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Chapter 5

The influence of the number of follicles on pregnancy rates in intrauterine insemination with ovarian stimulation: a meta-analysis

Minouche M.E. van Rumste, Inge M. Custers, Fulco van der Veen, Madelon van Wely, Johannes L.H. Evers, Ben Willem J. Mol

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ABSTRACT

BACKGROUND The influence of multifollicular growth on pregnancy rates in subfertile couples undergoing intrauterine insemination (IUI) with controlled ovarian hyperstimulation (COH) remained unclear.

METHODS Relevant papers were identified by searching MEDLINE, EMBASE and the Cochrane Library. A meta-analysis was performed and Mantel–Haenszel pooled odd ratios (ORs) and risk differences with 99% confidence intervals (CIs) were calculated to express the relation between the number of follicles and pregnancy rates.

RESULTS We included 14 studies reporting on 11 599 cycles. The absolute pregnancy rate was 8.4% for monofollicular and 15% for multifollicular growth. The pooled OR for pregnancy after two follicles as compared with monofollicular growth was 1.6 (99% CI 1.3 – 2.0), whereas for three and four follicles, this was 2.0 and 2.0, respectively. Compared with monofollicular growth, pregnancy rates increased by 5, 8 and 8% when stimulating two, three and four follicles. The pooled OR for multiple pregnancies after two follicles was 1.7 (99% CI 0.8 – 3.6), whereas for three and four follicles this was 2.8 and 2.3, respectively. The risk of multiple pregnancies after two, three and four follicles increased by 6, 14 and 10%. The absolute rate of multiple pregnancies was 0.3% after monofollicular and 2.8% after multifollicular growth.

CONCLUSIONS Multifollicular growth is associated with increased pregnancy rates in IUI with COH. Since in cycles with three or four follicles the multiple pregnancy rate increased without substantial gain in overall pregnancy rate, IUI with COH should not aim for more than two follicles. One stimulated follicle should be the goal if safety is the primary concern, whereas two follicles may be accepted after careful patient counselling.

INTRODUCTION

Controlled ovarian hyperstimulation (COH) with intrauterine insemination (IUI) is frequently used in couples that suffer from unexplained subfertility. In a meta-analysis on couples with unexplained subfertility, ovarian stimulation in combination with IUI was shown to result in significantly higher pregnancy rates per woman as compared with IUI in the natural cycle (OR 2.3, 95% confidence interval (95% CI) 1.5 – 3.7) (Verhulst *et al.*, 2006).

The drawback of multifollicular growth in IUI and COH is the risk of multiple pregnancies. Although there is debate whether a multiple pregnancy should be seen as a complication of assisted reproductive techniques, there is consensus that a multiple pregnancy carries increased risks on pregnancy complications, such as preterm delivery, growth retardation and preecclampsia (Land and Evers, 2003; van Wely et al., 2006). In view of this dilemma, the balance between a decrease of the number of follicles in women undergoing IUI with COH for a still acceptable pregnancy rate is extremely important.

Although the rationale for addition of COH with IUI is to increase the pregnancy rate by multifollicular growth (Cohlen, 1998), studies reporting on the number of preovulatory follicles in relation to pregnancy rates in ovarian stimulation with IUI show contradictory results. Whereas the majority of the studies report a positive association between the number of follicles and pregnancy rate (Tomlinson *et al.*, 1996; Nuojua-Huttunen *et al.*, 1999; Stone et al., 1999; Dickey et al., 2002; Ibérico et al., 2004), we failed to find such a positive association in previous studies (van Rumste *et al.*, 2006; Steures *et al.*, 2006). Moreover, two studies reported high ongoing pregnancy rates of 16.6 and 10.4% even though 60% of the cycles were monofollicular (Ragni *et al.*, 2004; Crosignani and Somigliana, 2007).

This contradiction raised the question whether multifollicular growth does increase pregnancy rates over that attributed to monofollicular growth in couples undergoing COH and IUI. To address this issue, we performed a systematic review of the literature on the subject.

