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IUI: review and systematic assessment of the evidence that supports global recommendations

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BACKGROUND: IUI with or without ovarian stimulation (OS) has become a first-line treatment option for many infertile couples, worldwide. The appropriate treatment modality for couples and their clinical management through IUI or IUI/OS cycles must consider maternal and perinatal outcomes, most notably the clinical complication of higher-order multiple pregnancies associated with IUI–OS. With a current global emphasis to continue to decrease maternal and perinatal mortality and morbidity, the World Health Organization (WHO) had established a multi-year project to review the evidence for the establishment of normative guidance for the implementation of IUI as a treatment to address fertility problems, and to consider its cost-effectiveness for lower resource settings.

OBJECTIVE AND RATIONALE: The objective of this review is to provide a review of the evidence of 13 prioritized questions that cover IUI with and without OS. We provide summary recommendations for the development of global, evidence-based guidelines based upon methodology established by the WHO.

SEARCH METHODS: We performed a comprehensive search using question-specific relevant search terms in May 2015. For each PICO (Population, Intervention, Comparison and Outcomes) drafted by WHO, specific search terms were used to find the available evidence in MEDLINE (1950 to May 2015) and The Cochrane Library (until May 2015). After presentation to an expert panel, a further hand search of references in relevant reviews was performed up to January 2017. Articles that were found to be relevant were read and analysed by two investigators and critically appraised using the Cochrane Collaboration's tool for assessing risk of bias, and AMSTAR in case of systematic reviews. The quality of the evidence was assessed using the GRADE system. An independent expert review process of our analysis was conducted in November 2016.

OUTCOMES: This review provides an assessment and synthesis of the evidence that covers 13 clinical questions including the indications for the use of IUI versus expectant management, the sperm parameters required, the best and optimal method of timing and number of inseminations per cycle, prevention strategies to decrease multiple gestational pregnancies, and the cost-effectiveness of IUI versus IVF. We provide an evidence-based formulation of 20 recommendations, as well as two best practice points that address the integration of methods for the prevention of infection in the IUI laboratory. The quality of the evidence ranges from very low to high, with evidence that may be decades old but of high quality, however, we further discuss where critical research gaps in the evidence remain.

WIDER IMPLICATIONS: This review presents an evidence synthesis assessment and includes recommendations that will assist health care providers worldwide with their decision-making when considering IUI treatments, with or without OS, for their patients presenting with fertility problems.

Key words: IUI / ovarian stimulation / expectant management / infertility / fertility problems / prevention of multiple pregnancies / assisted reproduction / evidence-based recommendations / gonadotrophins / clomiphene citrate

Introduction

Women and men may have fertility problems that can only be resolved through medically assisted interventions. The World Health Organization (WHO) invited experts to help to develop and provide draft recommendations based upon the available evidence for six prioritized areas, including the fertility treatment IUI with or without ovarian stimulation (OS). First, an IUI evidence synthesis team was formed and tasked to assist the WHO to formulate questions through a predefined process (Handbook for Guideline Development (World Health Organization, 2014)). Prioritization of questions was accomplished and stakeholders considered global relevance that included the importance of cost-effectiveness, safety and affordability. The evidence synthesis team was also asked if the quality of the evidence identified was sufficiently robust and complete. Could important research gaps be identified that might alter the future use of IUI? Was it possible to implement IUI procedures that also prevented complications such as (high-order) multiple pregnancies, effectively preventing maternal/perinatal morbidity and mortality? Thus, this review provides an overview of the process applied and the draft evidence-based recommendations generated plus discussions that expose key research gaps.

In this review OS refers to OS with gonadotropins unless stated otherwise.

Why should IUI be used as an intervention to resolve fertility problems?

The rationale of IUI

Decades ago very disappointing results were reported regarding the capacity of motile spermatozoa to reach the oviduct after intercourse with an important reduction in sperm number along the length of the female reproductive tract (Settlage *et al.*, 1973; Mortimer and Templeton, 1982). According to Settlage *et al.* (1973) only 0.1% of spermatozoa placed in the upper vagina were also present in the cervical canal, 1 h after insemination. Even more striking was the finding that only 1 in every 14 million motile sperm deposited in the vagina reached the site of fertilization in the oviduct.

The rationale behind IUI is to increase this gamete density at the site of fertilization even when sperm or cervical mucus abnormalities are present. The increasing use of IUI in idiopathic and male infertility is mainly the result of the refinement of techniques for the preparation of washed motile spermatozoa, as used in IVF procedures.

In order to improve the quality and outcome of IUI procedures, there is a need for simple, inexpensive, reliable and safe sperm preparation techniques that isolate and select sperm cells with intact functional and genetic properties, including normal morphology, minimal DNA damage and intact cell membranes with functional binding properties (World Health Organization, 2010). Seminal fluid acts as a

transport medium for sperm, prostaglandins, ions and anti-oxidants. Cells other than spermatozoa are also present in the ejaculate, including epithelial cells from the urinary tract, prostate cells, spermatogenic cells and leucocytes. Reactive oxygen species, either produced by the different germ cells or by leucocytes, can be detrimental for the fertilizing potential of the spermatozoa (Aitken and Clarkson, 1987; Aitken and De Iuliis, 2010). The seminal plasma also contains decapitation factor(s) that need to be removed for complete capacitation of the spermatozoa (Mortimer, 2000). This process of capacitation is essential for both fertilization *in vivo* or *in vitro*, and hence spermatozoa to be used in IUI must be separated from the seminal plasma and its decapacitating factors. Preparation of human semen samples should also result in the removal of non-viable spermatozoa, leucocytes and/or bacteria, and other sources of contamination. Donor sperm is mainly cryopreserved and kept in quarantine for at least 6 months to prevent the transfer of infectious diseases. Thawed sperm is mostly used for IUI as compared to intracervical insemination, as supported by older evidence (Besselink *et al.*, 2008).

IUI in a historical perspective

Over the last centuries the popularity of IUI has varied tremendously (Ombelet and Van Robays, 2010). After the first description of spermatozoa by Antoni van Leeuwenhoek and his assistant Johannes Ham in 1678 it took more than 100 years before the first IUI (in canine) was reported by Lazzaro Spallanzani in 1784 (Kremer, 1979; Moll, 2006). This insemination resulted in the birth of three puppies 62 days later (Belonoschkin, 1956; Zorgniotti, 1975). Before this, in 1770, John Hunter described the first case of human intravaginal insemination because of severe hypospadias. In the mid-1800s J. Marion Sims reported on 55 intravaginal inseminations. Only one pregnancy occurred, which is probably explained by the fact that Sims believed that ovulation occurred during menstruation. The first reports on human IUI originated from Guttmacher (1943) and Kohlberg (1953a, 1953b). This represents the start of a new era in assisted reproduction.

Dr Jerome K. Sherman (1953) introduced a simple method of preserving human sperm using glycerol and reported the first successful human pregnancy with frozen sperm in 1953. Due to the hostile climate for donor insemination (DI) at the time, nearly a decade passed before the first successful birth from frozen sperm was announcement in public (Sherman, 1964).

The renewed interest in sperm washing procedures owing to the introduction of IVF could be regarded as one of the most important milestones in the history of IUI (Steptoe and Edwards, 1978). Sunde *et al.* (1988) reported the data of a European collaborative report on IUI describing 127 births in 20 clinics as a result of IUI with pretreated sperm. In 1989 the results of the first prospective controlled trials were published describing the value of IUI in case of cervical hostility and male factor infertility (Friedman *et al.*, 1989; te Velde *et al.*, 1989). The evidence-based value of IUI as a treatment for cervical hostility, male factor and unexplained infertility was first described in 2004 (Cohlen, 2005). Recent reports of Bensdorp *et al.* (2015) and Tjon-Kon-Fat *et al.* (2015) have shown that according to the results of a prospective multi-centre trial, IUI–OS is recommended as the most cost-effective strategy for mild male factor or unexplained infertility with a poor prognosis of becoming pregnant with normal coitus (Bensdorp *et al.*, 2015; Tjon-Kon-Fat *et al.*, 2015).

Insemination of semen in humans was originally developed to help heterosexual couples to become pregnant in case of severe male factor infertility of a physical or psychological nature, however, insemination with homologous semen nowadays is most commonly used for unexplained and mild male factor infertility. In the previous century, DI was mainly used for male infertility caused by azoospermia or very low sperm count and for inherited genetic diseases linked to the Y-chromosome. At present, DI is commonly used for individual women who desire a pregnancy.

Globalization of IUI

Despite the lack of IUI registration or incorporation of IUI procedures reported within IVF/ICSI registries in most countries, it is possible to assume that IUI is one of the, if not the, most popular methods of assisted reproduction worldwide, for different reasons. Since IUI is a simple and non-invasive technique, it can be performed without expensive infrastructure resulting in IUI becoming the only treatment for male and unexplained infertility in resource-poor countries where IVF is either not available or not accessible for the majority of the population, owing to high costs (Ombelet *et al.*, 2008). In addition, it can be provided as a safe and simple treatment with minimal risks when appropriately monitored. These factors are responsible for a high couple compliance in IUI programmes when compared to IVF (Homburg, 2003). In a structured review of papers dealing with the value of sperm parameters on the prediction of IUI success, 55 studies could be selected: 21 from Europe, 18 from Asia, 11 from the USA, 4 from Africa and 1 from Australia, showing the worldwide application of IUI in male infertility (Ombelet *et al.*, 2014).

