Outcome measures in reproductive medicine trials
van Rumste, M.M.E.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 3

Monitoring of stimulated cycles in assisted reproduction (IVF and ICSI)

Irene Kwan, Siladitya Bhattacharya, Alex McNeil, Minouche M.E. van Rumste

The Cochrane Library, Cochrane Database of Systematic Reviews 2008; 2:CD005289
ABSTRACT

BACKGROUND  Traditional monitoring of ovarian hyperstimulation during in vitro fertilisation (IVF) treatment has included ultrasonography plus serum estradiol concentration to ensure safe practice by reducing the incidence and severity of ovarian hyperstimulation syndrome (OHSS). The need for intensive monitoring during ovarian stimulation in IVF is controversial. It has been suggested that close monitoring is time consuming, expensive and inconvenient for the woman and simplification of IVF therapy by using ultrasound only should be considered. This systematic review assessed the effects of ovarian monitoring by ultrasound only versus ultrasound plus serum estradiol measurement on IVF outcomes and the occurrence of OHSS in women undergoing stimulated cycles in IVF and intracytoplasmic sperm injection (ICSI) treatment.

OBJECTIVES  To quantify the effect of monitoring controlled ovarian stimulation in IVF and ICSI cycles with ultrasound plus serum estradiol concentration versus ultrasound only in terms of live birth rates, pregnancy rates and the incidence of OHSS.

SEARCH STRATEGY  We searched the Menstrual Disorders and Subfertility Group Specialised Register of controlled trials, Cochrane Central Register of Controlled Trials (CENTRAL) on the latest issue of The Cochrane Library, MEDLINE (1966 to May 2007), EMBASE (1980 to May 2007), CINAHL (1982 to May 2007), the National Research Register, and web-based trial databases such as Current Controlled Trials. There was no language restriction. Additionally all references in the identified trials and background papers were checked and authors were contacted to identify relevant published and unpublished data.

SELECTION CRITERIA  Only randomised controlled trials that compared monitoring with ultrasound plus serum estradiol concentration versus ultrasound only in women undergoing ovarian hyperstimulation for IVF and ICSI treatment were included.

DATA COLLECTION AND ANALYSIS  Two review authors independently examined the electronic search results for relevant trials, extracted data and assessed trial quality. They resolved disagreements by discussion with two other authors. Outcomes data were pooled when appropriate and summary statistics presented when limited data did not allow meta-analysis.

MAIN RESULTS  Our search strategy identified 1119 potentially eligible reports, of which two met our inclusion criteria. These involved 411 women who underwent controlled ovarian stimulation monitoring. Our primary outcome of live birth rate was not reported in either study. One trial reported clinical pregnancy rate per woman (33% versus 31%;
RR 1.07, 95% CI 0.77 to 1.49), the second trial reported clinical pregnancy rate per oocyte retrieval (22% versus 25%). There was no significant difference between the ultrasound plus estradiol group and the ultrasound alone group in the mean number of oocytes retrieved (WMD-0.55, 95% CI -1.79 to 0.69) and the incidence of ovarian hyperstimulation (RR 0.73, 95% CI 0.30 to 1.78) for the two studies.

**AUTHORS’ CONCLUSIONS** There is no evidence from randomised trials to support cycle monitoring by ultrasound plus serum estradiol as more efficacious than cycle monitoring by ultrasound only on outcomes of live birth and pregnancy rates. A large well-designed randomised controlled trial is needed that reports on live birth rates and pregnancy, with economic evaluation of the costs involved and the views of the women undergoing cycle monitoring. A randomised trial with sufficiently large sample size to test the effects of different monitoring protocols on OHSS, a rare outcome, will pose a great challenge. Until such a trial is considered feasible, cycle monitoring by transvaginal ultrasound plus serum estradiol may need to be retained as a precautionary good practice point.
BACKGROUND

A successful outcome from in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) in assisted reproduction depends on a preliminary phase of controlled ovarian hyperstimulation using exogenous gonadotrophins. The aim is to produce multiple follicles without incurring the risk of ovarian hyperstimulation syndrome (OHSS), which is the most serious iatrogenic complication of ovarian stimulation. OHSS is associated with development of a large number of follicles and is a potentially fatal condition as it can lead to ascites, pleural and pericardial effusion, haemoconcentration and coagulopathy (Schenker 1978). The incidence of OHSS is estimated to range from 0.2% to 2.7% of all assisted reproductive cycles, including with intra-uterine insemination (Asch 1991; MacDougall 1992; Nygren 2002; Roest 1996; Smitz 1990).

