A retrospective study in Chinese infertility patients to investigate pregnancy outcomes of gonadotropin-releasing hormone antagonist in *in vitro* fertilization/intracytoplasmic sperm injection cycles: The FASSION study

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Research

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Abstract

Background The prevalence of infertility among Chinese women of reproductive age was estimated to be 25.0%. Currently, assisted reproductive technology, such as in vitro fertilization (IVF), is considered the most effective treatment for infertility. Cetrorelix is a subcutaneously administered gonadotropin-releasing hormone antagonist approved for clinical use in IVF therapy. To improve IVF outcomes, there is a need to identify predictive markers of successful clinical pregnancy with gonadotropin-releasing hormone antagonists.

Methods The retrospective FASSION study assessed clinical outcomes and factors associated with clinical pregnancy rates of Chinese patients undergoing fertility treatment with cetrorelix and IVF/intracytoplasmic sperm injection (ICSI) cycles. We analyzed medical records of infertile women aged ≤ 35 years, with baseline serum follicle-stimulating hormone level ≤ 10 mIU/mL, body mass index ≤ 30 kg/m² and normal uterine cavity, who underwent IVF/ICSI cycles using cetrorelix at four centers in China. The primary objective was identifying factors associated with clinical pregnancy rates by validating a predictive model for clinical outcome evaluation. Secondary objectives were clinical outcomes and safety.

Results In total, 2972 women were included. After adjusting for confounders, on the day of human chorionic gonadotropin triggering, an increased endometrial thickness was associated with a higher probability of pregnancy outcome ($p=0.0001$) and a higher progesterone level was associated with a lower probability of pregnancy outcome after fresh embryo transfer (ET) per initiated cycle ($p=0.0256$). Per ET cycle, the ongoing pregnancy and clinical pregnancy rates were 45.2% and 53.0%, respectively, with an implantation rate of 37.3% per ET. The early miscarriage and cycle cancellation rates were 13.4% and 5.7%, respectively. A total of 970 live births were reported. The live birth rate per initiated cycle was 32.6% and that per ET cycle was 45.2%. Fifty-one patients (1.7%) reported an ovarian hyperstimulation syndrome event, with severe events in 17 (0.6%) patients.

Conclusions This prediction model may be useful for the preliminary screening of IVF patients and help improve clinical pregnancy outcomes.

Background

In China, the prevalence of infertility among women of reproductive age attempting to become pregnant was recently estimated to be 25.0%; this percentage is known to increase with age [1]. Currently, assisted reproductive technology (ART) is considered the most effective treatment for infertility worldwide because of the improvement of techniques such as controlled ovarian stimulation, in vitro fertilization (IVF), and embryo culture and transfer (ET).

Traditional gonadotropin-releasing hormone (GnRH) agonist downregulation was associated with a higher rate of ovarian hyperstimulation syndrome (OHSS), a known serious complication following ART treatment [2]. For this reason, GnRH agonist downregulation has progressively been replaced by GnRH

antagonist-based ART cycles, as these are associated with several advantages compared with GnRH agonist-based ART cycles and fewer complications [3–5]. Reportedly, GnRH antagonists could have some advantages such as a shorter duration of treatment with fewer injections; lower risk of vasomotor symptoms; lower risk of inadvertent administration during early pregnancy; lower risk of ovarian cyst formation; and the lower gonadotropin dose requirements per cycle. These advantages could potentially translate into increased convenience and patient satisfaction [3–5]. Additionally, it has been reported that GnRH antagonist protocols in combination with GnRH agonist triggering of final oocyte maturation may reduce and potentially prevent OHSS [6].

The latest Cochrane review [5] concluded that there is no difference between GnRH antagonists versus agonists with respect to cycle cancellation rate, number of mature oocytes, and clinical pregnancy rates. This is supported by a clinical study [7] and two meta-analyses [8, 9]. However, other studies have reported conflicting results regarding the advantages of GnRH antagonists versus GnRH agonists [10–13]. For instance, a recent retrospective study of 203,302 fresh, autologous cycles reported an increased risk of cycle cancellation and a decreased probability of implantation and live birth with GnRH antagonists compared with GnRH agonists [10].

