Power Doppler ultrasound assessment of ovarian perifollicular blood flow in women with polycystic ovaries and normal ovaries during in vitro fertilization treatment

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Objective: To evaluate whether ovarian perifollicular blood flow (PFBF) varies by ultrasound among women with polycystic and normal ovaries undergoing in vitro fertilization (IVF).
Design: Prospective observational cohort study of women undergoing IVF treatment.
Setting: Department of reproductive medicine at a university teaching hospital.
Patient(s): Thirty four women with regular spontaneous ovulatory menstrual cycles undergoing IVF divided into two groups according to findings on a baseline transvaginal ultrasound scan: group 1 consisted of 20 women with ultrasound-evident normal ovaries (USNO group), and group 2 consisted of 14 women with ultrasound-evident polycystic ovaries (USPCO group).
Intervention(s): Serial transvaginal power Doppler ultrasound assessments throughout the follicular phase of ovarian stimulation.
Main Outcome Measure(s): Ovarian PFBF and ovarian stromal artery pulsatility index.
Result(s): Women with USPCO had a significantly lower ovarian stromal artery pulsatility index at the time of the first ultrasound assessment before starting the FSH injections compared with USNO women. However, there was no difference in ovarian PFBF between women with USPCO and USNO during the follicular phase of ovarian stimulation for IVF.
Conclusion(s): There is no difference in ovarian follicular vascularity between women with polycystic and normal ovaries during ovarian stimulation at IVF treatment. (Fertil Steril® 2005;83:945–54. ©2005 by American Society for Reproductive Medicine.)

Key Words: Polycystic ovaries, Doppler ultrasound, IVF, ovarian perifollicular blood flow, follicular vascularity

Polycystic ovary syndrome (PCOS), characterized by chronic anovulation and hyperandrogenism, affects approximately 5% to 10% of women of reproductive age. This heterogeneous disorder has clinical, biochemical, and ultrasonographic features. One end of the PCOS spectrum comprises women who manifest ultrasound evidence of polycystic ovaries (PCO) without any clinical manifestations of the syndrome (1, 2). Polycystic ovaries have been reported to occur in about 20% of the general female population (3) and in up to 50% of women presenting to infertility clinics (1).

A recent study has shown that women who have PCO diagnosed by ultrasound without the clinical manifestations of PCOS (i.e., isolated PCO morphology) have a higher pregnancy rate from in vitro fertilization (IVF) treatment compared with women who have normal ovaries (4). The investigators believed that the probable reason for the better IVF outcome in women with isolated PCO was the production of more oocytes but of comparable quality to oocytes from normal ovaries on ultrasound, leading to a wider choice of embryos to select for transfer and thus to a higher chance of conception.

Doppler ultrasound studies have shown that ovarian stromal blood flow velocity measured before commencing gonadotrophin stimulation is predictive of good ovarian response and successful outcome of IVF treatment (5). Furthermore, recent studies using color Doppler ultrasound have shown that women with PCO have a higher ovarian stromal blood flow velocity before commencement of gonadotrophin therapy than do women with normal ovaries (6–8).

Ovarian perifollicular blood flow (PFBF) assessment during IVF using power Doppler ultrasound has been demon-

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strated to be a good marker of oocyte competence, embryo viability, and subsequent implantation potential (9). A number of studies have shown a higher pregnancy rate when embryos resulting from the fertilization of eggs from better perfused follicles are transferred (10–13).

Angiogenesis is the process by which new capillary blood vessels develop from pre-existing mature vessels, leading to neovascularization (14). The tissues of the female reproductive tract undergo cyclical physiologic angiogenesis in the processes of ovarian folliculogenesis, corpus luteum formation, and endometrial development (15). This physiologic angiogenesis in the reproductive tract is highly regulated by both proangiogenic and antiangiogenic factors (16).

In the ovary, primordial and preantral follicles have no special vascular supply of their own and derive their blood supply from the stromal blood vessels (17, 18). However, the subsequent growth of the primary follicles leads to the development of a vascular network with increased follicular blood flow. As the antral follicle grows, it acquires a vascular sheath in the theca layer that consists of two concentric networks of vessels in the theca externa and interna when fully established. The arterioles and venules of the outer network within the theca externa send tiny branches into the inner network of the single layered capillary plexus lying within the theca interna, immediately outside the basement membrane. This inner network of capillaries does not penetrate the basement membrane, nor does it enter the granulosa cell layer of the unruptured follicle. The venous capillaries draining the inner capillary plexus collect into a few small vessels which become continuous with the medullary veins (17).

