Risk factors for higher order multiples following stimulated intrauterine insemination

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Abstract

Higher Order Multiple Pregnancies (HOMP) are defined as pregnancies with three or more foetuses. Higher Order Multiple Births (HOMB) are defined as deliveries of three or more babies.
Over the last decades, there has been a four to eight fold increase of higher order multiple births. This increase can mainly be attributed to fertility treatments, but the exact attribution for stimulated intrauterine insemination (IUI COH) is not known, since IUI treatments are not always recorded. It is generally accepted that multiple gestations are high risk pregnancies. They are associated with maternal, obstetric, and perinatal complications, and neonatal and infant mortality In addition, they are associated with increased financial and negative psychological consequences. These risks and consequences are higher for HOMPS than for twins.
This overview summarizes briefly how to prevent higher order multiple pregnancies in IUI COH. In order to prevent HOMP, prediction models can be used to distinguish patients with a good prognosis for a spontaneous pregnancy. In this patient group expectant management needs to be considered. With mild stimulation protocols, and monitoring, particularly in young women and especially in their first cycles, most high order multiples can easily be prevented. Pregnancy rates can be increased by immobilisation following IUI, without a further increasing risk of HOMP. When primary prevention fails, cancelling of cycles is a low impact option for secondary prevention. Remedies such as aspiration of supernumerary follicles, or converting to IVF or should be considered as a last resort. This applies especially for Multifoetal Pregnancy Reduction (MFPR).

Key words: intrauterine insemination, higher order multiples, prevention.

Introduction

Higher Order Multiple Pregnancies (HOMP) are defined as pregnancies with three or more foetuses. Higher Order Multiple Births (HOMB) are defined as deliveries of three or more babies.

The frequency of HOMBS after natural conception is described by Hellin's law; if twin births occur once in N births, then triplet births occur once in N^2 births and quadruplet births occur once in N^3 births. (Fellman and Eriksson, 2009). Spontaneous twin births occur at a rate of 1 in 50 to 1 in 100 births (1% to 2%). Thus a spontaneous HOMB can be expected to occur in 0.01% to 0.025% of all deliveries.

Over the last decades there has been a four to eight fold increase in higher order multiple births exceeding the numbers predicted by Hellin's law by far. (Blickstein and Keith, 2003; Martin and Park, 1999). This explosive growth is mainly attributed to fertility treatments (Keith and Oleszczuk, 1999). The sparse data in the literature suggests that non IVF ovarian stimulation is responsible for 35-50% of all multiple pregnancies (Levene *et al.*, 1992; Bergh *et al.*, 1999; Tur *et al.*, 2001). Unfortunately, data on an increase of the higher order multiple births caused by intrauterine insemination with ovarian hyperstimulation are lacking.

It is generally accepted that multiple gestations are high risk pregnancies. They are associated with maternal, obstetric, and perinatal complications, and neonatal and infant mortality (Albrecht and Tomich, 1996; Luke and Brown, 2008). In addition, they are

associated with increased financial and negative psychological consequences (Ombelet *et al.*, 2005; Roca de *et al.*, 2009). These risks and consequences are higher for HOMPS than for twins (Seoud *et al.*, 1992; Gleicher *et al.*, 1995; Evans *et al.*, 1992).

Prevention of multiple pregnancy has become important, and at the European Society of Human Reproduction and Embryology consensus meeting in 2002 it was agreed that the preferred outcome of ART should be the birth of one healthy child, and that twin, and thus higher order multiple pregnancy should be considered a complication (Land and Evers, 2003).

For IVF and ICSI, various studies have demonstrated that elective SET is an effective treatment to prevent multiple pregnancies and this has resulted in a consistent trend of transferring fewer embryo's leading to a decrease of the number of HOMB (Gerris *et al.*, 1999; Martikainen *et al.*, 2001; Gardner *et al.*, 2004; Thurin *et al.*, 2004; Lukassen *et al.*, 2005; van Montfoort *et al.*, 2005).