Cetrorelix (Cetrotide®, Merck Serono Co., Ltd, China) is a subcutaneously administered GnRH antagonist approved in over 80 countries for clinical use in IVF therapy [14]. Further, the efficacy and safety of cetrorelix have been shown in several studies [15–17].

The success of ART is multifactorial, but it depends largely on the demographic and clinical characteristics of the couple seeking treatment [18]. The high rates of infertility among Chinese women [1] highlight a real need for an effective treatment for infertility in this setting.

Therefore, there is a need to identify predictive markers of successful clinical pregnancy with GnRH antagonists in order to improve IVF and intracytoplasmic sperm injection (ICSI) outcomes. This would allow us to carefully select patients who are better suited for such procedures and who are also more likely to achieve a clinical pregnancy. The objective of the study was to assess the clinical outcomes and factors associated with clinical pregnancy rates of Chinese patients undergoing fertility treatment with cetrorelix and IVF/ICSI cycles.

Methods

Study design and setting

The FASSION study (ClinicalTrials.gov; NCT02889380) was a retrospective, multicenter study conducted in China. Data from the medical records of women who underwent IVF/ICSI cycles using cetrorelix were collected at four IVF centers in China from 30 August 2016 to 21 April 2017. This study was approved by the ethics committees and institutional review boards of the four participating centers.

Patients

In this study, infertile women ≤ 35 years of age were included if they had undergone the first GnRH antagonist (IVF/ICSI-ET) cycle with an available ART outcome, used cetrorelix in a fixed or flexible antagonist protocol, had a baseline serum follicle-stimulating hormone (FSH) level ≤ 10 mIU/mL, body mass index (BMI) ≤ 30 kg/m², and a uterine cavity without any structural abnormalities.

Women with any of the following characteristics were excluded from the study: previously underwent three or more IVF/ICSI cycles, received a total dose of GnRH ≥ 2500 IU in the current cycle, administration of cetrorelix 0.125 mg daily, received an agonist trigger, used clomiphene citrate or letrozole during cycles, presence of confirmed or suspected endometriosis Grade 3 to 4, presence of uni- or bilateral hydrosalpinx, and a history of recurrent miscarriages.

These inclusion and exclusion criteria, which were representative of patients with a good prognosis, were determined to minimize the selection bias.

Data source and assessments

Data for this study were obtained from the medical records of women who underwent IVF/ICSI cycles using cetrorelix. Data consisted of demographics and clinical baseline characteristics of patients, infertility history, duration of infertility, previous/concomitant medications or procedures, and treatment compliance and exposure.

Study outcomes

The primary objective was to investigate the factors associated with clinical pregnancy rates by validating a predictive model used for clinical outcome evaluation. The secondary objectives (quantitative variables) were clinical pregnancy, implantation, and ongoing pregnancy rates; early miscarriage and canceled cycle rates; and live birth rates. Definitions of the quantitative variables are provided in an additional document (see Additional file 1). Safety was evaluated according to the incidence and severity of OHSS.

Subgroup analyses

Subgroup analyses were performed for primary and secondary objectives by age groups (≤ 30 years and > 30 years of age) and number of oocytes retrieved (0/1 to 3/4 to 9/10 to 15/ >15 /Not done).

Study size

A sample size of 3000 patients was planned according to the desired level of precision: 2000 patients were to be allocated into a test sample for modeling and 1000 patients were to be allocated into a validation sample to examine the sensitivity and specificity of the model. The precision (half width of 95% confidence interval [CI]) of the estimate was approximately 0.19 to 0.62.

Statistical methods

The full analysis set (FAS) was defined as the maximum number of patients having variables considered for univariate regression analyses. Continuous variables are presented using descriptive statistics and categorical variables, using frequency and percentage. Where applicable, 95% CIs were calculated. All statistical tests are of explorative nature and the corresponding p-values presented are purely descriptive. Missing data were not imputed.

We developed a predictive model to identify factors associated with clinical pregnancy rate, using univariate and multivariate logistic regression analyses, based on a random selection of two-thirds of patients from the FAS. The predictive model was validated by performing a sensitivity analysis on the remaining third of the patients from the FAS by comparing the predicted versus the observed clinical pregnancy outcomes using a 2 × 2 contingency table. The statistical analysis was performed using Statistical Analysis System (SAS) version 9.1.3 (SAS Institute, Cary, NC, USA).

