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Reproductive Medicine

The impact of ovarian stimulation on the outcome of intrauterine insemination treatment: an analysis of 8893 cycles

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Objective To evaluate the impact of ovarian stimulation on the outcome of intrauterine insemination (IUI).

Design Retrospective analysis.

Setting A single university-based centre.

Population A total of 5109 couples with 8893 cycles.

Methods The outcome of IUI with different protocols for ovarian stimulation was examined.

Main outcome measures The live birth rate (LBR), twin pregnancy rate and ovarian hyperstimulation syndrome (OHSS).

Results In ovulatory women without ovarian stimulation, the LBR was 7.6%. Stimulation with clomifene citrate (CC), letrozole (LE), human menopausal gonadotrophin (HMG), CC or LE combined with HMG achieved LBRs of 6.1, 5, 7.9, 8 and 12.2%, respectively. LE combined with HMG achieved a significantly improved LBR compared with no stimulation. HMG stimulation was associated with a higher rate of twins (7.4%) than no stimulation (0%, $P < 0.01$). In ovulatory women, the LBR appeared lower in CC and LE compared with no stimulation ($P > 0.05$). In anovulatory women, ovarian stimulation with CC, LE, HMG, CC or LE combined with HMG achieved LBRs of 11.3, 5.1, 11.8, 12.6 and 13.6%, respectively. No significant difference was observed. There were no triplet pregnancies or OHSS in stimulated cycles.

Conclusions In ovulatory women, ovarian stimulation with LE combined with HMG achieved a significantly improved live birth rate. HMG stimulation resulted in a high risk for twins.

Keywords Clomifene citrate, human menopausal gonadotrophin, intrauterine insemination, letrozole, live birth rate, ovarian stimulation.

Tweetable abstract In ovulatory women, ovarian stimulation with letrozole and HMG resulted in a significantly improved LBR.

目的: 分析不同促排卵方案对人工授精妊娠结局影响

设计: 回顾分析

背景: 单中心

样本: 8893周期

方法: 检验不同促排卵方案对妊娠结局影响

分析指标: 活产率、双胎率、卵巢过度刺激综合征

结果: 排卵正常者自然周期活产率为7.6%。枸橼氯米芬、来曲唑、尿促性素、枸橼氯米芬+尿促性素、来曲唑+尿促性素促排卵活产率6.1%、5%、7.9%、8%、12.2%,来曲唑+尿促性素明显较自然周期改善活产率。使用尿促性素较自然周期显著增加双胎率(7.4%、0%,($P < 0.05$))。排卵障碍者采用五种方案活产率11.3%、 5.1%、11.8%、12.6%、13.6%。组间无统计差异。

结论: 排卵正常者,来曲唑+尿促性素方案明显改善活产率,尿促性素增加双胎风险。

关键词 卵巢促排卵, 宫腔内人工授精, 尿促性素, 来曲唑, 活产率。

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Introduction

Intrauterine insemination (IUI) has been widely used as a common treatment for infertile couples. The reported clinical pregnancy rate varies considerably, ranging from 5 to 20%.[1–4] Although an encouraging clinical pregnancy rate (12–18%) has been reported,[5–8] the application of IUI in modern infertility practice has recently been questioned.

The UK National Institute for Health and Care Excellence (NICE) guideline suggests that IUI is of limited value for people with unexplained infertility, mild endometriosis or 'mild male factor infertility'.[9]

IUI is considered a first-line procedure among assisted reproductive techniques due to its simplicity, ease of management, relatively low incidence of complications and low cost. However, when IUI is used, should ovarian stimulation be used at the same time? Some investigators have advocated using the natural cycle[10,11] whereas others have claimed that ovarian stimulation may lead to better results.[12,13] Furthermore, there is still no consensus on the optimal protocol for ovarian stimulation. Various stimulation protocols have been applied, including clomifene citrate (CC), letrozole (LE), human menopausal gonadotrophin (HMG), urinary follicle-stimulating hormone (uFSH), recombinant FSH (rFSH) and combinations of these products. In this retrospective study we analysed the outcomes of 8893 cycles of IUI treatment with different protocols for ovarian stimulation and compared the risk of multiple pregnancy and ovarian hyperstimulation syndrome (OHSS) among various protocols.

