



www.sciencedirect.com  
www.rbmonline.com



## COMMENTARY


# The updated Cochrane review 2014 on GnRH agonist trigger: repeating the same errors



Shahar Kol <sup>a,\*</sup>, Peter Humaidan <sup>b</sup>, Birgit Alsbjerg <sup>b</sup>, Lawrence Engmann <sup>c</sup>,  
Claudio Benadiva <sup>c</sup>, Juan A García-Velasco <sup>d</sup>, Human Fatemi <sup>e</sup>,  
Claus Yding Andersen <sup>f</sup>

<sup>a</sup> IVF Unit, Rambam Health Care Campus, The Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel; <sup>b</sup> The Fertility Clinic, Skive Regional Hospital, Faculty of Health, Aarhus University, Skive, Denmark; <sup>c</sup> Department of Obstetrics and Gynecology, Center for Advanced Reproductive Services, University of Connecticut School of Medicine, Farmington, CT, USA; <sup>d</sup> IVI Madrid, Spain; <sup>e</sup> Nova-IVI, Abu Dhabi, United Arab Emirates; <sup>f</sup> Juliane Marie Centre for Women, Children and Reproduction University Hospital of Copenhagen Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

\* Corresponding author. E-mail address: ivfisrael@gmail.com (S Kol).

**Abstract** Cochrane reviews are powerful tools, internationally recognized as the highest standard in evidence-based health care. A Cochrane analysis makes use of precise, reproducible criteria in the selection of studies for review. In the context of a previous Cochrane review (2010) on the subject of gonadotrophin-releasing hormone agonist (GnRHa) trigger, we questioned whether a review should be conducted during the research phase when new concepts are being developed. Recently, an updated Cochrane review was published, reaching the same general conclusion as the first one, i.e., GnRHa triggers lower the chance of pregnancy in fresh autologous IVF and intracytoplasmic injection treatment cycles. We argue that the new review repeats previous errors by compiling data from studies that were not comparable as different luteal phase protocols were used. From the clinical point of view, the luteal support used is the variable which affects the pregnancy rate and not the use of the GnRHa trigger for final oocyte maturation. Therefore, a meaningful comparison between GnRHa and HCG trigger must be confined to outcome measures that are not affected by the luteal support used. We conclude that the updated review falls short of addressing meaningful clinical and fundamental questions in the context of GnRHa trigger. 

© 2015 Reproductive Healthcare Ltd. Published by Elsevier Ltd. All rights reserved.

**KEYWORDS:** Cochrane review, GnRHa triggering, luteal support, meta-analysis

We have previously stated that we consider Cochrane reviews to be internationally recognized as the highest standard in evidence-based health care (Humaidan and Polyzos, 2012). Obviously, this means that the conclusions of a Cochrane review may have significant legal implications for the recommended clinical practice. Undoubtedly, most Cochrane reviews provide valid messages that are important for daily clinical practice and, thus, our patients. During recent years, however, there has been an increasing focus on the

quality of some of the published Cochrane reviews and meta-analyses. Thus, several authors have pointed out that some meta-analyses are based on scant information, and, even worse, are conducted during the development of new concepts (Humaidan and Polyzos, 2012; Humaidan et al., 2011; Simon and Bellver, 2014; Simon et al., 2014).

Along this line, a recent updated Cochrane review on gonadotrophin-releasing hormone agonist (GnRHa) trigger (Youssef et al., 2014) reached the same general conclusions

of the previous review (Youssef et al., 2010), i.e. GnRHa trigger is associated with a lower ongoing pregnancy rate compared with the conventional human chorionic gonadotrophin (HCG) trigger. The first published review (Youssef et al., 2010) even concluded that 'no further studies are required in this field', and that 'GnRHa trigger as final oocyte maturation should not be used'. Interestingly, these statements are now replaced by the following statement: 'GnRH agonist triggers significantly reduce the risk of ovarian hyperstimulation, but also lower the chance of pregnancy in fresh autologous IVF-ICSI treatment cycles compared with HCG. GnRH agonist use as an oocyte maturation trigger could be useful for women who choose to avoid fresh transfers (for whatever reason), women who donate oocytes to recipients or women who wish to freeze their eggs for later use in the context of fertility preservation (Youssef et al., 2014)'.

