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Article

Do endometriomas grow during ovarian stimulation for assisted reproduction? A three-dimensional volume analysis before and after ovarian stimulation

Ayse Seyhan [a], ***Bulent Urman*** [a,b], ***Engin Turkgeldi*** [c], ***Baris Ata*** [b,*]

[a] *Assisted Reproduction Unit of the American Hospital of Istanbul, Güzelbahçe Sok, No:20 34365 Nişantaşı, Istanbul, Turkey*

[b] *Department of Obstetrics and Gynecology, Koç University School of Medicine, Davutpaşa Caddesi No:4 34010 Topkapı, İstanbul, Turkey*

[c] *Department of Obstetrics and Gynecology, Koç University Hospital, Davutpaşa Caddesi No:4 34010 Topkapı, İstanbul, Turkey*

Ayse Seyhan graduated from the Istanbul School of Medicine. After residency training in Obstetrics and Gynaecology, she completed a clinical fellowship in ultrasound in reproductive medicine at the McGill University Reproductive Center between 2010 and 2012. Her research is focused on clinical aspects of assisted reproduction.

KEY MESSAGE

Endometrioma volume significantly increased during ovarian stimulation for assisted reproduction techniques; however, the absolute increase is small and possibly transient and clinically insignificant.

A B S T R A C T

Whether endometriomas grow because of supraphysiological oestradiol levels attained during ovarian stimulation for assisted reproduction techniques is a concern. In this prospective study, 25 women with 28 endometriomas underwent three-dimensional ultrasound using sono-automated volume calculation software. Endometrioma volume was measured on the first day of gonadotrophin injection (V1) and the day of ovulation trigger (V2). Nine (36%) women were stimulated in a gonadotrophin releasing hormone antagonist protocol (GnRH), 13 (52%) in a long, and three (12%) in an ultra-long GnRH agonist protocol. Mean duration of stimulation was 10.3 days with median total gonadotrophin dose of 4500 IU/day. Median number of cumulus oocyte complexes was five, and metaphase-two oocytes was four. None of the endometriomas were punctured during oocyte retrieval. Median V1 was 22.2 ml (12–30 ml) and median V2 was 24.99 ml (11.2–37.4 ml) with $P = 0.001$. Twenty-three out of 28 endometriomas (82%) grew to some extent during ovarian stimulation. Endometrioma growth was positively correlated with prestimulation cyst volume (Correlation coefficient 0.664; $P < 0.01$). Although the 3-ml average growth was statistically significant, it could be regarded as clinically insignificant.

* Corresponding author.
E-mail address: barisata@ku.edu.tr (B Ata).

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Introduction

Endometriosis is a chronic condition that is characterized by the presence of endometrial glands and stroma outside the uterine cavity. Ovarian endometriotic cysts are present in about 20–40% women with endometriosis (Redwine, 1999; Vercellini et al., 2003). Endometriosis is associated with subfertility, and endometrioma is often diagnosed during infertility work-up. Many women with ovarian endometriomas will eventually undergo an assisted reproduction technique cycle for endometriosis-associated infertility or for other indications. Optimal management of endometrioma before an assisted reproduction technique cycle, however, is controversial. Current evidence supports a conservative approach, as the presence of an endometrioma does not decrease live birth rates (Hamdan et al., 2015). Moreover, surgical excision, rather than being beneficial, may adversely affect ovarian reserve thereby decreasing the number of collected oocytes (Hamdan et al., 2015). As a result, many women with endometriomas undergo an assisted reproduction technique cycle without surgical excision.

Endometriosis is an oestrogen-dependent condition. Oestrogen stimulates the growth of ectopic endometriotic foci, and supraphysiological oestradiol levels associated with ovarian stimulation could possibly lead to their growth (Garcia-Velasco and Somigliana, 2009). Previously published studies with conventional two-dimensional ultrasound reported that endometrioma size remained unchanged after ovarian stimulation for assisted reproduction techniques (Benaglia et al., 2009, 2011). Two-dimensional ultrasound measurements of ovarian follicles have notoriously poor accuracy and reproducibility, especially in the presence of multi-follicular growth in assisted reproduction technique cycles (Ata and Tulandi, 2011). Similar limitations can be anticipated in the assessment of endometriomas within stimulated ovaries. Three-dimensional ultrasound technology and automatic volume calculation software (SonoAVC) accurately measure ovarian structures with less inter- and intra-observer variation than conventional two-dimensional ultrasound (Ata and Tulandi, 2011). The aim of the present study was to determine whether ovarian stimulation is associated with an increase in endometrioma volume as measured by SonoAVC.