For intra-uterine insemination in a stimulated cycle (IUI COH), the methods of prevention of multiple pregnancies are more intricate. After COH, the higher number of released oocytes increases the chance of a pregnancy thus withholding COH will decrease pregnancy rates (Nyboe *et al.*, 2009; Verhulst *et al.*, 2006).

In this short overview we focus on 1) the increased incidence of multiple pregnancies following intra uterine insemination in a stimulated cycle (IUI COH); 2) on the maternal and neonatal risks of triplets and higher order pregnancies; 3) and on how these IUI induced HOMPs can be prevented.

IUI and the incidence of multiple pregnancy

IUI has been a common treatment since 1962 for a broad range of subfertility diagnoses such as unexplained subfertility, mild male subfertility, mild endometriosis, and cervical factor (Cohen, 1962).

Cumulative pregnancy rates with IUI COH vary between 20 and 30% after 6 cycles, depending on the cause and duration of subfertility (Ombelet *et al.*, 2005; Allen *et al.*, 1985; Ombelet *et al.*, 2005). Addition of ovarian hyperstimulation increases the pregnancy rates in couples with unexplained subfertility (OR of 2.07, 95% CI 1.22-3.50) (Verhulst *et al.*, 2006). In couples with mild male subfertility IUI COH is generally applied, but there is little evidence of its effectiveness (Bensdorp *et al.*, 2007).

As IUI is an intermediate step of low to moderate complexity before applying more sophisticated assisted reproductive technologies (ART) such as IVF with or without ICSI (Oehninger, 2001), it is in many countries more accessible than ART. Minor adjustments to current IUI practice, such as immobilization for 15 minutes after randomisation might increase pregnancy rates, without further increasing the risk of multiple pregnancies (Custers *et al.*, 2009).

Unfortunately, many of the countries performing IUI do not have national registries or reports that depict IUI numbers and success (Nyboe *et al.*, 2009).

In Europe, where countries are increasingly reporting IUI data, the number of cycles performed is still increasing. In 2001, 15 countries performed 52.939 IUI cycles, in 2004 19 countries performed almost twice as many cycles. Pregnancy rates per insemination have remained well above 12%. Twin rates and triplet rates were 10% and 1% respectively in 2005.(Nyboe *et al.*, 2009).

Although IUI data are not reported separately, US data from 2004, show that ovulation induction outside of IVF and other ART was estimated to be responsible for 28.912 twins and 1654 higher order multiples, of which 371 were quadruplet and even higher orders. These represent 22% of all twin and 40% of all triplet and 71% of all quadruplet and higher order babies born that year (CDC, 2008; Dickey, 2007).

It can be expected that the actual triplet conception rate following IUI is about twice as high as reported, since 50% of triplet and higher order pregnancies undergo spontaneous reduction to lower orders during the first trimester (Dickey and Pyrzak, 2002). Furthermore, in ongoing triplet and higher order pregnancies foetal reductions are often being performed thus reducing the HOMP and HOMB numbers. Without these costly foetal reductions, the proportion of triplet deliveries would have been higher, although it is unclear to what extent since national foetal reduction rates are not being registered (Nyboe *et al.*, 2009).

Maternal and neonatal risks of higher order multiple pregnancy

Women carrying HOMPS are at an increased risk of diabetes, pregnancy induced hypertension, preeclampsia, and delivery through a caesarean section as well as post partum haemorrhage.These risks are increased by an additional 20-50% in comparison to twin pregnancies, except for caesarean section, which is increased by 300-500% (Luke and Brown, 2008; Wen *et al.*, 2004). The largest cohort of triplets described a total of 198, and 94% were delivered by caesarean section (Newman *et al.*, 1989).

Neonatal complications associated with HOMPS are predominantly related to premature delivery. Prematurely delivered children are prone to suffer from respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular bleeding and pneumonia (Seoud *et al.*, 1992). Recent US data from 2006

supplied by 426 fertility clinics show that after 138.198 cycles of ART 95% of triplets or more, compared to 63% of twins were born preterm (CDC, 2008). There is no reason to assume that HOMPS after IUI treatment would behave differently. The risk of a very preterm delivery (birth at < 29 weeks of gestation) is increased for triplets and quadruplets compared with twins by a factor 4 and 8 respectively (Luke and Brown, 2008).