In previous debates (Humaidan et al., 2010; Kol and Humaidan 2013) we responded to the initial Cochrane review (Youssef et al., 2010), arguing that Cochrane reviews should not be conducted during the research phase when new concepts are developed. We also suggested that the meta-analysis was too premature because the number of trials was restricted and included a limited number of participants. Moreover, data were compiled from studies that were not comparable as different luteal phase protocols were used (Humaidan et al., 2011). Unfortunately, in the new Cochrane review, it seems that the authors repeat the same errors as in their initial review. Thus, a few more studies have been added, but again they are not comparable as they differ significantly in their luteal phase support after the trigger.

Importantly, we would like to underline that the main clinical variable is the luteal support used after GnRHa trigger. As mentioned, studies are still compiled as if a similar luteal support was used. Thus, it seems that the authors of the present Cochrane analysis have missed that the luteal support is indeed the variable which affects the pregnancy rate and not the use of the GnRHa trigger for final oocyte maturation (Yding Andersen and Vilbour Andersen, 2014). Combining studies that did not use any form of luteal phase support (Beckers et al., 2003) or studies that used standard luteal phase support (Humaidan et al., 2005; Kolibianakis et al., 2005) with other studies that have used some form of modified luteal phase support (Engmann et al., 2008; Humaidan et al., 2013) is scientifically flawed in view of the overwhelming evidence showing abnormal luteal phase after GnRHa trigger (Beckers et al., 2003; Nevo et al., 2003). As the luteal phase support differs between studies included in the new Cochrane analysis, in our opinion, it makes no sense to meta-analyse them in one pooled analysis. This fundamental flaw clearly prevents meaningful conclusions to be drawn, even worse, it reveals a lack of clinical insight and understanding of the studies analysed.

Three important questions relate to GnRHa trigger that are relevant to clinicians: does GnRHa trigger result in similar number of oocytes and mature oocytes compared with HCG trigger? Is GnRHa trigger effective in preventing the development of ovarian hyperstimulation syndrome (OHSS)? Does GnRHa trigger result in optimal pregnancy rates if a modified luteal phase support is used? Unfortunately the authors of the recent Cochrane review have failed to adequately answer these pertinent questions. A meaningful comparison between GnRH agonist and HCG trigger must naturally be confined to outcome

measures that are not affected by the luteal support used, and indeed the use of the GnRHa trigger for the first time allows us to separate the induction of final oocyte maturation from the luteal phase (Kol and Humaidan, 2013). Thus, variables to compare or meta-analyse are the number of oocytes obtained, the percentage of metaphase II oocytes, the fertilization rate, the oocyte and embryo quality and patient convenience during the luteal phase. Moreover, if a 'freeze all' approach was used, the OHSS rate and subsequently the reproductive outcome of the frozen-thawed cycle may be meta-analysed.

Indeed, previous studies indicate that GnRHa trigger may offer significant advantages over HCG trigger, taking these variables into account (Bodri et al., 2010; Cerrillo et al., 2009; Hernandez et al., 2009; Humaidan et al., 2011; Oktay et al., 2010). Interestingly, one co-author of the present Cochrane analysis previously published results showing that the implantation potential of frozen-thawed embryos deriving from GnRHa trigger is similar to that of embryos deriving from HCG trigger (Griesinger et al., 2007). This clearly demonstrates that the trigger as such is not the decisive parameter for successful implantation and ongoing pregnancy, but indeed the luteal phase support provided.

Importantly, we acknowledge that the optimal type of luteal phase support after GnRHa trigger followed by fresh transfer is still subject to research and has not reached its final form. The recent European Society of Human Reproduction and Embryology campus workshop in Thessaloniki (November 2014) clearly showed that many new aspects are currently being evaluated, and that GnRHa trigger is a perfect tool to study various ways to improve the current luteal phase support used in IVF. In this aspect, we urge authors of future meta-analyses to await the results of more studies, using the same luteal phase support, with or without the use of a GnRHa trigger, to avoid hasty and biased conclusions.