Differences in multiple pregnancy rates

Unacceptable high multiple pregnancy rates (MPR) after IUI with OS treatment are described; this can most often be attributed to uncontrolled use of gonadotrophins for OS prior to insemination. Considering the increased risk for multiple pregnancies after IUI, there are significant differences observed in the MPR in Europe versus the USA. Using data from the National ART Surveillance System (NASS) of the Centres for Disease Control and Prevention, it was shown that from 2004 onwards non-IVF fertility treatments including 'OS and IUI' became the most highly associated treatment procedure with triplet and higher-order births in the USA (Kulkarni *et al.*, 2013). The 2011 European data mentioned a mean twin pregnancy rate of 9.7% and a 0.6% triplet pregnancy rate after IUI with homologous semen. However, these European data have to be compared with 18.6% twins and 0.6% triplets for IVF which includes ICSI (Kupka *et al.*, 2016). For example, a study on IUI pregnancy rates in the Netherlands showed that in the year 2003, ~28 500 IUI cycles were performed as compared to 9761 IVF cycles, and the MPR following IUI was estimated to be 9% as compared to 21.6% after IVF (Steures *et al.*, 2007). Because economic aspects of provision of infertility interventions will surely become a major challenge in the near future, the lack of high quality studies on cost-effectiveness comparing the different methods of assisted reproduction represent a glaring research gap and will be discussed later on in this paper.

Lack of registration

Owing to the lack of registration of IUI and linkages to maternal health outcomes, data on indications, success rates and complications

associated with IUI are scarce and in most countries not available or incomplete.

For example, data on ART generated from European national registries by ESHRE have been published since 2004, describing various ART outcomes since the year 2000. However, IUI data were not collected by ESHRE until 2009, with the first publication including IUI data in the year 2013 (Ferraretti *et al.*, 2013). Fresh IVF (135 621 reported cycles) and ICSI (266 084 reported cycles) resulted in a multiple delivery rate of 20.2%. Although incomplete, the data on 162 843 reported IUI cycles showed an 8.3% delivery rate per cycle with a multiple delivery rate of 11.1%.

Different factors can explain why the registration of IUI data has only been established many years after IVF registration. In the early years of IVF, not all fertility specialists believed in the added value of IUI, especially if male factor infertility was involved. In addition, if IUI is practiced within general gynaecological services, collection of data from fertility centres alone will not be able to capture all procedures and their resultant pregnancies. Therefore, potentially due to the lack of complete data from all health providers providing IUI, when compared to IVF/ICSI it has been shown that individual IUI success rates appear to be low: even now the delivery rate in the European register for the year 2011 was 21.7% per aspiration for IVF (130 324 cycles) and 19.9% per aspiration for ICSI. In the same year (2011) the delivery rate was 8.3% for IUI using homologous semen (174 390 cycles) and 12.2% for IUI with donor semen (41 151 cycles) (Kupka *et al.*, 2016).

In addition, it is critical to note that results on the cumulative pregnancy rate after three or more IUIs were not often reported in the registries, with only a few research articles reporting on the value of IUI from a point of view of cost-effectiveness (Goverde *et al.*, 2000; Philips *et al.*, 2000).

When and how should IUI be used as an intervention to resolve fertility problems?

In order to address the when and how to provide IUI, a list of PICO (Population, Intervention, Comparison and Outcomes) questions was raised and prioritized through the WHO processes. We include the evidence-based draft recommendations that resulted from our evidence synthesis, as described below.

Methods

For each PICO that was drafted by the WHO, specific search terms were used to find the available evidence in MEDLINE (1950 to May 2015) and The Cochrane Library (until May 2015). We also hand searched references of relevant reviews and included studies, to find other potentially eligible studies. One investigator (A.B.) read all the abstracts of articles that were found by the search. Articles that were found to be relevant were read and analysed by two investigators (A.B. and B.C.) and critically appraised using The Cochrane Collaboration's tool for assessing risk of bias and AMSTAR in case of systematic reviews. The quality of the evidence was assessed using the GRADE system (Guyatt *et al.*, 2011). When recent updated systematic reviews were identified, we considered these the best available evidence, although we additionally searched for new randomized trials that were not (yet) included in the systematic review. Whether this new evidence would alter the outcome of the systematic reviews was assessed by analysing the outcomes and quality of the evidence by two investigators (A.B. and B.C.) and by discussion at the WHO guideline consensus meeting. Draft recommendations were made by the authors and presented at the first stakeholder WHO consensus meeting in September 2015. When no evidence or low quality evidence was available only, good practise points were formulated at the WHO expert meeting.

The final recommendations that are decided upon will be published by the WHO after extensive processes following WHO procedures which include independent review by individuals with relevant expertise as well as stakeholders, including patient groups. In this review generated by our evidence synthesis team identified by the WHO, these PICO questions will be briefly reviewed. Furthermore, the prevention of complications such as multiple pregnancies, key contributors to maternal and perinatal morbidity and mortality, will be discussed in more detail. During the process of identifying, retrieving, summarizing and grading all relevant studies on IUI it was also possible to identify several research gaps.

PICO questions with draft recommendations and identified research gaps

The evidence and draft recommendation for each PICO question are shown in Table I and summarized in Fig. 1.

Question 1: What are the indications for IUI versus intercourse or expectant management in infertile couples and when should treatment be initiated?

Draft recommendations

- In couples with unexplained infertility with a prognosis of becoming pregnant without assistance within the next 12 months (estimate >30%), IUI could be postponed for at least 6 months.
- In couples with solely a poor sperm quality in the male partner, it is not recommended either for or against use of IUI.
- In couples with unexplained infertility, IUI in natural cycles should not be offered although this recommendation is based on one trial only.

After 36 years of publication of the first RCT by Kerin *et al.* (1984), the indications for IUI remain a subject of debate. Widely used indications for IUI are unexplained infertility (including mild endometriosis), male factor infertility and female cervical factor. One might pose the question whether the global use of IUI is still substantiated by high quality evidence. Nowadays the evidence from earlier randomized trials, supporting the use of IUI for male and unexplained infertility, is often considered of too low quality. On the other hand, questionnaires among patients show that patients prefer IUI, with or without OS, over expectant management when their chance of spontaneous conception is below 50 or 40%, respectively, and they prefer IUI over IVF up to six treatment cycles (Steures *et al.*, 2005; van Weert *et al.*, 2007). Furthermore, clinicians seem to believe in IUI as a first line treatment option, because only 4% followed the National Institute for Health and Clinical Excellence (NICE) guidelines that advised to stop IUI in cycles with OS (Kim *et al.*, 2015).

Unexplained infertility and IUI

The evidence for IUI in unexplained infertility was analysed by a Cochrane systematic review (Veltman-Verhulst *et al.*, 2012). It was

Table I IUI: Summary of draft recommendations and strength of evidence.

Clinical questions	Recommendations through assessment of developed PICO question and associated evidence analysis	Strength of the evidence
1. What are the indications for IUI versus intercourse or expectant management in infertile couples and when should treatment be initiated	In couples with unexplained infertility with a prognosis of becoming pregnant without assistance within the next 12 months (estimate >30%), IUI could be postponed for at least 6 months	High
	In couples with unexplained infertility and men with a total motile sperm count (TMSC) >10 million and a prognosis of spontaneous pregnancy <30% within a year, it is recommended that IUI plus ovarian stimulation (OS) is the treatment of first choice.	High
	In couples with solely a poor sperm quality in the male partner, it is not recommended either for or against use of IUI.	High
2. When is OS required in an IUI cycle?	In couples with unexplained infertility and men with a TMSC above 10 million, IUI should be combined with OS to improve live birth rates.	Moderate
3. What is the influence of sperm quality on IUI outcome? Can we define threshold levels for successful IUI?	It is not possible to define clear lower cut-off levels of pre- or post-wash sperm parameters below which IUI should be withheld.	Low to moderate
4. When is the best timing of insemination in an IUI cycle? What is the optimal method of timing in natural or stimulated IUI cycles?	Providers can determine the method of triggering in IUI stimulated with gonadotrophins as there is no evidence to recommend for or against a method.	Moderate
	Providers can determine the method of timing IUI in natural cycles (no OS) as there is no evidence to recommend for or against a method.	Moderate
	If a HCG injection is used, single IUI can be performed any time between 24 and 40 hours after HCG injection without compromising pregnancy rates.	Moderate
	IUI in a natural (not ovarian stimulated) cycle should be performed 1 day after LH rise.	Moderate
5. What is the value of 'fallopian sperm perfusion' (FSP) compared to IUI.	The intervention FSP, when compared to IUI, should not be the treatment of choice.	High
6. What is optimal number of inseminations per cycle?	In both unexplained and male infertility there is insufficient evidence that the intervention, a double IUI, within the same cycle will lead to better pregnancy rates than a single IUI within a cycle.	Moderate
	Women undergoing IUI should be offered a single insemination per cycle.	Moderate
7 Is there a benefit of bed rest after IUI?	Women undergoing IUI, should have 10 to 15 minutes of bed rest after an insemination.	Moderate
8. What is the ultimate number of consecutive IUI cycles per couple/woman in which pregnancy rates still increase significantly?	In couples with an indication for IUI at least three consecutive IUI cycles should be performed.	Moderate
	There is insufficient evidence to recommend a maximum number of IUI treatment cycles.	Moderate
9. Which semen preparation technique used yields the best results (in terms of pregnancy rates) for IUI?	According to the available evidence, it is not possible to recommend any semen preparation technique over another (swim-up, gradient, wash and centrifugation).	Low
10. What is the cost-effectiveness of IUI versus IVF/ICSI	In couples with unexplained infertility and men with a TMSC of >10 million and a prognosis of a pregnancy without assistance <30% within a year, at least three cycles of IUI–OS is the most effective option.	High
11. How can you prevent infections in a IUI laboratory?	Good practice point: Couples and individuals undergoing IUI and males providing semen samples for IUI should be screened for infectious agents based on local, regional and national standards and regulations.	Very low
12. How can you prevent multiple pregnancies and ovarian hyperstimulation syndrome in an IUI programme?	In order to prevent high rates of multiple gestation pregnancies in IUI–OS, IUI should be withheld when more than two dominant follicles >15 mm or more than five follicles >10 mm at the time of HCG injection or LH surge are present.	Moderate
	When gonadotrophins are used in IUI, regiments with 75 IU or lower should be used because higher doses have similar pregnancy rates but increase multiple pregnancy rates.	High

Continued

Table I *Continued*

Clinical questions	Recommendations through assessment of developed PICO question and associated evidence analysis	Strength of the evidence
	Clomiphene citrate or tamoxifen are acceptable alternatives to low dose gonadotrophins for low multiple pregnancy and birth rates and with lesser costs, although at a lower live birth rate than with gonadotrophins.	Moderate
	Addition of GnRH agonist to gonadotrophins in IUI–OS is not recommended because there is no increase in pregnancy rate despite increased multiple pregnancy rates and increased costs.	Moderate
	Good practice point: As an alternative to cycle cancelation, aspiration of excess follicles at the time of HCG injection or LH surge might be additional options for reducing the risk of multiple pregnancy in IUI–OS.	Low
13. Is there a different perinatal outcome for IUI pregnancies and how does this perinatal outcome differ from normal coitus and IVF/ICSI pregnancies?	Individuals with infertility undergoing treatment with IUI–OS should be informed about a possible increased risk for preterm birth and low birthweight in singletons and twin pregnancies when compared to pregnancies in fertile couples not requiring assistance. (IVF/ICSI outcome comparisons are assessed in the IVF/ICSI prioritized guideline.)	Very low

found that IUI alone does not seem to improve live birth rates significantly in natural cycles [odds ratio (OR) = 1.60, 95% CI: 0.92–2.78] but this conclusion was based upon one trial only. Although this one trial by Bhattacharya *et al.* (2008) was graded as high quality, the findings should preferably be confirmed in other randomized trials.

