Journal Pre-proof

GnRHa trigger – The story of the ugly duckling

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PII: S2666-3341(23)00030-2

DOI: https://doi.org/10.1016/j.xfre.2023.02.011

Reference: XFRE 293

To appear in: *F&S Reports*

Received Date: 19 September 2022

Revised Date: 7 December 2022

Accepted Date: 22 February 2023

Please cite this article as: Humaidan P, Haahr T, GnRHa trigger – The story of the ugly duckling, *F&S Reports* (2023), doi: https://doi.org/10.1016/j.xfre.2023.02.011.

Title: GnRHa trigger – The story of the ugly duckling

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Running title: GnRHa trigger from ugly duckling to swan

Disclosures: PH received unrestricted research grants from MSD, Merck, and Ferring as well as honoraria for lectures from MSD, Merck, Gedeon-Richter, Theramex, Med.E.A and IBSA. TH received honoraria for lectures from Ferring, IBSA, Besins and Merck.

Abstract

The objective of this invited review is to describe the introduction and development of the GnRHa trigger protocol in modern IVF, focusing on OHSS prevention and equally important on the role of GnRHa trigger as an opener of the luteal phase "black box".

GnRHa trigger and freezing of all embryos is the ultimate weapon against OHSS in the OHSS risk patient. In the non OHSS risk patient, GnRHa trigger followed by a modified luteal phase support with LH activity and subsequent fresh embryo transfer results in excellent reproductive outcomes. Thus, GnRHa trigger has paved the way for a virtually OHSS free clinic, and equally important, is the fact that the early lessons learned from studying GnRHa trigger opened the "black box" of the luteal phase enabling improved reproductive outcome in both fresh and frozen embryo transfer cycles.

Key words: GnRHa trigger; OHSS; hCG; luteal phase rescue; pregnancy

Prologue

The ugly duckling is a famous fairy tale by the Danish poet Hans Christian Andersen, describing the troublesome early years of a duckling, who suffers verbal as well as physical abuse, because he does not fit in with the other ducklings. He moves from place to place like an outcast until he finally finds a flock of swans who welcome him. He is shocked and surprised when the swans welcome him, only to realize by looking at his own reflection in the water that he had not been a duckling, but a swan all this time. Like the "ugly duckling", GnRHa trigger after years of tribulations eventually turned into a wonderful white swan which now spreads its wings all over the world.

GnRHa trigger - physiology

Already in the early 1990'ies a bolus of GnRHa was shown to effectively trigger final oocyte maturation in two small case series of non-pituitary down-regulated IVF patients [1,2]. However, following this initial research, pituitary down-regulation with GnRHa prior to and during ovarian stimulation for many years ahead was the established way of avoiding a premature LH surge. On this basis the GnRHa trigger concept was abandoned and forgotten as the simultaneous use of GnRHa for down-regulation and ovulation trigger obviously is not possible.

Only when the GnRH antagonist protocol was introduced for the prevention of a premature LH surge [3–5], did it again become an option to trigger final oocyte maturation with GnRHa - now as an alternative to the gold standard hCG trigger in non-OHSS risk - as well as OHSS risk patients.

From a physiological point of view, a bolus of GnRHa displaces the GnRH antagonist from the GnRH receptor in the pituitary which induces an initial flare-up of gonadotropins (LH and FSH), similar to the natural cycle surge of gonadotropins. However, important differences in the bioactive profile and duration exist between the GnRHa induced surge, the natural cycle surge of gonadotropins, and the supraphysiological surge of LH activity induced by an hCG trigger. Comparing the three surges, the

LH surge of the GnRHa triggered cycle has a duration of 28-32 hours, only, compared to the natural cycle surge duration of 48 hours and the supra-physiological LH activity surge of an hCG trigger, lasting for approximately 6.5 days after oocyte retrieval (OR) [1,2,6,7].

Taking into account the bioactive profile and significantly shorter duration of the LH/FSH surge elicited by a bolus of GnRHa, this trigger concept leads to a significantly reduced total amount of LH (and FSH) released by the pituitary compared to the natural cycle - and particularly compared to the LH activity of cycles triggered with hCG[7]. In addition, the supraphysiological steroid levels (E_2 and P_4) produced during the early luteal phase of the GnRHa triggered IVF cycle reduce circulating endogenous LH via negative feed-back mechanisms, resulting in an overall profound suppression of LH after the initial flare-up – leading to demise of the corpus luteum (CL)[6].

