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human reproduction **ORIGINAL ARTICLE** ***Infertility***

A randomized double blind comparison of atosiban in patients undergoing IVF treatment

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STUDY QUESTION: Does atosiban (oxytocin/vasopressin V1A receptor antagonist), given around embryo transfer improve the live birth rate of women undergoing IVF treatment?

SUMMARY ANSWER: The use of atosiban around embryo transfer did not improve the live birth rate in a general population of IVF patients.

WHAT IS KNOWN ALREADY: Uterine contractions in IVF cycles were significantly increased following ovarian stimulation and women with frequent uterine contractions had a lower pregnancy rates. A few observational studies suggested that the use of atosiban around embryo transfer resulted in higher pregnancy rates in women with repeated implantation failure (RIF). A non-randomized trial of IVF patients also reported higher implantation and clinical pregnancy rates after the use of atosiban.

STUDY DESIGN, SIZE, DURATION: This multi-centre randomized double blind study recruited 800 general subfertile women undergoing IVF treatment between November 2011 and March 2013. Subjects were randomized into the atosiban ($n = 400$) and placebo ($n = 400$) groups according to a computer-generated randomization list.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Subjects were recruited and randomized in the three IVF units in Guangzhou, Hong Kong and Ho Chi Minh City. Women in the atosiban group received i.v. atosiban 30 min before embryo transfer with a bolus dose of 6.75 mg, and the infusion was continued at 18 mg/h for ~1 h. The dose of atosiban was then reduced to 6 mg/h continued for another 2 h. Those in the placebo group received i.v. normal saline only. The primary outcome measure was the live birth rate.

MAIN RESULTS AND THE ROLE OF CHANCE: There was no significant difference in the live birth rate between the atosiban and placebo groups (39.8 versus 38.0%, $P = 0.612$, rate ratio 1.051, 95% confidence interval: 0.884–1.251). No significant differences were found between the two groups in the positive pregnancy test, clinical pregnancy, ongoing pregnancy, miscarriage, multiple pregnancy, ectopic pregnancy rates and implantation rate per woman. Similar results were found between the groups at different IVF centres, with a repeated cycle, presence of uterine fibroids or a serum estradiol level on the day of hCG above the median level.

LIMITATIONS, REASONS FOR CAUTION: Limitations include the transfer of early cleavage embryos, no measurement of uterine contractions, no documentation of adenomyosis and incomplete tracking of congenital abnormalities in newborns.

WIDER IMPLICATIONS OF THE FINDINGS: This randomized double blind study demonstrated that the use of atosiban given around embryo transfer did not improve the live birth rate in a general population of IVF patients; therefore atosiban should be given only in the context of clinical research.

STUDY FUNDING/COMPETING INTEREST(S): Centres in Hong Kong and Vietnam received research funding from Ferring, which was not involved in study design, execution, data analysis and manuscript preparation. There are no conflicts of interest.

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Key words: atosiban / IVF / live birth / uterine contraction

Introduction

IVF treatment involving ovarian stimulation, oocyte retrieval and embryo transfer after fertilization is an effective treatment for various causes of infertility. Despite advances in ovarian stimulation regimens and laboratory conditions, the pregnancy and delivery rates remain ~29 and 20%, respectively, per aspiration in Europe in 2009 (Ferraretti *et al.*, 2013). The corresponding rates in the USA in 2010 were 39 and 32% (Centre for Disease Control and Prevention, 2013).

Ovarian stimulation is used in the great majority of IVF cycles so that multiple embryos are available for selection and transfer. However, supraphysiological serum estradiol (E_2) concentrations following ovarian stimulation may induce endometrial production of oxytocin, formation of oxytocin receptors, and indirectly the synthesis/release of prostaglandin (PG)F2a (Richter *et al.*, 2004; Liedman *et al.*, 2008). Fanchin *et al.* (1998) found that around 30% of patients undergoing embryo transfer have frequent uterine contractions (>5 per minute) which were associated with significantly lower pregnancy success. Uterine contractions in stimulated IVF cycles measured by ultrasound scanning were increased by ~6-fold when compared with that in the natural cycle (Ayoubi *et al.*, 2003). An increased frequency of uterine contractions following ovarian stimulation has been recently confirmed (Zhu *et al.*, 2012).