Male infertility and IUI

IUI for male infertility is still under debate. One of the major problems in male subfertility is the lack of validated definitions and strict cut-off values of sperm parameters to make a clear distinction between mild, moderate and severe male infertility. A Cochrane systematic review by Bensdorp *et al.* (2007) analysed IUI (with or without OS) in patients with male infertility. Since there was no harmonized definition, all studies with various definitions of male infertility were included. The authors of this review concluded that there was insufficient evidence to recommend for or against IUI (with or without OS) in male infertility, mainly because large high quality randomized trials are lacking (Bensdorp *et al.*, 2007). A recently published large RCT showed us that IUI–OS is non-inferior to IVF in couples with unexplained and mild male infertility, defined as a total motile sperm count (TMSC) of 3–10 million. However, the number of included couples in this study with mild male infertility was relatively low (only 10% of total inclusions) (Bensdorp *et al.*, 2015). Therefore, we were not able to recommend for or against IUI in couples with solely poor sperm quality.

Cervical factor infertility and IUI

A Cochrane systematic review by Helmerhorst *et al.* (2005) concluded that IUI with or without OS is not an effective treatment of cervical factor infertility (Helmerhorst *et al.*, 2005). Although more recent studies were published on this subject, most clinicians no longer support performing post-coital testing as part of a fertility check-up. Therefore, cervical factor is less often diagnosed, however, it is recognized that good practice indicates that for heterosexual couples where the male partner refuses semen analysis (e.g. for personal or cultural reasons) the post-coital test can be used to suggest that further evaluation of male factor infertility is indicated (evidence-based consensus to support this draft recommendation is reviewed by the WHO evidence synthesis team which addressed female infertility diagnosis and management).

Research gaps

With the lack of high quality randomized trials investigating the effectiveness of IUI in male infertility, the question whether IUI should be applied in male infertility remains. Furthermore, a clear and generally accepted definition of mild, moderate or severe male infertility, terms often used in IUI studies, is missing. Ideally, the results of the trial by Bhattacharya *et al.* (2008) regarding IUI in unexplained infertility should be confirmed.

Question 2: When is OS required in an IUI cycle?

Draft recommendations

- In couples with unexplained infertility with a prognosis of becoming pregnant without assistance within the next 12 months (estimate >30%), IUI could be postponed for at least 6 months.
- In couples with unexplained infertility and men with a TMSC above 10 million, IUI should be combined with OS to improve live birth rates.
- In couples with unexplained infertility and men with a TMSC > 10 million and a prognosis of spontaneous pregnancy <30% within a year, it is recommended that IUI plus OS are the treatments of first choice.

The rationale of OS is to achieve multifollicular growth. Van Rumste *et al.* (2008) showed that multifollicular growth resulted in significantly higher pregnancy rates compared to monofollicular growth (15 versus 8.4%). Compared to one dominant follicle, pregnancy rates increased by a further 5, 8 and 8% when two, three or four dominant follicles were present, respectively (van Rumste *et al.*, 2008).

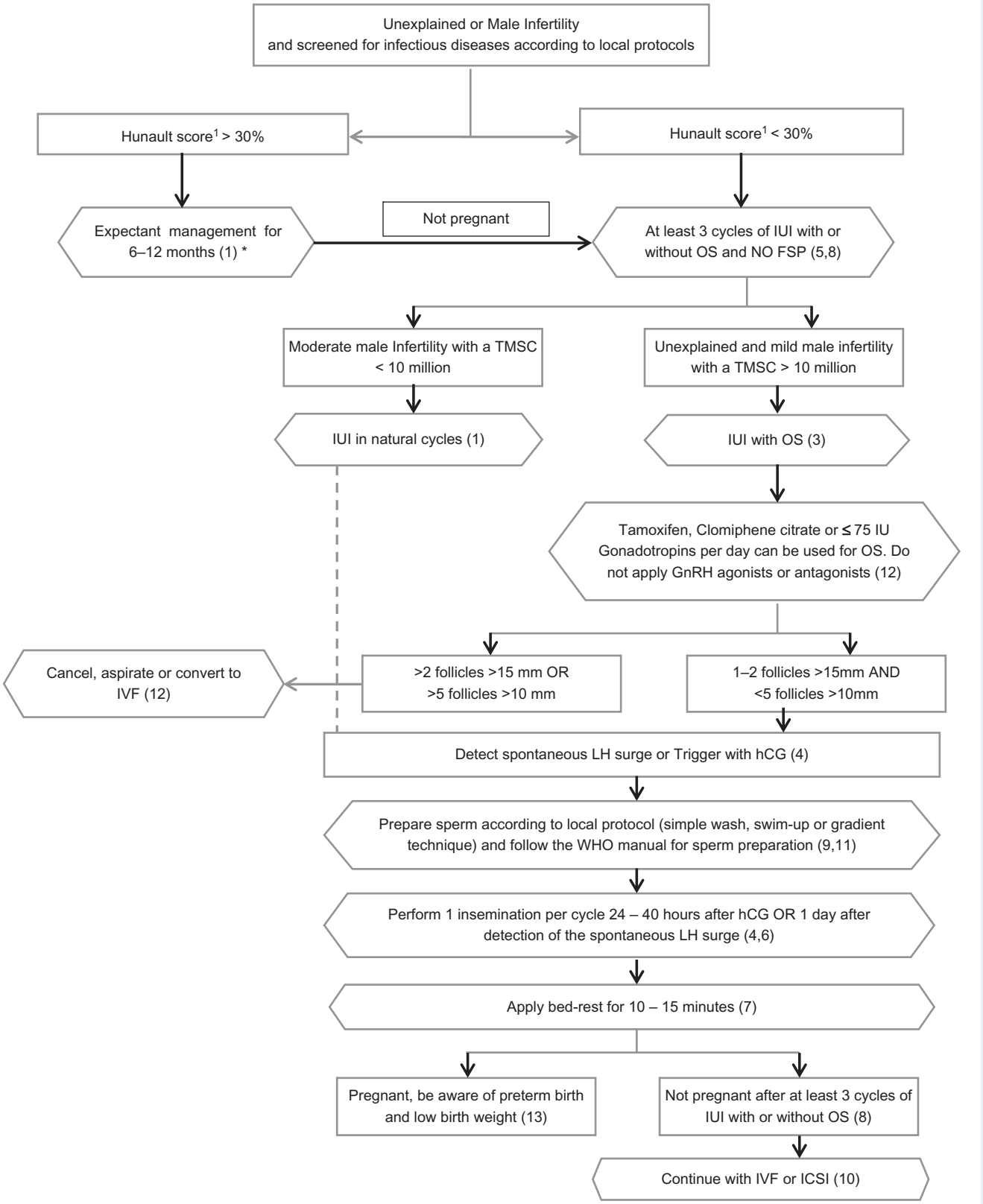

Figure 1 Flowchart for IUI with or without ovarian stimulation. FSP, fallopian sperm perfusion. *numbers between brackets refer to the PICO (question mentioned in the text). [1]https://www.freya.nl/probability.php.

Cohlen *et al.* conducted a RCT comparing IUI with or without OS in male infertility. In couples with a TMSC < 10 million, OS did not improve pregnancy outcome, while it did in couples with a TMSC > 10 million (high level of evidence) (Cohlen *et al.*, 1998).

For unexplained infertility, the Cochrane systematic review of Veltman-Verhulst *et al.* (2012) showed us that IUI without OS does not positively influence pregnancy outcomes. Adding OS to IUI significantly increases live birth rates in couples with unexplained infertility (OR = 2.07, 95% CI: 1.22–3.50, *n* = 396). However, when there is still a reasonable chance of becoming pregnant through normal intercourse (Hunault score 30–40%) (Hunault *et al.*, 2004, 2005), expectant management for at least 6 months should be the first option because in these good prognosis couples, IUI in cycles with OS does not improve live birth rates significantly [relative risk (RR) = 0.85, 95% CI: 0.63–1.1, *n* = 253] (Veltman-Verhulst *et al.*, 2012). Furthermore, OS is a well-known risk factor for (high order) multiple pregnancy as described above.

Recently the results of the TUI study were presented at ESHRE 2017, where IUI–OS cycles with clomiphene citrate were randomly compared to expectant management in couples with unexplained infertility and a Hunault score below 30% (Farquhar *et al.*, 2017). This trial showed that IUI–OS significantly increased cumulative live birth rates compared to expectant management (OR with 95% CIs: 3.4, 1.7–6.8). It remains unclear whether this positive effect is due to the OS, the insemination or the combination of both.

