

Ovarian stimulation for IVF - a balance between efficacy and safety

Akademisk avhandling

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av

Åsa Magnusson

Fakultetsopponent:
Professor Nick S. Macklon
Department of Obstetrics and Gynaecology
University of Copenhagen
Zealand University Hospital

Avhandlingen baseras på följande delarbeten:

- I. Magnusson Å, Nilsson L, Oleröd G, Thurin-Kjellberg A, Bergh C. **The addition of anti-Müllerian hormone in an algorithm for individualized hormone dosage did not improve the prediction of ovarian response-a randomized, controlled trial.** *Hum Reprod* 2017;1:811-819
- II. Magnusson Å, Oleröd G, Thurin-Kjellberg A, Bergh C. **The correlation between AMH assays differs depending on actual AMH levels.** *Hum Reprod Open* 2017;4:1-5
- III. Magnusson Å, Källén K, Thurin-Kjellberg A, Bergh C. **The number of oocytes retrieved during IVF; a balance between efficacy and safety.** *Hum Reprod* 2018;33:58-64
- IV. Magnusson Å, Wennerholm U-B, Petzold M, Källén K, Thurin-Kjellberg A, Bergh C. **The association between the number of oocytes retrieved for IVF, perinatal outcome and obstetric complications.** *Submitted 2018*

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Abstract

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Department of Obstetrics and Gynecology, Institute of Clinical Sciences, The Sahlgrenska Academy, University of Gothenburg, SE-413 45 Gothenburg, Sweden.

Background: To increase the chance of a live birth after in vitro fertilization (IVF) a controlled ovarian hormonal hyperstimulation (COH) is used to collect a certain number of oocytes for fertilization. COH is a potent hormonal treatment with a potential risk of serious adverse events.

Aim: To assess the ovarian response, expressed as the number of oocytes retrieved for IVF that results in an optimal balance between efficacy and safety.

Methods: *Paper I:* A randomized controlled trial (RCT), including 308 patients, comparing the performance of a dosage algorithm based on anti-Müllerian hormone (AMH) to one without AMH for prediction of the desired ovarian response, 5 to 12 oocytes. *Paper II:* A cohort study including 269 serum samples analyzed in a parallel setting investigating the correlation between the two AMH assays used in the RCT. *Paper III:* All fresh IVF cycles performed in Sweden 2007-2013 (n=77,956) and their subsequent frozen embryo transfer (FET) cycles (n=36,270) performed 2007-2014 were included in a population based registry study. Four major outcomes were investigated in relation to the number of oocytes retrieved; live birth rate (LBR), cumulative LBR per fresh and all subsequent FET cycles, incidence of severe ovarian hyperstimulation syndrome (OHSS) and incidence of thromboembolic events. *Paper IV:* All singletons born after fresh IVF cycles in Sweden 2002-2015 (n=27,359) were included in a population based registry study. Five main perinatal outcomes (preterm birth [PTB], very preterm birth [VPTB], small for gestational age [SGA], major birth defects and peri/neonatal death) and two main obstetric outcomes (hypertensive disorders of pregnancy [HDP] and placenta praevia) were investigated in relation to the number of oocytes retrieved. Data was adjusted for maternal age, parity, smoking, BMI, cause of infertility, maternal educational level, maternal country of birth, treatment period, embryo stage, fertilization method (IVF/ICSI), OHSS and vanishing twin.

Results: *Paper I:* There was no significant difference between the two algorithms regarding the primary outcome variable rate of patients with between 5 and 12 oocytes retrieved. *Paper II:* The correlation between the two assays was good, although there were considerable differences between the two assays depending on the actual AMH levels. *Paper III:* LBR after fresh cycles increased by the number of oocytes retrieved, although reaching a plateau at 11 oocytes while cumulative LBR evened out at 20 oocytes retrieved. OHSS increased rapidly if more than 18 oocytes were retrieved. Thromboembolic events were rare and occurred mainly if more than 15 oocytes were retrieved. *Paper IV:* There was no significant association between the number of oocytes retrieved and any of the perinatal outcomes or HDP. There was however a significant association between the number of oocytes retrieved and placenta praevia.

Conclusions: 1. Inclusion of AMH in dose decision did not result in a better prediction of ovarian response. 2. AMH assays have considerable and clinically important methodological problems 3. Ovarian stimulation up to 18 to 20 oocytes retrieved seems optimal from a cumulative live birth perspective, keeping severe adverse events at a reasonable level. 4. Ovarian response was not associated with adverse perinatal outcome though a significant association was found with the risk of placenta praevia.

Keywords: AMH/ovarian response/efficacy outcome/safety outcome

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