In addition to a gentle approach in the transfer procedure, methods or medications to reduce uterine contractions around embryo transfer are an attractive option to improve the IVF success. The use of beta-adrenergic agonists or non-steroidal anti-inflammatory drugs (NSAID) has not been shown to provide benefit (Tsirigotis *et al.*, 2004; Bernabeu *et al.*, 2006), although piroxicam has been shown to improve the success of fresh IVF and frozen transfer cycles (Moon *et al.*, 2004). Uterine contractions are stimulated by oxytocin and therefore inhibition of oxytocin receptors may improve IVF success by decreasing uterine contractions, interfering with PGF2a/oxytocin systems and possibly improving endometrial perfusion (Kalmantis *et al.*, 2012).

Atosiban, a combined oxytocin/vasopressin V1A antagonist, is currently registered for clinical use in women suffering from preterm labour. The first case of using atosiban in IVF treatment was reported by Pierzynski *et al.* (2007a), followed by Liang *et al.* (2009), Chou *et al.*, (2011) and Lan *et al.* (2012). All of the studies used atosiban in patients with repeated implantation failure (RIF). In a placebo-controlled trial of general IVF patients, Moraloglu *et al.* (2010) showed that the implantation and clinical pregnancy rates of the atosiban group were significantly higher than the placebo group. However, this was not a randomized study and only the clinical pregnancy rate was reported.

There is clearly a need for a randomized double blind study to compare the live birth rate between women receiving atosiban and placebo around embryo transfer. The hypothesis in the present study was that the live birth rate was significantly higher after the use of atosiban in women undergoing IVF treatment.

Materials and Methods

Study design

This multi-centre randomized double blind study was conducted in three IVF units: Reproductive Medical Center of Nanfang Hospital, Guangzhou, China; Centre of Assisted Reproduction and Embryology, The University of Hong Kong – Queen Mary Hospital, Hong Kong and An Sinh Hospital, Ho Chi Minh City, Vietnam. The study had been approved by the Institutional Review Board of each hospital and was registered under Clinicaltrials.gov (NCT01501214). All women were fully counselled and written consents were obtained prior to participation. They were recruited once and did not receive any monetary compensation for joining the study.

Study population

Consecutive subfertile women undergoing IVF treatment at the three centres were screened and recruited if they met the selection criteria. Inclusion criteria included: (i) age <43 years and (ii) normal uterine cavity shown on ultrasound scanning. Women were excluded if they had the following: (i) three or more previous IVF cycles; (ii) use of donor oocytes; (iii) natural IVF or *in vitro* maturation cycles; (iv) endometrial thickness <8 mm; (v) presence of hydrosalpinx on scanning; (vi) transfer cancelled because of no fertilization or risk of ovarian hyperstimulation syndrome (OHSS); (vii) blastocyst transfer; (viii) undergoing PGD, (ix) recruited in the same study before or (x) joined other studies in the centres.

Ovarian stimulation and IVF

All women started their IVF treatment with ovarian stimulation using either the long agonist or antagonist protocols. On Day 2–3 of the menstrual cycle, they underwent transvaginal ultrasound examination and serum E_2 measurement. Human menopausal gonadotrophin (hMG) or recombinant FSH were started at 150–300 IU per day based on the antral follicle count, age of women and previous ovarian response, according to the standard operation procedures of the centre. Ovarian response was monitored by serial transvaginal scanning with or without hormonal monitoring. Further dosage adjustments were based on the ovarian response at the discretion of the clinicians in charge.

When three leading follicles were ≥18 mm, hCG 10 000 IU or ovidrel 250 μg (Merck Serono S.p.A., Modugno, Italy) was given to trigger final maturation of oocytes. Oocyte retrievals were arranged around 36 h later. A maximum of two embryos in Hong Kong, three embryos in China and four embryos in Vietnam were transferred 2–3 days after the retrieval, depending on the age of the patient, the indication for IVF, the number of IVF cycle attempted, the number and quality of embryos available per transfer, and the couple's decision. Excess good quality embryos were frozen for subsequent transfer.