Another additional, more recent article was identified and screened to be relevant (Bensdorp *et al.*, 2015). Bensdorp *et al.* (2015) conducted a RCT in which they analysed the cost-effectiveness between three cycles of IVF with single embryo transfer (SET), six cycles of IVF in a modified natural cycle (MNC) and six cycles of IUI–OS in patients with unexplained or mild male infertility with a Hunault score <30%. Couples with a pre-wash TMSC above 10 million were classified as unexplained infertility, while a TMSC between 3 and 10 million was classified as mild male infertility. Birth rates of a healthy child in the IVF–SET group, the IVF–MNC group and the IUI–OS group were 52, 43 and 47%, respectively (RR = 1.1 [95% CI: 0.9 1–1.34] comparing IVF–SET to IUI–OS, and RR = 0.91 [95%CI: 0.73–1.14] comparing IVF–MNC to IUI–OS).

MPR per ongoing pregnancy were 6, 5 and 7%, respectively (Bensdorp *et al.*, 2015). Some have discussed whether the non-inferiority design applied was appropriate for this randomized trial.

We therefore provided a draft evidence-based recommendation that expectant management be attempted for at least 6 months in heterosexual couples with unexplained infertility and a prognosis of becoming pregnant without assistance within the next 12 months >30%, based on the Hunault score. When this prognosis is <30%, IUI with OS is recommended in couples with unexplained infertility and men with a TMSC > 10 million as the first treatment option. The quality of the evidence found was graded as moderate to high. In the above-mentioned study, the Hunault score was used (Bensdorp *et al.*, 2015). Although this score has been validated externally (van der Steeg *et al.*, 2007) one should keep in mind that prediction models are still under debate (Leushuis *et al.*, 2009).

Research gaps

Now that it has become clear that IUI–OS is a first line treatment option for mild male and unexplained infertility, the question arises whether IUI, with or without OS, is beneficial for moderate male infertility as well. Furthermore, as mentioned above, a clear definition of mild or moderate male infertility is mandatory.

Question 3: What is the influence of sperm quality on IUI outcome? Can we define threshold levels for successful IUI?

Draft recommendations

- It is not possible to define clear lower cut-off levels of pre- or post-wash sperm parameters below which IUI should be withheld.

A recent systematic review and meta-analysis clearly presents the lack of robust evidence for clear lower cut-off levels of sperm parameters in IUI treatment. Based on very low quality of evidence, a TMSC > 1 million and a morphology > 4% are of possible prognostic value, in such a case that below these cut-off levels IUI should be withheld (Ombelet *et al.*, 2014). Van Weert *et al.* (2004) found the post-wash TMSC to be predictive for non-pregnancy but the lower cut-off levels varied tremendously between 0.8 and 5 million (van Weert *et al.*, 2004). We, therefore, could not define clear lower cut-off levels of pre- or post-wash sperm parameters below which IUI should be withheld.

Research gaps

Because the lower cut-off level of semen parameters below which IUI is no longer cost-efficient has not be clearly identified, a randomized trial comparing IUI with either conventional IVF or IVF/ICSI to define these lower cut-off levels is required before any conclusion can be drawn.

Question 4: When is the best timing of insemination in an IUI cycle? What is the optimal method of timing in natural or stimulated IUI cycles?

Draft recommendations

- Providers can determine the method of triggering in IUI stimulated with gonadotrophins as there is no evidence to recommend for or against a method.
- Providers can determine the method of timing IUI in natural cycles (no ovarian stimulation) as there is no evidence to recommend for or against a method.
- If a HCG injection is used, single IUI can be performed any time between 24 and 40 h after HCG injection without compromising pregnancy rates.
- IUI in a natural (not ovarian stimulated) cycle should be performed 1 day after LH rise.

The timing of insemination is one of the most important factors influencing the outcome of IUI (Cantineau *et al.*, 2014). There are various methods for timing IUI of which LH testing or monitoring follicle growth by ultrasound combined with HCG injection are the most applied methods. In IUI–OS, HCG injections are most often used to trigger ovulation when the dominant follicle(s) reaches a mean diameter of ~18 mm. In IUI in natural cycles, LH testing is the most applied method for timing. Less frequently used methods for timing are administration of a GnRH agonist or recombinant LH for triggering ovulation. In a RCT of Kyrou *et al.* (2012) spontaneous triggering of ovulation was associated with

significantly higher ongoing pregnancy rates compared with administration of HCG in patients undergoing IUI in natural cycles. They concluded that use of LH for timing ovulation might be the best way to maximize the probability of pregnancy for patients undergoing IUI (Kyrou *et al.*, 2012). On the other hand, a recent Cochrane systematic review was identified that had analysed the methods of timing in infertile women (Cantineau *et al.*, 2014). They found no significant difference in live birth rates between HCG injection or LH surge (OR = 1.0, 95% CI: 0.06–18, one trial, $n = 24$), urinary HCG or recombinant HCG (OR = 1.17, 95% CI: 0.68–2.03, one trial, $n = 284$) or HCG versus GnRH agonist (OR = 1.04, 95% CI: 0.42–2.6, three trials, $n = 104$ women). Regarding the method of timing, it is concluded that there is insufficient evidence to advise one method over another. The quality of the evidence was graded from low to moderate because of suspected imprecision (Cantineau *et al.*, 2014).

Regarding the actual timing of the insemination after HCG administration, randomized trials were not able to detect significant differences in clinical pregnancy or live birth rates between various time frames that range from 24 to 48 h (Claman *et al.*, 2004; AboulGheit, 2010; Rahman *et al.*, 2011). It was therefore concluded that a more flexible approach (IUI between 24 and 40 h after HCG) will not compromise pregnancy rates. The quality of the evidence was graded as moderate because of suspected imprecision.

A large well-designed RCT by Blockeel *et al.* (2014) showed that IUI in natural cycles should be performed 1 day after detection of the spontaneous LH surge. Clinical pregnancy rates were significantly higher when IUI was performed after 1 day when compared with women undergoing IUI after 2 days (19.7 versus 11.1%, RR = 1.78, 95% CI: 1.11–2.88) (Blockeel *et al.*, 2014). The analysis, however, was performed on a per cycle level. When analysing the results per participant, results were no longer significant, probably due to the limited number of included participants. The quality of the evidence is therefore graded as moderate.

Question 5: What is the value of fallopian sperm perfusion compared to IUI?

Draft recommendations

- The intervention fallopian sperm perfusion (FSP), when compared to IUI, should not be the treatment of choice.

With regard to FSP, a technique that ensures the presence of higher sperm densities in the Fallopian tubes at the time of ovulation, the recommendation of this PICO is clear. Based on a recent Cochrane systematic review (Cantineau *et al.*, 2013), without any more recent papers identified, the review was not able to show a beneficial effect of FSP on live birth rates per couple compared to IUI (OR = 0.94, 95% CI: 0.59–1.49), therefore, a draft recommendation is that IUI is the treatment of choice and the quality of this evidence was graded as high.

Question 6: What is the optimal number of inseminations per cycle?

Draft recommendations

- In both unexplained and male infertility there is insufficient evidence that the intervention, a double IUI, within the same cycle will lead to better pregnancy rates than a single IUI within a cycle.
- Women undergoing IUI should be offered a single insemination per cycle.

An assumption can be made that increasing the number of inseminations per cycle from one to two (or more) might increase the probability of a pregnancy in IUI treatment since more spermatozoa may be present at the moment of ovulation. One Cochrane systematic review and two additional relevant systematic reviews were identified after a systematic search. One additional RCT not included in one of these systematic reviews was also identified. The Cochrane systematic review (Cantineau *et al.*, 2003) found a significant difference in favour of double insemination (OR = 1.8, CI 95%: 1.4–2.4) in heterosexual couples with unexplained or male infertility. This observed effect is largely due to the contribution of one study with a weight of 66.5%; however, this study yielded an unclear risk of bias because allocation concealment was not mentioned. Another systematic review (Zavos *et al.*, 2013) compared single versus double insemination in male infertility. This review showed a significant benefit of double IUI in male infertility but, again, this effect was largely due to the same dominant study.

A third systematic review (Polyzos *et al.*, 2010) analysed double versus single insemination in unexplained infertility. This meta-analysis showed that double IUI does not result in significantly higher pregnancy rates compared with single IUI in women with unexplained infertility. This was confirmed by a more recent RCT by Rahman *et al.* (2010). The overall quality of evidence from systematic reviews was graded as moderate, mainly because of the dominating effect of one study, which did not clearly described allocation concealment. Based upon our review it can be concluded that there is insufficient evidence for a beneficial effect of double insemination in couples with unexplained infertility. Yet, in the case of male infertility, there might be a positive effect. However, this was only proven by one study with an unclear risk of bias. We therefore provide a draft recommendation that women undergoing IUI should be offered a single insemination per cycle.

Research gaps

The number of inseminations per cycle is not well defined. Future large prospective cohort studies or randomized trials for each indication separately might help clinicians to advise couples or individuals about the number of inseminations per cycle.

Question 7: Is there a benefit of bed rest after IUI?

Draft recommendations

- Women undergoing IUI, should have 10–15 min of bed rest after an insemination.

Studies on the intrauterine behaviour of spermatozoa have shown that spermatozoa already reach the Fallopian tubes within 5–10 min after insemination (Suarez and Pacey, 2006). After vaginal intercourse, a large percentage of the semen is lost by 'flow back' and no more than 1% of the spermatozoa are retained in the female reproductive tract. Thus, an assumed hypothesis is that immobilization in supine position after IUI could prevent direct loss of a large percentage of the spermatozoa and this action will improve fertility outcomes.

A systematic search resulted in the identification of two relevant articles. Saleh et al. (2000) randomized 95 heterosexual couples to either direct mobilization after IUI or immobilization in supine position for 10 min. Groups were rather unbalanced with 40 couples in the mobilization group and 55 couples in the immobilization group. After three cycles, pregnancy rates per couple were significantly higher in the immobilization group. No information on live birth rates was reported (Saleh et al., 2000).

Custers et al. (2009) performed a well-designed RCT in 391 heterosexual couples. They randomized between immobilization in a supine position for 15 min (n = 199) or immediate mobilization (n = 192) after IUI. Live birth rates after three cycles were significantly higher in the immobilization group: 27 versus 17%, respectively (RR = 1.6, 95% CI: 1.1–2.4) (Custers et al., 2009).