GnRHa trigger - OHSS prevention

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of ovarian hyperstimulation for assisted reproductive technology (ART), characterized by enlargement of the ovaries and fluid shift from the intravascular compartment to the third space, caused by vascular hyperpermeability. OHSS is in its severe form a life-threatening condition triggered by either exogenous or endogenous hCG, which activates the LH/hCG receptor of the human ovary. Apart from progesterone production by the CL, hCG stimulates the release of vascular endothelial growth factor (VEGF), known to be the most prominent mediator of vascular hyperpermeability, which in the OHSS risk patient may lead to haemoconcentration, thromboembolic risk, ascites formation, and pleural effusion [8,9]. As GnRHa trigger induces a total demise of the CL within few days, if the luteal phase is not further supported with exogenous or endogenous LH activity, this trigger concept - in combination with a freeze-all policy - i.e., vitrification of oocytes/embryos, followed by embryo transfer in a subsequent cycle, has proven to be the most potent weapon against OHSS[10].

Importantly, the success of the GnRHa trigger for OHSS prevention was closely related to the improved reproductive results seen after vitrification and frozen/thaw embryo transfer, compared to previous slow-freeze protocols. However, an important issue when evaluating the success of the GnRHa trigger protocol is the classification and reporting of OHSS in the clinic as well as during research. In this aspect it is essential to distinguish between early and late OHSS as well as the severity of OHSS and to report it uniformly. This was why we proposed an easy adaptable OHSS flowchart to be used for reporting in clinical trials [11]. Although improved over the years, unfortunately, OHSS still remains poorly reported in daily clinical practice as well as in studies, which makes it difficult to evaluate the true risk of severe OHSS related to ovarian stimulation and ovulation trigger.

Taken together, GnRHa trigger revolutionized modern IVF, as GnRHa trigger followed by freeze all oocytes/embryos provides the OHSS risk patient a safe and efficacious treatment, outweighing the limited risks and additional costs involved with the freezing/thawing process [12,13].

GnRHa trigger and fresh embryo transfer – the early days

In hindsight we were quite naïve in 2003, when we planned our first RCT, comparing the outcomes of GnRHa trigger and fresh embryo transfer to hCG trigger and fresh embryo transfer[14]. Primarily the study was planned to include a total of 300 IVF cycles, in which patients were randomized to either GnRHa (Buserelin 0,5mg) or hCG trigger (10,000 IU) - and fresh embryo transfer. All patients were to receive a "standard" luteal phase support, in those days consisting of vaginal micronized progesterone 90 mg, once daily and oral estradiol, 4 mg daily from the day following OR and continuing until the day of the pregnancy test, i.e., day 12 after embryo transfer. However, when a total of 110 patients, i.e., 55 cycles in each group, had been completed, the study was discontinued due to a suspicion of extremely low clinical pregnancy rates in one of the two study arms, which subsequently appeared to be the GnRHa trigger group. In this group, the early pregnancy loss rate

was 79 % contrasted by 4 % in the hCG trigger group, resulting in a clinical pregnancy rate of 6 % versus 36 % in the GnRHa and hCG trigger groups, respectively. Four months later the Brussels/Lubeck group published their results from a similar RCT, which also had to be discontinued due to extremely low clinical pregnancy rates after GnRHa trigger[15]. This was obviously a tough lesson for our patients and us, which however was going to change our future understanding of the luteal phase dramatically.

After the two failed RCT`s there were just a few remaining believers in GnRHa trigger worldwide - at least this was our feeling during the subsequent years.

Instead of abandoning GnRHa trigger and fresh embryo transfer in patients not considered at risk of OHSS, we wanted to scrutinize the reasons for the poor reproductive outcome further. Our RCT had resulted in significantly more MII oocytes in the GnRHa trigger group, which we ascribed to the presence of an FSH surge in addition to the LH surge. In favor of GnRHa trigger was also publications, suggesting a negative effect in terms of endometrial advancement and oocyte quality induced by the gold standard hCG trigger dose.

