Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for the prevention of OHSS in ART cycles: an overview of Cochrane reviews (Protocol)

Mourad S, Brown J, Farquhar C

Mourad S, Brown J, Farquhar C.
Interventions for the prevention of OHSS in ART cycles: an overview of Cochrane reviews.
Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD012103.
DOI: 10.1002/14651858.CD012103.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Overview of Reviews Protocol]

Interventions for the prevention of OHSS in ART cycles: an overview of Cochrane reviews

Selma Mourad[1], Julie Brown[2], Cindy Farquhar[3]

[1]Radboud University Medical Centre, Nijmegen, Netherlands. [2]Liggins Institute, The University of Auckland, Auckland, New Zealand. [3]Department of Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand

Contact address: Selma Mourad, Radboud University Medical Centre, Nijmegen, Netherlands. Selma.Mourad@radboudumc.nl.

Editorial group: Cochrane Gynaecology and Fertility Group.
Publication status and date: New, published in Issue 2, 2016.

Citation: Mourad S, Brown J, Farquhar C. Interventions for the prevention of OHSS in ART cycles: an overview of Cochrane reviews. *Cochrane Database of Systematic Reviews* 2016, Issue 2. Art. No.: CD012103. DOI: 10.1002/14651858.CD012103.

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To summarize the evidence from Cochrane systematic reviews on interventions that reduce the risk of moderate, severe and overall OHSS in women undergoing ART cycles.

BACKGROUND

Description of the condition

Ovarian Hyperstimulation Syndrome (OHSS) is a serious complication of controlled ovarian hyperstimulation cycles used in assisted reproductive technologies (ART). OHSS is clinically characterized by abdominal tenderness and swelling due to an increased ovarian volume and a sudden increase in vascular permeability, which results in a shift of fluid to the extravascular space. However, the exact pathophysiology of OHSS has not been completely elucidated. Although cases of spontaneous OHSS are reported and are suspected to be linked to follicle-stimulating hormone (FSH) receptor gene mutations (Delbaere 2004). However, the development of OHSS in ART cycles is mainly an iatrogenic side effect of exogenous hormonal administration (aimed at controlled hyperstimulation and multifollicular growth), the administration of human chorionic gonadotrophin (hCG) for ovulation triggering, pregnancy-derived hCG in a situation where multiple follicles are present. A key role is suspected for vascular endothelial growth factor (VEGF), which is produced by the multiple follicles following ovarian stimulation (Agrawal 1999). Higher VEGF levels induce hyperpermeability of the ovarian blood vessels, which leads to a fluid shift from the intravascular to the third space. Also, administration of hCG in high-risk women and extensive luteinization, supraphysiological levels of oestradiol and progesterone in the presence of multiple corpora lutea trigger OHSS (Delbaere 2005).

Over the years, several criteria have been used to classify OHSS severity in women (Table 1; Aboulghar 2003; Golan 1989; Navot 1992; Schenker 1978). In general, when OHSS progresses to a moderate stage, women can suffer from abdominal pain, nausea and vomiting, and ascites can be seen around the ovaries on vaginal ultrasound. If it progresses to severe OHSS, extravascular fluid can be found in pleural and pericardial spaces and several haemodynamic changes take place, such as intravascular volume depletion, haemoconcentration, hypoalbuminaemia and electrolyte imbalances. These changes can lead to severe morbidity due to throm-

boembolic events (Stewart 1997), respiratory distress, and liver or renal failure. If left untreated, OHSS demonstrates a rapid progression, with potentially life-threatening or lethal complications (Braat 2006).