Recently, results of a large RCT comparing immobilization for 15 min versus direct mobilization were published. In total, 498 patients with either unexplained or mild male infertility were included. No significant difference in cumulative ongoing pregnancy rate was found (RR = 0.81, 95% CI: 0.63–1.02) (van Rijswijk et al., 2017). Pooling the data of the last two studies mentioned here showed a non-significant difference between mobilization and immobilization (OR = 1.00, 95% CI: 0.74–1.33) (Fig. 2). However, a substantial statistical heterogeneity (I^2 =88%) was found. Conclusions should therefore be drawn with caution.

The data of van Rijswijk et al. (2017) were not yet available at the time of the WHO guideline consensus meeting. Following the existing data at that time, immobilization for 10–15 min after IUI was determined to be an evidence-based draft recommendation. The overall quality of the evidence was considered to be moderate.

Question 8: What is the ultimate number of consecutive IUI cycles per couple/woman in which pregnancy rates still increase significantly?

Draft recommendations

- In couples with an indication for IUI at least three consecutive IUI cycles should be performed.
- There is insufficient evidence to recommend a maximum number of IUI treatment cycles.

The number of IUI cycles per patient is an important item to discuss when starting IUI treatment. An important factor to take into account is the pregnancy chances of additional IUI cycles. Three to six cycles of IUI has become common practice worldwide and the INeS-trial from Bensdorp et al. (2015) showed us that six cycles of IUI–OS is still cost-effective compared to direct IVF in patients with unexplained and mild male infertility (Bensdorp et al., 2015). But is there evidence to perform more cycles? Two relevant studies were found: Custers et al. (2008) and Aboulghar et al. (2001). Custers et al. (2008) performed a retrospective cohort study among 3714 women that had undergone 15 303 treatment cycles. Analysis was limited up to the ninth treatment cycle (15 245 cycles). There were 935 ongoing pregnancies, resulting in a mean ongoing pregnancy rate of 5.6% per cycle. The ongoing pregnancy rates were relatively high in the first two cycles, with 7.4 and 7.0%, respectively, compared with ~5% in higher order cycles. The cumulative clinical pregnancy rate after three cycles was 18%, which increases to 30 and 41% after six and nine cycles, respectively (Custers et al., 2008). Aboulghar et al. (2001) conducted an observational prospective study in 594 women with unexplained infertility. All participants had one to three cycles of treatment and 91 participants underwent four to six cycles of IUI–OS after failing to achieve pregnancy in the first three cycles. The clinical pregnancy rate per cycle was significantly higher in the first three cycles compared to the second three cycles ($P < 0.001$) (Aboulghar et al., 2001). The overall quality of the evidence was graded as low to moderate mainly because of the retrospective and observational design of the studies. Based on this moderate quality evidence, a draft recommendation was developed to perform at least three cycles of IUI. There is insufficient evidence to recommend a maximum number of IUI treatment cycles.

Research gaps

The number of IUI cycles that couples or single women should be offered is not well defined. Future large prospective cohort studies or randomized trials for each indication might help clinicians to advise couples or individuals when to switch to IVF.

Question 9: Which semen preparation technique used yields the best results (in terms of pregnancy rates) for IUI?

Draft recommendations

- According to the available evidence, it is not possible to recommend any semen preparation technique over another (swim-up, gradient, wash and centrifugation).

Currently, there are three semen preparation techniques that are routinely used worldwide: a simple dilution and washing technique, a swim-up technique and use of density gradient centrifugation. Whether one of these techniques is preferable was the subject of a Cochrane systematic review (Boomsma et al., 2007). Only one additional article was identified related to this subject, which has not yet been included in this Cochrane systematic review (Karamahmutoglu et al., 2014). The Cochrane systematic review analysed five RCTs comparing two or three techniques with each other. Heterogeneity concerning included indications might be suspected since they vary widely over the five studies or were not described clearly. The review found no significant difference in pregnancy rates among semen preparation techniques: swim up versus gradient technique (OR = 1.57, 95% CI :0.74–3.32); swim up versus wash and centrifugation (OR = 0.41, 95% CI: 0.41–1.10) or gradient technique versus wash and centrifugation (OR = 1.76, 95% CI: 0.71–5.44).

Karamahmutoglu et al. (2014) randomized 223 couples with unexplained and mild male infertility to either the swim up technique or the gradient technique. They found a significantly higher ongoing pregnancy rate per patient after the gradient technique compared to swim up: 23.4 versus 10.7%, respectively ($P < 0.05$). A subgroup analysis revealed that this difference was significant only in couples with unexplained infertility (Karamahmutoglu et al., 2014).

The overall quality was graded as low across all studies because of the suspected clinical heterogeneity, unclear descriptions of randomization and allocation in almost all included studies, and a low number of couples in the relevant comparisons. Therefore, according to

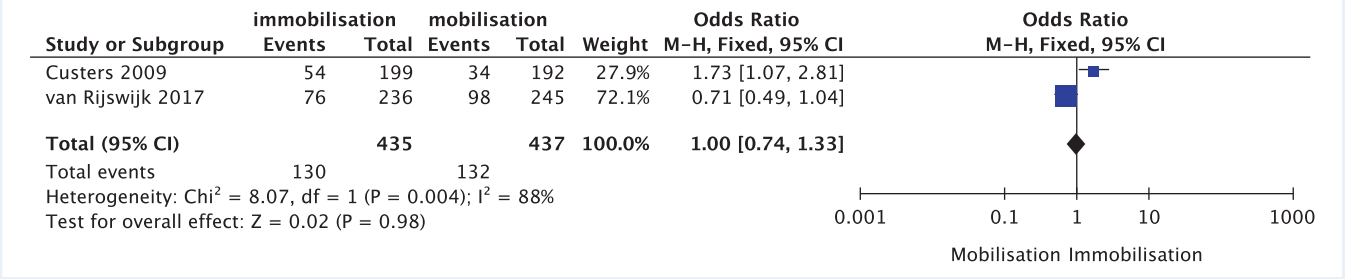

Figure 2 Meta-analysis of immobilization versus direct mobilization after IUI.

the available evidence it was not possible to recommend any semen preparation technique over another (swim-up, gradient, wash and centrifugation).

Research gaps

It remains unclear which semen preparation technique is superior (expressed as live birth rate per couple) in case of either unexplained or male infertility, therefore, a multi-center randomized trial comparing various techniques is recommended.

Question 10: What is the cost-effectiveness of IUI versus IVF/ICSI?

Draft recommendations

- In couples with unexplained infertility and men with a TMSC of >10 million and a prognosis of a pregnancy without assistance <30% within a year, at least three cycles of IUI–OS is the most effective option.

The goal of research on cost-effectiveness is to maximize health outcomes with a minimum use of resources. As costs linked to fertility care in many countries are not covered by government or insurance companies, the relative cost-effectiveness of fertility treatments is a very important consideration (Moolenaar *et al.*, 2014). Health care systems can become burdened by high costs associated with premature infants who are born from multiple gestations as a result from unregulated fertility treatments (Chambers and Ledger, 2014). Therefore, cost-effectiveness studies in fertility are important not only to the individual and family but also to health care systems and society.

Large randomized trials evaluating the relative cost-effectiveness of different infertility treatments are scarce. Moreover, the outcome most often reported is the cost per delivery of at least one child and this outcome parameter does not include the substantial costs of caring for premature infants owing to the high rates of multiple gestations. On the other hand, there is the potential to consider twins as perhaps eliminating the need for future fertility treatments for some couples or individuals. However, this comes with a clear understanding of the maternal and perinatal morbidity and mortality outcomes of twin pregnancies in a local context. All of these factors have to be considered when studying the cost-effectiveness of IUI and IUI–OS.

Many retrospective cohort cost-effectiveness studies have compared IUI, IUI–OS and conventional IVF in couples and individuals with differing causes of infertility. Most large cohort or randomized studies from individual centres have found IUI alone or IUI–OS to be the most cost-effective first line therapy for heterosexual couples with infertility linked to cervical factor, endometriosis, unexplained infertility and relatively mild male factor infertility (Van Voorhis *et al.*, 1997; Guzick *et al.*, 1998; Goverde *et al.*, 2000), but the retrospective designs make it difficult to draw firm conclusions.

For male factor infertility several studies have been identified that support the concept of threshold values for sperm parameters below which IUI becomes significantly less effective (Ombelet *et al.*, 2014; Moolenaar *et al.*, 2015). Moolenaar *et al.* (2015) studied the cost-effectiveness of interventions for male infertility according to the TMSC. A computer-simulated cohort of infertile women with a partner with a pre-wash TMSC of 0–10 million was investigated. They compared IUI with and without OS, conventional IVF and IVF/ICSI. Live birth rate was the main outcome parameter. Study results showed that above a pre-wash TMSC of 3 million, IUI is less costly than conventional IVF, and below a pre-wash TMSC of 3 million IVF/ICSI is less costly. However, these findings need to be confirmed in a large randomized trial.

Contradictory results are published concerning the cost-effectiveness of IUI in heterosexual couples with unexplained infertility (Guzick *et al.*, 1998; Goverde *et al.*, 2000; Pashayan *et al.*, 2006; van den Boogaard *et al.*, 2014; Wordsworth *et al.*, 2011). A multi-centre RCT from Scotland (graded as high quality evidence) compared the outcomes of 6 months of natural cycle IUI, clomiphene citrate stimulation followed by normal intercourse and expectant management in couples with 2 years of unexplained infertility (Bhattacharya *et al.*, 2008). Live birth rates were not significantly different with 32/193 (17%) for expectant management, 26/192 (14%) for clomiphene citrate-intercourse and 43/191 (23%) for natural cycle-IUI. The authors recommended that IUI–OS should be the subject of future trials for unexplained infertility.