What we noted in the Humaidan et al. 2005 study was a very low mid-luteal mean serum LH (OR+7) of 1.5 IU in the GnRHa trigger group – compared to 6.0 IU previously reported for the natural cycle. In the hCG trigger group the mid-luteal serum LH was even lower, 0.2 IU/l, caused by negative feed-back on the pituitary from high mid-luteal progesterone (283 nmol/l) boosted by the hCG trigger bolus. In comparison the mean mid-luteal progesterone level of the GnRHa trigger group was 39 nmol/l, more or less representing the contribution of the vaginal progesterone, only - and indicative of a total demise of the CL.

By coincidence, one of the co-authors of the 2005 paper met a co-author from the Brussels/Lubeck group in 2006. It appeared that both groups had supernumerary embryos from the studies cryopreserved, and we agreed to collaborate in a prospective frozen embryo transfer study, using

those frozen embryos from the two published 2005 papers to explore whether the negative impact seen in the fresh transfer studies was embryo related or rather related to luteal phase deficiency. The compiled data from this study showed excellent live birth rates in the GnRHa trigger group – numerically better than the frozen embryos deriving from hCG trigger[16].

In the meantime, from our center, we also published data from follicular fluids, deriving from the 2005 study[17]. Our aim was to test whether the poor reproductive outcomes seen were related to a defective follicular maturation, resulting in oocytes with a compromised developmental competence. From that study we concluded, that although pronounced differences existed in follicular fluid hormonal profiles between GnRHa trigger and hCG trigger – driven by the supraphysiological LH activity load induced by an hCG trigger – the gonadotropin signaling after the GnRHa trigger was sufficient to secure optimal pre-ovulatory follicular maturation and mature oocytes.

Finally, in 2011 during the continued development of the GnRHa trigger protocol, we explored the levels of the EGF-like peptide amphiregulin in follicular fluid from patients who received either a GnRHa trigger or hCG trigger, comparing those to amphiregulin levels in small antral follicles and natural cycle pre-ovulatory follicles aspirated **after** the midcycle surge, but **before** ovulation. From a physiological point of view, amphiregulin is the mediator of LH action inside the follicle, and after stimulation with LH-like activity, the granulosa cell responds with a rapid synthesis of amphiregulin which is known to be a potent mediator of oocyte maturation. The study showed that significantly more MII oocytes and more transferable embryos were obtained after GnRHa trigger as compared to hCG trigger. Thus, in concordance with previous studies, from this study we suggested that intrafollicular amphiregulin should neither be too high nor too low, and that amphiregulin levels from follicles triggered with GnRHa were significantly lower as compared to hCG trigger [18].

Taken together, we concluded that the poor reproductive outcome seen after GnRHa trigger did not derive from defect follicle maturation, defect LH signaling inside the follicle or impairment of the

embryo. In contrast, the poor reproductive outcome was caused by low LH levels, resulting in progesterone levels too low to support the early implant, which was the most likely biological rationale for the extremely high early pregnancy loss rate.

From a physiological point of view, luteal phase LH plays a pivotal role for the function of the CL, being totally responsible for the steroidogenic activity in terms of mainly progesterone and estradiol, but also for the production/secretion of among others inhibin A, relaxin, oxytocin, and growth factors involved in implantation. Thus, if the GnRHa triggered cycle is not supported with exogenous LH activity, the demise of the CL will inevitably occur approximately three days after OR, unless the early-mid luteal phase "LH gap" is covered by LH activity until the embryo implants on approximately day 8. After this period the embryo itself will support the CL function by trophoblast driven hCG production.

Importantly, in those days - 16 years ago this was an eye-opener which drove us to a new frontier of research, investigating optimal mid-luteal progesterone levels to maximize reproductive outcomes in both fresh and frozen IVF embryo transfer cycles.

Opening the black box of the luteal phase

Following the disappointing results of the 2005 study, over the years we set up a series of RCTs on GnRHa trigger and fresh embryo transfer to explore the amount of LH activity needed after the trigger to rescue the luteal phase[19–21]. In these studies, small boluses of hCG at different time points were used during the early luteal phase. The breakthrough came in the 2010 RCT, in which supplementation with 1.500 IU hCG on the day of oocyte retrieval after GnRHa trigger resulted in a non-significant difference in delivery rate (24% and 31%), and early pregnancy loss rate (21% and 17%) between the GnRHa trigger (152 patients) and a 10,000 IU hCG trigger comparator group (150 patients). Moreover, no OHSS was seen in the GnRHa trigger group versus 3 cases after HCG trigger

(20). Thus, supplementing the early luteal phase after the GnRHa trigger with a small bolus of 1500 IU hCG radically changed the outcomes, compared to the 2005 study in which the clinical pregnancy rate was 6% and the early pregnancy loss rate 79%.