Results

Patients and treatment exposure

A total of 2972 women were included in the FAS. Women had a mean ($\pm$ standard deviation [SD]) age of 29.7 ± 3.33 years; a mean BMI of 22.3 ± 2.96 kg/m²; and a mean duration of infertility of 43.0 ± 28.26 months. The types of infertility were female infertility alone (n=1223; 41.2%), male and female infertility (n=983; 33.1%), male infertility alone (n=650; 21.9%), and unexplained (n=116; 3.9%).

The most common reasons for female infertility included tubal factor infertility (n=1719; 57.8%), ovulatory dysfunction (n=896; 30.1%) and other reasons (n=358; 12.0%) such as intrauterine insemination failure (n=103; 3.5%), abdominal surgery (n=69; 2.3%), and pelvic disorders (n=28; 0.9%). The mean $\pm$ SD baseline FSH, luteinizing hormone, and estradiol levels within 3 months prior to initiating treatment were 6.2 ± 1.6 IU/L, 5.0 ± 4.0 IU/L, and 43.0 ± 22.0 pg/mL, respectively (**Table 1**). The mean duration of treatment with cetrorelix was 4.8 ± 1.56 days. The mean daily cetrorelix dose was 0.250 ± 0.0 mg, and the mean total dose of cetrorelix was 1.214 ± 0.4293 mg.

Table 1. Demographic and clinical baseline characteristics (Full analysis set)

Characteristic	Total
	N = 2972
Age, years	29.7 ± 3.33
Body mass index, kg/m ²	22.3 ± 2.96
Duration of infertility, months	43.0 ± 28.26
Type of infertility	
Female and male	983 (33.1)
Female only	1223 (41.2)
Male only	650 (21.9)
Unexplained	116 (3.9)
Causes of female infertility	
Tubal factor	1719 (57.8)
Endometriosis	30 (1.0)
Ovulatory dysfunction	896 (30.1)
Other	358 (12.0)
Follicle stimulating hormone level, IU/L	6.2 ± 1.6
Luteinizing hormone level, IU/L	5.0 ± 4.0
Estradiol level, pg/mL	43.0 ± 22.0

Data in the table are presented as (mean ± standard deviation) or n (%).

Study outcomes

Primary analysis: Factors associated with clinical outcomes

A multivariate logistic regression analysis was performed using data from 671 patients with available data for the independent variables considered in the model building process, with clinical pregnancy

outcome (yes/no) set as the dependent variable (**Table 2**). As only patients with a complete set of variables could be included in the statistical modeling by logistic regression, the total number of patients was substantially reduced in the development and validation of this model.

Table 2. Multivariate logistic regression analysis with clinical pregnancy outcome as the dependent variable

Total (N = 1981)					
Independent variables	n	Regression coefficient	Standard error	P-value	Odds ratio (95% CI)
Progesterone level on the day of hCG triggering, ng/mL	671	-0.5948	0.2036	0.0035	0.55 (0.37–0.82)
Endometrial thickness on the day of hCG triggering, mm	671	0.1744	0.0477	0.0003	1.19 (1.08–1.31)
Total number of embryos on Day 3/blastocysts on Day 5	671	0.0635	0.0138	<0.0001	1.07 (1.04–1.09)
Number of oocytes obtained	671	0.3518	0.1555	0.0236	1.42 (1.05–1.93)
Confounding factors adjusted ^a					
Progesterone level on the day of hCG triggering (ng/mL)	675	-0.4278	0.1916	0.0256	0.65 (0.45–0.95)
Endometrial thickness on the day of hCG triggering (mm)	675	0.1854	0.0474	0.0001	1.20 (1.10–1.32)

^aThe following factors were considered: serum luteinizing hormone and estradiol levels on the day of starting cetorelix, number of ≥ 14 mm follicles, endometrial thickness on the day of hCG triggering, number of oocytes obtained, number of good quality embryos/ blastocysts transferred, age, duration of infertility, type of infertility, cause of infertility, body mass index and smoking status. Of these, only the factors that showed >10% changed in the odds ratio of at least one independent variable were considered as the confounding factor.