Methods

Patients

This was a retrospective study using data accumulated over a 7-year period between 2006 and 2012 inclusive. A total of 5109 couples who underwent IUI treatment in our centre were included. The clinical details and outcome of treatment were retrieved from our clinical database. The inclusion criteria for IUI included: infertility for at least 1 year, at least one patent fallopian tube and absence of a severe male factor. Women were excluded if there was evidence of premature ovarian failure. This study was approved by the local hospital ethics committee.

Ovarian stimulation and follicle monitoring

This study used five types of ovarian stimulation protocol:

1 CC 50 mg/day starting from days 3–5 for 5 days.
2 LE 2.5 mg/day from days 3–5 for 5 days.
3 HMG 75 IU/day starting from days 3–5 for a variable duration depending on the response.
4 CC combined with HMG – CC 50 mg/day starting from days 3–5 for 5 days followed by the addition of 75 IU of HMG for a variable duration depending on the response.
5 LE combined with HMG – LE 2.5 mg/day starting from days 3–5 for 5 days followed by the addition of 75 IU of HMG for a variable duration depending on the response.

In all treatment cycles, whether natural or stimulated, a serial follicle scan was performed starting from day 11 or 12 of the cycle. We did not routinely perform any hormone monitoring. When at least one mature follicle had a diameter of 18 mm or more we triggered ovulation with intramuscular injection of urinary human chorionic gonadotrophin (hCG) (5000–10 000 IU) (Livzon, Zhuhai, China). Insemination was performed 36–40 hours after injection of hCG. We cancelled the IUI treatment cycle when there were more than three mature follicles.

Semen preparation and insemination

Semen was collected by masturbation after abstinence for 3–7 days and prepared with two-layer density gradient centrifugation after liquefaction. Only one insemination procedure was performed in each treatment cycle. The volume of washed semen sample used for insemination 0.3–0.5 ml.

Luteal support and follow-up

The luteal phase was used routinely in all patients, commencing the day after IUI. It consisted of microniSed progesterone (Dydrogesterone Tablets, 20mg/day, Abbott, Chicago, U.S.A) for 13 days. A blood sample was obtained 14 days after insemination for hCG assay to confirm whether pregnancy had occurred. In women with positive hCG, ultrasound examination was performed at 7 weeks' gestation to confirm fetal viability. A clinical pregnancy was defined as one in which there was ultrasonographic evidence of an intrauterine insemination gestational sac.

Statistical analysis

SPSS 16.0 software was used for data analysis. A chi-square test was used to compare categorical data between groups. Student's t-test was used to compare continuous variables between groups. A P-value <0.05 was considered statistically significant.

Results

A total of 8893 cycles of IUI treatment were included; 2591 of these in natural cycles and 6302 in stimulated cycles. Patient demographics are presented in Table 1. The mean age, body mass index (BMI), antral follicle count (AFC) and duration of infertility were not significantly different among natural and stimulated cycles ($P > 0.05$); the mean number of dominant follicles in stimulated cycles was 1.68 ± 0.81. In the past 6 years, the pregnancy rate in our centre for IUI with a natural cycle did not vary significantly year by year (8.3, 9.7, 10.4, 8.1, 9.4 and 8.7%, respectively; $P = 0.52$). No triplet pregnancies or OHSS were observed in stimulated cycles.

Table 1. Demographics of patients who underwent natural or stimulated IUI cycles

Parameters	Natural cycles (*n* = 2591)	Stimulated cycles (*n* = 6302)*	*P*-value
Mean age (years)**	29.5 ± 3.5	29.3 ± 3.3	0.65
Body mass index (kg/m^2)**	21.5 ± 2.5	21.7 ± 2.5	0.6
Antral follicle count**	12.6 ± 5.9	12 ± 5.7	0.59
Duration of infertility (years)**	3.5 ± 2.1	3.4 ± 2.1	0.69
Infertility			
Primary	1762 (68%)	4096 (65%)	0.003
Secondary	875 (32%)	2206 (35%)	
Diagnosis			
Endometriosis	268 (10.3%)	311 (4.9%)	<0.001
Tubo-peritoneum	826 (31.9%)	1418 (22.5%)	
Male factors	622 (24%)	1195 (19%)	
Unexplained infertility	875 (33.8%)	1815 (28.8%)	
Pregnancies	241 (9.3%)	734 (11.7%)	0.001
Miscarriages	35 (14.5%)	144 (19.6%)	0.05
Twin pregnancies	0 (%0)	36 (4.9%)	<0.001
Ectopic pregnancies	10 (4.2%)	44 (6.0%)	0.18
Live births	196 (7.6%)	546 (8.7%)	0.05

*This total includes 4246 ovulatory women and 2056 anovulatory women.
**Results shown are mean ± SD.