MATERIAL AND METHODS

Search strategy

The meta-analysis was performed according to the MOOSE criteria (Stroup et al., 2000). We performed a computerized search in MEDLINE (1966 – July 2007), EMBASE (1988 – July 2007) and the Cochrane Library (2006: 2) to identify articles reporting on the number of follicles and pregnancy rates in couples undergoing treatment with IUI and COH. Keywords used were follicle number, controlled ovarian stimulation, hyperstimulation, IUI, clomiphene citrate, follicle stimulating hormone, human menopausal gonadotrophin,

subfertility and fertility, with a limitation to humans and 'not IVF'. No restriction on language was used. References detected with the related articles function in Pubmed were also checked to identify cited articles not captured by electronic searches. The reference lists of all identified articles and eligible primary studies were examined for identification of additional articles. Studies were included if they reported on the number of preovulatory follicles and subsequent pregnancy rates in couples undergoing IUI with COH. All couples undergoing IUI with COH, irrespective of their diagnosis of subfertility, were included.
The number and size of follicles during the ovarian stimulation were detected by ultrasound. The size of a follicle was measured in millimetres. All follicles above a certain cut-off diameter at time of human chorionic gonadotrophin (hCG) administration were recorded. The cut-off diameter varied per study. We defined monofollicular growth as one follicle on the day of hCG administration. Multifollicular growth was defined as more than one follicle counted, irrespective of their diameter. Pregnancy was defined as a positive urine or serum hCG test. Clinical pregnancy was defined as a pregnancy confirmed by ultrasound at 6 weeks of gestation. Ongoing pregnancy was defined as a pregnancy with fetal cardiac activity seen at ultrasound at 12 weeks of gestation.
All studies were scored on methodological quality. We assessed whether the study was prospective, whether it was a randomized controlled trial (RCT), a cohort study or a case – control study, whether the study was blinded and whether the assessment of the number of follicles, as well as the outcome, was defined. Assessment of methodological quality and data extraction was done by two reviewers independently (MvR, IC). In case of disagreement, the judgement of a third reviewer (BWM) was decisive.

Statistical analysis

For each study, we constructed tables comparing the number of follicles counted in relation to the pregnancy rate. To do so, several categories of multifollicular growth (two follicles, three follicles or four follicles or more) were classified against monofollicular growth, which was the reference strategy.
The analysis was then stratified for different levels of multifollicular growth. First, we assessed pregnancy rates in cycles with two follicles compared with cycles with monofollicular growth, then we assessed all studies in which pregnancy rates in cycles with three follicles were compared with cycles with monofollicular growth. We performed the same analysis comparing four or five follicles to monofollicular growth.
Homogeneity was tested by means of the Breslow–Day test. P-values less than 0.05 were considered to indicate statistical significance. If homogeneity could not be rejected, i.e. if the P-value of the Breslow-Day test was .0.05, a pooled odd ratios (ORs) with a 99% CI was calculated for each exposure by means of a fixed effect model (Mantel – Haenszel method), thus pooling the ORs of the evaluated studies. If homogeneity had to be rejected, the range of point estimates of individual studies was reported. A similar analysis

was done for multiple pregnancies. The analysis on multiple pregnancies was limited to those cycles in which a pregnancy had occurred. The risk differences (RDs) with 99% CI were calculated for pregnancy and multiple pregnancy for the various cut-off values for multifollicular growth as compared to monofollicular cycles.

Post hoc subgroup analyses were performed, in which we pooled studies that used comparable cut-off values for follicle diameter. In a sensitivity analysis, we repeated the main analysis while excluding studies that used donor semen and studies that did not specify the exact number of follicles.