From a clinical point of view, the most significant benefit of GnRHa trigger is its ability to induce a quick luteolysis and thus eliminate or reduce the risk of developing OHSS. Further, this trigger concept allows the practitioner to mold the luteal phase in a patient-specific manner, thus, introducing the new term, 'individualized luteal phase support (iLPS)' in which the ovarian response of each specific patient is taken into account when deciding the type of luteal phase support to be used (Humaidan et al., 2013; Kol and Humaidan, 2013). This will further impair the possibility to conduct meaningful meta-analyses, illustrating the shortcoming of the mathematical tool that a meta-analysis constitutes. In comparison, the gold standard HCG trigger induces not only a continuous luteotrophic effect for 8-9 days, but also supra-physiological luteal steroid levels, which, according to more recent studies, might hamper the reproductive outcome (Evans and Salamonsen, 2013; Shapiro et al., 2011; Valbuena et al., 2001). As recently stated, the early luteal supra-physiological steroid level induced by HCG trigger is the main culprit of the luteal phase defect, seen after all ovarian hyperstimulation (Yding Andersen and Vilbour Andersen, 2014).

In conclusion, the new meta-analysis on GnRHa trigger (Youssef et al., 2014) might be seen as yet another example of the fact that the meta-analysis has become a convenient way to get published rather than being able to address meaningful clinical and fundamental questions (Humaidan and Polyzos, 2012). In the worst case scenario, the present analysis might hinder scientific progress, and deprive our patients

from one of the best tools we currently have to prevent severe OHSS. We sincerely call upon authors to refrain from further meta-analysing studies using GnRHa trigger without considering differences in luteal phase support as a variable.