Randomization, intervention and blinding

On the day of embryo transfer, women were randomized into the atosiban or placebo groups in a 1 to 1 ratio according to a computer-generated randomization list with blocks of 10 in sealed envelopes by a research nurse not involved in the present study. Women in the atosiban group received i.v. atosiban 30 min before the transfer with a bolus dose of 6.75 mg, and the infusion was continued with an infusion rate of 18 mg/h for ~1 h. The dose of atosiban was then reduced to 6 mg/h after embryo transfer and the infusion was continued for another 2 h. Therefore, the total administered dose was 37.5 mg. Those in the placebo group received only normal saline infusion for the same duration. In both the atosiban and placebo groups, women were medicated by intravenous bags which looked identical and were prepared by a dedicated nurse in the centre not involved in the study. Subjects, clinicians and laboratory staff were therefore blinded to the group assignment. The codes for the treatment groups were revealed to investigators only after the completion of the whole study and statistical analysis.

Pregnancy outcomes

Women received vaginal or i.m. progesterone only as the luteal phase support according to the standard operation procedures of the centre. A urine pregnancy test was performed ~16 days after embryo transfer. If it was positive, ultrasound examination was performed 10–14 days later to confirm intrauterine pregnancy and to determine the number of gestational sacs present. Antenatal management was as usual, if pregnant. All pregnant women were contacted or traced for the pregnancy outcome after delivery or miscarriage.

Outcome measures

The primary outcome measure was the live birth rate and the secondary outcome measures include positive pregnancy test, clinical pregnancy, ongoing pregnancy, miscarriage, multiple pregnancy and ectopic pregnancy rates. A baby born alive after 20 weeks gestation was classified as a live birth. Clinical pregnancy was defined as the presence of at least one gestational sac on ultrasound at 6 weeks. Ongoing pregnancy was defined as the presence of at least one fetus with heart pulsation on ultrasound beyond 8 weeks. Miscarriage rate was defined as the number of miscarriages before 20 weeks divided by the number of women with positive pregnancy test. Multiple pregnancy was defined as a pregnancy with more than one gestational sac detected on ultrasound at 6 weeks. Implantation rate per subject was calculated as the number of gestational sacs seen on scanning divided by the number of embryos replaced and was considered as a continuous variable.

Sample size calculation

The average live birth rate for the three centres in 2009 was 35% per transfer. Assuming 10% increase in the live birth rate to 45% after the use of atosiban, 396 women in each arm were required at a power of 80% and a significance level of 5% (Sigmastat, Jandel Scientific, San Rafael, CA, USA). A total of 800 patients were recruited in this study to account for some drop-outs.

Statistical analysis

Analysis was performed based on the intention-to-treat principle. Statistical comparisons were carried out using Mann–Whitney *U*-test, Chi-square test, Fisher's exact test and Student *t*-test where appropriate with the Statistical Program for Social Sciences (SPSS, Inc., Version 21.0, Chicago, IL, USA). Subgroup analysis was performed for different centres, repeated cycles, having fibroids and serum E_2 level on the day of hCG above the median level. Logistic regression analysis was used to analyse factors predicting the live birth rate. A two-sided $P < 0.05$ was taken as statistically significant.

Results

Participant flow

Between November 2011 and March 2013, 1268 women were screened, 293 women did not meet the selection criteria and 175 women declined to participate (Fig. 1—Consort 2010 Flow Diagram). Therefore, 800 women were recruited: 250 in China, 250 in Hong Kong and 300 in Vietnam. Two women with an ongoing pregnancy in Hong Kong were lost to follow-up for documentation of live birth and were not considered to have a live birth.

Baseline and cycle characteristics

Baseline characteristics of women in the atosiban and placebo groups are shown in Table I. No significant differences were detected in the demographic characteristics of women of in any features of the IVF cycles, including dosage/duration of FSH/hMG, serum E_2 concentration on the day of hCG, endometrial thickness, number of oocytes aspirated/fertilized, number of transferrable embryos and number of embryos transferred (Table I).

Primary outcome

There was no significant difference in the live birth rate between the atosiban and placebo groups (39.8 versus 38.0%, $P = 0.612$, rate ratio 1.046, 95% confidence interval (CI): 0.874–1.253) (Table II).