However, although non-significant there was still a 7% difference in delivery rate between the two trigger concepts in favor of hCG trigger, which prompted us to continue with further RCT´s, elaborating on hCG doses and the optimal day(s) to supplement during the early luteal phase[19,21]. After further modifications of the protocol, in the 2013 RCT (384 patients randomized) we obtained a non-significant difference in ongoing pregnancy rates, however now in favor of GnRHa trigger; moreover, fewer OHSS cases were seen after GnRHa trigger.

Taken together, over the years, by modifications of the hCG rescue bolus after GnRHa trigger, we continuously increased the mean mid-luteal progesterone level (OR+5) from 39 nmol/l[14], using vaginal micronized progesterone, 90 mg daily, only, to 74 nmol/l with the addition of 1500 IU HCG on the day of OR[20] – and finally to 409 nmol/l using two boluses of 1500 IU HCG – one on day of OR and another bolus on OR+5[19].

Through these LPS modifications we were able to significantly increase ongoing pregnancy rates from 6% (Humaidan et al., 2005) to 29% (Humaidan et al., 2013) and 48% (Humaidan et al., 2021) and, equally important , significantly reduce early pregnancy losses from 79% (Humaidan et al., 2005) to 12% (Humaidan et al., 2013), showing the important correlation between progesterone, early pregnancy loss, and ongoing pregnancy, table 1.

GnRHa trigger - fresh transfer - and meta-analysis

During the development of the GnRHa trigger protocol fresh transfer protocol, our studies were being meta-analyzed by the Cochrane institution [22–24]. Importantly, the first published analysis (Youssef et al., 2010) even went so far as to conclude that ‘there is no indication for further research with

GnRH agonists for oocyte triggering in ART in fresh autologous cycles', and that 'GnRHa trigger as final oocyte maturation should not be used routinely'. We from our side urged meta-analysts not to meta-analyze during concept development, stating that this kind of analysis "in the worst-case scenario might hinder scientific progress, and deprive our patients from one of the best tools we currently have to prevent severe OHSS" [25]. Thus, the scene was set for verbal confrontation, which occurred at the ESHRE Istanbul meeting in 2012. At this meeting, the first author of the present manuscript was invited to speak about GnRHa trigger and the ongoing clinical research in fresh embryo transfer after GnRHa trigger. The lecture was followed by an intense and energetic debate between the presenter and the first author of the aforementioned Cochrane review which, according to comments from the audience, reminded them of a debate "from the good old days". A few days later, however, it appeared that a letter of complaint had been handed over to the ESHRE committee by the Cochrane group of authors, first and foremost posing allegations of racism - a very serious complaint with serious implications. Fortunately, the session had been videotaped, and subsequently allegations were completely dismissed; however, this event shows how passionate feelings – pro et con - were regarding GnRHa trigger during the early days. Nevertheless, as a results of the lively ESHRE debate on the impact of meta-analyses during concept development we were invited to give our opinion on the increasing number of meta-analyses being performed in reproductive science, and their risk of losing credibility due to lack of robust evidence [26].

Present and future perspectives of GnRHa trigger

In contrast to what was believed after the initial pioneering studies on GnRHa trigger, fresh embryo transfer can certainly be performed after GnRHa trigger, provided that some kind of LH activity is supplemented during the luteal phase. We chose one or two small boluses of hCG (table 1) in combination with vaginal micronized progesterone and oral estradiol during the initial dose finding

studies. More recently, we showed that exogenous progesterone and oral estradiol are not necessary, when the CL function is supported by small boluses of hCG, only(21). In the same line others used repeat boluses of daily GnRHa after GnRHa trigger to boost the endogenous release of LH by the pituitary(27,28). As regards fresh embryo transfer after GnRHa trigger and luteal phase rescue, however, we suggest an upper follicle cut off level of 19 follicles ≥ 11 mm to minimize the risk of OHSS development(21) – very much in line with what was suggested after hCG trigger and fresh embryo transfer(29).