Controlled ovarian stimulation is traditionally monitored by means of ultrasound (US) in order to gain information on the number and size of developing follicles and to assist in determining the optimal time for human chorionic gonadotrophin (hCG) administration prior to oocyte retrieval. The overall aim is to ensure safe practice by reducing the incidence and severity of OHSS. Some fertility units also measure serum estradiol concentration during the course of stimulation, to provide added information about ovarian response and the potential risk of hyperstimulation. This combination of ultrasonography and serum estradiol concentration has been suggested to be the gold standard for monitoring stimulated cycles in IVF and ICSI procedures (Rizk 1992).

US monitoring alone has been reported to provide more accurate information on follicular number and size than can be obtained by serum estradiol concentration alone, in women with anovulatory infertility undergoing gonadotrophin induction therapy (Haning 1982; Hardiman 1990; Shoham 1991).

A cohort study comparing US only versus US plus hormonal determinations, including serum estradiol concentrations, for ovarian monitoring in women undergoing IVF reported no differences in live birth rate and the incidence of OHSS. There was a significant economic benefit in the US only monitoring protocol (Murad 1998). Another cohort study reported that US alone, performed during ovarian stimulation in IVF and intrauterine insemination, predicted 88% of cycle decisions as compared to 100% of cycle decisions that were predicted using combined monitoring (Confino 1996).

A third non-randomised study reported no differences in IVF outcomes and incidence of OHSS between women whose ovarian response was monitored by US and serum estradiol concentration on the day of human chorionic gonadotrophin (hCG) administration and women who were monitored with US and only had the serum estradiol concentration checked if the risk of OHSS was deemed to be high (Thomas 2002).

The need for intensive monitoring during ovarian stimulation in IVF is controversial. It has been suggested that close monitoring is time consuming, expensive and inconvenient for
the woman (Howard 1988; Rainhorn 1987; Tan 1992). Simplification of IVF therapy by minimal monitoring has been reported to have no adverse effects on treatment outcome and incidence of OHSS (Abdalla 1989; Roest 1995; Tan 1994). Some IVF programs have abandoned the use of hormone assay completely (Kemeter 1989; Tan 1994; Vlaisavljevic 1992).

This systematic review aimed to assess the effect of ovarian monitoring by US only versus US plus serum estradiol measurement on IVF outcomes and the occurrence of OHSS in women undergoing stimulated cycles in IVF and ICSI.

**OBJECTIVES**

To quantify the effect of monitoring controlled ovarian stimulation in IVF and ICSI cycles with ultrasound only versus ultrasound plus serum estradiol concentration in terms of live birth rates, pregnancy rates and the incidence of OHSS.

**METHODS**

Criteria for considering studies for this review

Types of studies
Randomised controlled trials only. Quasi-randomised controlled trials and randomised controlled trials of cross-over design were excluded because data from the precrossover phase could not be isolated.

Types of participants
All women undergoing ovarian stimulation with gonadotrophins in IVF and ICSI procedures.

Types of interventions
Monitoring with ultrasound versus monitoring with ultrasound plus serum estradiol concentrations.

Types of outcome measures
Primary outcomes
• Live birth rate per woman
Secondary outcomes
Chapter 3

• Pregnancy rate and multiple pregnancy rate per woman (pregnancy as established by pregnancy test or ideally confirmed by ultrasound)
• Number of oocytes recovered
• Number of cancelled cycles
• Rate of ovarian hyperstimulation syndrome (OHSS) per woman
• Costs of monitoring with ultrasound versus monitoring with ultrasound plus serum estradiol concentrations

Search methods for identification of studies

We searched the Menstrual Disorders and Subfertility Group Specialised Register of controlled trials, Cochrane Central Register of Controlled Trials (CENTRAL) on the latest issue of The Cochrane Library, MEDLINE (1966 to May 2007), EMBASE (1980 to May 2007), CINAHL (1982 to May 2007), the National Research Register, and web-based trial databases such as Current Controlled Trials. There was no language restriction. Additionally, all references in the identified trials and background papers were checked and authors contacted to identify relevant published and unpublished data. The search strategy was adapted to fit individual databases which use different subject headings. The search strategy for MEDLINE was as follows:

