Pirard C, Donnez J, Loumaye E. GnRH agonist as luteal phase support in assisted reproduction technique cycles: results of a pilot study. *Hum Reprod* 2006; **21**:1894–1900.

E.M. Kolibianakis[1,*], G. Griesinger[2] and C.A. Venetis[1]
[1]*Unit for Human Reproduction, 1st Department of Obstetrics and Gynaecology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece*
[2]*Department of Obstetrics and Gynecology, University Clinic of Schleswig-Holstein, Campus Luebeck, Luebeck, Germany*
**Correspondence address. E-mail: stratis.kolibianakis@gmail.com*

doi:10.1093/humupd/dmr055
Advanced Access publication on January 24, 2012

Reply: GnRH agonist for triggering final oocyte maturation: time for a critical evaluation of data

Sir,

We read with interest the letter by Kolibianakis *et al.*, concerning our consensus paper by The Copenhagen GnRH agonist Triggering Workshop Group (Humaidan *et al.*, 2011).

In their letter, the authors conclude that ovarian hyperstimulation syndrome (OHSS) is reduced only in the OHSS high-risk patient and not in the normal OHSS-risk patient, by further subdividing the population of six recently published studies into normo-ovulatory (normal OHSS-risk patients) (Humaidan *et al.*, 2006, 2010; Pirard *et al.*, 2006; Papanikolaou *et al.*, 2011) and high-risk OHSS patients—mainly polycystic ovary syndrome patients (Babayof *et al.*, 2006; Engmann *et al.*, 2008), using a modified luteal phase support after GnRHa trigger.

Clearly, the authors of the current letter focus on statistical significance when analyzing the results of the four trials in the normal OHSS-risk patient, using a modified luteal phase support; however, still not 1 patient of a total of 188 patients triggered with GnRHa developed OHSS, compared with 3 of 189 patients (2%) triggered with hCG.

Moreover, the findings of the four studies performed in a donor oocyte population are completely ignored (Acevedo *et al.*, 2006; Galindo *et al.*, 2009; Melo *et al.*, 2009; Sismanoglu *et al.*, 2009). When analyzing the data from these studies, the OHSS incidence is 0% (0/230) after GnRHa trigger versus 8% (19/230) after hCG trigger. Importantly, the oocyte donor is a normo-ovulatory volunteer and special care is, therefore, taken to avoid OHSS. However, as mentioned, 8% of oocyte donors developed early-onset OHSS after hCG trigger. This further supports the OHSS preventive effect of GnRHa trigger even in the normal OHSS-risk patient.

The concept of modified luteal phase support after GnRHa trigger aims at transferring fresh embryos with a reproductive outcome comparable to that seen after hCG trigger. We are still in the process of describing the most optimal luteal phase protocol after GnRHa trigger—a protocol which should secure the reproductive outcome of the patient as well as eliminate the risk of OHSS. On this basis, we founded The Copenhagen GnRH Agonist Triggering Workshop Group—an international network of clinical scientists with a specific interest in GnRHa triggering.

Based on our present knowledge, we disagree with the authors' statement that after further subdividing the data, 'the picture is significantly different'. Although low-risk patients by definition will have a lower risk of developing OHSS, when hCG is used for triggering final oocyte maturation, only the use of a GnRHa trigger will completely eliminate that risk. Considering the medical, social and economical consequences of even one single case of OHSS, the clinical implications are not insignificant.

Although we understand that hCG triggering still remains the standard of care for triggering final oocyte maturation for the OHSS low-risk patient, we maintain that based on the available data, GnRHa triggering is a valid alternative to hCG triggering for both the low-risk and the high-risk patients.

Finally, we certainly agree that the time has come for a 'critical evaluation of data' as the health and well-being of a patient undergoing controlled ovarian stimulation is beyond the confidence interval of statistical significance.

References

Acevedo B, Gomez-Palomares JL, Ricciarelli E, Hernandez ER. Triggering ovulation with gonadotropin-releasing hormone agonists does not compromise embryo implantation rates. *Fertil Steril* 2006;**86**:1682–1687.