The analysis revealed that an increased endometrial thickness on the day of human chorionic gonadotropin (hCG) triggering ($p=0.0003$; odds ratio: 1.19; 95% CI: 1.08–1.31), a higher total number of embryos on Day 3/blastocysts on Day 5 ($p < 0.0001$; OR: 1.07; 95% CI: 1.04–1.09), a higher number of good quality embryos/blastocysts transferred ($p=0.0236$; OR: 1.42; 95% CI: 1.05–1.93), and a lower progesterone level on the day of hCG triggering ($p=0.0035$, OR: 0.55, 95% CI: 0.37–0.82) were associated with a higher probability of pregnancy outcome after fresh ET per initiated cycle.

After adjusting for confounding factors, an increased endometrial thickness on the day of hCG triggering was associated with a higher probability of pregnancy outcome ($p=0.0001$, OR: 1.20; 95% CI: 1.10–1.32). A higher progesterone level on the day of hCG triggering was associated with a lower probability of pregnancy outcome after fresh ET per initiated cycle ($p=0.0256$; OR: 0.65; 95% CI: 0.45–0.95).

Data from 326 patients were used for model validation. The sensitivity and specificity analyses results are shown in **Table 3**. A predictive model was established with a sensitivity and specificity of 53.3% and 64.6%, respectively. The overall accuracy of the model was 58.9%.

Table 3. Sensitivity and specificity analyses

		Clinical pregnancy outcome (observed) (N = 326)		
		Yes	No	Total
Clinical pregnancy outcome (predicted)	Yes	88	57	145
	No	77	104	181
	Total	165	161	326

The value 0.56 was considered as the cut-off point of the Youden Index for the prediction of clinical pregnancy outcome (Yes [>0.56]/ No [≤ 0.56]).

Secondary analysis: Clinical outcomes

Clinical outcomes are shown in **Table 4**. In the FAS, 2972 patients initiated a cycle. Of these, the beta-hCG test was positive in 1215 patients (40.9% per initiated cycle). A total of 1138 patients had confirmed clinical pregnancies (38.3% per initiated cycle) and 970 patients had ongoing pregnancies (32.6% per initiated cycle). The mean number of viable fetuses per initiated cycle was 1.3 ± 0.48 fetuses. The ongoing pregnancy and clinical pregnancy rates per ET cycle were 45.2% and 53.0%, respectively, and the implantation rate was 37.3% per ET.

Table 4. Clinical outcomes (full analysis set)

Clinical outcomes	Total
	N = 2972
No. of initiated cycles, n	2972
No. of embryo transfer cycles, n	2147
No. of clinical pregnancies, n	1138
No. of ongoing pregnancies, n	970
No. of early miscarriages, n	152
No. of live births reported, n	970
Proportion of patients reaching clinical outcomes	
Clinical pregnancy rate, ^a (%)	53.0
Per embryo transfer cycles	
Ongoing pregnancy rate, ^b (%)	45.2
Per embryo transfer cycles	
Live birth rate, ^c (%)	45.2
Per embryo transfer cycles	
Implantation rate, ^d (%)	37.3
Cycle canceled rate, (%)	5.7
Early miscarriage rate, ^e (%)	13.4

^aClinical pregnancy rate = (Number of clinical pregnancies/Total number of cycles performed) × 100

^bOngoing pregnancy rate per embryo transfer cycle = (Number of ongoing pregnancy/No. of embryo transfer cycles) × 100

^cLive birth rate = (Number of live births/Total number of cycles performed) × 100

^dImplantation rate = (Number of gestational sacs observed/No. of embryos transferred) × 100

^eEarly miscarriage rate = (Number of early miscarriages/No. of clinical pregnancies) × 100

A total of 152 early miscarriages were reported out of 1138 clinical pregnancies resulting in an early miscarriage rate of 13.4%. The rate of cancelled cycles was 5.7%. A total of 970 live births were reported with a live birth rate of 32.6% per initiated cycle and a live birth rate of 45.2% per ET cycle.