Epilogue

From a clinical point of view GnRHa trigger revolutionized modern IVF and in combination with vitrification this trigger concept provides an almost total elimination of OHSS as well as excellent live birth rates in subsequent frozen/thaw cycles. The problem is no longer to obtain too many follicles after ovarian stimulation, but rather too few follicles. Thus, GnRHa trigger radically changed stimulation policies worldwide and paved the way for the "OHSS free clinic". Equally important is the fact that GnRHa trigger opened the "black box" of the luteal phase, and that pivotal lessons were learnt from those initial failing studies, which completely changed our luteal phase support policies – moving from "standard" to" personalized" luteal phase support – taking into account mid-luteal progesterone levels. Thus, in many clinical practices it is now common routine to monitor mid-luteal progesterone prior to frozen/thaw embryo transfer and to intervene if levels are too low. In very near future, we predict that luteal phase progesterone monitoring will also be performed in fresh embryo transfer cycles.

The story of GnRHa trigger is the typical example of the four phases along the journey of acceptance of novel concepts: resistance – resignation – acceptance – and embracing. In line with the Hans

Christian Andersen fairy tale, the ugly duckling - GnRHa trigger - turned into a wonderful white swan and was finally embraced by the IVF community worldwide.

Disclosures

PH received unrestricted research grants from MSD, Merck, and Ferring as well as honoraria for lectures from MSD, Merck, Gedeon-Richter, Theramex, Med.E.A and IBSA. TH received honoraria for lectures from Ferring, IBSA, Besins and Merck.

References:

[1] Gonen Y, Balakier H, Powell W, Casper RF. Use of gonadotropin-releasing hormone agonist to trigger follicular maturation for in vitro fertilization. J Clin Endocrinol Metab 1990;71:918–22. https://doi.org/10.1210/jcem-71-4-918.

[2] Itskovitz J, Boldes R, Levron J, Erlik Y, Kahana L, Brandes JM. Induction of preovulatory luteinizing hormone surge and prevention of ovarian hyperstimulation syndrome by gonadotropin-releasing hormone agonist. Fertil Steril 1991;56:213–20.

[3] European and Middle East Orgalutran Study Group. Comparable clinical outcome using the GnRH antagonist ganirelix or a long protocol of the GnRH agonist triptorelin for the prevention of premature LH surges in women undergoing ovarian stimulation. Hum Reprod 2001;16:644–51.

[4] Itskovitz-Eldor J, Kol S, Mannaerts B, Coelingh Bennink H. First established pregnancy after controlled ovarian hyperstimulation with recombinant follicle stimulating hormone and the gonadotrophin-releasing hormone antagonist ganirelix (Org 37462). Hum Reprod 1998;13:294–5. https://doi.org/10.1093/humrep/13.2.294.

[5] Albano C, Smitz J, Camus M, Riethmüller-Winzen H, Van Steirteghem A, Devroey P. Comparison of different doses of gonadotropin-releasing hormone antagonist Cetrorelix during controlled ovarian hyperstimulation. Fertil Steril 1997;67:917–22. https://doi.org/10.1016/s0015-0282(97)81407-0.

[6] Vuong TNL, Ho MT, Ha TD, Phung HT, Huynh GB, Humaidan P. Gonadotropin-releasing hormone agonist trigger in oocyte donors co-treated with a gonadotropin-releasing hormone antagonist: a dose-finding study. Fertil Steril 2016;105:356–63. https://doi.org/10.1016/j.fertnstert.2015.10.014.

[7] Vuong LN, Ho TM, Pham TD, Ho VNA, Andersen CY, Humaidan P. The early luteal hormonal profile in IVF patients triggered with hCG. Hum Reprod 2020;35:157–66. https://doi.org/10.1093/humrep/dez235.

[8] Humaidan P, Quartarolo J, Papanikolaou EG. Preventing ovarian hyperstimulation syndrome: guidance for the clinician. Fertil Steril 2010;94:389–400. https://doi.org/10.1016/j.fertnstert.2010.03.028.