The live birth and pregnancy rates of *ovulatory* women undergoing IUI treatment in a natural cycle were 7.6 and 9.3%, respectively. The results of IUI using the different protocols of ovarian stimulation are summarised in Table 2a. Only ovarian stimulation with LE combined with HMG produced a significantly higher live birth and clinical pregnancy rates (12.2 and 16.8%, respectively). The results of other forms of stimulation were not significantly different from those with natural cycles. HMG stimulation (all three groups combined) was associated with a significantly higher twin pregnancy rate (14/189, 7.4%) than no stimulation (0%) ($P < 0.001$). We also observed that the live birth rate appeared to be lower in those stimulated with CC (6.1%) and LE (5.0%) compared with no stimulation (7.6%) ($P = 0.05$ and 0.14, respectively).

The live birth and pregnancy rates achieved in *anovulatory* women with the different protocols of ovarian stimulation are compared in Table 2b. The live birth rate was the lowest with LE (5.1%) and the highest with combined LE and HMG (13.6%). But contingency table analysis showed no statistical difference among the groups. When we combined all types of stimulation together, the pregnancy rate in anovulatory women was 16%, significantly higher than that of ovulatory women without stimulation (9.3%) ($P < 0.01$).

Figure 1 compares the outcomes of IUI in ovulatory and anovulatory women for each ovarian stimulation protocol. The live birth and pregnancy rates achieved in anovulatory women were consistently higher than in ovu-

Table 2. A comparison of pregnancy outcomes among ovulatory and anovulatory women undergoing IUI and receiving different protocols of stimulation

	NC (*n* = 2591)	CC (*n* = 2246)	LE (*n* = 264)	HMG (*n* = 559)	CC + HMG (*n* = 980)	LE + HMG (*n* = 197)	*P*-value
(a) Ovulatory women							
Pregnancies (%)	241 (9.3)	196 (8.7)	20 (7.6)	55 (9.8)	101 (10.3)	33 (16.8)***	0.004
Miscarriages (%)	35 (14.5)	46 (23.5)	5 (25)	8 (14.5)	15 (14.9)	8 (24.2)	0.13
Twin pregnancies (%)	0 (0)	8 (4.1)**	0 (0)	3 (7.3)**	9 (8.9)***	2 (6.1)*	0.001
Ectopic pregnancies (%)	10 (4.2)	12 (6.1)	2 (10)	3 (5.5)	8 (7.9)	1 (3.0)	0.66
Live births (%)	196 (7.6)	138 (6.1)	13 (5.0)	44 (7.9)	78 (8)	24 (12.2)***	0.01

	CC (*n* = 515)	LE (*n* = 79)	HMG (*n* = 85)	CC + HMG (*n* = 1025)	LE + HMG (*n* = 352)	*P*-value
(b) Anovulatory women						
Pregnancies (%)	78 (15.2)	7 (8.9)	13 (15.3)	169 (16.5)	62 (17.6)	0.38
Miscarriages (%)	18 (23.1)	2 (28.6)	2 (15.4)	26 (15.4)	14 (22.6)	0.5
Twin pregnancies (%)	3 (3.8)	0 (0)	0 (0)	8 (4.7)	3 (4.8)	0.9
Ectopic pregnancies (%)	2 (2.6)	1 (11.1)	1 (7.7)	14 (8.3)	0 (0)	0.07
Live births (%)	58 (11.3)	4 (5.1)	10 (11.8)	129 (12.6)	48 (13.6)	0.28

NC, natural cycle.
**P* < 0.05.
***P* < 0.01.
****P* < 0.001.
The *P*-value indicates a statistically significance difference compared with the NC group.