Growth retardation is another risk factor for children delivered from multiple pregnancies, and is increased by 42 to 57%. Low birth weight infants are more at risk for short and long term disability such as cerebral palsy, mental retardation and limited motor and cognitive skills (Collins and Bleyl, 1990; Seoud *et al.*, 1992). US data show that low birth weight (< 2500 gram) was found in 90% of the triplets and higher order multiples, compared with 57% of the twins, and 8% of the singleton pregnancies (CDC, 2008). Mortality rates are 6 times higher for HOMP when compared to singletons (Alexander *et al.*, 2005).

Financial consequences

Higher order pregnancies are expensive; medical costs, obstetric costs and perinatal costs are substantially higher than in singleton or twin pregnancies.

Medical costs include medication, as well as hospital admission and sometimes even emergency surgery, often to delay preterm labour. Obstetric costs are 4 to 5 times higher for triplets, and 7 fold for quadruplets compared to singletons (Mugford, 1995). Perinatal costs are enormous; and mostly associated with prematurity and dysmaturity (Petrou and Henderson, 2003; Ombelet *et al.*, 2005).

Admission costs to the neonatal intensive care unit are high and result in a two to four fold increase in cost per child born. It has been estimated that the costs of an infant with Extremely Low Birth Weight (ELBW) which is defined as < 1000 g, vary between £ 30.000 and £ 40.000 depending on the country of treatment (some 40.000 to 60,000 Euro at 2005 exchange rates) (Ombelet *et al.*, 2005). Additionally, the long-term costs due to handicaps like spastic cerebral palsy are substantial, and subsequently a burden for society (Mugford, 1995).

Primary prevention

There are several ways to prevent HOMPS after IUI-COH:

Selection of patients

Patients should be carefully selected. Prediction models can be used to do this. Several models have been published which estimate a couples' chance of conceiving naturally. Hunault's model is a combination of the three models of Eimers, Snick and Collins, and predicts a couples chances of natural conception leading to live birth within 1 year (Hunault *et al.*, 2004). This model includes independent patient characteristics like age of the woman, referral status, duration of subfertility, whether subfertility is primary or secondary, and sperm quality. From 2002 to 2004 this model has been calibrated and externally validated in a subfertile population in 38 centres in the Netherlands. In this cohort study, the model was used to predict the chance of spontaneous pregnancy in 3021 couples. Calibration of the prediction model was almost perfect; of the couples who had a calculated chance of > 40% of conceiving, the cumulative pregnancy rate without treatment was 46% (van der Steeg *et al.*, 2007).

As pregnancy can be predicted, this model was then used in a randomised controlled trial, also in the Netherlands. In 253 couples with unexplained or mild male subfertility and an intermediate prognosis (30-40% probability of spontaneous ongoing pregnancy within 12 months) no differences in pregnancy rates were found between expectant management for six months and IUI COH for six months, demonstrating that expectant management should be advocated for this patient group (Steures *et al.*, 2006).

Use of low dose stimulation protocols

An effective method to prevent twins and HOMPS in IUI, even in an unselected population, is abiding by low dose stimulation protocols. Already in 1970, no multiple pregnancies or HOMB were found after a starting dosage of 75 IU HMG compared to a 13% twinning rate and 4.8% HOMB when stimulating with 150 IU of HMG (Thompson and Hansen, 1970).

In a retrospective Italian study, of 1259 cycles with a low starting dose of 50 IU good pregnancy rates (15.8-21.9%) were obtained with 10% twins, without any higher order pregnancies (Ragni *et al.*, 2006). Approximately 5% of cycles had to be cancelled because of hyperresponse (predefined as three or more follicles ≥ 16 mm, and/or five or more follicles ≥ 11 mm).