The mild form of OHSS is quite common and of less clinical importance, and occurs in an estimated 20% to 33% of ART cycles. Moderate and severe forms of OHSS occur in an estimated 3% to 8% of ART cycles, with around 3% to 6% moderate and 0.5% to 5% severe forms (Delvigne 2002; Golan 1989; Schenker 1994). The large differences in reported OHSS incidence are mainly because most reports concern single-centre data, use different definitions of OHSS, do not require diagnosis to be ascertained by a formal classification system or adequate follow-up, and lack the reporting of mild or moderate forms. A large European report on 2010 ART practice, Kupka 2014, reported OHSS data for 25 participating countries and found a prevalence of 0.3% in 349,402 simulated ART cycles. However, the report lacked data for some countries with a high volume of ART cycles (e.g. France, Sweden, the Netherlands and the UK) and for some countries the OHSS rates were extremely low, possibly due to reporting bias. A large Swiss retrospective cohort study reported a decline in OHSS incidence from 3.6% to 1% from 2005 to 2009 (De Geyter 2015). Globally, OHSS incidence is declining, with a steady decrease reported since peak incidence in the 1990s, when the main goal in ART was to get a high number of oocytes (Kol 2011) and the incidence of severe OHSS was considered to be around 0.2% to 1% (Abramov 1999). With new treatment regimens emerging, more judicious use of gonadotropins, increased cycle monitoring and more knowledge of OHSS risks, the incidence gradually fell in the following decades.

Although still relatively rare, OHSS is thus an iatrogenic disease in ART cycles, and women who are affected should be carefully monitored to avoid life-threatening complications. Early recognition of risk factors for OHSS development can help clinicians tailor their treatment regimens. Women with a priori risk for the development of OHSS are those with polycystic ovaries (PCO) (with or without PCO syndrome) or a high antral follicle count (e.g. in young age). During a controlled ovarian stimulation cycle, women can acquire a 'high risk' status when they prove to have high oestradiol levels, excessive follicle growth or a high number of oocytes retrieved. Besides the early OHSS type that develops during, or immediately following, ovarian stimulation, we can also distinguish a late type, which appears after embryo implantation is established. The presence of a multiple gestation can moreover trigger or exacerbate this late type of OHSS (Delbaere 2005; Mathur 2000).

Description of interventions and how the interventions might work

Interventions that aim to reduce OHSS incidence can target diverse parts of stimulated ART cycles:

- selection or identification of 'high risk' populations to tailor stimulation regimens;
- prevention of recurrent OHSS by adjustment of the dose of gonadotrophins in a next cycle;
- prevention of a large numbers of follicles by tailoring ovarian stimulation in specific risk groups (e.g. use of different treatment regimens or use of adjuvant medication);
- prevention of the rise in VEGF levels (e.g. by prevention of development of large numbers of follicles) or by targeting VEGF receptors (e.g. by dopamine agonists);
- dose-reduction or withholding hCG administration for ovulation trigger or luteal support;
- prevention of the rise in oestradiol by withholding gonadotrophins ('coasting');
- prevention of a further rise in oestradiol and preventing ovulation triggering and pregnancy by cycle cancellation;
- prevention of intravascular volume depletion by administration of plasma expanding intravenous (IV) fluids;
- prevention of pregnancy by freezing all embryos and transferring them back in a subsequent cycle.

Moreover, trials of interventions within an ART cycle that are not specifically aimed at preventing OHSS, may also report on OHSS as an outcome. These interventions are also of interest to this overview and might reveal new mechanisms to lower the risk of OHSS.

Why it is important to do this overview

OHSS in ART cycles is an iatrogenic disease with an estimated incidence of 3% to 6%, and up to 5% for the severe form (Delvigne 2002). If left untreated, it can lead to severe morbidity and be potentially life-threatening. There are multiple treatment options available for the prevention of OHSS in ART cycles, and it is therefore important to provide consumers, health professionals, policy makers and guideline developers with a summary of evidence from the Cochrane Library on OHSS prevention. We will comment upon this evidence in light of the overall effectiveness of the studied interventions in the separate reviews. By doing so, we will also identify any existing knowledge gaps or reporting flaws within the Cochrane systematic reviews published in the Cochrane Library concerning OHSS in ART cycles. This means we can give recommendations on future research.

OBJECTIVES

To summarize the evidence from Cochrane systematic reviews on interventions that reduce the risk of moderate, severe and overall OHSS in women undergoing ART cycles.

METHODS

Criteria for considering reviews for inclusion

Types of reviews

For this overview of reviews, we will include all published Cochrane systematic reviews of randomized controlled trials (RCTs) that study:

- interventions that aim to prevent OHSS and have the incidence of moderate, severe or overall OHSS as a primary outcome;
- other interventions in ART cycles and report on the incidence of moderate, severe or overall OHSS as a secondary outcome.

