

## Unilateral ovarian endometriotic cysts do not impair follicles development, oocyte and embryo quality: report on eight controlled ovarian hyperstimulations and ICSI cycles

Sir,

We thank Benaglia *et al.* (2009) for their interesting study. In contrast to Nakagawa *et al.* (2008), they found that spontaneous ovulation is impaired in ovaries affected by endometriotic cysts. The same group previously observed hypo-responsiveness of the affected ovaries to gonadotrophin-induced controlled ovarian hyperstimulation (COH) (Somigliana *et al.*, 2006a, b). In all studies, ovulation was only presumed by ultrasound (US) criteria.

We report herein on three infertile patients with unilateral ovarian endometriotic cysts diagnosed according to current US criteria (Mais *et al.*, 1993) and undergoing three minimally stimulated (one patient) and five COH ICSI cycles (two patients). All health information regarding the patients have been rendered anonymous and they consented to this publication. Institutional Review Board approval has been obtained for this clinical study. This study is in accordance with the Helsinki Declaration of 1975 regarding human experimentation.

Patient #1: L.P. aged 37, secondary infertility, was diagnosed with one 16 mm endometriotic cyst on her right ovary. She was offered a minimally stimulated ICSI cycle using rFSH (Gonal F, Merck Serono, Rome, Italy) and GnRH antagonist (Cetrorelix, Cetrotide, Merck Serono, Rome, Italy) due to severely impaired ovarian reserve (3rd day FSH > 16 mUI/ml, estradiol > 80 pg/ml and anti-mullerian hormone < 2 pmol/l on two different occasions) and lack of response to COH. In three consecutive ICSI cycles, one follicle reached 17 mm mean diameter and after hormonal and US check, ovulation was triggered by using 10 000 U hCG from two different batches. Cycle #1: one follicle grew from the right ovary, one meta-phase II (MII) oocyte was retrieved and microinjected and one first-grade (top quality) embryo (according to a three-grade score, based on the size and equality of the blastomeres) was transferred. No pregnancy ensued. Cycle #2: the same protocol as for Cycle #1 was used and one follicle grew from the right ovary, but no oocyte was retrieved. Cycle #3: the same protocol as for Cycle #1 was used, one follicle grew from the right ovary, one MII oocyte was retrieved and microinjected and one second-grade embryo was transferred. No pregnancy ensued.

Patient #2: A.D., aged 33, primary infertility, was diagnosed with two endometriotic cysts (mean diameter 22 and 12 mm) on her right ovary. After discussing the arguments for and against the surgical

removal of endometriomas (Somigliana *et al.*, 2006a, b) and the success rates of intrauterine insemination and ICSI, the patients chose to be treated by ICSI. In two consecutive ICSI cycle, a 'long' protocol was offered by using rFSH (Puregon, Organon, the Netherlands) and agonist (buserelin acetate, Suprefact; Aventis Farma, Milan, Italy) and after hormonal and US check, ovulation was triggered by using 10 000 U hCG from two different batches: Cycle #1: 7/10 follicles grew on the right ovary. No oocyte was retrieved; Cycle #2: 6/10 follicles grew on the right ovary. Two MII oocytes were retrieved and one second-grade embryo was transferred. No pregnancy ensued. In two other ICSI cycle, a 'short' protocol was offered using rFSH and GnRH antagonist (ganirelix, Orgalutran, Organon, the Netherlands) and after hormonal and US check, ovulation was triggered by using 10 000 U hCG from two different batches: Cycle #3: five of eight follicles grew on the right ovary. Five MII oocytes were retrieved and microinjected, and two first-grade embryos were transferred. No pregnancy ensued; Cycle #4: 9/16 follicles grew on the right ovary. Four of five MII oocytes were retrieved from the right ovary. All oocytes were microinjected and two of three oocytes were fertilized from the right ovary. From the right ovary oocytes, one first-grade and one second-grade embryos ensued, while from the left ovary oocyte, one third-grade embryo ensued. All embryos were transferred on Day 2. Pregnancy outcome is still pending.

Patient #3: T.D., aged 35, primary infertility, was diagnosed with one 10 mm endometriotic cyst on her right ovary. After seminal fluid and tubal controls, she was offered intrauterine insemination, which was reverted to ICSI due to hyper-responsiveness to low dosage rFSH (Puregon, Organon, the Netherlands). GnRH antagonist (ganirelix, Orgalutran, Organon, the Netherlands) was therefore added to the protocol to inhibit ovulation: four of eight follicles grew on the right ovary. Peak estradiol and LH were found at 1600 pg/ml and 3 mUI/ml, respectively. Ovulation was triggered by using 10 000 U of hCG from two different batches. No oocyte was retrieved.