In a review including ten studies that followed a low dose protocol administering ≤ 75 IU FSH clinical pregnancy rates per cycle varied from 9% to 20%, with a mean clinical pregnancy rate of 11% per cycle. Triplets and higher order pregnancy rates were kept to a minimum and varied between 0 and 2.4%. When cancellation criteria were applied in addition

to the low dose protocol, the mean clinical pregnancy rate was 10% per cycle, and the HOMP frequency was further reduced to 0.3% (Ragni *et al.*, 2006).

Cycle monitoring

In a recent meta-analysis of 14 studies with 11.599 IUI cycles multifollicular growth was associated with increased pregnancy rates in IUI with COH. Absolute pregnancy rates were 8.4% for monofollicular growth, and 15% for multifollicular growth. In cycles with 3 to 4 follicles the multiple pregnancy rate increased without a substantial gain in overall pregnancy rate (van Rumste *et al.*, 2008).

In addition to the number of developing follicles, various authors have found a relation between multifollicular growth, age of the woman, estradiol levels and HOMP rates. In 3347 stimulated IUI cycles the incidence of triplets and higher order pregnancies was significantly related to the total number of follicles ≥ 7 mm and E2 concentration ≥ 1385 pg/mL (CHL assay). No HOMP occurred when there were fewer than 10 total follicles ≥ 7 mm. The rate of HOMP was 3.8% if there were fewer than 15 follicles ≥ 7 mm and E2 concentration was below the earlier mentioned threshold. If there were more than 15 follicles ≥ 7 mm and E2 concentration was above the threshold, the HOMP rate reported was 22.2%. (Gleicher *et al.*, 2000).

These results were confirmed in a Spanish study albeit with slightly different thresholds. In 1878 stimulated IUI cycles the HOMP rate was 3.3% if the woman's age was above 33 years, and the E2 concentration was above the equivalent of 1051 pg/mL (CHL assay) and the number of follicles ≥ 10 mm was fewer than six. For the younger women (< 33 years) who had six or more follicles ≥ 10, with the E2 concentration above the previously mentioned threshold, the rate of triplets and higher order pregnancies was 22.0% (Tur *et al.*, 2001).

Findings from the most recent study on this subject concur; for women of 38 years and older, no triplets and higher order pregnancies occurred in 4062 cycles of stimulated IUI. For the slightly younger women (33-37 years) the HOMP rate was 16.7%, and for the even younger ones (< 32 yrs) the HOMP rate was 23.1% when there were seven or more follicles ≥ 10 mm present with an E2 concentration ≥ 1000 pg/mL by CHL (Dickey *et al.*, 2005).

Also, as women are more prone to conceive in their first treatment cycles, it is in these cycles that they are at risk for HOMP. This is clearly demonstrated by figure 1. Four large retrospective studies show that practically no HOMP occurred after the third cycle (Dickey *et al.*, 2001; Dickey *et al.*, 2005; van Rumste *et al.*, 2006; Custers *et al.*, 2007).

Secondary prevention

Cancellation of cycles

Cancellation is the most frequently applied strategy in the secondary prevention of HOMPs during IUI cycles, but international guidelines show different