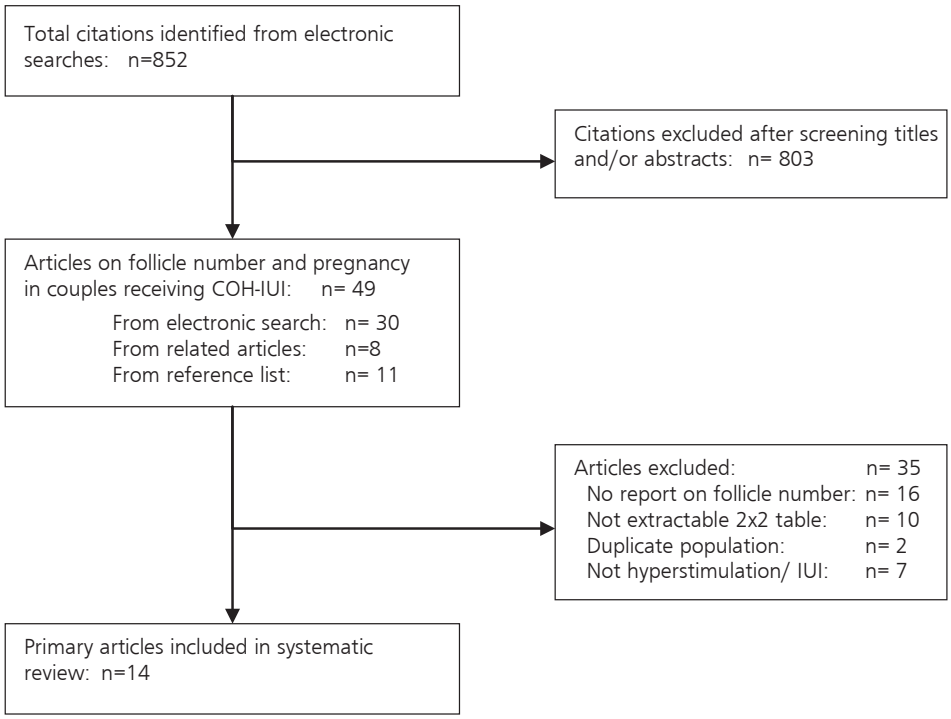

Figure 1. Study selection process for systematic review of relation between follicle number and pregnancy rates in IUI with COH.

RESULTS

Literature identification and study characteristics

The process of literature identification and selection is summarized in Fig. 1. Of the 49 detected articles, 14 studies met the inclusion criteria. The included studies and their characteristics are listed in Table I. The studies reported on a total of 11 599 cycles in

Table I. Study characteristics of included studies.

Study (year)	Quality	Patient characteristics	Number of patients	Number of cycles
Dodson and Haney (1991)	Retrospective cohort	All types of subfertility	371	720
Tomlinson et al. (1996)	Retrospective cohort	All types of subfertility	134	260
Vollenhoven et al. (1996)	Retrospective cohort	All types of subfertility	107	237
Nuojua-Huttunen et al. (1999)	Retrospective cohort	All types of subfertility	n.s.	811
Dickey et al. (2001)	Prospective cohort	All types of subfertility	4000	2728
Khalil et al. (2001a)	Retrospective cohort	Unexplained, mild male factor, anovulation	893	2466
Khalil et al. (2001b)	Retrospective cohort	Donor semen	351	1118
Özcakir et al. (2002)	Retrospective cohort	Not stated, excluded male or unilateral tube factor	180	180
Ibérico et al. (2004)	Retrospective cohort	Unexplained	470	1010
Steures et al. (2004)	Retrospective cohort	Cervical factor	181	213
Goverde et al. (2005)	Randomized controlled trial	Unexplained, mild male factor	85	334
Sikandar et al. (2005)	Retrospective cohort	Unexplained, mild male factor	290	290
van Rumste et al. (2006)	Retrospective cohort	Unexplained	300	879
Steures et al. (2006)	Randomized controlled trial	Unexplained	127	353

CC, clomiphene citrate; FSH, follicle stimulating hormone; hCG, humane chorionic gonadotrophin; hMG, human menopausal gonadotrophin; n.s., not stated; US, ultrasound

7489 couples. Eleven studies were retrospective cohort studies, one was a prospective cohort study (Dickey *et al.*, 2001) and two were RCTs (Goverde *et al.*, 2005; Steures *et al.*, 2006). In the first RCT, pregnancy outcome of IUI in natural cycles and IUI in stimulated cycles were compared in couples with unexplained subfertility and mild male subfertility (Goverde et al., 2005). In the second RCT, couples with unexplained subfertility were randomly assigned to IUI with COH or to expectant management (Steures *et al.*, 2006). Only the subset of couples receiving IUI in stimulated cycles were included in this review. The excluded studies are summarized in Table II.