Secondary outcomes

No significant differences were found between the atosiban and placebo groups in the positive pregnancy test, clinical pregnancy, ongoing pregnancy, miscarriage, multiple pregnancy, ectopic pregnancy rates and implantation rate per subject (Table II).

Subgroup analyses and logistic regression

Subgroup analysis was performed by stratifying women into those in different centres, in a repeated cycle, having fibroids and a serum E_2 level on the day of hCG above the median level (7356 pmol/l). The clinical pregnancy, ongoing pregnancy and live birth rates were also comparable between the two groups in different centres, in a repeated cycle, having fibroid or serum E_2 level on the day of hCG above the median level (Fig. 2).

Binary logistic regression using the enter method was used to analyse the prediction for live birth in the fresh IVF cycle by the women's age, duration of infertility, cycle number, presence of fibroids, treatment centres, stimulation protocol (agonist/antagonist), insemination method, antral follicle count, FSH/HMG dosage, number of oocytes obtained, number of embryos replaced and atosiban/placebo. The number of embryos replaced was the only significant factor which independently predicted the likelihood of a live birth [Exp(B) 1.521, 95% CI 1.084–2.134; $P = 0.015$].

Adverse events and congenital abnormalities

All women had received the atosiban or placebo infusion as prescribed without any complaint. There were no serious adverse events documented. One and three cases of OHSS were noted in the atosiban and placebo groups, respectively.

Data for congenital abnormalities in the newborns were available only in the centre in China. Four cases (3.2%, 4/125) of congenital abnormality (cleft lip 1; cleft palate 1; hypospadia 1; Dandy-Walker syndrome 1) were found in the atosiban group while two cases (1.6%, 2/125) of congenital abnormality (truncus arteriosus 1; ventricular septal defect & syndactylia 1) were in the placebo group.

Discussion

To the best of our knowledge, this is the first randomized double blind trial on the use of atosiban in IVF. Our results did not show any improvement in pregnancy outcome, including the positive pregnancy test, clinical pregnancy, ongoing pregnancy and live birth rates, in women receiving atosiban infusion around the time of embryo transfer. Patients with RIF (Pierzynski *et al.*, 2007a; Liang *et al.*, 2009; Lan *et al.*, 2012) or having uterine fibroids (Fujiwara *et al.*, 2004; Somigliana *et al.*, 2007; Yoshino *et al.*, 2010) may have more uterine contractions. However, our subgroup analysis revealed no difference in all pregnancy outcomes between the two groups in