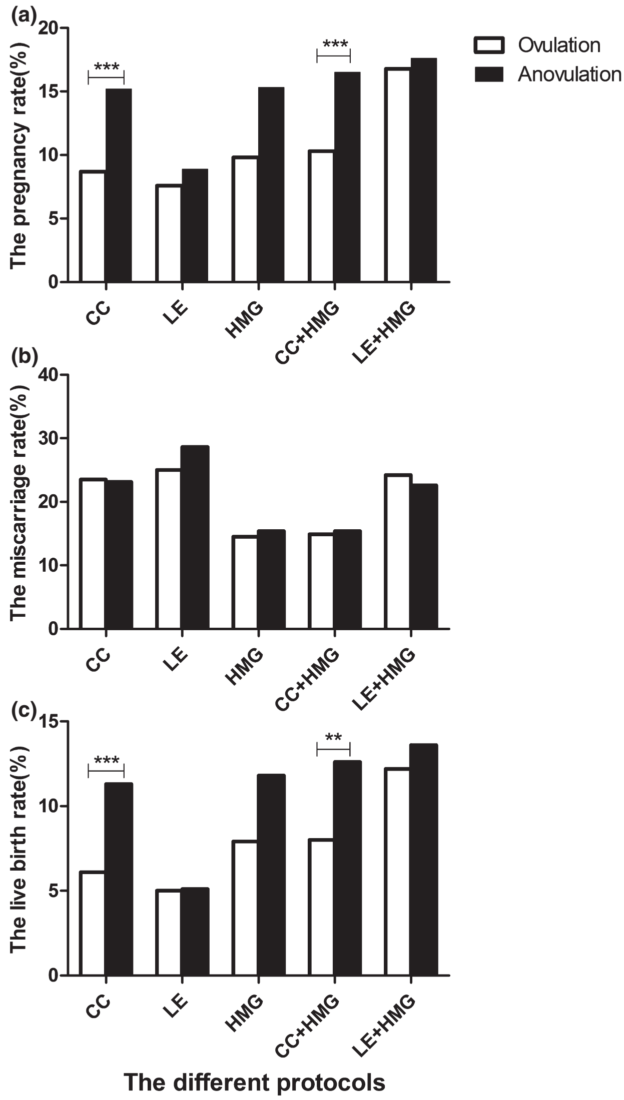

Figure 1. A comparison of the impact of different protocols of ovarian stimulation on intrauterine insemination treatment outcome between women with and without ovulation: (A) pregnancy rate, (B) miscarriage rate, (C) live birth rate (**$P < 0.01$; ***$P < 0.001$).

latory women. Statistical significance ($P < 0.01$) was achieved in CC and CC combined with HMG but not for other forms of stimulation.

Discussion

Main findings

Our study found that in ovulatory women undergoing IUI, ovarian stimulation with CC, LE, HMG, or CC combined with HMG did not improve the pregnancy or live birth rates but stimulation with LE combined with HMG significantly increased these rates. On the other hand, in anovulatory women undergoing ovarian stimulation and IUI, different protocols did not affect the outcomes, although LE on its own seemed to have the lowest pregnancy and live birth rates, whereas LE combined with HMG appeared to have the highest pregnancy and live birth rates.

Strengths and limitations

Our study represents the largest ever reported series of cases on IUI treatment from a single centre. We have also analysed separately the results for women with or without an ovulatory disorder and found that ovarian stimulation had different impacts on these two groups of women. The limitation, however, is the retrospective nature of our study with its potential, inherent bias. The conclusion should therefore be considered tentative pending confirmation from randomised controlled trials.

Interpretation

It remains controversial whether ovarian stimulation improved the outcome of IUI treatment in *ovulatory* women. Some investigators have suggested a beneficial effect,[12,14] whereas others observed no benefit.[11] In some cases, the protocols of ovarian stimulation were clearly defined,[12,15] but in others, different protocols were grouped together.[13,14] In our study when all ovarian stimulation protocols were lumped together, we could not find any difference in pregnancy or live birth rate. The same applied to our case series if we grouped all cases of ovarian stimulation together, in which case the live birth and pregnancy rates were 7 and 9.5% compared with no stimulation, for which the corresponding rates were 7.6 and 9.3% ($P = 0.39$ and 0.77, respectively). However, a further analysis of the impact of the different types of ovarian stimulation showed that whereas stimulation with CC, LE, HMG or CC combined with HMG did not improve the outcome, stimulation with LE combined with HMG did significantly increase the pregnancy and live birth rates.

LE causes androgens to accumulate in the ovarian follicles by blocking the conversion of androgens to estrogens. The accumulated androgens may increase the sensitivity of the growing follicles to FSH by increasing the expression of FSH receptors;[16] this may explain the special advantage of combining LE with HMG in ovarian stimulation.