Most of the large retrospective cohort studies on cost-effectiveness tend to become 'dated' as both costs and outcomes change over time. It is well known that IVF clinical pregnancy rates have increased steadily over time and high order multiple births have declined, as there has been increased emphasis on the value of transferring less embryos. These changes have made conventional IVF a more attractive option from a cost-effective point of view when compared to IUI or IUI–OS. van Rumste *et al.* (2014) stated in an economic analysis comparing IVF with elective transfer of a single embryo (eSET) with IUI–OS that when IVF–eSET would result in an ongoing pregnancy rate of more than 38%, IVF would be the preferred treatment (van Rumste *et al.*, 2014).

Only a few prospective randomized trials have compared natural cycle IUI, IUI–OS and conventional IVF.

In couples with male factor and unexplained infertility, Goverde et al. (2000) compared three treatment arms; IUI alone, HMG–IUI and conventional IVF, each performed for up to six cycles. The costs in this study were calculated through 12 weeks of pregnancy and neglecting the high costs associated with multiple gestations. According to this study, IUI was as effective as IVF, and IUI–OS did not yield higher pregnancy rates when compared with natural cycle IUI. They conclude that IUI was the most cost-effective first line therapy for the infertile heterosexual couple. Furthermore, IUI was better tolerated by couples while IVF was associated with a higher drop-out rate (Goverde et al., 2000). A big criticism against this study was an extremely low IVF pregnancy rate of 12.2% per cycle, a value that is clearly out-dated. Even after careful monitoring and using low doses of FSH (75 IU/day) the MPR was 27% in the IUI–OS arm demonstrating the risky nature of this treatment.

In the prospective randomized Fast Track and Standard Treatment (FASTT) trial, graded as high quality, Reindollar et al. (2010) addressed the important issue of time to pregnancy, both to alleviate the suffering and disappointment of infertile couples and to avoid the negative effects of aging on their reproductive potential. Only women between the ages of 21 and 39 years with unexplained infertility and a normal ovarian reserve were included in the study. Cost-effectiveness was calculated by summing all insurance charges divided by the number of women having at least one live birth. Out-of-pocket expenses (indirect costs) to the patient and the cost of multiple gestations as well as their associated increased hospital perinatal costs were included in the analysis. They concluded that clomiphene citrate-IUI seems to be the best first-line therapy for couples with unexplained infertility and, if not pregnant after three cycles, moving directly to conventional IVF was the most cost-effective approach (Reindollar et al., 2010).

As mentioned before, in a recent multi-centre randomized non-inferiority trial in the Netherlands, the effectiveness of IVF with SET or IVF in a MNC was compared with the effectiveness of IUI–OS, with an outcome indicator of a healthy live birth (Bensdorp et al., 2015). The data of this trial showed that IUI–OS was non-inferior as the two alternative strategies of IVF had a reasonably low multiple birth rate and was a more cost-effective strategy for heterosexual couples with mild male factor or unexplained infertility with a poor prognosis of becoming pregnant with expectant management. In another cost-effectiveness study on the same cohort of participants and investigating direct health care costs, it was concluded that both IVF strategies were significantly more expensive when compared with IUI–OS, without being significantly more effective (Tjon-Kon-Fat et al., 2015). Therefore, based on high quality evidence, IUI–OS is recommended as the initial treatment for mild male factor and unexplained infertility with a poor prognosis of becoming pregnant through normal coitus. As mentioned before, there are no strict criteria for how to define mild male factor. Bensdorp et al. (2015) used a TMSC of between 3 and 10 million although Cohlen et al. (1998) showed that OS was only effective in couples with a TMSC above 10 million, which they defined as mild male infertility.

A significant increase in pregnancy rates has been observed with IVF and IVF/ICSI during the last decade, however, similar increases have not been reported with IUI treatments. If the singleton delivery rate per cycle can be improved, IVF or IVF/ICSI may become the favoured first line treatment for most causes of infertility (van Rumste et al., 2014). On the other hand it might be that a better selection of patients for IUI treatment and further improvement of the methodology of IUI may increase the success rates of IUI as well, and, hopefully not at the expense of increased multiple pregnancies. At present the balance of all randomized trials still favours starting with a more conservative treatment regimen of IUI–OS before moving to IVF for the treatment of heterosexual couples with unexplained and mild male infertility.

Research gaps

Clear definitions of mild or moderate male infertility should be established before randomized trials can be started to define lower threshold levels of sperm parameters below which IUI with or without OS is no longer cost-effective and IVF or IVF/ICSI should be the first line treatment option.

Question 11: How can you prevent infections in an IUI laboratory?

Draft recommendations

- Good practice point: Couples and individuals undergoing IUI and males providing semen samples for IUI should be screened for infectious agents based on local, regional and national standards and regulations.

In this era of semen preparation, infection is a lesser problem especially when managed in higher income settings. In some lower and middle-income countries and settings prevention of infections remains a critical issue. It is generally recommended that couples and individuals undergoing IUI and/or males providing semen samples for IUI should be screened for infectious agents based on local, regional and national standards and regulations. Furthermore, facilities for performing semen preparation for IUI should meet the criteria of the WHO laboratory safety manual for reducing the risk of infection. Studies are lacking concerning the prevention and transmission of viral diseases in IUI treatment and thus these guidelines are therefore based upon best practice, guidelines associated with prevention of sexually transmitted infections, and local regulatory guidelines (good practise point).

Research gaps

We recommend to compare various sperm preparation techniques in multi-center randomized trials both for success rates concerning the elimination of transmission of infectious diseases to both partners, and to offspring (Zafer et al., 2016).

Question 12: How can you prevent multiple pregnancies and OHSS in an IUI programme?

Draft recommendation

- In order to prevent high rates of multiple gestation pregnancies in IUI–OS, IUI should be withheld when more than two dominant follicles >15 mm or more than five follicles >10 mm at the time of HCG injection or LH surge are present.

- When gonadotrophins are used in IUI, regiments with 75 IU or lower should be used because higher doses have similar pregnancy rates but increase multiple pregnancy rates.
- Clomiphene citrate or tamoxifen are acceptable alternatives to low dose gonadotrophins for low multiple pregnancy and birth rates and with lesser costs, although at a lower live birth rate than with gonadotrophins.
- Addition of GnRH agonist to gonadotrophins in IUI–OS is not recommended because there is no increase in pregnancy rate despite increased multiple pregnancy rates and increased costs.
- Good practice point: As an alternative to cycle cancellation, aspiration of excess follicles at the time of HCG injection or LH surge might be additional options for reducing the risk of multiple pregnancy in IUI–OS.

The most common side effects of IUI in cycles with OS are multiple pregnancies and ovarian hyperstimulation syndrome (OHSS). Multiple pregnancies carry increased risks of pregnancy complications and diminished neonatal outcome, such as preterm delivery, growth retardation and pre-eclampsia. High MPRs are mainly caused by multifollicular growth following OS. Measures to prevent multiple pregnancies can be divided into primary and secondary measures. Primary measures include attempting to prevent the growth of more than two to three dominant follicles, as showed by van Rumste *et al.* (2008) in a systematic review and meta-analysis including 14 studies (11 599 IUI cycles) (moderate quality of evidence). Multifollicular growth resulted in significantly higher pregnancy rates compared to monofollicular growth (15 versus 8.4%). Compared with one dominant follicle, pregnancy rates increased by a further 5, 8 and 8%, respectively, when two, three or four dominant follicles were present. Subsequently, the risk of multiple pregnancies after two, three and four dominant follicles increased, at 6, 14 and 10%, respectively (van Rumste *et al.*, 2008).

Another primary measure to prevent multiple pregnancies is to apply the appropriate drug and doses, and to individualize the doses when possible. Clomiphene citrate (100 mg per day for 5 days) or tamoxifen are acceptable alternatives to low dose gonadotrophins for low multiple birth rates and also result in lower costs, although at a lower live birth rate (Cantineau *et al.*, 2007) (moderate quality of evidence). In this systematic review of Cantineau *et al.* (2007), significantly higher pregnancy rates were found with gonadotrophins compared to anti-oestrogens (OR = 1.8, 95% CI 1.2–2.7, $n = 556$, moderate quality of evidence). Two more recent high quality evidence RCTs confirmed the outcomes of the Cochrane systematic review. In these trails, compared to clomiphene citrate, gonadotrophins showed significantly higher live birth rates and comparable, relatively low MPRs of between 3.6 and 12.5% (Erdem *et al.*, 2015; Peeraer *et al.*, 2015).

The Cochrane systematic review concluded also that there is no benefit in using Letrozole compared to clomiphene citrate (pregnancy rate per couple: OR = 1.2, 95% CI: 0.64–2.1) based upon moderate quality evidence. High level evidence shows that when gonadotrophins are used in IUI, regiments with 75 IU or lower should be used as higher doses have similar pregnancy rates while increasing MPRs (Cantineau *et al.*, 2007; Erdem *et al.*, 2015; Peeraer *et al.*, 2015). Currently an ongoing large multi-centre trial is attempting to identify factors that might predict ovarian response with low dose gonadotrophin stimulation and thus might help to individualize stimulation doses in the future (PRORAILS study, NCT01662180). Based upon moderate quality evidence, addition of GnRH agonist or antagonist is not recommended for our draft evidence-based guideline, because there is no increase in pregnancy rate despite increased MPRs and costs (Cantineau *et al.*, 2007). Cycles should be closely monitored by regular vaginal ultrasounds and when more than two to three follicles larger than 15 mm, or when more than five follicles larger than 10 mm are seen, secondary measures can be advocated (moderate quality of evidence) (van Rumste *et al.*, 2008). Of course, cycles can be cancelled and heterosexual couples should be advised to abstain from unprotected intercourse. As an alternative to cycle cancellation, aspiration of excess follicles at the time of HCG injection or LH surge, or conversion to IVF, might be additional options for reducing the risk of multiple pregnancy (good practice point). Finally, multifetal reduction can be proposed when a multiple pregnancy is observed (Dodd *et al.*, 2015). However, multifetal reduction should be prevented at all costs with the above-mentioned measures for prevention of multiple pregnancies with IUI (good practice point).

OHSS is very rare in IUI–OS treatment because the aim of the stimulation protocol should be two to three dominant follicles (van Rumste *et al.*, 2008). Regular ultrasound monitoring should identify any hyper-response early, such that HCG to induce ovulation can be withheld to avoid OHSS. With an adequate programme to prevent multiple pregnancies, OHSS should be rarely encountered.