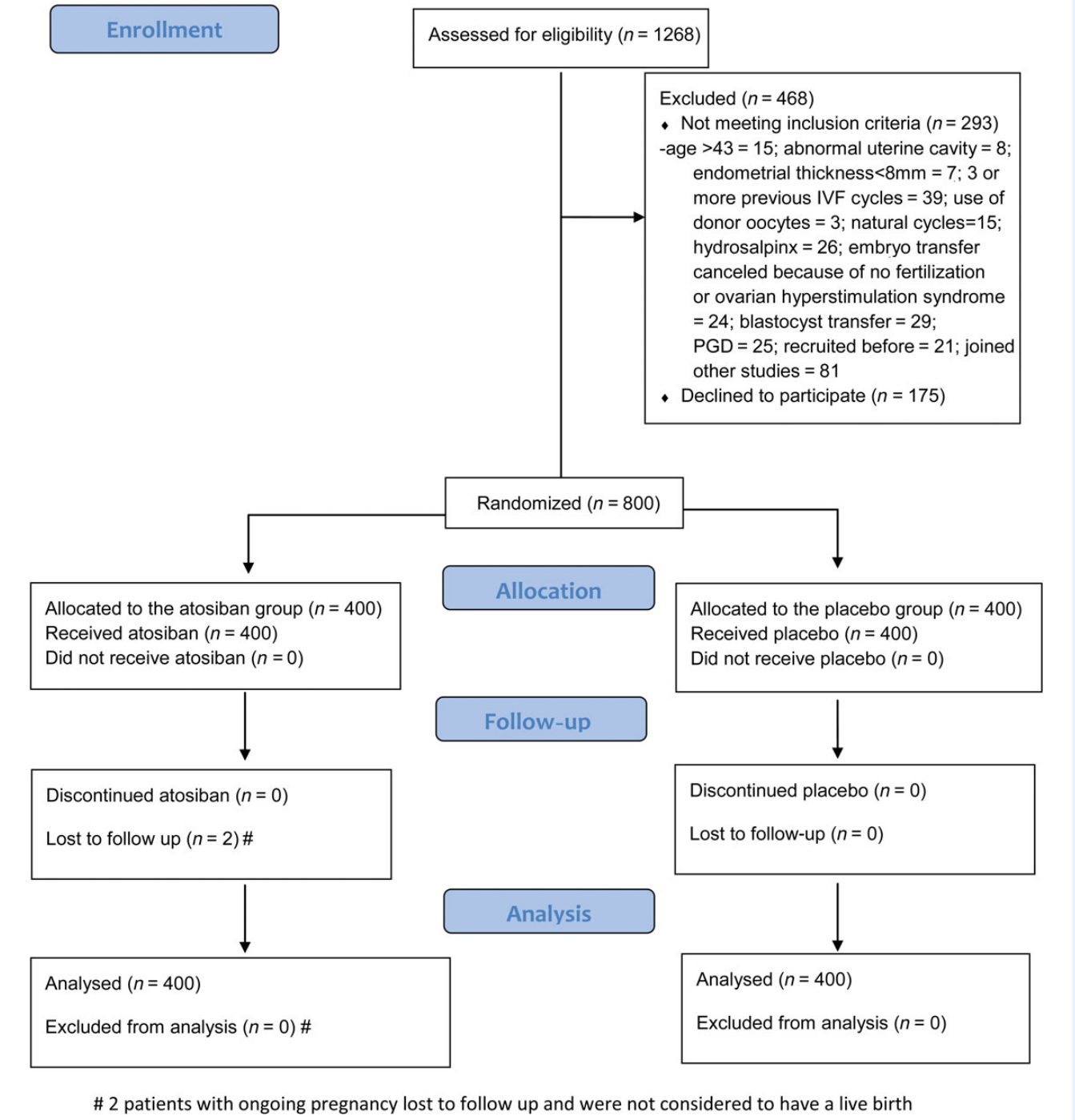

Figure 1 CONSORT 2010 Flow Diagram.

different centres, in a repeated cycle, having uterine fibroids or a serum E_2 level on the day of hCG above the median level.

Moraloglu *et al.* (2010) reported a placebo-controlled trial of atosiban in 160 general IVF patients and showed significant improvements in both implantation and clinical pregnancy rates with atosiban. Unfortunately, this is not a truly randomized study as randomization was performed using the weekdays and live birth rate was not reported. Our study is a randomized trial and the randomization codes were revealed only after completion of the statistical analysis. Therefore, subjects, clinical and laboratory staff, researchers and the one performing statistical analysis were all blind to the randomization group in order to avoid any bias in conducting this clinical trial including data analysis. The sample size calculation was based on the live birth rate, which should be the gold standard in a clinical trial of subfertility.

Uterine contraction or peristalsis plays a key role in the human reproductive process. During the early follicular phase, peristalsis starting from

Table I Comparison of the demographic characteristics and ovarian response in patients undergoing IVF treatment in a randomized trial of atosiban versus placebo.