Babayof R, Margalioth EJ, Huleihel M, Amash A, Zylber-Haran E, Gal M, Brooks B, Mimoni T, Eldar-Geva T. Serum inhibin A, VEGF and TNFalpha levels after triggering oocyte maturation with GnRH agonist compared with HCG in women with polycystic ovaries undergoing IVF treatment: a prospective randomized trial. *Hum Reprod* 2006;**21**:1260–1265.

Engmann L, DiLuigi A, Schmidt D, Nulsen J, Maier D, Benadiva C. 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* 2008;**89**:84–91.

Galindo A, Bodri D, Guillen JJ, Colodron M, Vernaeve V, Coll O. Triggering with HCG or GnRH agonist in GnRH antagonist treated oocyte donation cycles: a randomised clinical trial. *Gynecol Endocrinol* 2009;**25**:60–66.

Humaidan P, Bungum L, Bungum M, Yding Andersen C. Rescue of corpus luteum function with peri-ovulatory HCG supplementation in IVF/ICSI GnRH antagonist cycles in which ovulation was triggered with a GnRH agonist: a pilot study. *Reprod Biomed Online* 2006;**13**:173–178.

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**:847–854.

Humaidan P, Kol S, Papanikolaou EG. GnRH agonist for triggering of final oocyte maturation: time for a change of practice? *Hum Reprod Update* 2011;**17**:510–524.

Melo M, Busso CE, Bellver J, Alama P, Garrido N, Meseguer M, Pellicer A, Remohi J. GnRH agonist versus recombinant HCG in an oocyte donation programme: a randomized, prospective, controlled, assessor-blind study. *Reprod Biomed Online* 2009;**19**:486–492.

Papanikolaou EG, Verpoest W, Fatemi H, Tarlatzis B, Devroey P, Tournaye H. A novel method of luteal supplementation with recombinant luteinizing hormone when a gonadotropin-releasing hormone agonist is used instead of human chorionic gonadotropin for ovulation triggering: a randomized prospective proof of concept study. *Fertil Steril* 2011;**95**:1174–1177.

Pirard C, Donnez J, Loumaye E. GnRH agonist as luteal phase support in assisted reproduction technique cycles: results of a pilot study. *Hum Reprod* 2006; **21**:1894–1900.

Sismanoglu A, Tekin HI, Erden HF, Ciray NH, Ulug U, Bahceci M. Ovulation triggering with GnRH agonist vs. hCG in the same egg donor population undergoing donor oocyte cycles with GnRH antagonist: a prospective randomized cross-over trial. *J Assist Reprod Genet* 2009;**26**:251–256.

P. Humaidan[1,*], S. Kol[2], C. Benadiva[3], L. Engmann[3], E.G. Papanikolaou[4] and on behalf of the 'The Copenhagen GnRH Agonist Triggering Workshop Group'[5]

[1]*The Fertility Clinic, Department D, Odense University Hospital, Odense, Denmark*
[2]*Department of Obstetrics and Gynecology, IVF Unit, Rambam Medical Center, Haifa, Israel*
[3]*Department of Obstetrics and Gynecology, Center for Advanced Reproductive Services, University of Connecticut School of Medicine, Farmington, CT, USA*
[4]*Assisted Reproduction Unit, Aristotle University of Thessaloniki, Thessaloniki, Greece*

[5]*P. Humaidan, S. Kol, E.G. Papanikolaou, L. Engmann, C. Benadiva, J. Itskovitz-Eldor, E.J. Margalioth, E. Ricciarelli, D. Bodri, J.C. Castillo-Farfan, J.A. Garcia-Velasco, C. Yding Andersen, P. Devroey and B. Tarlatzis*

**Correspondence address. E-mail: peter.humaidan@ouh.regionsyddanmark.dk*

doi:10.1093/humupd/dmr056
Advanced Access publication on January 24, 2012