal menstruations and to improve pregnancy outcomes. Thus far, no effective method for the prevention of IUAs exists, at least to the best of our knowledge. The endometrium lining is typically non-renewable, and if the basal layer is severely traumatized, IUAs are unavoidable, and the probability of re-adhesions following uterine adhesion removal is high. The key for the fundamental prevention of IUAs is to minimize ‘avoidable’ uterine operations particularly abortions.

Effects of age and ovarian functional status on pregnancy outcome following IVF-ET. A number of women tend to wait a long time before attempting to have their first child, and with the opening of the second child policy in China, older-aged women are again having fertility needs. Age is associated with the female reproductive capacity (12), and the number of patients with diminished ovarian reserves (DORs) has increased. The ovarian reserve reflects the reproductive potential left within a woman’s two ovaries; the ability of the ovarian cortex to form fertile oocytes is mainly determined by the number and quality of the antral follicles in that ovary (13). Due to the smaller number of oocytes available to patients with DORs, the number of embryos that can be obtained is lower, the cycle cancellation rate is higher, and the clinical pregnancy rate is lower than that in patients without DORs (14). This has been a difficult problem to solve during IVF-ET treatment cycles (15). Fernandez et al (16) and others have demonstrated that the post-operative pregnancy rates of patients with IUAs are 23.5% in the >35-year-old group and 66.6% in the <35-year-old group; in addition, the live birth rates have been shown to be 14.7 and 53.5%, respectively, with the difference being statistically significant. A patient with a diminished ovarian reserve has an increased basal serum FSH/LH ratio, and this ratio is a good predictor of ovarian function (17). In this study, the ratio of FSH/LH in the non-pregnancy group (2.35±1.99) was higher than that in the pregnancy group (1.79±1.03), and the difference was statistically significant.
this effect include traditional hormone therapy (24), vasoactive
with which to improve clinical pregnancy rates. Measures to
of endometrial thickness is the most direct and effective means
endometrial receptivity is equally important. The improvement
requirement of the treatment of IUAs, and the improvement of
thickness on the hCG trigger day correlates with age, and has
other hand, Gonen
revealed no significant correlation (r=‑0.185; P=0.029). On the
between age and endometrial thickness on the hCG trigger day
95% CI, 1.222-3.697; P<0.01). Our analysis of the correlation
had a significant effect on the pregnancy outcome (OR, 2.125;
higher than that in the non-pregnancy group (10.35±1.96 mm),
trial thickness in the pregnancy group was 11.23±1.73 mm,
is significantly reduced (20). In this study, the mean endome
implantation, and thinning of the intima is an important cause
a certain thickness is a pre-requisite condition for embryo
embryos should be reduced from 3 to 2, and the remaining
embryos can be cryopreserved, to avoid embryo waste and reduce
the multiple pregnancy incidence. In this study, the number of
embryos transferred in the pregnancy group (1.96±0.19) was
higher than that in the non-pregnancy group (1.86±0.39), and
the difference was statistically significant (t=2.093; P=0.039);
however, our multivariate logistic regression analysis revealed
no statistically significant differences (P>0.05).
In the presence of an appropriate endometrial condition,
the number of embryos to transfer can be determined jointly
by the doctor and the patient. The decision affects not only the
pregnancy outcome, but also the mother-child and postpartum
health. In recent years, single embryo transfers have become
the focus of many assisted reproductive centers worldwide to
ensure safe outcomes (29).
In conclusion, for patients undergoing IVF-ET treatment
following the surgical removal of IUAs, age and endometrial
thickness on the day of triple layer appearance are the most
important predictors of pregnancy outcomes. Future studies
are required however, to focus on identifying methods with
which to effectively improve endometrial thickness and
ovarian response in patients with a diminished ovarian reserve
and in data collection, and in the writing of the manuscript.

Acknowledgements
Not applicable.

Funding
No funding was received.

Availability of data and materials
The datasets used and/or analyzed during the current study are
available from the corresponding author on reasonable request.

Authors' contributions
XW was involved in the conception and design of the study
and in data collection, and in the writing of the manuscript.
JY was involved in the conception and design of the study and in the editing of the manuscript. XX was involved in the data interpretation and editing of the manuscript. SD and LL were involved in data collection. XZ was involved in data collection. All authors have read and approved the final manuscript.

**Ethics approval and consent to participate**

The Ethics Committee of the Fujian Provincial Maternity and Children's Hospital approved this retrospective medical record review (approval no. 20192006). Informed written consent was obtained from all patients for the surgical procedures. For the present study, patient consent was waived as it was a retrospective analysis, with no direct contact between the authors and the patients, and personal privacy was protected through anonymization.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**References**