Medication	Follicle size at count (mm)	On hCG day: at least one follicle of length (mm)	Cancellation criteria	Cycles with multifollicular growth	Pregnancy test	PR per cycle
hMG	17	17	n.s.	635	serum hCG	15%
FSH, hMG	18	18	>3 follicles >18 mm	153	n.s.	21%
hMG	14	18	E2>2500 pg/ml	218	US at 6 weeks	9.3%
Combination of CC and hMG	16	16	n.s	634	US at 12 weeks	13%
hMG, CC and both in the same cycle	12	16 (hMG) 18 (cc/ hMG) or LH surge	n.s	2319	serum hCG and US at 6 and 12 weeks	15%
Combination of CC and hMG	14	18	>5 follicles >15 mm	1942	US at 6 weeks	12%
Combination of CC and hMG	16	16	>4 follicles >16 mm	777	US at 6 weeks	22%
FSH, hMG	18	18	n.s.	103	US at 5.5 weeks	18%
hMG	16	18	>5 follicles >15 mm	564	Urine test	9.2%
CC and FSH	14	16	>4>14 mm or >3>16 mm	113	US at 12 weeks	13%
FSH	14	18	>6>14 mm or >3>18 mm	239	US at 12 weeks	9.9%
hMG, CC and both in the same cycle	16	16	n.s.	113	serum hCG	10%
hMG	14	18	>4 follicles >14 mm	600	US at 12 weeks	8.3%
FSH, hMG	11	16	>5>12 mm or >3>16 mm	247	US at 12 weeks	4.5%

In all studies, couples with primary and secondary subfertility were included. All couples had undergone a fertility work-up, including confirmation of ovulation by ultrasound, semen analysis and evaluation of tubal function by hysterosalpingography and/or laparoscopy, before treatment with IUI and COH was started. The mean female age varied from 31 to 34 years. Patients received gonadotrophins and/or clomiphene citrate. All patients received hCG to induce ovulation. Definitions of multifollicular growth varied greatly between studies with the minimal diameter of a follicle ranging from 11 to 18 mm. Two studies used multiple cut-off points for follicle diameters (Dickey *et al.*, 2001; Steures *et al.*, 2006). One of the included studies reported a specific definition of multifollicular

Table II. Excluded studies.

Study (year)	Reason for exclusion
Schenker *et al.* (1981)	Not hyperstimulation/IUI
Stone *et al.* (1987)	Not extractable 2x2 table
Deaton *et al.* (1990)	No report per follicle number
Dickey *et al.* (1991)	Not hyperstimulation/IUI
Martinez *et al.* (1991)	No report per follicle number
Silverberg *et al.* (1991)	Not hyperstimulation/IUI
Dickey *et al.* (1992)	Not hyperstimulation/IUI
Ben-Nun *et al.* (1993)	No report per follicle number
Chang *et al.* (1993)	Not extractable 2x2 table
Plosker *et al.* (1994)	Not hyperstimulation/ IUI
Pittrof *et al.* (1996)	No report per follicle number
Valbuena *et al.* (1996)	Not extractable 2x2 table
Goldfarb *et al.* (1997)	No report per follicle number
Hughes (1997)	No report per follicle number
Cohlen *et al.* (1998)	No report per follicle number
Hughes *et al.* (1998)	No report per follicle number
Pasqualotto *et al.* (1999)	Not extractable 2x2 table
Stone *et al.* (1999)	Not hyperstimulation/ IUI
Gleicher *et al.* (2000)	Not extractable 2x2 table
Tsai *et al.* (2000)	No report per follicle number
Dickey *et al.* (2002)	Duplicate population
Go¨ker *et al.* (2002)	Not extractable 2x2 table
Kaplan *et al.* (2002a)	Not extractable 2x2 table
Kaplan *et al.* (2002b)	Not extractable 2x2 table
Filicori *et al.* (2003)	No report per follicle number
Makkar *et al.* (2003)	Not extractable 2x2 table
Cantineau *et al.* (2004)	No report per follicle number
Deng and Clark (2004)	No report per follicle number
Papageorgiou *et al.* (2004)	No report per follicle number
Wang *et al.* (2004)	No report per follicle number
Dickey *et al.* (2005)	Duplicate population
Filicori *et al.* (2005)	Not hyperstimulation/IUI
Richmond *et al.* (2005)	Not extractable 2x2 table
Al-Inany *et al.* (2006)	No report per follicle number
Park *et al.* (2007)	No report per follicle number

growth, i.e. the growth of more than one follicle with a diameter of ≥14 mm on the day of hCG administration (Goverde *et al.*, 2005).

In four studies, the end-point was a clinical pregnancy and in six studies, ongoing pregnancy. Two studies proved pregnancy by rising levels of hCG in blood serum (Dodson and Haney, 1991; Sikandar *et al.*, 2005), one study used a urine pregnancy test (Ibérico *et al.*, 2004) and another study did not state the method of pregnancy test (Tomlinson *et al.*, 1996). Seven studies did report on live birth, but none of these studies reported on live birth per number of preovulatory follicles (Dodson and Haney, 1991; Nuojua-Huttunen *et al.*, 1999; Dickey *et al.*, 2001; Khalil *et al.*, 2001a,b; Goverde *et al.*, 2005; Steures *et al.*, 2006).