Moreover, we will list the protocols of reviews and title registrations on OHSS prevention in a table in the overview. Thus we will be able to identify and add new reviews, once published, in the next overview update. We will exclude reviews on non-ART cycles and reviews on ART cycles that did not report on OHSS as an outcome.

Types of participants

We will include reviews that include women who undergo fresh ART cycles, including women who act as oocyte donors. We will also consider Cochrane systematic reviews that report on 'high risk' subgroups (e.g. minimum number of follicles, minimum number of oocytes retrieved, minimum oestradiol level or women with PCOS) as well as those that report on unselected populations. We will exclude reviews of non-ART cycles, such as ovulation induction or intrauterine insemination cycles.

Types of interventions

We will consider two types of intervention reviews:

- interventions specifically aimed at prevention of OHSS, where OHSS is reported as a primary outcome;
- any interventions in ART cycles, where OHSS is reported as a secondary outcome.

Search methods for identification of reviews

We will search for reviews within the Cochrane Database of Systematic Reviews and Archie (the Cochrane information management system) for the keywords in vitro fertilisation (IVF), intracytoplasmic sperm injection (ICSI), ART, adverse events and OHSS. The recently updated overview 'Assisted reproductive technology: an overview of Cochrane Reviews' by Farquhar 2015 identified all current reviews in ART that report on OHSS as a primary or secondary outcome and we will use it as complementary guidance.

Data collection and analysis

We will base the methodology for data collection and analysis for this overview on Chapter 22 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Becker 2011; Higgins 2011*)*.

Primary outcomes

The primary outcome measure will be the incidence of moderate, severe and overall OHSS, per woman randomized.
We will define the OHSS subgroups of moderate and severe by the criteria set by Aboulghar 2003, Golan 1989, Navot 1992, Rabau 1967, Rizk 1999 and Schenker 1978 or any other classification used (Table 1).

Secondary outcomes

Secondary outcomes studied will be live birth rate, clinical pregnancy rate, miscarriage rate, multiple pregnancy rate and any adverse effects reported that derive from the interventions studied (as reported by the separate reviews, e.g. side-effects of medication, admission to the hospital).

Selection of reviews

Two overview authors will independently select reviews for inclusion according to the criteria stated. A third overview author will act as a referee and discuss any disagreements. We will add the following to the overview for future overview updates: protocols of reviews and title registrations submitted to the Cochrane Library on the prevention of OHSS or reviews on ART interventions that will report on OHSS as a secondary outcome.

Data extraction and management

Two overview authors will perform data extraction and will use a Microsoft Excel spreadsheet. If any data from the reviews are unclear or seem to be missing, we will contact the review authors for clarification, search the primary RCTs or contact the primary study authors for details. A third overview author will be a referee and discuss any discrepancies or disputes.
We will extract and summarize data in the additional tables on the following:

- population demographics: participant characteristics, definition of high risk groups whenever applicable;
- review characteristics: the number of included trials, the number of participants, the date that the review was assessed as up to date (date of search), interventions and comparisons, all primary and secondary outcomes and limitations of the review;

- timing of intervention: e.g. pretreatment selection of participants, pretreatment adjuvant therapy, stimulation phase, stimulation phase adjuvant treatment, ovulation trigger, embryo transfer phase and luteal support phase;
- statistical summary: the summary effects from relevant comparisons on our primary outcomes moderate, severe or overall OHSS.

We will use the same summary effect measures as the original reviews, in most cases odds ratios.

Assessment of methodological quality of included reviews

Two overview authors will independently assess the quality of the evidence from the included systematic reviews. We will resolve any discrepancies by discussion and a third overview author will arbitrate.

Quality of evidence from primary studies in included reviews

Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, we will summarize the quality of the evidence from the primary studies in the included reviews (Guyatt 2008; Schünemann 2013). We will prepare 'Summary of findings' tables using GRADEpro Guideline Development Tool (GDT) software (GRADEpro GDT) for the overview outcomes for each comparison by either taking ratings from the original review, or we will appraise the review ourselves if the review was not yet assessed using the GRADE approach:

- the risk of bias of included trials;
- directness of evidence;
- precision of the evidence;
- heterogeneity;
- risk of publication bias.

We will summarize the evidence for each of the selected clinical outcomes in a 'Summary of findings' table, which we will populate with the summary risk estimate and 95% confidence intervals. We will allocate the quality of the evidence for the clinical outcome with a score for the strength of the evidence, which will range from 'high' to 'very low'.