[9] Mocanu E, Redmond ML, Hennelly B, Collins C, Harrison R. Odds of ovarian hyperstimulation syndrome (OHSS) - time for reassessment. Hum Fertil (Camb) 2007;10:175–

81. https://doi.org/10.1080/14647270701194143.
[10] ESHRE guideline: ovarian stimulation for IVF/ICSI† | Human Reproduction Open | Oxford Academic n.d. https://academic.oup.com/hropen/article/2020/2/hoaa009/5827574 (accessed September 11, 2022).
[11] Humaidan P, Nelson SM, Devroey P, Coddington CC, Schwartz LB, Gordon K, et al. Ovarian hyperstimulation syndrome: review and new classification criteria for reporting in clinical trials. Hum Reprod 2016;31:1997–2004. https://doi.org/10.1093/humrep/dew149.
[12] Castillo JC, Haahr T, Martínez-Moya M, Humaidan P. Gonadotropin-releasing hormone agonist for ovulation trigger - OHSS prevention and use of modified luteal phase support for fresh embryo transfer. Ups J Med Sci 2020;125:131–7. https://doi.org/10.1080/03009734.2020.1736696.
[13] Kol S, Humaidan P. IVF and the exogenous progesterone-free luteal phase. Curr Opin Obstet Gynecol 2021;33:188–95. https://doi.org/10.1097/GCO.0000000000000682.
[14] Humaidan P., Bredkjaer HE., Bungum L., Bungum M., Grøndahl ML., Westergaard L., et al. GnRH agonist (buserelin) or hCG for ovulation induction in GnRH antagonist IVF/ICSI cycles: a prospective randomized study. Human Reproduction (Oxford, England) 2005;20:1213–20. https://doi.org/10.1093/humrep/deh765.
[15] Kolibianakis EM, Schultze-Mosgau A, Schroer A, van Steirteghem A, Devroey P, Diedrich K, et al. 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 2005;20:2887–92. https://doi.org/10.1093/humrep/dei150.
[16] Griesinger G., Kolibianakis EM., Papanikolaou EG., Diedrich K., Van Steirteghem A., Devroey P., et al. Triggering of final oocyte maturation with gonadotropin-releasing hormone agonist or human chorionic gonadotropin. Live birth after frozen-thawed embryo replacement cycles. Fertility and Sterility 2007;88:616–21. https://doi.org/10.1016/j.fertnstert.2006.12.006.
[17] Andersen CY, Humaidan P, Ejdrup HB er, Bungum L, Grøndahl ML, Westergaard LG. Hormonal characteristics of follicular fluid from women receiving either GnRH agonist or hCG for ovulation induction. Human Reproduction 2006;21:2126–30. https://doi.org/10.1093/humrep/del119.
[18] Humaidan P, Westergaard LG, Mikkelsen AL, Fukuda M, Yding Andersen C. Levels of the epidermal growth factor-like peptide amphiregulin in follicular fluid reflect the mode of triggering ovulation: a comparison between gonadotrophin-releasing hormone agonist and urinary human chorionic gonadotrophin. Fertil Steril 2011;95:2034–8. https://doi.org/10.1016/j.fertnstert.2011.02.013.
[19] Humaidan P, Polyzos NP, Alsbjerg B, Erb K, Mikkelsen AL, Elbaek HO, et al. 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 2013;28:2511–21. https://doi.org/10.1093/humrep/det249.
[20] Humaidan P, Ejdrup Bredkjaer H, Westergaard LG, Yding Andersen C. 1,500 IU human chorionic gonadotropin administered at oocyte retrieval rescues the luteal phase when gonadotropin-releasing hormone agonist is used for ovulation induction: a prospective, randomized, controlled study. Fertil Steril 2010;93:847–54. https://doi.org/10.1016/j.fertnstert.2008.12.042.
[21] Humaidan P, Alsbjerg B, Elbaek HO, Povlsen BB, Laursen RJ, Jensen MB, et al. The exogenous progesterone-free luteal phase: two pilot randomized controlled trials in IVF patients. Reprod Biomed Online 2021;42:1108–18. https://doi.org/10.1016/j.rbmo.2021.03.011.
[22] Youssef M.A., Van der Veen F., Al-Inany H.G., Mochtar M.H., Griesinger G., Nagi Mohesen

M., et al. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology. The Cochrane Database of Systematic Reviews 2014.

