with the latest research, adding LH activity to the luteal phase after
GnRHa triggering in addition to the standard luteal phase support with
estradiol and progesterone, it thus seems that we have detected the
problems of the luteal phase insufficiency previously seen.

Youssef et al. (2009) refer to their Cochrane review, presented at
this year ESHRE meeting. This review includes a total of 713 patients
randomized to either GnRHa or hCG for triggering of final oocyte
maturation. The authors conclude that although GnRHa triggering sig-
nificantly reduces moderate/severe OHSS, ‘GnRHa triggering results
in significantly lower birth rate and ongoing pregnancy likelihood—
and should, therefore, not be used in general practice for final
ovocyte maturation’.

We, like others, believe in the strength and relevance of
meta-analyses. However, the relevance of a meta-analysis including
713 cycles only, should be critically questioned, especially if studies
included also have employed different modes of luteal phase
support. In addition, although moderate/severe OHSS has a low inci-
dence after ovarian stimulation, it still represents the main morbidity
and mortality cause in IVF. In this context, GnRHa triggering is of para-
mount importance in high responder patients (Griesinger et al., 2007;
Humaidan et al., 2009b).

Moreover, the fact, that the implantation rate after hCG triggering in
IVF is approximately 30% at its best, indicates that the luteal phase is
probably the last black box in ART, irrespective of the mode of trig-
gerriging. Therefore, the understanding of the luteal phase is of
immense importance for the improvement of our results to the
benefit of the patient.

GnRHa triggering of final oocyte maturation has taught us that the
commonly used luteal phase support in IVF does not secure a func-
tional endometrium. Instead of meta-analyzing studies employing
different luteal phase support schemes, lessons from the luteal
phase support from GnRHa triggering, should be extended to luteal
phase support after hCG triggering in order to find the most appro-
piate protocol for luteal phase support.

In conclusion, we have only just started to understand the problems
concerning the luteal phase insufficiency seen after GnRHa triggering.
The results of the largest RCT, using a supplementary bolus of 1500 IU
hCG on the day of oocyte aspiration in addition to a standard luteal
phase support, now show a non-significant difference in live birth
rate (24 versus 31%). We are thus on the right path. Moreover, the
fact that no OHSS was seen and that more MII oocyte were retrieved
in the GnRHa group further encourages us to refine the GnRHa trig-
gerriging protocol. This could eventually lead to a paradigm shift from
hCG triggering to GnRHa triggering, coinciding with the increasing
use of GnRHa antagonist protocols.

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Reply: GnRHa to trigger final oocyte maturation: a time to reconsider

Sir

We are pleased by the feed-back from Dr Youssef et al., regarding our
latest review on the most recent clinical trials employing a GnRH
agonist (GnRHa) to trigger final oocyte maturation (Humaidan et al.,
2009c). In this review we conclude, from our own published results
and the results of other trials, that GnRHa triggering of final oocyte
maturation is now a valid alternative to hCG triggering, taking into
account that additional luteal phase support in terms of LH activity
supplementation is mandatory.

In our review we, among others, refer to the results of the largest
RCT (302 patients) until now on GnRHa triggering of final oocyte
maturation (Humaidan et al., 2009a), reporting a non-significant differ-
ence in live birth rate between GnRHa triggering and hCG triggering
(24 versus 31%, respectively). These results thus corroborate the
results of a previous pilot study (Humaidan et al., 2006), showing that
supplementation with a small bolus of 1500 IU hCG on the day of
ovocyte aspiration, rescues the luteal phase and secures the repro-
ductive outcome when GnRHa is used to trigger final oocyte
maturation.

We have thus come a very long way since the disappointing reports
from the first RCTs focusing on the reproductive outcome when
GnRHa was used to trigger final oocyte maturation (Humaidan et al.,
2005; Kolibianakis et al., 2005). In these studies an extremely
low ongoing pregnancy rate (6%) and an unacceptably high early preg-
nancy loss rate (80%) was reported, despite standard luteal phase
support with vaginal progesterone and estradiol.