Data on pregnancy rates

The overall mean pregnancy rate of all included cycles was 13.3% per cycle. In 8657 cycles, multifollicular growth was achieved (74.6%), ranging from 39 to 85% per study. Data on pregnancy rates in cycles with two follicles versus cycles with monofollicular growth are shown in Fig. 2A. Homogeneity was not rejected (χ^2 = 14.7, P = 0.33). The pooled OR for pregnancy after two follicles as compared with monofollicular growth was 1.6 (99% CI 1.3 – 1.9). The RD was 0.05 (99% CI 0.03 – 0.06), meaning an increase in pregnancy rate of 5% when two follicles were stimulated as compared with monofollicular growth. Two studies compared multifollicular growth to monofollicular growth without specifying the number of follicles. One study compared the pregnancy rate in cycles with two till six follicles with the pregnancy rate in cycles with monofollicular growth, whereas another study compared the pregnancy rate in cycles with two and three follicles with the pregnancy rate in cycles with monofollicular growth (Goverde *et al.*, 2005; Steures *et al.*, 2006). These studies were only included in the analysis of two follicles versus one follicle and left out in the subsequent analyses of three and four follicles.

Twelve studies reported on three follicles versus cycles with monofollicular growth. Data on pregnancy rates of these cycles are shown in Fig. 2B. Homogeneity was not rejected (χ^2 = 18.4, P = 0.07). The pooled OR for the pregnancy rate after three follicles as compared with monofollicular growth was 2.0 (99% CI 1.6 – 2.5). The chance on a pregnancy increased by 8% (RD 0.08, 99% CI 0.05 – 0.10).

Data on pregnancy rates in cycles with four follicles versus cycles with monofollicular growth are shown in Fig. 2C. Eleven studies reported on this item. Again, homogeneity could not be rejected (χ^2 = 7.5, P = 0.67). The pooled OR for the pregnancy rate after four follicles as compared with monofollicular growth was 2.0 (95% CI 1.5 – 2.7). The chance on a pregnancy increased by 8% (RD 0.08, 99% CI 0.04 – 0.11).

Six studies reported on pregnancy rates in cycles with five follicles versus cycles with monofollicular growth. Again, homogeneity was not rejected (χ^2 = 0.88, P = 0.97). The pooled OR for the pregnancy rate after five follicles as compared with monofollicular growth was 2.8 (95% CI 2.1 – 3.8).

The number of studies that reported on pregnancy rates after six follicles or more, as well as the number of patients in these categories, was limited, making meta-analysis not

useful. Overall, the absolute pregnancy rate in these 14 studies increased from 8.4 to 15% when multifollicular growth was achieved as compared to monofollicular stimulation.
In subgroup analyses, we calculated the odd ratios for pregnancy after two follicles versus one follicle from studies that reported on cut-off values for follicle diameter of 11 – 12, 13 – 14, 15 – 16 and 17 – 18 mm, respectively. We found that pooled odd ratios at these cut-off values were 2.4 for 11 – 12 mm [99% CI 1.5 – 4.0 (Dickey *et al.*, 2001; Steures *et al.*, 2006)], 1.4 for 13 – 14 mm [99% CI 0.9 – 2.0 (Vollenhoven et al., 1996; Khalil *et al.*, 2001a; Steures *et al.*, 2004; Goverde *et al.*, 2005; van Rumste *et al.*, 2006)], 1.6 for 15 – 16 mm [99% CI 1.3 – 2.1 (Nuojua Huttunen *et al.*, 1999; Dickey *et al.*, 2001; Khalil *et al.*, 2001b; Ibérico *et al.*, 2004; Sikandar *et al.*, 2005; Steures *et al.*, 2006)] and 1.8 for 17 – 18 mm [99% CI 1.3 – 2.4 (Dodson and Haney, 1991; Tomlinson et al., 1996; Dickey et al., 2001; Özcakir *et al.*, 2002)]. Leaving out the study that used donorsperm (Khalil *et al.*, 2001b) and the studies that did not specify the exact number of follicles (Goverde et al., 2005; Steures *et al.*, 2006) did not alter the outcome of the analysis (OR of 1.6 with a 99% CI 1.3 – 2.0).