There have been no published studies evaluating ovarian PFBF in PCO. We hypothesized that follicular vascularity in isolated PCO during IVF may be different from normal ovaries due to the increased stromal blood flow and pregnancy rate observed in women with isolated ultrasound PCO morphologic features. To improve our understanding of the physiology of PCO, we therefore decided to perform a study to assess and compare the ovarian PFBF of women with polycystic and normal ovaries undergoing IVF.

MATERIALS AND METHODS

Patients

This prospective observational cohort study recruited 34 women undergoing IVF treatment between May 2002 and March 2003 at IVF-Australia, Royal Hospital for Women, Sydney, Australia. All women underwent IVF treatment because of unexplained, male factor, or tubal factor infertility.

Based on clinical menstruation history, physical examination, and ultrasound findings, the women were divided into two groups. Group 1 consisted of 20 women (the normal ovaries group or USNO group) who had regular, spontaneous ovulatory menstrual cycles ranging from 25 to 32 days and a baseline transvaginal ultrasound scan showing normal ovaries. Group 2 consisted of 14 women (the ultrasound PCO group or USPCO group) who had regular, spontaneous ovulatory menstrual cycles ranging from 25 to 32 days, no clinical manifestations of PCOS, and a baseline transvaginal ultrasound scan showing polycystic ovaries.

The ovaries were categorized as polycystic if 10 or more subcapsular follicles of 2 to 8 mm in diameter in one plane were detected in either ovary (19, 20). Ovarian volume, stromal volume, and stromal echogenicity were not used as criteria because neither Adams et al. (19, 20) nor any other available definitions (21) provide objective criteria or precise cutoff values to determine them (22).

The study was approved by the South-Eastern Sydney Area Health Service Research Ethics Committee, Eastern Section and the Human Research Ethics Committee at the University of New South Wales.

Controlled Ovarian Stimulation

All patients underwent one of three ovarian stimulation protocols: IVF long protocol (IVFLP), IVF short protocol (IVFSP), and IVF gonadotrophin-releasing hormone (GnRH) antagonist protocol (IVFANT).

In the IVFLP, patients were pretreated with an oral contraceptive pill (OCP) (Brevinor 21; Pharmacia Australia, Rydalmere, NSW, Australia) from day 5 of the menstrual cycle preceding the treatment cycle for 21 days. Fifteen days after starting the OCP, a GnRH agonist was introduced either as a nasal spray (nafarelin acetate; Pharmacia Australia), 200 μg twice daily, or as a subcutaneous injection (leuprorelin acetate; Abbott Australasia, Cronulla, NSW, Australia), 1 mg daily for at least 10 days, until pituitary down-regulation was confirmed by a serum estradiol (E_2) level of $<$120 pmol/L. Follicle-stimulating hormone (FSH) injections (Gonal F; Serono Laboratories, Frenchs Forest, NSW, Australia; or Puregon; Organon Laboratories, Lane Cove, NSW, Australia) were then commenced for ovarian stimulation, with the starting dose being determined according to the patient's age and the presence or absence of polycystic ovaries on ultrasound.

In the IVFSP, a GnRH agonist was administered from menstrual cycle day 1 and FSH injections were commenced on cycle day 2 or 3. In both of these protocols, daily FSH injections and the GnRH agonist were continued until the day of human chorionic gonadotropin (hCG) injection (Profasi; Serono Laboratories).

In the IVFANT protocol, daily FSH injections commenced from cycle day 1 or 2 and continued until the day of hCG injection. A single 3-mg dose of GnRH antagonist (cetrorelix acetate; Serono Laboratories) was administered on cycle day 6 or 7. If ovarian follicular growth did not allow ovulation induction with hCG injection on the 5th day after injection of GnRH antagonist, 250 μg of cetrorelix acetate was administered once daily beginning 96 hours after the