Quality of included reviews

We will assess the methodological quality of included reviews using the AMSTAR instrument (Shea 2007). This instrument evaluates the methods used in the reviews and the degree to which reviews are biased by comparing with distinct criteria. The ratings used in AMSTAR are: yes (clearly done), no (clearly not done), cannot answer and not applicable (Table 2).

Data synthesis

We will undertake a narrative description of the included trials. We will include an 'overview of reviews' table, which will show the characteristics of the included reviews. Moreover, we will display a summary of the quality of the evidence within individual reviews based on the GRADE judgements, and will provide an AMSTAR rating for each included review. We will not perform a network meta-analysis.

We will summarize the main results of the included systematic reviews and the effect on OHSS rate of their individual comparisons using the following framework:

- effective interventions: indicate that the review found evidence of effectiveness for an intervention;
- promising interventions (more evidence needed): indicate that the review found some evidence of effectiveness for an intervention, but more evidence is needed;
- ineffective interventions: indicate that the review found evidence of lack of effectiveness for an intervention;
- probably ineffective interventions (more evidence needed): indicate that the review found evidence that suggests lack of effectiveness for an intervention, but more evidence is needed;
- no conclusions possible due to lack of evidence: indicates that the review found insufficient evidence to comment on the effectiveness of an intervention.

The choice of category to be allocated will reflect the conclusions stated by the authors of the individual reviews and we will be base it on our judgements as overview authors. We will resolve any disagreements by discussion.

We have based our approach to summarizing the evidence on Farquhar 2015.

ACKNOWLEDGEMENTS

We acknowledge the support of the Cochrane Gynaecology and Fertility Group editorial base, particularly Jane Marjoribanks, Assistant Managing Editor and Helen Nagels, Managing Editor for their help with the protocol.

REFERENCES

Additional references

Aboulghar 2003

Aboulghar MA, Mansour RT. Ovarian hyperstimulation syndrome: classifications and critical analysis of preventive measures. *Human Reproduction Update* 2003;**9**(3):275–89.

Abramov 1999

Abramov Y, Elchalal U, Schenker JG. Severe OHSS: An 'epidemic' of severe OHSS: a price we have to pay?. *Human Reproduction* 1999;**14**(9):2181–3.

Agrawal 1999

Agrawal R, Tan SL, Wild S, Sladkevicius P, Engmann L, Payne N, et al. Serum vascular endothelial growth factor concentrations in in vitro fertilization cycles predict the risk of ovarian hyperstimulation syndrome. *Fertility and Sterility* 1999;**71**(2):287-93.

Becker 2011

Becker LA, Oxman AD. Chapter 22: Overviews of reviews. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from www.cochrane-handbook.org 2011.

Braat 2006

Braat D, Bernardus R, Gerris J. Anonymous reports of lethal cases of ovarian hyperstimulation syndrome. In: Gerris J, Olivennes F, Delvigne A editor(s). *Ovarian Hyperstimulation Syndrome*. London: Informa UK Limited, 2006:59–66.

De Geyter 2015

De Geyter C, Fehr P, Moffat R, Gruber IM, von Wolff M. Twenty years' experience with the Swiss data registry for assisted reproductive medicine: outcomes, key trends and recommendations for improved practice. *Swiss Medical Weekly* 2015;**145**:w14087. [DOI: 10.4414/smw.2015.14087]

Delbaere 2004

Delbaere A, Smits G, Olatunbosun O, Pierson R, Vassart G, Costagliola S. New insights into the pathophysiology of ovarian hyperstimulation syndrome. What makes the difference between spontaneous and iatrogenic syndrome?. *Human Reproduction* 2004;**19**(3):486–9.

Delbaere 2005

Delbaere A, Smits G, De Leener A, Costagliola S, Vassart G. Understanding ovarian hyperstimulation syndrome. *Endocrine* 2005;**26**(3):285–90.

Delvigne 2002

Delvigne A, Rozenberg S. Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review. *Human Reproduction Update* 2002;**8**(6):559–77.

