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human reproduction DEBATE

Should Cochrane reviews be performed during the development of new concepts?

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ABSTRACT: Cochrane reviews are internationally recognized as the highest standard in evidence-based health care. A Cochrane analysis conducts systematic reviews of primary research in human health care, and the analysis includes a comprehensive search of all potentially relevant studies and the use of explicit, reproducible criteria in the selection of studies for review. Thus, Cochrane reviews, undoubtedly provide many useful clinical guidelines. In this opinion paper, however, it is questioned at what level of clinical development of a new strategy a Cochrane review should be conducted in order not to draw premature conclusions that may not be sustained later on. Previous examples of this are debated together with the most recent Cochrane review regarding GnRH agonist triggering of final oocyte maturation, in which debatable conclusions are drawn from early studies, when the concept was still under development. We question the current policy of meta-analysis and recommend that in the future, the meta-analysts should await the results of a sufficient number of well-performed studies with an established new regime before an analysis is performed in order to avoid too early and possibly biased conclusions.

Key words: Cochrane review / meta-analysis / GnRHa triggering

Cochrane reviews are internationally recognized as the highest standard in evidence-based health care. A Cochrane analysis conducts systematic reviews of primary research in human health care and health policy. The strategy includes a comprehensive search of all potentially relevant studies and the use of explicit, reproducible criteria in the selection of studies for review. Thus, it is difficult to argue against a Cochrane review, which undoubtedly provides many useful clinical guidelines. However, one might question at which level of clinical development a Cochrane review should be performed. Clearly, the development of new strategies demands many clinical trials; trials which obviously are in progress towards the optimal protocol. Thus, during this process, the results of previous trials serve to improve the set-up and outcome of subsequent trials.

The issue of the current debate is whether or not a Cochrane review should be conducted during the process of development of a new clinical strategy. According to the aims of a Cochrane review, it should include all potentially relevant studies; however, if studies included are part of the groundwork research efforts, they will inevitably skew the review results, undermining further clinical research. If, for instance, a Cochrane review on IVF treatment had been conducted in the mid-1980s, it would have shown appalling results: just a few babies born after thousands of unsuccessful cycles worldwide. The premature results of such a review might have prevented the IVF era.

Previous examples of early Cochrane reviews from the field of reproductive medicine include, among others, the meta-analysis on the use of intravenous albumin in the prevention of ovarian hyperstimulation syndrome (OHSS). Two Cochrane reviews concluded that intravenous albumin administration at the time of oocyte retrieval was an effective method of OHSS prevention in the high-risk patient (Aboulghar *et al.*, 2000, 2002). Subsequent publications seriously questioned this conclusion, and finally, a larger recent meta-analysis concluded that albumin does not prevent OHSS (Venetis *et al.*, 2011).

Another example is the comparison between the long GnRH agonist (GnRHa) and the GnRH antagonist protocol. An early Cochrane analysis concluded that GnRH antagonist co-treatment

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resulted in a significantly lower reproductive outcome (Al-Inany and Aboulghar, 2001). However, the most recent meta-analysis concluded that the two GnRH analogues are comparable in reproductive outcome (Kolibianakis et al., 2006).

The latest example of the prevailing meta-analytical impatience is the Cochrane review (Youssef et al., 2010), comparing GnRHa versus hCG for triggering of final oocyte maturation—a clinical approach which is clearly a concept in progress, not yet finally developed. The review in the 'Implications for practice' section of the manuscript concludes: 'We recommend that GnRH agonists as a final oocyte maturation trigger in fresh autologous cycles should not be routinely used due to the associated significantly lower live birth rate, ongoing pregnancy rate (pregnancy beyond 12 weeks) and higher early miscarriage (less than 12 weeks)'. Furthermore, the 'Implications for research' section concludes: 'In view of the poor reproductive outcomes following oocyte triggering with GnRH agonist we believe there is no indication for further research with GnRH agonists for oocyte triggering in ART in fresh autologous cycles'.

If one penetrates the story deeper, it is obvious that the first large clinical trials (Humaidan et al., 2005; Kolibianakis et al., 2005) delineated the fact that GnRHa triggering induced a luteal phase insufficiency, which could not be solved by the standard luteal phase support currently used in IVF. Importantly, the luteal phase insufficiency resulted in an unacceptably low reproductive outcome; both trials are included in the meta-analysis by Youssef et al. (2010).