Data on multiple pregnancy rates

In 12 of the 14 studies multiple pregnancies were reported. Of the 1481 pregnancies found in these 12 studies, there were 274 multiple pregnancies (18.5%). In nine studies with 1286 pregnancies, the number of twin pregnancies was specified. Of these pregnancies, 181 were twins (79.7% of the multiple pregnancies).

Data on multiple pregnancy rates after two follicles versus monofollicular growth of the five studies that reported on this topic are shown in Fig. 3. Homogeneity was not rejected ($\chi^2 = 5.9$, P = 0.21). The pooled OR for multiple pregnancies per conceived cycle after two follicles as compared with monofollicular growth was 1.7 (99% CI 0.8 – 3.6). The risk of multiple pregnancies for two follicles as compared with monofollicular growth increased by 6% (RD 0.06, 99% CI 20.02 to 0.15).
The absolute pregnancy rate in these five studies was 7.4% after monofollicular growth versus 13.4% after multifollicular growth. The absolute rate of multiple pregnancies was 0.3% after monofollicular growth versus 2.8% after multifollicular growth. Consequently, the multiple pregnancy rate in case of pregnancy was 3.7% after monofollicular growth and 17% after multifollicular growth.
The three studies that reported on multiple pregnancy rates per conceived cycle after growth of three follicles versus monofollicular growth showed an OR of 2.8 (99% CI 1.2 – 6.4, χ^2 for homogeneity 2.8, P = 0.25) and an increased risk of a multiple pregnancy of 14% (RD 0.14, 99% CI 0.03 – 0.24). Three studies reported on multiple pregnancy rates per conceived cycle after four or more follicles as compared with monofollicular growth.

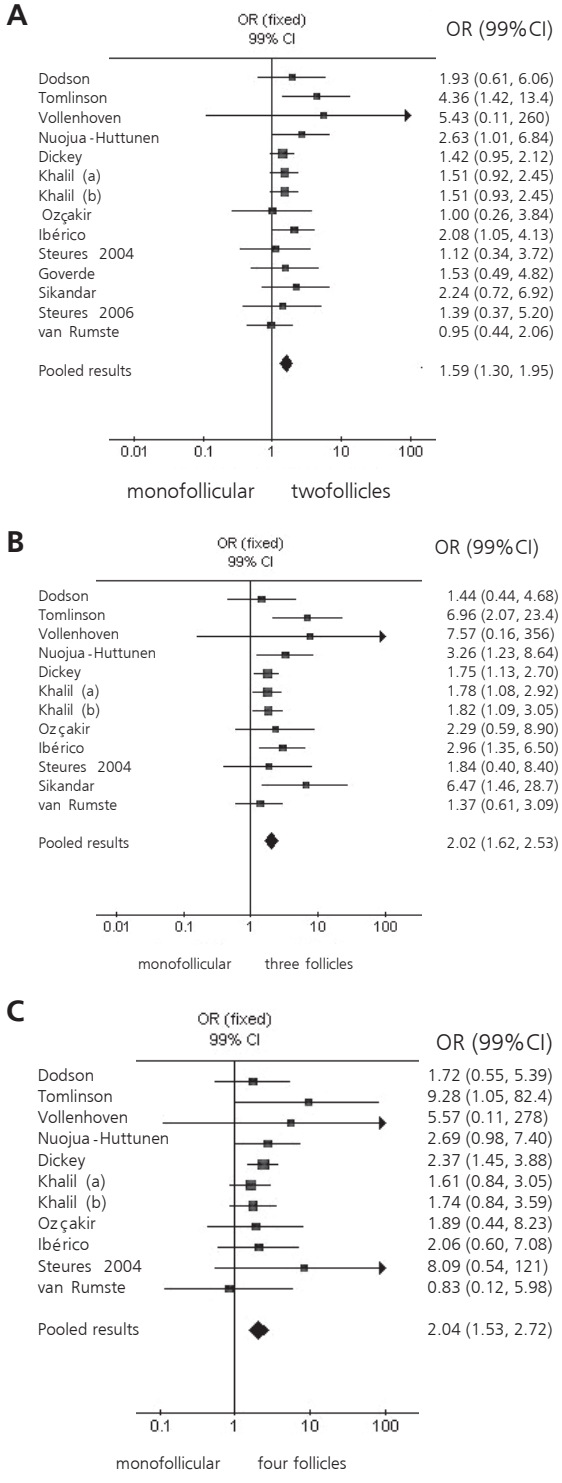

Figure 2: (A) Odd ratios (95% CI) on pregnancy rates, two follicles versus monofollicular growth. Reported on the x-axis is the OR for pregnancy rate, where one means no difference between multifollicular growth and monofollicular growth, less than one favours monofollicular growth and more than one favours multifollicular growth. (B) Odd ratios (95% CI) on pregnancy rates, three follicles versus monofollicular growth. (C) Odd ratios (95% CI) on pregnancy rates, four follicles versus monofollicular growth.