1. randomized controlled trial.pt.
2. double-blind method/
3. random allocation/
4. random$.ti,ab,sh.
5. Randomized Controlled Trials/
6. ((single or double or triple or treble) adj5 (blind$ or mask$)).ti.
7. single-blind method/
8. clinical trial.pt.
9. exp clinical trials/
10. (clin$ adj5 trial$).ti,ab,sh.
11. meta analysis/
12. meta analysis.pt.
13. (metaanaly$ or meta-analy$ or (meta adj analy$)).tw.
14. (systematic$ adj5 (review$ or overview$)).ti.
15. (methodologic$ adj5 review$).tw.
16. (methodologic$ adj5 overview$).tw.
17. (“review” or “review academic” or “review tutorial”).pt.
18. (medline or medlars or embase).tw,sh.
19. (scisearch or psychinfo or psycinfo).tw,sh.
20. (psychlit or psychlit).tw,sh.
21. cinahl.tw,sh.
22. ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.
23. (electronic database$ or bibliographic database$ or computeri? ed database$ or online database$).tw,sh.
24. (pooling or pooled or mantel haenszel).tw,sh.
25. (peto or dersimonian or der simonian or fixed effect).tw,sh.
26. or/1-25
27. Ovulation Induction/
28. Ovarian Hyperstimulation Syndrome/
Data collection and analysis

**Trial identification**

Two review authors (IK, AMN) independently examined the electronic search results for reports of possibly relevant trials. These reports were retrieved in full. Both authors independently applied the selection criteria to the trial reports and resolved disagreements by discussion with two other review authors (SB, MM).

**Quality assessment**

Since there is evidence that the quality of allocation concealment particularly affects the results of studies (Schulz 1995), two review authors independently scored this quality as shown.

A: randomised trial deemed to have taken adequate measures to conceal allocation (i.e. central randomisation; serially numbered, opaque, sealed envelopes; or other description that contained elements convincing of concealment).

B: randomised trial in which the authors either did not report an allocation concealment approach at all or did not clarify the process involved as 'sealed envelopes', 'random
C: randomised trial in which allocation concealment was inadequate (such as quasi-randomised trials in which allocation was by alternation or reference to case record numbers or to dates of birth). These trials were excluded from this review.

If the method used to conceal allocation was not clearly reported, the author was contacted for clarification. We then compared the scores allocated and resolved differences by discussion. From the published data, the following were assessed independently by two review authors:

- criteria for including participants and assessing outcomes;
- use of intention-to-treat analysis;
- use of valid prospective power calculations;
- numbers lost to follow up;
- blinding of outcome assessment.

**Data extraction**

Two review authors (IK, AMN) independently extracted the data and information on the following: method of allocation concealment, number of randomised patients, types of participants, interventions and outcomes. The review authors were not blinded to the authors or publication journal when doing this. Results were compared and any differences resolved by discussion (SB, MM). We contacted the authors for clarification where there was insufficient information in the published report.

**Analysis**

Data extracted from the trials were analysed on an intention-to-treat basis (when this was not done in the original report, re-analysis was performed with the implicit assumption of outcome by including patients with missing data in the denominator but not the numerator). The primary analysis included only reported data. When live birth rates were not available, we reported pregnancy rates. The effects of the interventions on the outcome measures were meta-analysed based on clinical judgment as to whether the studies were addressing similar questions. Outcomes which were dichotomous (such as pregnancy rates and OHSS rates) were analysed as relative risks (RR) with 95% confidence intervals (CI) and outcomes which were continuous (such as number of oocytes retrieved) were analysed using weighted mean difference (WMD). We used RevMan software with the Mantel-Haenszel method and a fixed-effect model. Due to the limited number of studies identified, pooling of data was carried out on similar outcomes when such data were available; when these data were not available summary statistics were presented for individual studies.

Details of the studies, including methods, participants, intervention, outcomes, allocation concealment and any other details such as incidence of violation of protocol, were entered into the table ‘Characteristics of included studies’. Studies which were excluded from...
the review were presented in the table ‘Characteristics of excluded studies’ with a brief statement of the reason for exclusion, but no further information.
It is the intention of the review authors that the review is updated regularly.