Our study is consistent with earlier reports with regard to the lack of benefit of CC,[15] LE[17] or HMG alone[18] in ovulatory women undergoing IUI. However, we showed that LE combined with HMG increased the pregnancy and live birth rates in these women.

However, in *anovulatory* women undergoing IUI, ovarian stimulation is essential. Various stimulation protocols produced similar live birth and pregnancy rates (12.1 and 16%, respectively), both of which rates are significantly higher than those of ovulatory women undergoing IUI without stimulation (7.6 and 9.3%, respectively; both $P < 0.01$). Moreover, if we compared the outcomes of ovarian stimulation and IUI between anovulatory women and ovulatory women for each stimulation protocol, the pregnancy and live birth rates in anovulatory women were consistently higher, although only the rates for CC and CC combined with HMG were statistically significant ($P < 0.01$). The overall result suggested that anovulatory women undergoing ovarian stimulation and IUI appeared to have a better prognosis compared with women who were ovulatory.

Taking the above observations together, one can conclude that ovarian stimulation in ovulatory women undergoing IUI appears to have a limited role, with the exception of LE and HMG. It is possible that women who are ovulatory but remain infertile are more likely to have additional or subtle infertility factors compared with those who are anovulatory.

In our series, the overall twin pregnancy rate in women who underwent ovarian stimulation and IUI was 4.9%, which was modestly but not excessively high. In women not receiving ovarian stimulation, the twin pregnancy rate was 0% in our series. It should be noted that the use of LE combined with HMG to produce a modest increase in pregnancy rate to 16.8% was achieved at the expense of a modest increase in the twin pregnancy rate to 6.1%. As for other protocols of ovarian stimulation, including CC, LE, HMG or CC combined with HMG, there was a similar modest increase in the twin pregnancy rate but no increase in pregnancy rate compared with no stimulation. In our study we did not encounter any cases of triplet or higher-order pregnancies among 6302 ovarian stimulation cycles, probably due to gentle HMG stimulation policy adopted in our centre. It has now been recognised that aggressive ovarian stimulation can increase the pregnancy rate, but at the expense of increasing the likelihood of higher-order pregnancy, and that an increasing number of follicles does not increase the pregnancy rate but only leads to a higher risk of multiple pregnancies.[19]

Some reports,[20] but not all,[21] have suggested that the miscarriage rate following IUI and ovarian stimulation is higher than for IUI without stimulation. Our series failed to confirm this (20.0% with stimulation versus 14.5% without; $P = 0.07$). Further studies on this issue are needed.

Finally, the role of IUI in infertility treatment remains controversial. Our study showed that IUI in general, even in a young age group, had an overall pregnancy rate of only about 10%, and a live birth rate of only about 8%. The results are significantly inferior to those achieved with IVF. However, the treatment is simpler and less expensive than IVF. In our view, IUI still has a role in women with infertility.

Conclusion

In ovulatory women undergoing IUI, ovarian stimulation with LE and HMG, but not with CC, LE, HMG or CC combined with HMG, significantly improved the pregnancy and live birth rates. In anovulatory women undergoing ovarian stimulation and IUI, there are no significant differences in pregnancy and live birth rates among the various stimulation protocols.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as Supporting Information.

Contribution to authorship

JYL coordinated the data collection, analysis, interpretation and wrote the first draft of the paper. JL designed the study and data collection form. TCL critically revised and co-wrote the manuscript. JW, WW and ZH assisted in data collection.

Details of ethics approval

This study was approved by the medical ethics committee of First Affiliated Hospital of Nanjing Medical University (2016-SR-049).