Subgroup analysis: Clinical outcomes by age and number of oocytes retrieved

In patients aged ≤ 30 years, implantation rates, clinical pregnancy rates, ongoing pregnancy rates and live birth rates per ET cycles, were slightly higher compared to those aged >30 years. However, clinical pregnancy rates, ongoing pregnancy rates and live birth rates per initiated cycle and aspiration cycle were slightly lower in patients aged ≤ 30 years than in those aged >30 years. Patients aged ≤ 30 years had a similar cycle cancellation rate, but a lower early miscarriage rate compared with patients aged >30 years.

Clinical outcomes in terms of implantation rates, clinical pregnancy rates, ongoing pregnancy rates and live birth rates per ET cycle, aspiration cycle, and initiated cycle, were higher in patients for which 4–9 or 10–15 oocytes were retrieved compared with the other subgroups. Overall, clinical outcomes were lower in patients with 1–3 oocytes retrieved, except for ongoing pregnancy rates per initiated cycle, which was lowest in patients with >15 oocytes retrieved (23.7% vs 22.1%).

Safety

Of 2972 patients (100%), 51 patients (1.7%) reported an OHSS event. These events were mild in 24 (0.8%), moderate in 10 (0.3%), and severe in 17 (0.6%) patients. Signs, symptoms, or risk of OHSS led to a freeze-all cycle in 443 (14.9%) patients.

Discussion

We conducted a retrospective analysis using real-world demographic and clinical data of 2972 women less than 35 years of age treated for infertility at four IVF centers in China to evaluate the clinical outcomes and factors associated with clinical pregnancy rates of these patients undergoing IVF/ICSI cycles in conjunction with cetrorelix. The primary analysis of this study was to identify factors associated with clinical pregnancy rates in a GnRH antagonist cycle. We found that an increased endometrial thickness on the day of hCG triggering remained significantly associated with a higher probability of achieving pregnancy (OR: 1.20; $p = 0.0001$) after adjustment for confounding factors.

A previous retrospective study in China reported a similar finding. In that study, the clinical pregnancy group had a thicker endometrium and endometrial thickness was identified as a significant independent prognostic factor of clinical pregnancy, and the results also suggested that a higher pregnancy rate could be achieved with an endometrial thickness ≥ 8 mm [19]. Another retrospective study analyzing medical

chart data of Chinese women reported that the miscarriage rate was higher in patients with endometrial thickness < 7 mm. In that same study, clinical pregnancy rate, ongoing pregnancy rate, and implantation rate were highest in patients with endometrial thickness ≥ 14 mm; however, no statistical difference was observed with an endometrial thickness between 8 and 14 mm [20]. Similarly, a recent retrospective study on a large cohort (N = 9952) of patients undergoing their first IVF/ICSI treatment with autologous oocytes concluded that a thin endometrium on the day of hCG triggering could have an adverse effect on live birth rates and clinical pregnancy rates [21].

After adjusting for confounders in the present study, a higher progesterone level on the day of hCG triggering was found to significantly lower the probability of achieving clinical pregnancy (Odds ratio: 0.65, 95% CI 0.45–0.95; $p = 0.0256$). As with endometrial thickness, there is some controversy regarding the association of clinical outcomes with elevated serum progesterone levels at the time of ovulation triggering. However, a meta-analysis comprising 63 eligible studies (55,199 fresh IVF cycles using either agonist or antagonist protocols) found that a high progesterone level (defined as progesterone levels ≥ 0.8 ng/mL) on the day of triggering is associated with a decreased probability of pregnancy [22]. In contrast, a recent review of the available evidence suggested that debate remains regarding the impact of late follicular phase progesterone elevation on fresh ET IVF/ICSI outcomes [23]. To further validate this prediction model, we performed a sensitivity analysis. Our prediction model had a sensitivity, specificity, and overall accuracy of 53.3%, 64.6%, and 58.9%, respectively, suggesting the possible usefulness of our prediction model for predicting clinical pregnancy outcomes.