Research gaps

There is still debate regarding the most cost-effective drug for mild stimulation in IUI programmes. Many randomized trials comparing gonadotrophins with clomiphene citrate or letrozole have been published but the results are contradictory and often these trials are of (very) low quality. A large multi-center trial comparing gonadotrophins with clomiphene citrate is ongoing in the Netherlands (SUPER trial NTR4057) and might be able to answer the question as to which strategy is the most cost-effective when addressing side effects and maternal and neonatal morbidity, and mortality associated with multiple pregnancies.

Question 13: Is there a different perinatal outcome for IUI pregnancies and how does this perinatal outcome differ from normal coitus and IVF/ICSI pregnancies?

Draft recommendations

- Individuals with infertility undergoing treatment with IUI–OS should be informed about a possible increased risk for preterm birth and low birthweight in singletons and twin pregnancies when compared to pregnancies in fertile couples not requiring assistance. (IVF/ICSI outcome comparisons are assessed in the IVF/ICSI prioritized guideline.)

The perinatal outcome of pregnancies caused by ART and IUI is substantially worse when compared to pregnancies after normal coitus (Helmerhorst *et al.*, 2004). This is mainly attributed to a higher rate of multiple births.

Few studies have been published reporting the obstetric and perinatal outcome after IUI in a direct comparison with medically unassisted pregnancies, with contradictory results. According to

Nuojua-Huttunen et al. (1999) using the data obtained from the Finnish Medical Birth Register, IUI treatment did not increase obstetric or perinatal risks compared with matched pregnancies through normal coitus or IVF pregnancies (Nuojua-Huttunen et al., 1999). Wang et al. (2002) examined preterm birth in 1 015 IUI/artificial insemination by donor (AID) singletons compared to 1 019 IVF/ICSI and 1 019 medically unassisted singletons. Singleton IUI/AID births were ~1.5 times more likely to be born preterm than medically unassisted singletons, whereas the IVF/ICSI group were 2.4 times more likely to be born preterm. They found no significant difference in the risk of preterm birth for IUI with partner or donor semen (7.0 versus 7.5%, respectively) (Wang et al., 2002).

In a retrospective cohort study, Gaudoin et al. (2003) described a poorer perinatal outcome of singletons born to infertile mothers through OS–IUI compared to matched medically unassisted pregnancies within the Scottish national cohort. The difference in perinatal outcome was caused by a higher incidence of prematurity and low-birthweight infants. The poor perinatal outcome of singletons after OS–IUI was associated with low birthweight, but only when IUI was performed with partner's semen and not with donor semen (Gaudoin et al., 2003). In a matched case–control study, De Sutter et al. (2005) did not observe a difference in pregnancy outcome in IUI versus IVF gestations (De Sutter et al., 2005).

Two large cohort studies comparing the perinatal outcome after OS and/or IUI with medically unassisted pregnancies or IVF/ICSI pregnancies were performed in Flanders, Belgium (Ombelet et al., 2006). Data were obtained from the Study Centre for Perinatal Epidemiology of Flanders. In the first study the outcome from 661 065 births could be investigated. All women were matched for maternal age, parity, foetal sex, plurality, place and year of birth. A significantly higher incidence of extreme prematurity (<32 weeks), very low birthweight (<1500 g), stillbirths and perinatal death for OS–IUI singletons could be observed. Twin pregnancies resulting from OS–IUI showed a higher rate of neonatal mortality, assisted ventilation and respiratory distress syndrome when compared to medically unassisted twin pregnancies.

In the second study (Ombelet et al., 2016) 1 039 415 singletons and 39 041 twins were available for analysis. Following logistic regression analyses, it was shown that IVF/ICSI singletons had a significantly worse outcome when compared to OS–IUI and medically unassisted pregnancies for almost all investigated perinatal parameters. OS singletons were also significantly disadvantaged for birthweight and prematurity when compared to pregnancies obtained through normal coitus. The outcome of twin pregnancies was similar for the three groups unless only unlike-sex twins were studied separately. Among this subgroup, IVF/ICSI carried a higher risk for low birthweight when compared to medically unassisted pregnancies.

In a retrospective cohort study, Poon also observed that perinatal outcomes after IUI/clomiphene citrate pregnancies represent an intermediate risk between IVF/ICSI and pregnancies obtained through normal coitus (Poon and Lian, 2013).

A national cohort study in Denmark on 6338 singletons born after IUI showed an increased risk of adverse perinatal outcomes compared with children born after normal coitus. Stimulation with clomiphene citrate was associated with higher risk of small for gestational age compared with natural cycle IUI (Malchau et al., 2014).

The reason why perinatal health problems occur more frequently after IUI is still unknown, but can be explained by the procedures itself, the endocrine changes caused by OS medication or the underlying reason for infertility (Simpson, 2014). In a structured review Pinborg et al. (2013) concluded that infertility is a major risk factor for adverse perinatal outcome for singletons, and even in the same mother an ART singleton has a poorer outcome than the non-ART sibling (Pinborg et al., 2013). This could mean that factors related to the hormone stimulation and/or ART methods per se may play a role.

Both OS–IUI and IVF/ICSI are associated with an increased risk for multiple pregnancies.

It has been shown that spontaneous reduction of multiple pregnancies causes a higher risk for adverse obstetric and perinatal outcome compared to pregnancies without spontaneous reduction. More than 10% of IVF/ICSI singletons are the result of a vanishing twin, and the same can be expected after OS–IUI. Survivors of a vanishing co-twin have a higher risk for prematurity and low birthweight compared to singletons from single gestations, the higher the gestational age at foetal demise, the higher the risk for the surviving co-twin (Pinborg et al., 2007). This phenomenon can explain, at least partly, the worse perinatal health outcome after OS–IUI compared to singleton and twin pregnancies born without medical assistance.

Pregnancies resulting from DI carry no increased risk compared to pregnancies obtained through normal coitus (Hoy et al., 1999; Gaudoin et al., 2003; Wang et al., 2002). In a large French population study it was shown that after DI the miscarriage and tubal pregnancy rate, the children's weight and the prematurity rate was not different from that of the general French population (Lansac et al., 1997). The rate of birth defects was comparable to the figures reported in a general population. The chromosomal abnormality rate was normal and correlated not only to the mother's age but also to the sperm donor's age. In addition, and not further elaborated upon here, according to the available literature, the use of frozen spermatozoa does not seem to affect the health of children.

On the other hand, a clinical pregnancy resulting from IUI with donor sperm appears to increase the incidence of pre-eclampsia (Kyrou et al., 2010). In a structured review and meta-analysis, it was shown that pregnancy using donor sperm was associated with an increased risk of pre-eclampsia (OR = 1.63, 95% CI: 1.36–1.95) compared with using partner's sperm. No difference was observed in any risk for gestational hypertension (Gonzalez-Comadran et al., 2014).

Couples and single women undergoing treatment with IUI require counselling concerning the increased risk of perinatal mortality and morbidity in twins compared to singletons. They should also be informed about an increased risk for perinatal health problems if they become pregnant after IUI with homologous and donor sperm, even for singletons, although this draft recommendation is based upon low quality evidence. A close follow-up of IUI-pregnancies from the early beginning of pregnancy is mandatory to detect spontaneous reduction of multiple pregnancies, which might be very important for that particular pregnancy.

Other prognostic factors influencing IUI success

Female age is the most relevant predictor of the probability of clinical pregnancy in IUI treatment and moderate quality evidence-based data show that a sharp decline of IUI success rate is observed in women over the age of 40 years, which is presumably related to

oocyte quality (Yarde and Broekmans, 2014). In heterosexual couples with unexplained infertility, IUI treatment should be limited to women with female age under 40 years, although IUI may be encouraged to continue up to 42 years when donor sperm is used (Veltman-Verhulst *et al.*, 2012). Whether IVF or ICSI should be recommended as a first line therapy when the female is in her late 30s or above 40 years of age is still debatable and more studies are needed to examine the cost-effectiveness of such an approach (Yarde and Broekmans, 2014).

Male age seems to have no profound effect when the female partner or sperm recipient is younger than 35 years but a synergistic adverse effect seems to exist when the woman is older than 35 years and the man as well (Mathieu *et al.*, 1995). A possible explanation may be a decline in sperm quality with increased male age, especially for semen volume, sperm motility and sperm morphology, but not for sperm count (Kidd *et al.*, 2001). Therefore, men in a heterosexual relationship (or identified as sperm donor) with a female partner above 35 years should be informed that increasing paternal age (40 years and above) has a potential negative impact on IUI success rates (De Brucker and Tournaye, 2014). Moreover, oxidative stress-induced mitochondrial DNA damage and nuclear DNA damage in aging men may put them at a higher risk for transmitting multiple genetic and chromosomal defects (Desai *et al.*, 2010).

Additional parameters can also influence the IUI success rates although well-organized prospective randomized trials are not available.

In a structured review Ombelet *et al.* (2014) investigated which sperm parameter in the native and washed semen sample influences success rates after IUI. Their search indicated a lack of prospective studies, a lack of standardization in semen testing methodology and a huge heterogeneity of patient groups and IUI treatment strategies. The review identified an urgent need for more and better prospective cohort trials investigating the predictive value of semen parameters on IUI success rates.

The four sperm parameters most frequently examined were: inseminating motile count after washing: cut-off value between 0.8 and 5 million; sperm morphology using strict criteria: cut-off value >4% normal morphology; total motile sperm count in native sperm sample: cut-off value of 5–10 million; and total motility in native sperm sample: threshold value of 30%.

Several studies support the concept of threshold values for sperm parameters below which IUI becomes significantly less effective. Most important are sperm morphology with a threshold value of 4% (Van Waart *et al.*, 2001; Ombelet *et al.*, 2014) and the TMSC either in the ejaculate (an average of 10 million total motile sperm in at least two samples) or in the post-wash inseminating motile count (between 0.8 and 5 million motile sperm) (van Weert *et al.*, 2004; Ombelet *et al.*, 2014). When using these threshold values, a poor sensitivity for predicting pregnancy but high specificity for predicting failure to become pregnant with IUI could be observed.