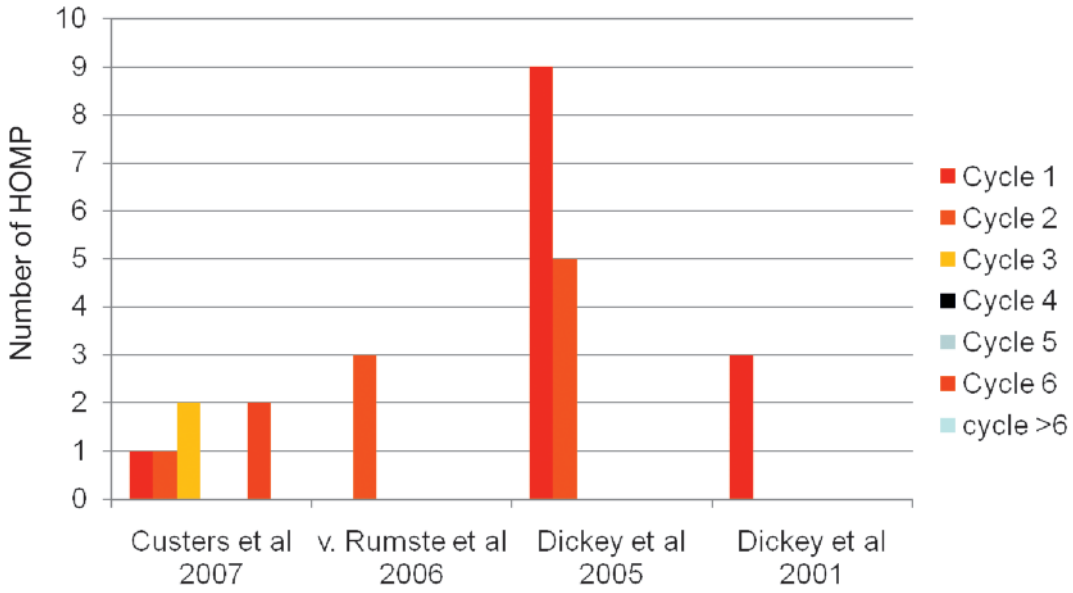

Fig. 1. — The number of HOMP each cycle in 4 different retrospective studies

cut off points.The American college of Obstetrics and Gynaecology (ACOG) recommend cancelling cycles or withholding hCG when more than three follicles are > 15 mm and the Royal College of Obstetrics and Gynaecologists sets this threshold at > 16 mm. Yet there is no consistent evidence to support either of these precautionary measures. In Europe only three other countries have issued IUI guidelines (Denmark, France, the Netherlands and England and Wales) and the ESHRE Capri Workshop has considered them to be of sufficient quality for use in clinical practice, even if their recommendations and references differ considerably. The varying indications for stimulated IUI in the Danish, French, English and Dutch guidelines are mainly due to the difference in selection of evidence (Haagen *et al.*, 2006; Nyboe *et al.*, 2009; 2009).

Aspiration of supernumerary follicles

An alternative secondary prevention is transvaginal ultrasound-guided aspiration of supernumerary ovarian follicles. This technique was first described in 1984 to increase the efficacy and the safety of IUI with gonadotropins (Hazout *et al.*, 1984). One of the few, small cohort studies of 26 IUI cycles performed found that aspiration of supernumerary is a valid approach to avoid multiple pregnancies without affecting pregnancy rate. (Albano *et al.*, 2001).

Inn 257 of 571 COH IUI cycles aspiration was performed of four or more follicles >- 14 mm before administrating hCG. Pregnancies occurred in approximately 21%, with 8% twinning rate and triplets of 1.7% (De Geyter *et al.*, 1996).

Coasting

Whether coasting, a possible third option for secondary prevention, is effective in IUI remains a matter of debate. Whereas gonadotropin stimulation can be discontinued in IVF cycles and hCG administration can be delayed to avoid ovarian hyperstimulation syndrome (OHSS), it is uncertain that applying the same technique to IUI cycles to prevent multiple pregnancies is effective. Trials that have investigated this technique for IUI are sparse and of poor quality (Urman *et al.*, 1992; Ulug *et al.*, 2004).

Conversion to IVF

The fourth option, conversion to IVF, is an invasive strategy to reduce HOMP. For the patient the follicle aspiration is unanticipated, as are the concomitant higher costs. In countries where only a limited number of IVF cycles are reimbursed by the insurance companies this clearly is an issue, and therefore seems not a viable option.