RESULTS

Description of studies

See Table 1 and 2 for a summary of the characteristics of respectively the included and excluded studies. Our search strategy identified 1119 potentially eligible reports, of which three appeared to meet the inclusion criteria. We excluded one study (Murad 1998) because it was a non-randomised comparison. We did not identify any quasi-randomised

Table 1. Characteristics of included studies
Golan 1994

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised controlled trial (method not reported) No report of sample size calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>114 women undergoing IVF/embryo transfer programme (first IVF attempt only)</td>
</tr>
<tr>
<td>Interventions</td>
<td>US + serum estradiol concentration (n=57) versus US alone (n=57)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Pregnancy rate/ oocyte retrieval. No of oocytes retrieved No of cases of OHSS</td>
</tr>
<tr>
<td>Notes</td>
<td>Intention-to-treat. No of cycles not reported Author contacted: no data details were made available</td>
</tr>
</tbody>
</table>

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B Unclear</td>
</tr>
</tbody>
</table>

Lass 2003

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised controlled trial (computer-generated randomisation, assignment code in individual sealed envelopes, sample size calculation carried out before trial) Patient-blinded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>297 women undergoing IVF treatment (had &lt; 3 previous attempts; ICSI excluded)</td>
</tr>
<tr>
<td>Interventions</td>
<td>US + serum estradiol concentration (n=148) versus US alone (n=149) (one cycle only)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Pregnancy rate / woman No of oocytes retrieved No of cases of OHSS</td>
</tr>
<tr>
<td>Notes</td>
<td>Nine women (3%) dropped out Not Intention to treat One cycle only Author contacted: no data details were made available</td>
</tr>
</tbody>
</table>

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B Unclear</td>
</tr>
</tbody>
</table>

US ultrasonography
OHSS ovarian hyperstimulation syndrome
or crossover trials. The two papers which met our inclusion criteria (Golan 1994; Lass 2003) involved 411 women who underwent controlled ovarian stimulation monitoring. They were published in 1994 and 2003.

**Golan 1994**

This trial involved 114 women (mean age 30.6 +/4.2 years versus 31 +/4.4 years; mean duration of infertility 5.2 +/3 years versus 4.6 +/3 years, in the two groups respectively). The women were randomly assigned to ultrasound and serum determinations of estradiol, progesterone and luteinizing hormone concentrations versus ultrasound alone. Only women undergoing their first IVF attempt were included. The outcomes measured were number of oocytes retrieved, pregnancy rate per oocyte retrieval, pregnancy rate per embryo transfer and number of OHSS cases. The criteria for ovarian hyperstimulation were not defined. The number of pregnancies and cancelled cycles were not documented. Live birth rates were not provided.

**Lass 2003**

This trial involved 297 women (mean age 33.2 +/3.4 years versus 33.0 +/34 years, in the two groups respectively; mean duration of infertility not reported) randomly assigned to daily ultrasound and serum estrogen E2 level assessments versus daily ultrasound assessment alone. Only one cycle of treatment was given to these women who had no more than three previously failed IVF attempts. Women undergoing ICSI were excluded. The outcomes measured were pregnancies per oocyte pick up, number of oocytes retrieved, pregnancy outcome and OHSS rates. The criteria for ovarian hyperstimulation were not defined. There was no report of the number of cancelled cycles. Live birth rate was not documented.

**Risk of bias in included studies**

**Methods of randomisation**

The method of randomisation was not reported in one trial (Golan 1994); the author was not able to provide these methodological details. In the other trial, randomisation was performed using a computer-generated randomisation list and sealed envelopes (Lass 2003).

**Methods of allocation concealment**

The method of allocation concealment was not reported in either trial. Both authors were not able to provide these methodological details. Women were described as blinded in one trial (Lass 2003) but no further information was available.
Use of a prospective power calculation
This was not reported in one trial (Golan 1994). In the other study, a power calculation was described and, based on pregnancy as an outcome; about 230 women per group were required in order to have a power of 70% to show a difference of 5%. The final number of women recruited was 148 and 149 in each arm, respectively (Lass 2003).

Criteria for including participants
Only women undergoing the first IVF attempt were included in one trial (Golan 1994). In the other study, women with no more than 3 previous unsuccessful IVF were included and given only one single cycle of treatment (Lass 2003). Women undergoing ICSI were excluded in both trials.