	Atosiban group (n = 400)	Placebo group (n = 400)
Age of women (years)[a]	32 (29–36)	33 (29–37)
Body mass index (kg/m^2)[a]	21.8 (20.1–23.8)	21.6 (20.0–23.7)
Smoker[b]		
Yes	9 (2.2%)	15 (3.8%)
No	381 (95.3%)	378 (94.5%)
Ex-smoker	10 (2.5%)	7 (1.7%)
Primary infertility[b]	240 (60.0%)	243 (60.8%)
Duration of infertility (years)[a]	4 (2–6)	4 (2–6)
Cause of infertility[b]		
Tuboperitoneal	119 (29.8%)	111 (27.8%)
Endometriosis	18 (4.5%)	21 (5.2%)
Male	142 (35.5%)	144 (36.0%)
Unexplained	57 (14.2%)	70 (17.5%)
Mixed	64 (16.0%)	54 (13.5%)
Cycle number[b]		
First cycle	319 (79.8%)	283 (70.8%)
Repeated cycle	81 (20.2%)	117 (29.2%)
Antral follicle count[a]	11 (8–15)	11 (8–15)
FSH/HMG dosage (IU)[a]	2150 (1575–2775)	2250 (1650–2900)
FSH/HMG duration (days)[a]	10 (9–11)	10 (9–11)
Estradiol on day of hCG (pmol/l)[a]	7422 (4741–10808)	7106 (3542–10 852)
Endometrial thickness (mm)[a]	11.2 (10.0–12.7)	11.5 (10.0–13.0)
No. of oocytes obtained[a]	11 (7–15)	11 (7–14)
No. of oocytes fertilized[a]	6 (4–10)	7 (4–10)
No. of transferrable embryos[a]	4 (3–6)	4 (3–6)
No. of embryos transferred[b]		
One	29 (7.2%)	31 (7.7%)
Two	211 (52.8%)	204 (51.0%)
Three	92 (23.0%)	94 (23.5%)
Four	68 (17.0%)	71 (17.8%)

[a]Data are median (25th and 75th percentile).
[b]Data are number (%).

the fundus to the cervix may help to empty the uterine cavity. In the late follicular and periovulatory phases, peristalsis from the cervix to the fundus dominates and increases in intensity towards ovulation, promoting sperm transport. During the luteal phase, the uterus shows a relative quiescence, thereby facilitating embryo implantation. Ovarian stimulation commonly employed in IVF cycles increases uterine contractions (Ayoubi *et al.*, 2003; Zhu *et al.*, 2012).

Embryo transfer is the final step of an IVF cycle and its success may be affected by uterine contractions as well as embryo quality and endometrial receptivity (Fanchin, 2009). Excessive uterine contractions may expel embryos from the uterus and decrease the implantation potential of embryos (Fanchin *et al.*, 1998; Zhu *et al.*, 2014a). Frequency of uterine peristalsis was positively correlated with the distance that fluid moved after it was deposited in the uterine cavity, as shown in ultrasound scanning (Zhu *et al.*, 2014a). Women with more uterine contractions before embryo transfer have a lower IVF success rate (Fanchin *et al.*, 1998; Zhu *et al.*, 2014b). A stepwise decrease in ongoing pregnancy rates was observed when the frequency of the contractions increased from 3 to >5 per minute (Fanchin *et al.*, 1998). Similarly, patients with uterine contractions of <3/min before embryo transfer had a significantly higher pregnancy rate (Zhu *et al.*, 2014b). Although the frequency of uterine contractions was not correlated with serum E_2 concentration in stimulated IVF cycles (Fanchin *et al.*, 1998; Zhu *et al.*, 2012), we performed a subgroup analysis to evaluate any improvement in the pregnancy outcomes in those with serum E_2 level on the day of hCG above the median level.

Atosiban, a combined oxytocin/vasopressin V1A antagonist, reduced the frequency and amplitude of uterine contractions in egg donors,

Table II Comparison of pregnancy outcomes.

	Atosiban group	Placebo group	*P*-value^	Rate ratio 95% confidence interval
Positive pregnancy test rate[a]	54.3 (217/400)	49.5 (198/400)	0.203	1.096 (0.959–1.253)
Clinical pregnancy rate[a]	50.3 (201/400)	46.8 (187/400)	0.322	1.075 (0.927–1.246)
Ongoing pregnancy rate[a]	42.8 (171/400)	38.3 (153/400)	0.195	1.118 (0.939–1.331)
Live birth rate[a]	39.8 (159/400)[#]	38.0 (152/400)	0.612	1.046 (0.874–1.253)
Miscarriage rate[a]	17.1 (37/217)	17.7 (35/198)	0.866	0.965 (0.634–1.468)
Multiple pregnancy rate[a]	30.0 (65/217)	34.3 (68/198)	0.339	0.872 (0.650–1.172)
Twin[a]	84.6 (55/65)	86.8 (59/68)		
Triplet[a]	12.3 (8/65)	13.2 (9/68)		
Quadruplet[a]	3.1 (2/65)	0 (0/68)		
Ectopic pregnancy rate[a]	4.1 (9/217)	5.1 (10/198)	0.660	0.811 (0.319–2.061)
Implantation rate per woman[b]	0.5 (0.33–0.75)	0.5 (0.33–1.00)	0.550^^	