Multifoetal pregnancy reduction

Finally multifoetal pregnancy reduction (MFPR), was introduced in 1978 to selectively eliminate a foetus affected by a genetic order in a twin pregnancy (Aberg *et al.*, 1978). Nowadays it is also carried out to improve the chances of survival and health of the remaining foetus in twin and high order multiple pregnancies. This is the most invasive technique to prevent HOMP in an IUI programme, morally questionable, but may reduce associated risks. As the risk for adverse perinatal and maternal outcomes increases with a greater number of foetuses within the uterus, patients and doctors are faced with dilemmas. The high risk pregnancy can be continued, terminated entirely, or the number of foetuses can be reduced in an attempt to decrease the maternal and perinatal morbidity. Risks associated with MFPR are pregnancy loss, and prematurity. Pregnancies reduced to twins do not seem to have worse outcomes than conceived twin gestations. (Evans *et al.* 1992, 1994, 2004).

Conclusion

Triplets and higher order pregnancies remain a major problem in artificial insemination. To prevent HOMP, prediction models can be used to distinguish patients with a good prognosis for a spontaneous pregnancy. In this patient group expectant management needs to be considered. With mild stimulation protocols, and monitoring, particularly in young women and especially in their first cycles, most high order multiples can easily be prevented. Pregnancy rates can be increased by immobilisation following IUI, without further increasing the risk of HOMP. When primary prevention fails, cancelling of cycles is a low impact option for secondary prevention. Remedies such as aspiration of supernumerary follicles, or converting to IVF or MFPR should be considered as a last resort.

References

Intrauterine insemination. Hum Reprod Update. 2009;15: 265-77.

Aberg A, Magiste M, von SH *et al.* Screening for twin pregnancy detection. Prog Clin Biol Res. 1978;24:113-6.

Albano C, Platteau P, Nogueira D *et al.* Avoidance of multiple pregnancies after ovulation induction by supernumerary preovulatory follicular reduction. Fertil Steril. 2001;76:820-2.

Albrecht JL, Tomich PG. The maternal and neonatal outcome of triplet gestations. Am J Obstet Gynecol. 1996;174: 1551-6.

Alexander GR, Slay WM, Salihu H *et al.* Fetal and neonatal mortality risks of multiple births. Obstet Gynecol Clin North Am. 2005;32:1-16, vii.

Allen NC, Herbert CM, III, Maxson WS *et al.* Intrauterine insemination: a critical review. Fertil Steril. 1985;44:569-80.