Criteria for assessing outcomes
In one study, pregnancy rate was presented as pregnancy per oocyte retrieval; the definition of pregnancy was not provided (Golan 1994). In the other trial clinical pregnancy, presented as pregnancy per cycle, was defined as a pregnancy in which a fetal sac (with or without fetal heart activity) was visualised by ultrasound on day 28 to 42 after hCG administration (Lass 2003). The definition of OHSS was not provided in either trial.

Numbers lost to follow up
No dropouts were reported in one trial and the number of women at randomisation and in the analyses was the same (Golan 1994). In the other trial, nine patients (3%) dropped out (Lass 2003).

Use of intention-to-treat analysis
In one trial, data analysed were based on the same number of women as at randomisation, satisfying the intention-to-treat criteria (Golan 1994). In the other trial, nine patients (3%) dropped out and analysis was not based on the intention-to-treat principle (Lass 2003).

Blinding of outcome assessment
There was no report of blinding of assessment in either trial.

Table 3. Comparison of US + estradiol versus US only

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Clinical pregnancy per woman</td>
<td>1</td>
<td>297</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.07 [0.77, 1.49]</td>
</tr>
<tr>
<td>2 Mean number of oocytes retrieved</td>
<td>2</td>
<td>411</td>
<td>Mean Difference (IV, Fixed 95% CI)</td>
<td>-0.55 [-1.79, 0.69]</td>
</tr>
<tr>
<td>3 OHSS rate</td>
<td>2</td>
<td>1233</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.74 [0.40, 1.37]</td>
</tr>
<tr>
<td>3.1 OHSS rate (all)</td>
<td>2</td>
<td>411</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.73 [0.30, 1.78]</td>
</tr>
<tr>
<td>3.2 OHSS rate (severe)</td>
<td>2</td>
<td>411</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.43 [0.06, 2.89]</td>
</tr>
<tr>
<td>3.3 OHSS rate (non-severe)</td>
<td>2</td>
<td>411</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.88 [0.32, 2.38]</td>
</tr>
</tbody>
</table>
Effects of interventions

Summary of comparison

Live birth rate
No data were available.

Pregnancy rate (Table 4)
One trial (Golan 1994) reported the clinical pregnancy rate per oocyte retrieval (22% in the ultrasound plus estradiol group versus 25% in the ultrasound only group), the number of pregnancies in each group was not reported. It was not clear if each woman only had one treatment cycle initiated. Although the number of women randomised was known, the number of women who underwent oocyte retrieval was not reported hence the actual number of pregnancies could not be calculated.

In the second trial (Lass 2003), the clinical pregnancy rate was 33% in the ultrasound plus estradiol group versus 31% in the ultrasound only group (RR 1.07, 95% CI 0.77 to 1.49).

Table 4. Clinical pregnancy per woman

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>US + estradiol</th>
<th>US only</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lass 2003</td>
<td>49/148</td>
<td>46/149</td>
<td></td>
<td>100%</td>
<td>1.07 [0.77, 1.49]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>148</td>
<td>149</td>
<td></td>
<td>100%</td>
<td>1.07 [0.77, 1.49]</td>
</tr>
</tbody>
</table>

Multiple pregnancy rates
No data were available.

Number of oocytes recovered (Table 5)
The mean number of oocytes retrieved between the two arms was (11.7 +/- 8.4 versus 13.4 +/- 7.5) in one trial (Golan 1994) and (11.4 +/- 6.1 versus 11.7 +/- 5.9) in the other trial (Lass 2003). Combining the data from the two trials, the weighted mean difference

Table 5. Mean number of oocytes retrieved

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>US + estradiol</th>
<th>US only</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Golan 1994</td>
<td>57</td>
<td>57</td>
<td>1.75</td>
<td></td>
<td>-1.70 [-4.62, 1.22]</td>
</tr>
<tr>
<td>Lass 2003</td>
<td>148</td>
<td>149</td>
<td>0.17</td>
<td></td>
<td>-0.30 [-1.67, 1.07]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>205</td>
<td>206</td>
<td>-0.55 [-1.79, 0.69]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: CH² = 0.72, df = 1 (P = 0.40); I² = 0.0%
Test for overall effect: Z = 0.87 (P = 0.38)
(WMD) for the number of oocytes retrieved was -0.55 (-1.79 to 0.69, I² = 0%). For this outcome, there was no significant difference between the two treatments.