Farquhar 2015

Farquhar C, Rishworth JR, Brown J, Nelen WLDM, Marjoribanks J. Assisted reproductive technology: an overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews* 2015, Issue 7. [DOI: 10.1002/14651858.CD010537.pub4]

Golan 1989

Golan A, Ron-El R, Herman A, Soffer Y, Wainraub Z, Caspi E. Ovarian Hyperstimulation Syndrome: an update review. *Obstetrical and Gynecological Survey* 1989;**44**(6):430–40.

GRADEpro GDT

GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime Inc.). Available from www.gradepro.org.

Guyatt 2008

Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ, GRADE Working Group. Rating quality of evidence and strength of recommendations: What is "quality of evidence" and why is it important to clinicians?. *BMJ* 2008;**336**(7651):995–8.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration 2011. Available from www.cochrane–handbook.org.

Kol 2011

Kol S. Ovarian hyperstimulation syndrome prevention. Global Library of Women's Medicine 2011. [DOI: 10.3843/GLOWM.10466; ISSN:1756–2228]

Kupka 2014

Kupka MS, Ferraretti AP, de Mouzon J, Erb K, D'Hooghe T, Castilla JA, et al. Assisted reproductive technology in Europe, 2010: results generated from European registers by ESHRE. *Human Reproduction* 2014;**29**(10):2099–113.

Mathur 2000

Mathur RS, Akande AV, Keay SD, Hunt LP, Jenkins JM. Distinction between early and late ovarian hyperstimulation syndrome. *Fertility and Sterility* 2000;**73**(5):901–7.

Navot 1992

Navot D, Bergh PA, Laufer N. Ovarian hyperstimulation syndrome in novel reproductive technologies: prevention and treatment. *Fertility and Sterility* 1992;**58**(2):249–61.

Rabau 1967

Rabau E, David A, Serr DM, Mashiach S, Lunenfeld B. Human menopausal gonadotropins for anovulation and sterility. Results of 7 years of treatment. *American Journal of Obstetrics and Gynecology* 1967;**98**(1):92–8.

Rizk 1999

Rizk B, Aboulghar, MA. Classification, pathophysiology and management of ovarian hyperstimulation syndrome. In: Brinsden P editor(s). *In-Vitro Fertilization and Assisted Reproduction*. New York, London: The Parthenon Publishing Group, 1999:131–155.

Schenker 1978

Schenker JG, Weinstein D. Ovarian hyperstimulation syndrome: a current survey. *Fertility and Sterility* 1978;**30**(3):255–68.

Schenker 1994
Schenker JG, Ezra Y. Complications of assisted reproductive techniques. *Fertility and Sterility* 1994;**61**(3):411–22.

Schünemann 2013
Schünemann H, Brozek J, Guyatt G, Oxman A (editors). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated March 2013. http://gdt.guidelinedevelopment.org/central_prod/_design/client/handbook/handbook.html (accessed 15 November 2015).

Shea 2007
Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology* 2007;**7**:10.

Stewart 1997
Stewart JA, Hamilton PJ, Murdoch AP. Thromboembolic disease associated with ovarian stimulation and assisted conception techniques. *Human Reproduction* 1997;**12**(10):2167–73.

* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Clinical classification of ovarian hyperstimulation syndrome (OHSS)

Study	Mild	Moderate	Severe	
Rabau 1967	Grade 1: oestrogen > 150 µg and pregnanediol > 10 mg 24 hr Grade 2: Grade 1 + enlarged ovaries and possibly palpable cysts Grade 1 and 2 were not included under the title of mild OHSS	Grade 3: grade 2 + confirmed palpable cysts and distended abdomen Grade 4: grade 3 + vomiting and possibly diarrhoea	Grade 5: grade 4 + ascites and possibly hydrothorax	Grade 6: grade 5 + changes in blood volume, viscosity and coagulation time
Schenker 1978	Grade 1: oestrogen > 150 µg/24 hr and pregnanediol > 10 mg 24 hr Grade 2: Grade 1 + enlarged ovaries, sometimes small cysts	Grade 3: grade 2 + abdominal distension Grade 4: grade 3 + nausea, vomiting and/or diarrhoea	Grade 5: grade 4 + large ovarian cysts, ascites and/or hydrothorax	Grade 6: marked haemoconcentration + increased blood viscosity and possibly coagulation abnormalities
Golan 1989	Grade 1: abdominal distension and discomfort Grade 2: Grade 1 + nausea, vomiting and/or diarrhoea, enlarged ovaries 5 cm to 12 cm	Grade 3: grade 2 + ultrasound evidence of ascites	Grade 4: grade 3 + clinical evidence of ascites and/or hydrothorax and breathing difficulties	Grade 5: grade 4 + haemoconcen- tration, increase blood viscosity, coagulation abnormality and diminished renal perfusion
Navot 1992	NA	NA	Severe OHSS: variable enlarged ovary; massive ascites ± hydrothorax; Hct > 45%; WBC > 15,000; oliguria; creatinine 1.0 to 1.5; creatinine clearance ≥ 50 mL/min; liver	Critical OHSS: variable enlarged ovary; tense ascites ± hydrothorax; Hct > 55%; WBC > 25,000; oliguria; creatinine > 1.6; creatinine clearance