The pooled OR for the pregnancy rate was 2.3 (99% CI 0.9 – 5.9, χ^2 for homogeneity 2.9, P = 0.24). The risk of a multiple pregnancy was 10% (RD 0.10, 99% CI 20.03 to 0.24).

DISCUSSION

In this review, we included 14 studies reporting on 11 599 cycles of IUI with COH in 7489 couples. The pooled OR for pregnancy after two follicles as compared with monofollicular growth was 1.6 (99% CI 1.3 – 2.0), whereas for three and four follicles as compared with monofollicular growth this was 2.0 (99% CI 1.6 – 2.5) and 2.0 (99% CI 1.5 – 2.7), respectively. The chance of a pregnancy was 5% higher when two follicles were stimulated as compared with monofollicular growth (RD of 0.05, 99% CI 0.03 – 0.06) and 8% higher when three or four follicles were present (RD of 0.08, 99% CI 0.05 – 0.10 and RD of 0.08, 99% CI 0.04 – 0.11, respectively). Pregnancy rates increased from 8.4% to 15% per cycle when multifollicular growth was achieved as compared with monofollicular stimulation. The pooled OR for multiple pregnancies after two follicles as compared with monofollicular growth was 1.7 (99% CI 0.8 – 3.6), whereas for three and four follicles as compared with monofollicular growth this was 2.8 (99% CI 1.2 – 6.4) and 2.3 (99% CI 0.9 – 5.9). The risk of multiple pregnancies in case of pregnancy was 6% higher when two follicles were present as compared with monofollicular growth (RD of 0.06, 99% CI 0.00 – 0.13). Multiple pregnancy rates increased from 3.7% to 17% per conceived cycle when multifollicular growth was achieved as compared with monofollicular stimulation. To achieve one additional pregnancy, 16 cycles of multifollicular growth instead of monofollicular growth are necessary (number needed to treat = 16) at the cost of two additional multiple pregnancies (number needed to harm = 8).

The validity of a meta-analysis depends on the quality of the individual studies included. When combining observational studies heterogeneity among groups is to be expected (Stroup *et al.*, 2000). In this analysis, 12 cohort studies and two RCTs were included, using

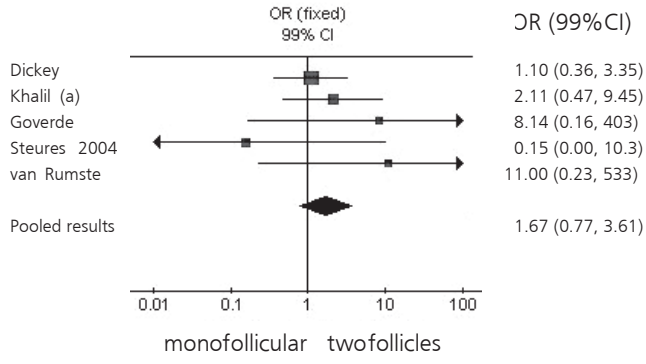

Figure 3: Odd ratios (95% CI) on multiple pregnancy rates, two follicles versus monofollicular growth. Analysis was limited to cycles in which women conceived.