**Number of cancelled cycles**

No data were available

**Rate of ovarian hyperstimulation syndrome (OHSS), including severe OHSS (Table 6)**

In one trial (Golan 1994), the incidence of non-severe OHSS was 2/57 in the ultrasound plus estradiol arm compared with 3/57 in the ultrasound only arm (3.5% versus 5.3%; RR 0.67, 95% CI 0.12 to 3.84). The figures in the second trial (Lass 2003) for nonsevere OHSS were 5/148 versus 5/149 (3.4% versus 3.4%; RR 1.01, 95% CI 0.32 to 2.38). Pooling the results of these two trials, the relative risk for non-severe OHSS was 0.88 (95% CI 0.32 to 2.38, I² = 0%).

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>US + estradiol n/N</th>
<th>US only n/N</th>
<th>Risk Ratio M-H Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 OHSS rate (all)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Golan 1994</td>
<td>3/57</td>
<td>4/57</td>
<td>1.78</td>
<td>0.75</td>
<td>0.18, 3.20</td>
</tr>
<tr>
<td>Lass 2003</td>
<td>5/148</td>
<td>7/149</td>
<td>3.11</td>
<td>0.72</td>
<td>0.23, 2.21</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>205</strong></td>
<td><strong>206</strong></td>
<td><strong>48.9 %</strong></td>
<td><strong>0.73</strong></td>
<td><strong>0.30, 1.78</strong></td>
</tr>
<tr>
<td></td>
<td>Total events: 8 (US + estradiol), 11 (US only)</td>
<td></td>
<td>Heterogeneity: Ch² = 0.00, df = 1 (P = 0.99); P² = 0.0%</td>
<td>Test for overall effect: Z = 0.69 (P = 0.49)</td>
<td></td>
</tr>
<tr>
<td>2 OHSS rate (severe)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Golan 1994</td>
<td>1/57</td>
<td>1/57</td>
<td>4.5 %</td>
<td>1.00</td>
<td>0.06, 15.60</td>
</tr>
<tr>
<td>Lass 2003</td>
<td>0/148</td>
<td>2/149</td>
<td>11.1 %</td>
<td>0.20</td>
<td>0.01, 4.16</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>205</strong></td>
<td><strong>206</strong></td>
<td><strong>15.6 %</strong></td>
<td><strong>0.43</strong></td>
<td><strong>0.06, 2.89</strong></td>
</tr>
<tr>
<td></td>
<td>Total events: 1 (US + estradiol), 3 (US only)</td>
<td></td>
<td>Heterogeneity: Ch² = 0.60, df = 1 (P = 0.44); P² = 0.0%</td>
<td>Test for overall effect: Z = 0.87 (P = 0.39)</td>
<td></td>
</tr>
<tr>
<td>3 OHSS rate (non-severe)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Golan 1994</td>
<td>2/57</td>
<td>3/57</td>
<td>13.4 %</td>
<td>0.67</td>
<td>0.12, 4.84</td>
</tr>
<tr>
<td>Lass 2003</td>
<td>5/148</td>
<td>5/149</td>
<td>22.2 %</td>
<td>1.01</td>
<td>0.36, 3.41</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>205</strong></td>
<td><strong>206</strong></td>
<td><strong>35.6 %</strong></td>
<td><strong>0.88</strong></td>
<td><strong>0.32, 2.38</strong></td>
</tr>
<tr>
<td></td>
<td>Total events: 7 (US + estradiol), 8 (US only)</td>
<td></td>
<td>Heterogeneity: Ch² = 0.14, df = 1 (P = 0.70); P² = 0.0%</td>
<td>Test for overall effect: Z = 0.25 (P = 0.80)</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>615</strong></td>
<td><strong>618</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.74</strong></td>
<td><strong>0.40, 1.37</strong></td>
</tr>
<tr>
<td></td>
<td>Total events: 16 (US + estradiol), 22 (US only)</td>
<td></td>
<td>Heterogeneity: Ch² = 1.02, df = 5 (P = 0.96); P² = 0.0%</td>
<td>Test for overall effect: Z = 0.99 (P = 0.34)</td>
<td></td>
</tr>
</tbody>
</table>

Although severe OHSS was not listed as an outcome in the protocol, we considered it clinically important to include as part of the analyses. The incidence of severe OHSS was 1.8% versus 1.8% in one trial (Golan 1994) and 0% versus 1.3% in the other trial (Lass 2003). Pooling the results of these two studies, the relative risk for severe OHSS was 0.43.
(95% CI 0.06 to 2.89, I² = 0%). Available data from the two trials favoured combined monitoring with ultrasound plus estradiol but with wide confidence intervals.