[a]Data are %.
[b]Data are median (25th and 75th percentile).
[#]Two patients with ongoing pregnancy lost to follow-up.
^Fisher's exact test except ^^Mann–Whitney *U*-test.

assessed by direct measurement (Blockeel *et al.*, 2009; Pierson *et al.*, 2009; Visnova *et al.*, 2009). Lan *et al.* (2012) evaluated the frequency of uterine contractions by ultrasound in patients with RIF and showed similar findings after atosiban infusion. The proportion of cycles with uterine contractions of >3/min was only 6.2% (18/292) in the study of Zhu *et al.* (2014b) but 65.0% (143/220) in the study of Fanchin *et al.* (1998). We did not measure uterine contractions in the present study due to logistic reasons and the use of atosiban unlikely offers benefit if the proportion of women with uterine contractions >3/min constitutes a small proportion only.

Another reason why we did not observe any benefit of atosiban may be related to the regimen of atosiban infusion used in the present study, which was based on that of Moraloglu *et al.* (2010). Atosiban, which has to be given i.v. and is a very short acting drug, was administered for ~3 h around embryo transfer, with the delivery 2 h after the transfer. Therefore, the reduction in uterine contractions may not last long enough after stopping the atosiban infusion to produce appreciable effects on the outcome measures. A prolonged atosiban infusion over 1–2 days or a maintenance therapy using oral non-steroidal anti-inflammatory therapy after the atosiban infusion may be associated with a sustained reduction in uterine contractions after embryo transfer, leading to a higher live birth rate. Further randomized trials are warranted to answer these questions.

The first case of clinical use of atosiban in IVF was reported by Pierzynski *et al.* (2007a). Atosiban was administered to a 42-year-old patient who had previously undergone eight transfers of 12 good quality embryos and she conceived in that cycle. In a prospective cohort study, Lan *et al.* (2012) showed that atosiban may benefit women with RIF undergoing transfer of cryopreserved embryos in a hormonal replacement cycle. Our primary goal in the present study was to evaluate the use of atosiban in a general population of patients undergoing IVF. Patients undergoing repeated IVF cycles obviously cannot be compared with those with RIF; therefore, our results should not be extrapolated to RIF management. One clinical trial on the use of atosiban in patients with RIF has been registered in Clinicaltrials.gov and it will be interesting to find out whether the benefit of atosiban can be observed in RIF patients.

There was a lack of an embryotoxic effect of atosiban in concentrations up to 50-fold therapeutic blood concentrations: atosiban did not affect the survival of 1-cell rabbit embryos or decrease the percentage of hatched rabbit blastocysts (Pierzynski *et al.*, 2007b). The human sperm motility bioassay also showed no adverse influence. We did not find a significant increase in congenital abnormalities in the newborns in China, although the sample size was too small to show statistical significance and no data on congenital abnormalities were available in the other two centres.

The limitations of the study include transfer of early cleavage embryos, no measurement of uterine contractions, no documentation of adenomyosis and no tracking of congenital abnormalities in newborns in Hong Kong and Vietnam. Although we recorded the presence of uterine fibroids, the number and size of the uterine fibroids were not documented. Multiple embryos are still being transferred in many Asian countries, leading to a 40% multiple pregnancy rate with 13–15% triplets or quadruplets in the present study. Patients should