Following these trials, however, it was evident that precautions needed to be taken during the luteal phase to secure the reproductive outcome when GnRHa was used to trigger the final oocyte maturation. In order to approach this question, an international scientific network—'The Copenhagen GnRHa Triggering Workshop Group'—was formed and a number of clinical studies were performed to explore different means of correcting the insufficient luteal phase induced after GnRHa triggering. This lead to the development of the so-called 'modified luteal phase support' (Humaidan et al., 2006, 2010; Humaidan, 2009; Engmann et al., 2008; Castillo et al., 2010; Papanikolaou et al., 2011).

Recently, this concept has been described in a consensus paper by the workshop group (Humaidan et al., 2011), in which a new meta-analysis of the most recent studies employing the modified luteal phase support shows a non-significant difference of 6% in live birth rate when GnRHa triggering is compared with hCG triggering (Humaidan et al., 2011). Moreover, with a further modification of the luteal phase support, a large randomized clinical trial (RCT) in normo-gonadotropic patients comparing hCG and GnRHa triggering now shows no statistical difference in the reproductive outcome between the two triggering concepts (Humaidan et al., unpublished). Thus, it appears that the conclusions of the Cochrane Review are possibly too hasty and the recommendation to refrain from further research is, in our opinion, unprecedented.

Furthermore, among the reasons for excluding one of the studies from the Cochrane Review (Engmann et al., 2008) was that it 'achieved comparable reproductive outcomes in both groups'. Despite some of the debatable methodological flaws of the study, obtaining results which are contrary to the preconceived ideas of the authors of the meta-analysis should definitely not be one of the reasons for exclusion. Moreover, it questions on which basis any given study qualifies for the inclusion in a Cochrane analysis.

Clearly, the GnRHa triggering concept has not yet reached a plateau in development and further fine-tuning is needed. Therefore, the Cochrane meta-analysis is premature. Moreover, beyond the 'academic' discussion, the conclusions of the Cochrane Review could deprive patients of one of the main advantages of GnRHa triggering: an OHSS-free ovarian stimulation, as the efficiency of GnRHa triggering to prevent OHSS has been proven beyond any doubt.

Cochrane Reviews are considered the highest standard in evidence-based medicine. Therefore, the choice of words in its publications is extremely important, especially since the Cochrane library addresses non-professionals by including 'plain language' summaries. These summaries are readily available to every patient online and will invariably affect patients' attitudes and decisions.

In the above meta-analysis, the authors concluded that 'We do not recommend that GnRH agonist be routinely used as a final oocyte maturation trigger in fresh autologous cycles because of lowered live birth rates and ongoing pregnancy rates. An exception could be made for women with high risk of OHSS, after appropriate counseling'. However, in the 'plain language' summary, it bluntly reads: 'We recommend that GnRH agonist as a final oocyte maturation trigger should be not used'.

We maintain that this statement is premature since it is based on a meta-analysis compiling some of the GnRHa triggering studies performed until now, without taking into account that the earlier studies provided very poor results, unacceptable to any clinician. These early studies cannot be compared with the newer studies as significant modifications of the luteal phase support have been performed; thus apples are compared with oranges. The recommendation also clearly disregards the beneficial effect of GnRH agonist trigger in the prevention of OHSS, an iatrogenic condition with significant severe side effects and potential morbidity.

Importantly, we do not question the Cochrane analysis as an important tool in evidence-based medicine. However, we suggest that these important meta-analyses should await a solid clinical experience based on many trials before they are conducted. Furthermore, due to the significant impact of a Cochrane analysis, the conclusions may have legal implications for the recommended clinical practice—a further reason not to perform the analysis prematurely.

During recent years, meta-analyses have obtained an increasingly dominating role in the field of reproduction. In comparison with epidemiology, however, the meta-analyses in our 'field' often include a very limited number of studies, a fact that significantly increases the risk of drawing wrong conclusions. Instead of awaiting a sufficient number of well-performed RCTs to be published, the meta-analysis could become a way of not only publishing, but also disputing protocols and 'hard' scientific clinical research.

In conclusion, the meta-analysis is an important tool for clinical guidelines and decision-making. However, we should realize that the current way of performing meta-analyses bears flaws and biases which need to be taken into consideration. Finally, we suggest that the Cochrane Review by Youssef et al. (2010) should be considered for withdrawal.

Authors' roles

P.H. is the corresponding author. P.H., S.K., L.E., C.B., E.G.P. and C.Y.A. accept direct responsibility for the manuscript. All members of the consensus group actively participated in the design, drafting and final approval of the manuscript.

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