Table 1. Clinical classification of ovarian hyperstimulation syndrome (OHSS) (*Continued*)

			dysfunction; anasarca	< 50 mL/min; renal failure; thromboembolic phenomena; ARDS
Aboulghar 2003	NA	Discomfort, pain, nausea, distension, ultrasonic evidence of ascites and enlarged ovaries, normal haematological and biological profiles	Grade A: dyspnoea, oliguria, nausea, vomiting, diarrhoea, abdominal pain, clinical evidence of ascites, marked distension of abdomen or hydro-thorax, US showing large ovaries and marked ascites, normal biochemical profile Grade B: grade A plus massive tension ascites, markedly enlarged ovaries, severe dyspnoea and marked oliguria, increased Hct, elevated serum creatinine and liver dysfunction	Grade C: complications as respiratory distress syndrome, renal shut-down or venous thrombosis

Table adapted from Aboulghar 2003
Abbreviations: ARDS = acute respiratory distress syndrome; Hct = haematocrit; US = ultrasound; WBC = white blood cells.

Table 2. AMSTAR ratings

1	Was an 'a priori' design provided? (Yes: the review authors established the research question and inclusion criteria before conducting the review.) *
2	Was there duplicate study selection and data extraction? (Yes: at least two people independently extracted the data and the review authors reported the method for reaching consensus if disagreements arose.)
3	Was a comprehensive literature search performed? (Yes: the review authors searched at least two electronic sources; they provided details of the databases, years searched and search strategy; and also searched the reference lists of included studies and specialized registers, and contacted experts.)
4	Was status of publication used as an inclusion criterion? (Yes: the review authors stated that they excluded studies from the review based on publication status. No: review authors searched for reports irrespective of publication type. They did not exclude reports from the systematic review based on publication.)
5	Was a list of studies (included and excluded provided)? (Yes: the review authors provided a list.)
6	Were the characteristics of the included studies provided? (Yes: the review authors provided data on participants, interventions and outcomes, and reported the range of relevant characteristics.)

Table 2. AMSTAR ratings (*Continued*)

7	Was the scientific quality of the included studies assessed and reported? (Yes: the review authors reported predetermined methods of assessing quality.)
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? (Yes: the review authors used the quality and limitations of included studies in the analysis, conclusions and recommendations of the review.)
9	Were the methods used to combine the findings of studies appropriate? (Yes: if results were pooled statistically, the review authors assessed heterogeneity and used it to help decide which statistical model to use. If heterogeneity was present, the review authors considered the appropriateness of combining studies.)
10	Was the likelihood of publication bias assessed? (Yes: the review authors explicitly considered and assessed publication bias.)
11	Was the conflict of interest stated? (Yes: the review authors clearly acknowledged the sources of funding and support.)

* Possible answers to all questions are: Yes, No, Can't answer and Not applicable.

CONTRIBUTIONS OF AUTHORS

Dr Mourad, Dr Brown and Professor Farquhar all contributed to the development of this Cochrane protocol.

DECLARATIONS OF INTEREST

Dr Mourad, Dr Brown and Professor Farquhar are authors of reviews that might be considered for inclusion. The overview authors have no conflicts of interest that relate to industry.

SOURCES OF SUPPORT

Internal sources

- Department of Obstetrics and Gynaecology, University of Auckland, New Zealand.

This department provided infrastructure support.

External sources

- None, Other.