the data of the IUI with COH arm of the RCTs. We noticed heterogeneity between studies regarding inclusion criteria for couples involved, use of ovarian stimulation medication, follicle size at count and use of pregnancy test. Seven studies included various kinds of subfertility (Dodson and Haney, 1991; Tomlinson *et al.*, 1996; Vollenhoven *et al.*, 1996; Nuojua-Huttunen *et al.*, 1999; Dickey *et al.*, 2001; Khalil *et al.*, 2001a; Özcakir et al., 2002), whereas five studies only included couples with unexplained subfertility (Ibérico *et al.*, 2004; Goverde *et al.*, 2005; Sikandar *et al.*, 2005; van Rumste *et al.*, 2006; Steures *et al.*, 2006). One study included only couples with donor insemination (Khalil et al., 2001b). In that study, the male partners had azoospermia, severe oligozoospermia or severe genetic disorders. Donor sperm was used and at least two million motile spermatozoa were inseminated during IUI. Women underwent hormonal screening for confirmation of a spontaneous ovulation and tubal patency was established. Since the male factor was overcome by using donor sperm and the women were ovulatory with patent tubes, we classified those couples as having 'unexplained subfertility'. These women did receive ovarian stimulation and IUI and we therefore decided to include these cycles in our review. The odd ratios were comparable to the other studies. Another difference in the studies was the definition of a pregnancy. Although nowadays live birth is by many preferred as the primary outcome in subfertility studies, data on this outcome could not be extracted from the studies. However, 10 out of 14 studies in this review report on viable pregnancy. It is known that 95% of these pregnancies will end in the birth of a healthy child. The included studies also showed heterogeneity in the cut-off value for follicle counting at time of hCG administration. Cut-off values varied between 11 and 18 mm. Pregnancies can occur in cycles with follicles of <15 mm (Richmond et al., 2005). Two studies used multiple cut-off values for follicle diameter (Dickey *et al.*, 2001; Steures *et al.*, 2006). Dickey *et al.* (2001) reported that in monofollicular cycles pregnancy rates were 7.1 and 11.9% at cut-off values of 12 and 18 mm, respectively, whereas in multifollicular cycles pregnancy rates were 16.4 and 18.4%. Steures *et al.* (2006) reported, in a much smaller study, a similar trend. Apparently, larger follicles will provide more often a viable oocyte, thus resulting in higher pregnancy rates.

The cut-off value for follicle size is also important in the light of occurrence of multiple pregnancies. Whereas only the large follicles are considered in clinical management, the accompanying smaller follicles may well lead to an increased risk of a multiple pregnancy. In more than half of the studies included in this review only follicles larger than 15 mm were counted at the time of hCG administration. These are mainly the older studies in which the stimulation protocol was usually more aggressive and cut-off values for follicle size were higher. Therefore, multiple pregnancies could be found in supposedly monofollicular cycles. It may be due to the increased awareness to prevent multiple pregnancies that methods of IUI and cancellation criteria are more clearly described nowadays (Land and Evers, 2003). Five of the included studies in this review did not state their cancellation criteria. Nearly all these studies were older than 5 years. The other studies did all describe

cancellation criteria, but none of them used the same criteria (Table I). In studies published before 2003, the multiple pregnancy rate in monofollicular cycles was 5.6% (Dickey *et al.*, 2001; Khalil *et al.*, 2001a), while 0.4% monozygotic twins would be expected (The ESHRE Capri workshop group, 2000). We found no multiple pregnancies in monofollicular cycles (out of 37 pregnancies) in studies published in the last 5 years (Goverde *et al.*, 2005; van Rumste *et al.*, 2006; Steures *et al.*, 2006).

We are also aware that the previous treatment cycles might be of influence on subsequent treatment cycles. Some women will only achieve one dominant follicle during the treatment with IUI and COH. Part of the hyperstimulation cycles producing only one follicle may reflect decreased ovarian reserve and hence impaired oocyte quality. Since none of the studies included restricted their outcomes to the first treatment cycle of IUI with COH, women were included who only achieved monofollicular growth in second and third cycles as well, resulting in more monofollicular cycles with lower pregnancy rates. Nowadays, cancellation criteria are defined more precisely. Two studies reported a very high percentage of monofollicular cycles of 60% due to strict cancellation criteria of two follicles >14 mm and two follicles >15 mm, respectively (Ragni et al., 2004; Crosignani and Somigliana, 2007). In the first study, no multiple pregnancies occurred whereas in the second study the multiple pregnancy rate was 8.3%. In spite of the high percentage of monofollicular growth, the ongoing pregnancy rate was 16.6 and 10.4%, respectively.

In conclusion, multifollicular growth is associated with increased pregnancy rates in IUI with COH. Since in cycles with three or four follicles, the multiple pregnancy rate increased without substantial gain in overall pregnancy rate, ovarian stimulation in IUI should not aim for more than two follicles. One stimulated follicle should be the goal if safety is the primary concern, whereas two follicles may be accepted after careful counselling of the patient.

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