Although no conclusion can be drawn from our small series, we found that 33/55 (60%) follicles grew on the endometriotic cyst affected ovary, whatever the COH protocol used. Interestingly, in our series, oocyte and embryo quality was also checked and found widely optimal (Suzuki *et al.*, 2005). In one cycle (Patient #2, Cycle #4), oocyte and embryo quality from both ovaries were separately assessed and no impaired function, specific to the endometrioma-bearing ovary, was observed. Instead, the absence of retrieved oocytes in three out of eight (37%) cycles and the absence of pregnancy (one case still pending), despite good embryo quality and young patients' age in most cases, suggest a general impairment of spontaneous and induced folliculogenesis and/or implantation problems in these patients, independently from the presence of endometriomas, even though Patient #1 (severely impaired ovarian reserve) is excluded from the analysis. These observations may confirm that

removal of endometriomas may not be beneficial to COH (Somigliana *et al.*, 2006a, b); however, the discussion is still open in term of pregnancy rate.

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Angelo Tocci<sup>1,3</sup>, Caterina Lucchini<sup>1</sup>, Maria Giulia Minasi<sup>2</sup> and Ermanno Greco<sup>2</sup>  
<sup>1</sup>Reproductive Medicine, Nuova Villa Claudia Clinic, Rome, Italy  
<sup>2</sup>Reproductive Medicine, European Hospital Clinic, Rome, Italy

<sup>3</sup>Correspondence address. E-mail: info@donnamed.it

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## Reply: Report of three infertile patients with unilateral ovarian endometriotic cysts diagnosed by ultrasound

Sir,

We appreciate Tocci *et al.*'s consideration of our study (Benaglia *et al.*, 2009) and adding new insight to this topic. The endometrioma-related damage to ovarian reserve is still debated.

We agree that it is difficult to measure ovarian function directly and that the ovarian response to gonadotrophin stimulation is currently considered the most appropriate surrogate measurement for ovarian function. Therefore, we consider the investigation of IVF outcome on patients with ovarian endometriomas at the time of oocyte retrieval to be very interesting.

In 2006, Somigliana *et al.* recruited 36 patients with monolateral endometrioma that were undergoing IVF. The presence of ovarian endometriomas was associated with a reduced responsiveness to gonadotrophin stimulation. In this study, the number of codominant follicles developing in affected gonads was reduced when compared with

the contralateral intact ovaries of the same patients. However, the number of analyzed cases was quite small because only patients at first cycle of hyperstimulation were considered for the study, as should be done, and the difference between the affected ovary and the healthy ovary was not statistically significant (Somigliana *et al.*, 2006).

Tocci *et al.* reported three patients but they lack the description of the ovarian responsiveness of the whole population that underwent IVF and were affected by ovarian endometriomas. Moreover, the reduced ovarian responsiveness seems to be further supported by the observation that this effect is dependent on the size and number of the cysts, and they reported four cysts with a mean diameter <3 cm. Moreover, we do not necessarily deny that women with endometriomas at the time of IVF may have a high-quality responsiveness but it is necessary to confirm this conclusion in a larger group.

Finally, in our article 'Endometriotic ovarian cysts negatively affect the rate of spontaneous ovulation' (Benaglia *et al.*, 2009), our conclusion was that the presence of endometriomas *per se* may negatively influence ovarian function but the magnitude of the negative effect on ovarian reserve is unknown. A minimal difference in quantity of ovarian damage may reflect a remarkable difference in ovulation rate.

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Laura Benaglia<sup>1</sup> and Edgardo Somigliana  
 Department of Obstetrics and Gynecology,  
 Fondazione Ospedale Maggiore Policlinico,  
 Mangiagalli e Regina Elena, Italy

<sup>1</sup>Correspondence address. E-mail: laurabenaglia@hotmail.it

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## Reply: A new method for testing a hypothesis on a cause of polycystic ovary syndrome

Sir,

I was delighted to see Dr James' brilliantly simple suggestion for testing the hypothesis that exposure to high levels of androgens *in utero* is a cause of polycystic ovary syndrome, a hypothesis which was re-iterated in my recent article (Homburg, 2009). We have taken up the idea with relish and thanks and have started a sibling-sex survey and counting.

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