## References

- Beckers, N.G., Macklon, N.S., Eijkemans, M.J., Ludwig, M., Felberbaum, R.E., Diedrich, K., Bustion, S., Loumaye, E., Fauser, B.C., 2003. Nonsupplemented luteal phase characteristics after the administration of recombinant human chorionic gonadotropin, recombinant luteinizing hormone, or gonadotropin-releasing hormone (GnRH) agonist to induce final oocyte maturation in in vitro fertilization patients after ovarian stimulation with recombinant follicle-stimulating hormone and GnRH antagonist cotreatment. *J. Clin. Endocrinol. Metab.* 88, 4186–4192.
- Bodri, D., Guillen, J.J., Trullenque, M., Schwenn, K., Esteve, C., Coll, O., 2010. Early ovarian hyperstimulation syndrome is completely prevented by gonadotropin releasing-hormone agonist triggering in high-risk oocyte donor cycles: a prospective, luteal-phase follow-up study. *Fertil. Steril.* 93, 2418–2420.
- Cerrillo, M., Rodriguez, S., Mayoral, M., Pacheco, A., Martinez-Salazar, J., Garcia-Velasco, J.A., 2009. Differential regulation of VEGF after final oocyte maturation with GnRH agonist versus hCG: a rationale for OHSS reduction. *Fertil. Steril.* 91, 1526–1528.
- Engmann, L., DiLuigi, A., Schmidt, D., Nulsen, J., Maier, D., Benadiva, C., 2008. The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled study. *Fertil. Steril.* 89, 84–91.
- Evans, J., Salamonson, L.A., 2013. Too much of a good thing? Experimental evidence suggests prolonged exposure to hCG is detrimental to endometrial receptivity. *Hum. Reprod.* 28, 1610–1619.
- Griesinger, G., Kolibianakis, E.M., Papanikolaou, E.G., Diedrich, K., Van, S.A., Devroey, P., Ejdrup, B.H., Humaidan, P., 2007. Triggering of final oocyte maturation with gonadotropin-releasing hormone agonist or human chorionic gonadotropin. Live birth after frozen-thawed embryo replacement cycles. *Fertil. Steril.* 88, 616–621.
- Hernandez, E.R., Gomez-Palomares, J.L., Ricciarelli, E., 2009. No room for cancellation, coasting, or ovarian hyperstimulation syndrome in oocyte donation cycles. *Fertil. Steril.* 91, 1358–1361.
- Humaidan, P., Polyzos, N.P., 2012. (Meta)analyze this: systematic reviews might lose credibility. *Nat. Med.* 18, 1321.
- Humaidan, P., Bredkjaer, H.E., Bungum, L., Bungum, M., Grøndahl, M.L., Westergaard, L., Andersen, C.Y., 2005. GnRH agonist (buserelin) or hCG for ovulation induction in GnRH antagonist IVF/ICSI cycles: a prospective randomized study. *Hum. Reprod.* 20, 1213–1220.
- Humaidan, P., Kol, S., Engmann, L., Benadiva, C., Papanikolaou, E.G., Andersen, C.Y., Copenhagen GnRH Agonist Triggering Workshop Group, 2010. Should Cochrane reviews be performed during the development of new concepts? *Hum. Reprod.* 27, 6–8.
- Humaidan, P., Westergaard, L.G., Mikkelsen, A.L., Fukuda, M., Yding, A.C., 2011. Levels of the epidermal growth factor-like peptide amphiregulin in follicular fluid reflect the mode of triggering ovulation: a comparison between gonadotropin-releasing hormone agonist and urinary human chorionic gonadotropin. *Fertil. Steril.* 95, 2034–2038.
- Humaidan, P., Polyzos, N.P., Alsbjerg, B., Erb, K., Mikkelsen, A.L., Elbaek, H.O., Papanikolaou, E.G., Andersen, C.Y., 2013. GnRHa trigger and individualized luteal phase hCG support according to ovarian response to stimulation: two prospective randomized controlled multi-centre studies in IVF patients. *Hum. Reprod.* 28, 2511–2521.
- Kol, S., Humaidan, P., 2013. GnRH agonist triggering: recent developments. *Reprod. Biomed. Online* 26, 226–230.
- Kolibianakis, E.M., Schultze-Mosgau, A., Schroer, A., van Steirteghem, A., Devroey, P., Diedrich, K., Griesinger, G., 2005. A lower ongoing pregnancy rate can be expected when GnRH agonist is used for triggering final oocyte maturation instead of HCG in patients undergoing IVF with GnRH antagonists. *Hum. Reprod.* 20, 2887–2892.
- Nevo, O., Eldar-Geva, T., Kol, S., Itskovitz-Eldor, J., 2003. Lower levels of inhibin A and pro-alphaC during the luteal phase after triggering oocyte maturation with a gonadotropin-releasing hormone agonist versus human chorionic gonadotropin. *Fertil. Steril.* 79, 1123–1128.
- Oktaç, K., Turkuoglu, I., Rodriguez-Wallberg, K.A., 2010. GnRH agonist trigger for women with breast cancer undergoing fertility preservation by aromatase inhibitor/FSH stimulation. *Reprod. Biomed. Online* 20, 783–788.
- Shapiro, B.S., Daneshmand, S.T., Garner, F.C., Aguirre, M., Hudson, C., Thomas, S., 2011. Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfers in high responders. *Fertil. Steril.* 96, 516–518.
- Simon, C., Bellver, J., 2014. Scratching beneath 'The Scratching Case': systematic reviews and meta-analyses, the back door for evidence-based medicine. *Hum. Reprod.* 29, 1618–1621.
- Simon, C., Bosch, E., Bellver, J., 2014. Reply: endometrial scratching for women with repeated implantation failure. *Hum. Reprod.* 29, 2856–2857.
- Valbuena, D., Martin, J., de Pablo, J.L., Remohi, J., Pellicer, A., Simon, C., 2001. Increasing levels of estradiol are deleterious to embryonic implantation because they directly affect the embryo. *Fertil. Steril.* 76, 962–968.
- Yding Andersen, C., Vilbour Andersen, K., 2014. Improving the luteal phase after ovarian stimulation: reviewing new options. *Reprod. Biomed. Online* 28, 552–559.
- Youssef, M.A., Van der Veen, F., Al-Inany, H.G., Griesinger, G., Mochtar, M.H., van Wely, M., 2010. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist assisted reproductive technology cycles. *Cochrane Database Syst. Rev.* (11), CD008046. doi:10.1002/14651858.CD008046.pub2.
- Youssef, M.A., Van der Veen, F., Al-Inany, H.G., Mochtar, M.H., Griesinger, G., Nagi Mohesen, M., Aboulfoutouh, I., van Wely, M., 2014. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology. *Cochrane Database Syst. Rev.* (10), CD008046. doi:10.1002/14651858.CD008046.pub4.

*Declaration: The authors report no financial or commercial conflicts of interest.*

Received 6 December 2014; accepted 18 February 2015.