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References

1 Custers IM, Steures P, Hompes P, Flierman P, van Kasteren Y, van Dop PA, et al. Intrauterine insemination: how many cycles should we perform? *Hum Reprod* 2008;23:885–8.
2 McClamrock HD, Jones HW Jr, Adashi EY. Ovarian stimulation and intrauterine insemination at the quarter centennial: implications for the multiple births epidemic. *Fertil Steril* 2012;97:802–9.
3 Group ECW. Intrauterine insemination. *Hum Reprod Update* 2009;15:265–77.
4 Merviel P, Heraud MH, Grenier N, Lourdel E, Sanguinet P, Copin H. Predictive factors for pregnancy after intrauterine insemination (IUI): an analysis of 1038 cycles and a review of the literature. *Fertil Steril* 2010;93:79–88.
5 Andersen AN, Goossens V, Ferraretti AP, Bhattacharya S, Felberbaum R, de Mouzon J, et al. Assisted reproductive technology in Europe, 2004: results generated from European registers by ESHRE. *Hum Reprod* 2008;23:756–71.
6 Demir B, Dilbaz B, Cinar O, Karadag B, Tasci Y, Kocak M, et al. Factors affecting pregnancy outcome of intrauterine insemination cycles in couples with favourable female characteristics. *J Obstet Gynaecol* 2011;31:420–3.
7 Jeon YE, Jung JA, Kim HY, Seo SK, Cho S, Choi YS, et al. Predictive factors for pregnancy during the first four intrauterine insemination cycles using gonadotropin. *Gynecol Endocrinol* 2013;29:834–8.
8 Ghaffari F, Sadatmahalleh SJ, Akhoond MR, Eftekhari Yazdi P, Zolfaghari Z. Evaluating the effective factors in pregnancy after intrauterine insemination: a retrospective study. *Int J Fertil Steril* 2015;9:300–8.
9 O'Flynn N. Assessment and treatment for people with fertility problems: NICE guideline. *Br J Gen Pract* 2014;64:50–1.
10 Goverde AJ, McDonnell J, Vermeiden JP, Schats R, Rutten FF, Schoemaker J. Intrauterine insemination or in-vitro fertilisation in idiopathic subfertility and male subfertility: a randomised trial and cost-effectiveness analysis. *Lancet* 2000;355:13–8.
11 Honda T, Tsutsumi M, Komoda F, Tatsumi K. Acceptable pregnancy rate of unstimulated intrauterine insemination: a retrospective analysis of 17,830 cycles. *Reprod Med Biol* 2015;14:27–32.
12 Bedaiwy MA, Abdelaleem MA, Hussein M, Mousa N, Brunengraber LN, Casper RF. Hormonal, follicular and endometrial dynamics in letrozole-treated versus natural cycles in patients undergoing controlled ovarian stimulation. *Reprod Biol Endocrinol* 2011;9:83.
13 Luco SM, Agbo C, Behr B, Dahan MH. The evaluation of pre and post processing semen analysis parameters at the time of intrauterine insemination in couples diagnosed with male factor infertility and pregnancy rates based on stimulation agent. A retrospective cohort study. *Eur J Obstet Gynecol Reprod Biol* 2014;179:159–62.
14 Goverde AJ, Lambalk CB, McDonnell J, Schats R, Homburg R, Vermeiden JP. Further considerations on natural or mild hyperstimulation cycles for intrauterine insemination treatment: effects on pregnancy and multiple pregnancy rates. *Hum Reprod* 2005;20:3141–6.
15 Gomez R, Schorsch M, Steetskamp J, Hahn T, Heidner K, Seufert R, et al. The effect of ovarian stimulation on the outcome of intrauterine insemination. *Arch Gynecol Obstet* 2014;289:181–5.
16 Kar S. Clomiphene citrate or letrozole as first-line ovulation induction drug in infertile PCOS women: a prospective randomized trial. *J Hum Reprod Sci* 2012;5:262–5.
17 Khanna SC, Kumar A, Joy SG, Tanwar R, Sharma S, Prasad S. Is letrozole superior to clomiphene for ovarian stimulation prior to intrauterine insemination? *Arch Gynecol Obstet* 2013;287:571–5.
18 Cantineau AE, Cohlen BJ, Heineman MJ. Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility. *Cochrane Database Syst Rev* 2007;(2): Cd005356.
19 van Rumste MM, Custers IM, van der Veen F, van Wely M, Evers JL, Mol BW. The influence of the number of follicles on pregnancy rates in intrauterine insemination with ovarian stimulation: a meta-analysis. *Hum Reprod Update* 2008;14:563–70.
20 Steures P, van der Steeg JW, Hompes PG, Habbema JD, Eijkemans MJ, Broekmans FJ, et al. Intrauterine insemination with controlled ovarian hyperstimulation versus expectant management for couples with unexplained subfertility and an intermediate prognosis: a randomised clinical trial. *Lancet* 2006;368:216–21.
21 Bensdorp AJ, Cohlen BJ, Heineman MJ, Vandekerckhove P. Intra-uterine insemination for male subfertility. *Cochrane Database Syst Rev* 2007;(4):CD000360.