Ultrasound parameters can also be used to provide important information on egg quality and endometrial receptivity that will optimize the chances of success in an IUI programme. However, robust evidence is lacking and the role of Doppler assessment in the ovaries and endometrium needs to be studied in future randomized trials (Bhal *et al.*, 2001; Nargund *et al.*, 2014).

Endometrial thickness is another important factor predicting endometrial receptivity. It has been shown that endometrial thickness in stimulated IUI cycles is lower than in IVF cycles and is lower in cycles stimulated with clomiphene citrate compared with natural non-stimulated cycles (Randall and Templeton, 1991). A recent systematic review and meta-analysis on pre-ovulatory endometrial thickness in IUI treatment (n = 3846) showed that women treated with clomiphene citrate had a significantly thinner endometrial thickness than women treated with gonadotrophins [n = 383, mean difference (MD): −0.33, 95% CI: −0.64 to −0.01]. However, pooling of seven relevant studies (n = 1525) did not reveal an association between endometrial thickness and pregnancy rates (MD: 0.51, 95% CI: −0.05 to 1.07). Also, after a sensitivity analysis, the results remained non-significant. The authors therefore concluded that endometrial thickness is not a good prognostic factor for IUI treatment success (low to moderate quality of evidence)(Weiss *et al.*, 2017).

Studies on the influence of the BMI and obesity on IVF success rates are contradictory. In a population-based cohort study Petersen *et al.* (2013) showed that an increased female and male BMI, both independently and combined, negatively influenced live birth rates after IVF treatments (Petersen *et al.*, 2013). In another prospective cohort study, weight status did not influence fecundity among heterosexual couples undergoing IVF treatment (Schliep *et al.*, 2015). However, the influence of weight on IUI outcome remains unclear. Contradictory results were published in two retrospective analyses investigating the influence of BMI on IUI success: in one study a BMI of 25 kg/m^2 or more in the woman was associated with higher success rates (Soria *et al.*, 2012), while in the second study a BMI of <25 kg/m^2 was positively correlated with clinical pregnancy rates after IUI (Yavuz *et al.*, 2013). In most studies, it seems that a woman's BMI is not a determining factor for success rate after IUI although obese women require higher doses of medication. Once medication is adjusted to overcome the weight effect, the success rate is comparable for obese and normal weight women (Dodson *et al.*, 2006; Souter *et al.*, 2011; Isa *et al.*, 2014; Petrozza *et al.*, 2014; Thijssen *et al.*, 2017a, 2017b). In addition, an underweight BMI may also be associated with poor fertility (Thijssen *et al.*, 2017b). However, the advice to patients should be focused not only on ensuring optimal treatment outcomes, but also promoting the best obstetrical outcomes because a high BMI is undoubtedly associated with adverse obstetrical and perinatal outcome (Petrozza *et al.*, 2014).

Studies on the influence of the smoking status on IUI success rates are almost non-existent. It was shown that female smokers undergoing IUI–OS need significantly more gonadotrophins than non-smokers in order to achieve a comparable clinical pregnancy rate (Farhi and Orvieto, 2009). However, smoking was not significantly associated with a chance of becoming pregnant after secondary analyses of data from a prospective, randomized, multi-center 'Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation' (AMIGOS) clinical trial (Hansen *et al.*, 2016). However, focus would need to be placed on obstetrical and perinatal outcome because of the detrimental effects of smoking.

Future developments

Increasing success rates following IVF/ICSI with better implantation rates per embryo are reported year-on-year, however, similar increases have not been reported following IUI. This could eventually lead to an unacceptable high difference in cost-effectiveness between IVF/ICSI and IUI, subsequently encouraging those who prefer IVF above IUI in all cases.

There has been an overall trend to transfer fewer embryos, which automatically results in lower MPRs, subsequently increasing the cost-effectiveness of IVF/ICSI compared to other fertility treatment procedures. IVF may become the favoured first line treatment for most causes of infertility if the singleton delivery rate per cycle can be improved through the use of SET (Moolenaar et al., 2014; van Rumste et al., 2014).

However, such a statement does not take into account the couple's or the individual woman's preference, and the difference in complications related to the various treatment strategies. van Weert et al. (2007) conducted interviews in 73 couples undergoing IUI. For up to six IUI cycles, couples preferred IUI over IVF (van Weert et al., 2007).

Nevertheless, IUI will remain an effective first-line treatment in unexplained infertility and mild male factor infertility, as well as the use of donor sperm in same sex female couples and single women, if we succeed in increasing the delivery rate per cycle without increasing the risk for complications such as a higher MPRs and increased risk for OHSS.

A well-controlled mild OS with gonadotrophins aiming for two dominant follicles is the most effective strategy when performing IUI for unexplained infertility, minimal to mild endometriosis and moderate to mild male factor infertility.

A standardized methodology for IUI taking into account evidence-based data on how to perform IUI as described in this paper will likely increase IUI singleton pregnancy rates worldwide. Other methods to increase the delivery rate per IUI cycle will be a better selection of patients who have a reasonable prognosis with IUI. The evidence has identified several factors that might influence IUI outcome as presented and will require further confirmation by well-designed and adequately powered randomized trials.

A recent study reported a negative effect of human papilloma virus (HPV) positivity in women on clinical pregnancy rates following IUI (Depuydt et al., 2016). On the other hand, a reduction in medically unassisted and assisted cumulative pregnancy rates, and an increase in miscarriage rates are related to the presence of HPV sperm. The exact mechanism by which sperm infection is able to impair fertility remains unclear, and more studies are urgently needed (Foresta et al., 2015; Garolla et al., 2016). If confirmed, these results could change the clinical and diagnostic approach to infertile couples and HPV-positive women and men would, for example, not be recommended to receive IUI as a first-line treatment. Furthermore, it is unknown if HPV positivity has an effect on pregnancy rates following IVF or IVF/ICSI.

In a prospective multi-centre cohort study in France it was shown that the time interval from the end of sperm preparation to IUI in the range of 40–80 min has a potential positive effect on pregnancy rate, while not requiring the investment of supplemental resources (Fauque et al., 2014).

Pre-washing the catheter with culture medium prior to IUI seems to increase the success rate per cycle and could be recommended in Good Laboratory Practice Guidelines, as is already the case for embryo transfer catheters (Pont et al., 2012).

In a prospective cohort study Duran et al. (2002) showed that sperm DNA fragmentation and age of the man were the only two parameters that were able to predict IUI outcome. No samples with >12% of sperm having DNA fragmentation have resulted in a pregnancy (Duran et al., 2002).

It is clear that more studies are needed examining the influence of certain infections, sperm DNA abnormalities and other (unknown) factors on IUI outcome results. More evidence-based research is also needed to optimize IUI outcome in terms of a better selection of couples or individual women who are the best candidates for IUI, therefore, these practices and appropriate strategies are not provided as additions to the draft guidelines yet.

In this article the draft recommendations on why and how to perform IUI in the forthcoming years is based on a literature search of all available evidence performed by experts invited by WHO. These draft recommendations are different from the most recent NICE guidelines (NICE, 2013). According to the NICE guidelines, most couples would no longer be offered IUI, as NICE says the results are no better than those for normal intercourse. An exception to this is if there are circumstances where vaginal intercourse would not be appropriate or possible. According to these guidelines couples with unexplained infertility, women with mild endometriosis, or men who have 'mild male infertility', should normally attempt to become pregnant through regular unprotected intercourse for a total of 2 years. After this time IVF should be offered. Interesting to note is that the NICE guidelines were partly based on a study in which mathematical modelling was used to estimate comparative clinical and cost-effectiveness of either a primary offer of one full IVF cycle or 'IUI + IVF' to a hypothetical cohort of infertile couples who are eligible for both treatment strategies. The data used in their calculations were not based on prospective randomized trials but derived from the published peer-reviewed literature as well as activity data of local infertility units (Pashayan et al., 2006). The methods used were criticized and according to Bahadur et al. (2016) the evidence strongly favours IUI over IVF in selected couples and therefore national funding strategies should include IUI treatment options before IVF is recommended (Bahadur et al., 2016). They refer to the results of the multi-centre RCT reported by Bensdorp et al. (2015), which clearly shows that from a cost-benefit point of view IUI–OS is the best first-choice treatment in patients with moderate male infertility and poor prognosis unexplained infertility (Bensdorp et al., 2015).

Conclusion

After collecting and appraising the most recent evidence on IUI in infertility care it is possible to conclude that most of the presented 'evidence' does not stand up to modern quality parameters, and is of moderate or (very) low quality. Issues such as randomization method, allocation concealment, blinding, adequate power and outcome measures are often not dealt with adequately and thus most evidence is often graded from moderate to low. Especially in an 'old treatment option', as IUI is often viewed, many RCTs are published in the previous century and firm conclusions are hard to draw.

Nevertheless, recently published higher quality multi-center RCTs fail to devalue IUI in the world of more advanced medically assisted reproductive treatments. Therefore, IUI, often in combination with OS, remains a first line treatment option for many heterosexual and same-sex infertile couples and single women as this strategy is supported by the results of cost-effectiveness trials.

However, applied inappropriately, IUI–OS could be a harmful treatment. In the delivery of fertility care interventions and treatments, the prevention of multiple pregnancies should be as important as optimizing live birth rates. In low and middle-income countries and settings, the prevention of infections with a high risk of transmission, including

endemic viral diseases such as HIV or hepatitis, is equally important. We presented several factors that might influence IUI outcome, such as women's age, BMI and ultrasound parameters, and that need further confirmation by randomized trials so that in future it might become possible to select those patients who would benefit most from IUI with a low risk of adverse events. Finally, we presented gaps in current research, with recommendations for future research.

Authors' roles

All authors contributed to this review. A.B. did all the searches and A.B. and B.C. graded the evidence found. All authors wrote parts of the review and reviewed the complete manuscript.

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Conflicts of interest

None declared.

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