For the secondary analysis, we assessed the clinical outcomes based on qualitative variables. In this retrospective study, the clinical pregnancy rate per ET cycle in the studied population was 53.0%. This rate is comparable with the pregnancy rate of 44.9% reported in another retrospective study on 2106 Chinese women who underwent treatment with cetrorelix [20]. The pregnancy rate observed in the present study is also comparable with the pregnancy rate of 43.7% achieved in a study of another GnRH antagonist, ganirelix, in Chinese normal responders [24]. Of note, there were methodological differences between these studies, so these comparisons need to be interpreted with care. Nevertheless, the present results suggest that GnRH antagonist protocol with cetrorelix is an effective ART protocol in Chinese patients with good prognosis leading to the achievement of high rates of clinical pregnancy, ongoing pregnancy, and live birth.

Age has been reported as one of the strongest factors affecting pregnancy outcomes after IVF, with marked differences among patients aged < 34 years and between 43 and 45 years [25, 26]. However, clinical outcomes by age in the present subgroup analyses, as well as the implantation, clinical pregnancy, ongoing pregnancy, and live birth rates per ET cycle, were only slightly higher in patients aged < 30 years compared with those aged > 30 years. Further, we found the cycle cancellation rates were similar in both age groups, most likely due to the fact that the study population is enriched with high responders/good prognosis patients.

Regarding the subgroup analysis of clinical outcomes by number of oocytes retrieved, clinical outcomes were poorer in patients with 1–3 oocytes retrieved and ongoing pregnancy rates per initiated cycle were the lowest in patients with > 15 oocytes retrieved. This is consistent with previous reports in which lower numbers of oocytes retrieved result in poor outcomes [27, 28]. Furthermore, retrieval of > 15 oocytes has been associated with a higher risk of OHSS without necessarily resulting in improved pregnancy or live birth rates [29].

A total of 51 (1.7%) out of 2972 patients experienced OHSS with mild (0.8%), moderate (0.3%) or severe (0.6%) intensity. A similar incidence of OHSS (1.21%) was reported in a recent retrospective study with Chinese women treated with a GnRH antagonist protocol [30]. The freeze-all policy was implemented as a prevention of OHSS in 14.9% of patients who presented signs, symptoms or risk of OHSS. Currently, there is no global definition for risk of OHSS; thus, different OHSS criteria in routine clinical practice and fresh cycle ET cancellation rates were observed across the study centers. However, several studies have reported that freezing embryos and transferring frozen embryos later may not only help prevent OHSS but also yield a higher success rate in this subgroup of patients [31–33].

Limitations

One limitation of this study was the selection bias inherent to retrospective chart review studies; however, the study was designed with stringent inclusion and exclusion criteria to restrict participation only to patients with good prognosis as a way of minimizing selection bias. There may also be limited feasibility in implementation of the prediction model to the real-world clinical setting as the results of the multivariate logistic regression analyses are based on a heavily reduced subset of patients; thus, they may not be representative of the overall study population.

Conclusions

On the day of hCG triggering, endometrial thickness contributed positively, and progesterone level contributed negatively to achieving clinical pregnancy. This prediction model may be useful to conduct a preliminary screening of IVF patients in order to improve clinical pregnancy outcomes after fresh ET.

List Of Abbreviations

ART, assisted reproductive technology

BMI, body mass index

CI, confidence interval

ICSI, intracytoplasmic sperm injection

IVF, in vitro fertilization

ET, embryo transfer

FAS, full analysis set

FSH, follicle stimulating hormone

GnRH, gonadotropin-releasing hormone

hCG, human chorionic gonadotropin

OHSS, ovarian hyperstimulation syndrome

SD, standard deviation

Declarations

Ethical approval and consent to participate

This study was approved by the ethics committees and institutional review boards of the four participating centers. As this is a retrospective study of anonymized patient information, informed consent was not required.

Consent for publication

Not applicable.

Availability of data and materials

Additional deidentified data and other related supporting documents are available from the corresponding author on reasonable request.

Competing interests

YD and PC are employees of Merck Serono Co., Ltd (an affiliate of Merck KGaA Darmstadt, Germany). All other authors have no conflicts of interest to declare.

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Authors' contributions

RL, RY, YS, FG, JL, and JQ contributed to protocol development, and data collection and management. YD contributed to protocol development and writing and editing of this manuscript. PC analyzed the data and contributed to writing and editing of this manuscript.

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