As we discuss in our review, the reason for the low reproductive
outcome seen previously when GnRHa was used to trigger final
ovocyte maturation, seems to be an LH depleted luteal phase,
induced not only by differences in the profile and duration of the
surge of gonadotrophines, elicited by a bolus of GnRHa (Gonen et al.,
1990; Tsiskovitz et al., 1991), but also by the supraphysiological
steroid level (estradiol and progesterone), exerting a negative feed-
back on LH secretion by the pituitary (Tavaniotou et al., 2001;
Tavaniotou and Devroey, 2006).

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A fatal case of ovarian hyperstimulation syndrome with perforated duodenal ulcer

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Ovarian hyperstimulation syndrome (OHSS) is a disturbing complication in infertility treatment. OHSS treatments aim to reduce vascular permeability, and include antiprogestin, anti vascular endothelial growth factor (VEGF), dopamine agonist and inhibition of VEGFR-2 phosphorylation (SU5416) (Soares et al., 2008). We wish to draw attention to a recent case of ours, a giant perforated duodenal ulcer, an extremely rare associated disorder of OHSS. Only one similar case has been reported previously (Uhler et al., 2001). Psychological stress from infertility and IVF may be instrumental in inducing peptic ulcers (Reed, 2002), and therefore prophylactic treatment of stress ulcers is critical in hyperstimulation situations (Barletta et al., 2002).

We recently treated a 30-year-old nulligravid woman with amenorrhea and infertility (>8 years). She had no history of serious clinical illness, clinical examination was normal; she had normal hysterosalpingography and slight galactorrhoea, ultrasonic pelvic examination showed a small uterus, endometrial diameter of 3 mm and normal ovaries. Laboratory data showed slightly increased serum level of prolactin (601 mlU/ml).

A treatment regime, Cabergoline 0.5 mg twice per week and human menopausal gonadotrophin (hMG) 225 IU per day for 6 days, was begun. Vaginal ultrasound at Day 7 showed numerous small follicles with the largest diameter of 13 mm. In order to prevent hyperstimulation syndrome, human chorionic gonadotrophin (hCG) administration was retarded for 4 days and she received only one ampoule 75 IU hMG every other day. In total, 20 hMG ampoules (18 + 2) were administered, and after 4 days 5000 hCG was injected. Three days after injection of hCG, patient was admitted in hospital with abdominal pain and vomiting. Blood examination showed WBC 14 900/ml, haemoglobin 14.5 g/dl, hematocrit 45.2%, platelet count 250 000/ml albumin 4 g/l, creatinine 1.5 mg/dl.

Abdominal ultrasound demonstrated large ovaries (12–13 cm) with numerous follicles and some fluid in the posterior cul-de-sac. One day after admission she was transferred to intensive care unit (ICU) because of cyanois and severe abdominal pain. Peritoneal fluid was aspirated under abdominal ultrasound guide, which contained elevated protein (8 g/dl), WBC (2000/ml), RBC (2200/ml) counts. She developed upper mid abdominal pain on the seventh day, and her status continued to deteriorate. High fever appeared 2 days after ICU admission. Patient was intubated and mechanical ventilation started immediately. A laparotomy was performed to investigate cystic ovarian torsion or rupture of ovary. Little fluid was detected in abdomen, ovaries were large and very soft, the right ovary contained a yellowish fluid, and no rupture or torsion and no injured intestine was observed. A large fragment of the ovaries were removed and a pelvic drain was inserted. Three to four days after laparotomy large volume of yellow discharge from the abdominal drain was observed, and after opaque meal X-ray, duodenal perforation was diagnosed. A surprising, 3–4 cm, giant perforated duodenal ulcer in anterior wall of duodenum was observed in the second laparotomy. A large drain was inserted into the duodenum via the ulcer opening, and another one was left in the peritoneum close to the ulcer to collect the probable remaining secretions (Gupta et al., 2005).

Despite broad spectrum antibiotic therapy, high fever continued 25 days after the operation. Forty eight days after arrival, a third laparotomy was performed but after 2 h the patient died.

In the final week, the patient developed symptoms of disseminated intravascular coagulation, hematuria and low platelet count.

To our knowledge, only one previous case of duodenal perforation with critical OHSS has been reported (Uhler et al., 2001). This case thus poses the question; should stress ulcer and duodenal perforation be included in complications of OHSS or not?