Costs of monitoring with ultrasound versus monitoring with ultrasound plus serum estradiol concentration
No data available

Discussion

Principal findings
The pooled data from the two trials did not show any significant differences between the monitoring procedures and confidence intervals were wide for all the identified outcomes with reported data. Therefore, the evidence is insufficient to determine the comparative effectiveness of cycle monitoring by transvaginal ultrasound plus serum estradiol estimation and transvaginal ultrasound alone in women undergoing IVF.

Strengths and weaknesses of the review
This study is the first comprehensive systematic review to assess the effects of cycle monitoring with ultrasound plus estradiol estimation versus ultrasound only. As a Cochrane review it will be updated regularly.

The methodological quality of the trials was variable (see section under ‘Methodological quality of included studies’). The small number of trials identified and the lack of detail provided in each trial, despite requests to the authors, limited our ability to aggregate data meaningfully, especially in terms of pregnancy rates per cycle. There was a possibility that some of the randomised women may not have reached oocyte recovery due to cycles cancelled for inappropriate ovarian stimulation (either an under or over response). This is important in a trial where ovarian response may be affected by the monitoring regimen. The studies reviewed were limited by their small sample sizes. As the definition of OHSS was not presented in the two trials, it was uncertain if the reported cases of severe OHSS were similar in nature. The criteria for inclusion in the two trials also varied. Only first IVF attempts were included in one study and the number of cycles of treatment given was not reported (Golan 1994). In the other study, women with no more than three previous unsuccessful IVF treatments were included and they were given only one single cycle of treatment (Lass 2003). These population characteristics could influence the success of the IVF treatment.
Implications of extra monitoring tests
Cycle monitoring with both ultrasound and estradiol measurement is likely to involve higher costs (to cover technicians and laboratory costs, outpatient attendance) when compared with ultrasound alone. Unnecessary monitoring may cause women anxiety, though it is unclear if women will be more satisfied because of a placebo effect of being monitored. The trials reviewed were not designed to test the cost effectiveness of the two interventions. However, it was suggested in one trial (Golan 1994) that avoiding serum hormone determination might save over US$150 (at early 1990 prices) in each cycle and compensate for the cost of the gonadotropin releasing hormone analogues (GnRHa).
Based on the results of this review, there is no evidence from randomised trials to support cycle monitoring by ultrasound plus serum estradiol as more efficacious than cycle monitoring by ultrasound only, relating to live birth and pregnancy rate outcomes.
To find a difference in rare outcome such as OHSS, a large randomised study requiring the recruitment of about 5000 women is needed, which would pose a great challenge. The interpretation of ultrasound involves some degree of inter-observer variability and, at present, a cycle monitoring protocol including both ultrasound and serum estradiol may need to be retained as a precautionary good clinical practice point.

AUTHOR’S CONCLUSIONS

Implications for practice
There is no evidence from randomised trials available to determine if cycle monitoring by transvaginal ultrasound plus serum estradiol concentrations is more effective than by transvaginal ultrasound alone in women undergoing IVF, relating to live birth and pregnancy rates. There is unlikely to be a trial sufficiently large to prove or disprove conclusively if either intervention can reduce OHSS rates, an important but rare outcome of ovarian stimulation. Until such a trial is considered feasible, cycle monitoring by transvaginal ultrasound plus serum estradiol may need to be retained as a good practice point.

Implications for research
A large well-designed randomised controlled trial that reports on live birth and pregnancy rates as outcomes and provides an economic evaluation of the costs involved and the views of the women undergoing cycle monitoring is needed to show if both monitoring protocols are equivalent. A randomised trial with sufficiently large sample size to test the effect of different cycle monitoring protocols on OHSS will pose a great challenge.
Acknowledgements

We are grateful thank the author for responding to our queries. We also thank Debbie Pledge for her help in updating the search strategy.
REFERENCES

References to studies included in this review


References to studies excluded from this review


Additional references