Bensdorp AJ, Cohlen BJ, Heineman MJ, Vandekerckhove P (2007) Intra-uterine insemination for male subfertility. Cochrane Database Syst Rev, CD000360.
Bergh T, Ericson A, Hillensjo T *et al.* Deliveries and children born after in-vitro fertilisation in Sweden 1982-95: a retrospective cohort study. Lancet. 1999;354:1579-85.
Blickstein I, Keith LG. Outcome of triplets and high-order multiple pregnancies. Curr Opin Obstet Gynecol. 2003;15: 113-7.
CDC. 2006 Assisted Reproductive Technology Success Rates: National Summary and Fertility Clinic Reports. In Centers for Diseas Control and Prevention ASfRMSfART (ed) Atlanta: US Department of Health and human Services, Centers for Disease Control and Prevention; 2008.
Cohen MR. Intrauterine insemination. Int J Fertil. 1962;7: 235-40.
Collins MS, Bleyl JA. Seventy-one quadruplet pregnancies: management and outcome. Am J Obstet Gynecol 1990;162: 1384-91.
Custers IM, Flierman PA, Maas P *et al.* Immobilisation versus immediate mobilisation after intrauterine insemination: randomised controlled trial. BMJ. 2009;339:b4080.
Custers IM, Steures P, van der Steeg JW *et al.* External validation of a prediction model for an ongoing pregnancy after intrauterine insemination. Fertil Steril. 2007;88:425-31.
De GC, De GM, Castro E, Bals-Pratsch M *et al.* Experience with transvaginal ultrasound-guided aspiration of supernumerary follicles for the prevention of multiple pregnancies after ovulation induction and intrauterine insemination. Fertil Steril. 1996;65:1163-8.
Dickey RP. The relative contribution of assisted reproductive technologies and ovulation induction to multiple births in the United States 5 years after the Society for Assisted Reproductive Technology/American Society for Reproductive Medicine recommendation to limit the number of embryos transferred. Fertil Steril. 2007;88:1554-61.
Dickey RP, Pyrzak R. Prevention of high order multiple pregnancy. Hum Reprod. 2002;17:1411-2.
Dickey RP, Taylor SN, Lu PY *et al.* Relationship of follicle numbers and estradiol levels to multiple implantation in 3,608 intrauterine insemination cycles. Fertil Steril. 2001;75: 69-78.
Dickey RP, Taylor SN, Lu PY *et al.* Risk factors for high-order multiple pregnancy and multiple birth after controlled ovarian hyperstimulation: results of 4,062 intrauterine insemination cycles. Fertil Steril. 2005;83:671-83.
Evans MI, Ciorica D, Britt DW. Do reduced multiples do better? Best Pract Res Clin Obstet Gynaecol. 2004;18:601-12.
Evans MI, Goldberg JD, Dommergues M *et al.* Efficacy of second-trimester selective termination for fetal abnormalities: international collaborative experience among the world's largest centers. Am J Obstet Gynecol. 1994;171:90-4.
Evans MI, Littmann L, King M *et al.* Multiple gestation: the role of multifetal pregnancy reduction and selective termination. Clin Perinatol. 1992;19:345-57.
Fellman J, Eriksson AW. Statistical analyses of Hellin's law. Twin Res Hum Genet. 2009;12:191-200.
Gardner DK, Surrey E, Minjarez D *et al.* Single blastocyst transfer: a prospective randomized trial. Fertil Steril. 2004;81:551-5.
Gerris J, De ND, Mangelschots K, Van RE *et al.* Prevention of twin pregnancy after in-vitro fertilization or intracytoplasmic sperm injection based on strict embryo criteria: a prospective randomized clinical trial. Hum Reprod. 1999;14:2581-7.
Gleicher N, Campbell DP, Chan CL *et al.* The desire for multiple births in couples with infertility problems contradicts present practice patterns. Hum Reprod. 1995;10:1079-84.
Gleicher N, Oleske DM, Tur-Kaspa I *et al.* Reducing the risk of high-order multiple pregnancy after ovarian stimulation with gonadotropins. N Engl J Med. 2000;343:2-7.
Haagen EC, Hermens RP, Nelen WL *et al.* Subfertility guidelines in Europe: the quantity and quality of intrauterine insemination guidelines. Hum Reprod. 2006;21:2103-9.
Hazout A, Prorchier J, Frydman R. Une alternative & la reduction embryonaire; la reduction folliculaire. 1984, In pp. 119-121.
Hunault CC, Habbema JD, Eijkemans MJ *et al.* Two new prediction rules for spontaneous pregnancy leading to live birth among subfertile couples, based on the synthesis of three previous models. Hum Reprod. 2004;19:2019-26.
Keith L, Oleszczuk JJ. Iatrogenic multiple birth, multiple pregnancy and assisted reproductive technologies. Int J Gynaecol Obstet. 1999;64:11-25.
Land JA, Evers JL. Risks and complications in assisted reproduction techniques: Report of an ESHRE consensus meeting. Hum Reprod. 2003;18:455-7.
Levene MI, Wild J, and Steer P. Higher multiple births and the modern management of infertility in Britain. The British Association of Perinatal Medicine. Br J Obstet Gynaecol. 1992;99:607-13.
Lukassen HG, Braat DD, Wetzels AM *et al.* Two cycles with single embryo transfer versus one cycle with double embryo transfer: a randomized controlled trial. Hum Reprod. 2005; 20:702-8.
Luke B, Brown MB. Maternal morbidity and infant death in twin vs triplet and quadruplet pregnancies. Am J Obstet Gynecol. 2008;198:401-10.
Martikainen H, Tiitinen A, Tomas C *et al.* One versus two embryo transfer after IVF and ICSI: a randomized study. Hum Reprod. 2001;16:1900-3.
Martin JA, Park MM. Trends in twin and triplet births: 1980-97. Natl Vital Stat Rep. 1999;47:1-16.
Mugford M. The cost of neonatal care: reviewing the evidence. Soz Praventivmed. 1995;40:361-8.
Newman RB, Hamer C, Miller MC. Outpatient triplet management: a contemporary review. Am J Obstet Gynecol. 1989;161:547-53.
Nyboe AA, Goossens V, Bhattacharya S *et al.* Assisted reproductive technology and intrauterine inseminations in Europe, 2005: results generated from European registers by ESHRE: ESHRE. The European IVF Monitoring Programme (EIM), for the European Society of Human Reproduction and Embryology (ESHRE). Hum Reprod. 2009;24:1267-87.
Oehninger S. Strategies for the infertile man. Semin Reprod Med. 2001;19:231-7.
Ombelet W, De SP, Van der Elst J *et al.* Multiple gestation and infertility treatment: registration, reflection and reaction – the Belgian project. Hum Reprod Update. 2005;11:3-14.
Petrou S, Henderson J. Preference-based approaches to measuring the benefits of perinatal care. Birth. 2003;30:217-26.
Ragni G, Caliari I, Nicolosi AE *et al.* Preventing high-order multiple pregnancies during controlled ovarian hyperstimulation and intrauterine insemination: 3 years' experience using low-dose recombinant follicle-stimulating hormone and gonadotropin-releasing hormone antagonists. Fertil Steril. 2006;85:619-24.
Roca de BM, Gutierrez MJ, Gris Martinez JM. Psychosocial risks associated with multiple births resulting from assisted reproduction: a Spanish sample. Fertil Steril. 2009;92:1059-66.
Seoud MA, Toner JP, Kruithoff C *et al.* Outcome of twin, triplet, and quadruplet in vitro fertilization pregnancies: the Norfolk experience. Fertil Steril. 1992;57:825-34.
Steures P, van der Steeg JW, Hompes PG *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.
Thompson CR, Hansen LM. Pergonal (menotropins): a summary of clinical experience in the induction of ovulation and pregnancy. Fertil Steril. 1970;21:844-53.
Thurin A, Hausken J, Hillensjo T *et al.* Elective single-embryo transfer versus double-embryo transfer in in vitro fertilization. N Engl J Med. 2004;351:2392-2402.