[23] Youssef MA, Van der Veen F, Al-Inany HG, Griesinger G, Mochtar MH, van Wely M. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist assisted reproductive technology cycles. Cochrane Database Syst Rev 2010:CD008046. https://doi.org/10.1002/14651858.CD008046.pub2.

[24] Youssef MA, Al-Inany HG, Aboulghar M, Mansour R, Abou-Setta AM. Recombinant versus urinary human chorionic gonadotrophin for final oocyte maturation triggering in IVF and ICSI cycles. Cochrane Database Syst Rev 2011:CD003719. https://doi.org/10.1002/14651858.CD003719.pub3.

[25] Kol S, Humaidan P, Alsbjerg B, Engmann L, Benadiva C, Garcia-Velasco JA, et al. The updated Cochrane review 2014 on GnRH agonist trigger: repeating the same errors. Reprod Biomed Online 2015;30:563–5. https://doi.org/10.1016/j.rbmo.2015.02.009.

[26] Humaidan P, Polyzos NP. (Meta)analyze this: Systematic reviews might lose credibility. Nat Med 2012;18:1321. https://doi.org/10.1038/nm0912-1321.

[27] Bar Hava I, Blueshtein M, Ganer Herman H, Omer Y, Ben David G. Gonadotropin-releasing hormone analogue as sole luteal support in antagonist-based assisted reproductive technology cycles. Fertil Steril 2017;107:130-135.e1. https://doi.org/10.1016/j.fertnstert.2016.10.011.

[28] Bar-Hava I., Mizrachi Y., Karfunkel-Doron D., Omer Y., Sheena L., Carmon N., et al. Intranasal gonadotropin-releasing hormone agonist (GnRHa) for luteal-phase support following GnRHa triggering, a novel approach to avoid ovarian hyperstimulation syndrome in high responders. Fertility and Sterility 2016. http://www.elsevier.com/locate/fertnstert (accessed January 1, 106AD).

[29] Griesinger G., Verweij P.J.M., Gates D., Devroey P., Gordon K., Stegmann B.J., et al. Prediction of ovarian hyperstimulation syndrome in patients treated with corifollitropin alfa or rFSH in a GnRH antagonist protocol. PLoS ONE 2016. http://www.plosone.org/article/fetchObject.action?uri=info:doi/10.1371/journal.pone.0149615&representation=PDF.

365 **Table 1:** GnRH agonist ovulation trigger protocol used in the present studies

Study	Progesterone at OR+ 7 days	Positive HCG /ET	Pregnancy loss/ET	Clinical pregnancy/ET	Luteal phase support
Humaidan *et al*., 2005	**Mean 39±30 nmol/l**	**29% (14/48)**	**79 % (11/14)**	**6% (3/48)**	**Mic P4 90 mg/day and estradiol 4mg/day**
Humaidan *et al*., 2010	**Mean 74±52 nmol/l**	**48% (63/130)**	**21% (13/63)**	**38% (50/130)**	**1500 IU hCG at OR plus Mic vaginal P4 90 mg/day and E2 4mg/day**
Humaidan *et al*., 2013	**Median 440 IQR, 238-574 nmol/l**	**43% (47/110)**	**9% (4/47)**	**39% (43/110)**	**1500 IU hCG at OR, 1500 IU hCG at OR+5 days as well as vaginal Mic P4 90 mg/twice daily and E2 4 mg/day**
Humaidan *et al*., 2021					**No exogenous P4 or E2 in either group**
OHSS low risk:	**Median 231 IQR, 120-317 nmol/l**	**56% (28/50)**	**10% (5/50)**	**46% (23/50)**	**1500 IU hCG at OR and 1000 IU hCG at OR+4 days.**
OHSS risk:	**Median 249 IQR, 120-313 nmol/l**	**59% (29/49)**	**4% 2/49**	**55% (27/49)**	**1500 IU hCG at OR and 500 IU hCG at OR+4 days.**

366 Legend table 1: GnRHa trigger (Buserelin 0,5mg used in all studies). Abbreviations below.

367 Mic=Micronized, P4=progesterone, E2= estradiol, OR=Oocyte retrieval, ET=embryo transfer