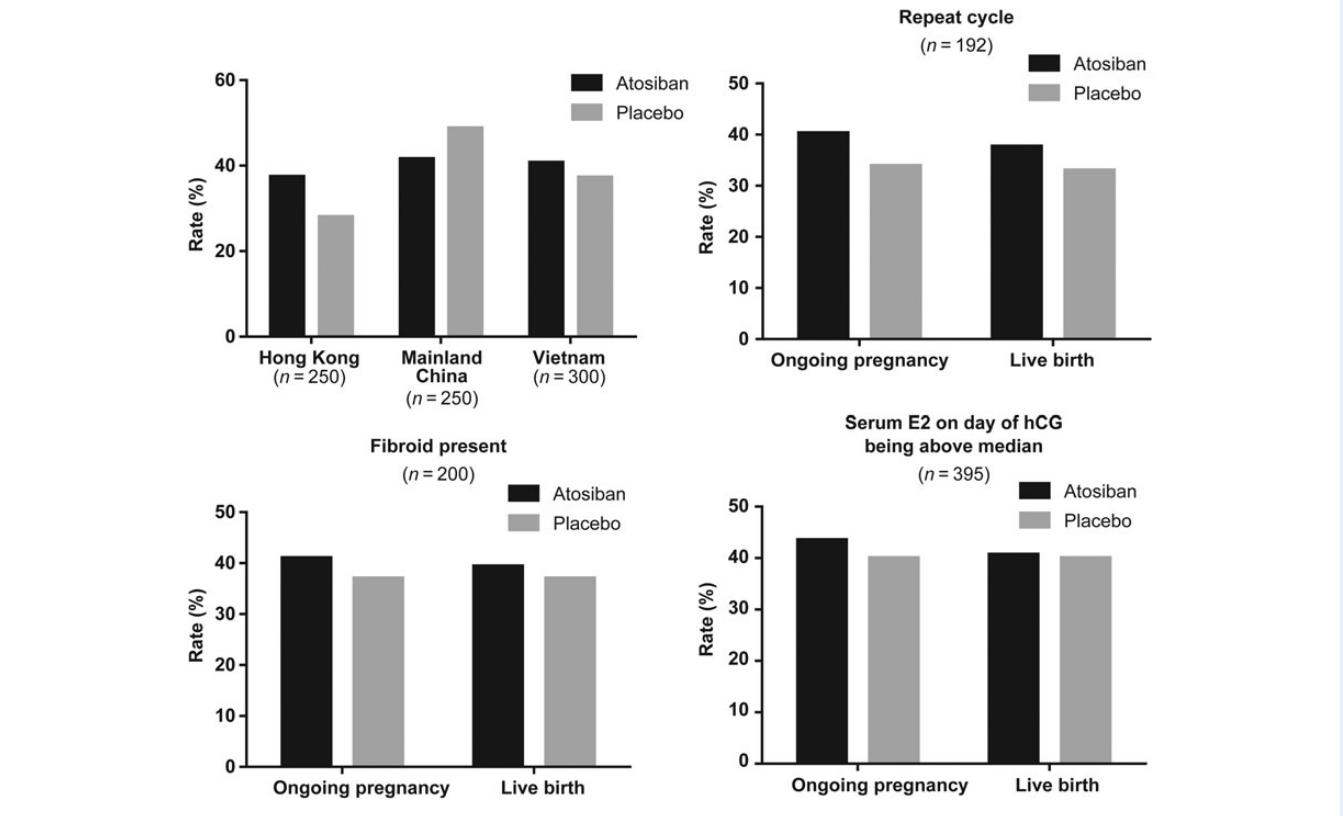

Figure 2 Subgroup analysis of the effect of atosiban. Subgroup analysis was performed for different centres, repeated cycles, having fibroids and serum estradiol (E_2) level on the day of hCG above the median level. No statistically significant differences between the groups were demonstrated ($P > 0.05$).

be counselled to transfer 1–2 embryos per cycle to avoid a higher multiple pregnancy rate and the associated adverse obstetric and perinatal outcomes.

In conclusion, the use of atosiban given around embryo transfer did not improve the live birth rate in a general population of IVF patients. Similar results were found in three different IVF centres, in repeated cycles, in the presence of uterine fibroids or a serum estradiol level on the day of hCG above the median level. Atosiban should, therefore, be administered only in the context of clinical research.

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Authors' roles

E.H.Y.N. was involved in study design, execution, analysis, manuscript drafting, critical discussion and final approval of the manuscript. L.C., V.T.N.L., H.M.T. and S.Q. were involved in study design, execution, critical discussion and final approval of the manuscript. R.H.W.L. was involved in execution, data analysis, critical discussion and final approval of the manuscript.

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Conflict of interest

None declared.

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