Tur R, Barri PN, Coroleu B *et al.* Risk factors for high-order multiple implantation after ovarian stimulation with gonadotrophins: evidence from a large series of 1878 consecutive pregnancies in a single centre. Hum Reprod. 2001; 16:2124-9.

Ulug U, Ben-Shlomo I, Bahceci M. Predictors of success during the coasting period in high-responder patients undergoing controlled ovarian stimulation for assisted conception. Fertil Steril. 2004;82:338-42.

Urman B, Pride SM, Yuen BH. Management of overstimulated gonadotrophin cycles with a controlled drift period. Hum Reprod. 1992;7:213-7.

van der Steeg JW, Steures P, Eijkemans MJ *et al.* Pregnancy is predictable: a large-scale prospective external validation of the prediction of spontaneous pregnancy in subfertile couples. Hum Reprod. 2007;22:536-42.

van Montfoort AP, Dumoulin JC, Land JA *et al.* Elective single embryo transfer (eSET) policy in the first three IVF/ICSI treatment cycles. Hum Reprod. 2005;20:433-6.

van Rumste MM, Custers IM, van der Veen F *et al.* 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.

van Rumste MM, den Hartog JE, Dumoulin JC *et al.* Is controlled ovarian stimulation in intrauterine insemination an acceptable therapy in couples with unexplained non-conception in the perspective of multiple pregnancies? Hum Reprod. 2006;21:701-4.

Verhulst SM, Cohlen BJ, Hughes E *et al.* Intra-uterine insemination for unexplained subfertility. Cochrane Database Syst Rev. 2006;CD001838.

Wen SW, Demissie K, Yang Q *et al.* Maternal morbidity and obstetric complications in triplet pregnancies and quadruplet and higher-order multiple pregnancies. Am J Obstet Gynecol. 2004;191:254-8.