Materials and methods

This prospective study was conducted in the Assisted Reproduction Center of the American Hospital of Istanbul, between April 2015 and March 2016. Koc University Clinical Research Ethics Committee approved the study protocol on December 26, 2014 (reference number: 2014.199.IRB1.013), and all participants provided written informed consent. All women who were due to start ovarian stimulation for assisted reproduction techniques were eligible for participation if they had at least one endometrioma. An endometrioma was defined by the visualization of an ovarian cyst with regular margins and ground-glass echogenicity on transvaginal ultrasound examination. The presence of the cyst was confirmed at least on two separate examinations carried out at least one month apart to rule out other haemorrhagic cysts that could be confused with an endometrioma (Exacoustos et al., 2014; Savelli, 2009).

Ovarian stimulation protocols are defined elsewhere (Ata et al., 2017). Briefly, the long gonadotrophin releasing hormone (GnRH) agonist involved daily subcutaneous injections of 0.5 mg leuprolide acetate (Lucrin Daily, Abbot), starting from the mid-luteal phase of the preceding cycle until the day of ovulation trigger. The GnRH antagonist protocol involved daily subcutaneous injection of 0.25 mg cetrorelix acetate (Cetrotide, MerckSerono) starting from the sixth day of ovarian stimulation until the day of ovulation trigger. Gonadotrophin injections were started on the second or third day of menstrual bleeding, and daily dosage ranged between 150 and 450 IU at the physician's discretion. When two or more follicles reached 18 mm or over in diameter, 250 µg recombinant HCG (Ovitrelle, MerckSerono) was administered to be followed by transvaginal oocyte retrieval 36 h later. In patients who underwent an embryo transfer, one or two embryos were transferred on day 3 or 5 using a Wallace or Cook catheter.

Assessment of endometrioma volume

Participants underwent two- and three-dimensional ultrasound monitoring of ovarian stimulation with a Voluson E8 using SonoAVC software (General Electric, Kratz, Austria). A single investigator (AS) conducted all scans with a 5–9 mHz intravaginal probe. Endometrioma volume was measured on the first day of gonadotrophin injection (V1) and the day of ovulation trigger (V2).

A three-dimensional volume of each ovary was captured without taking any automated measurements. Raw ovarian volumes were labelled with an identification number and stored. One month after completion of data collection, the ovarian volumes were analysed with SonoAVC in random order to prevent remembering the participants and the day of measurements, i.e. V1 or V2. SonoAVC automatically analyses the captured volume in voxels, i.e. three-dimensional equivalent of two-dimensional pixel, and checks for differences between echogenicity of adjacent voxels. When the difference between the echogenicity of two adjacent voxels exceeds a predefined threshold, they are identified as separate structures by the software. Thus, hypoechogenic follicles within the captured ovarian volume are identified and a set of measurements are generated for each follicle. The volume calculation is based on the voxel count within the identified follicle. Mean follicular diameter (MFD) is the arithmetic mean of the three longest orthogonal diameters.

SonoAVC provides post-processing options. Briefly, any follicles that are overlooked by the software can be added to, and any hypoechoic regions, such as free fluid around the ovaries or blood vessels adjacent to the ovaries, which could be erroneously included in the follicle count, can be excluded from the follicle count by simply using the 'add/remove' function. The 'cut' function is used to separate any adjacent follicles with thin follicular walls, which could have been erroneously identified and measured as a single follicle by the software, and to trim follicular borders to fit to the exact shape of the follicle. Rarely, a single follicle with heterogenous echogenicity can be identified as separate follicles by the software, and the 'merge' function is used to combine them to be counted as a single follicle. The settings of growth and separation within the software were kept uniform at default values of 'mid' for all follicle measurements.

Although SonoAVC is developed for follicle measurements, the unique echogenicity of endometriomas differ from both ovarian follicles and ovarian tissue, and therefore enable their identification as separate structures by SonoAVC (**Figure 1**). In the case of incomplete identification, endometrioma borders can be precisely marked by using the above mentioned post-processing options.