Short-Term GnRH-Analogue Administration in Patients with PCOS and Its Impact on Hemodynamics and Hormonal Profile

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Purpose: The ovarian response to 14 days of GnRH-analogue (GnRHa) application in patients with polycystic ovary syndrome (PCOS) was evaluated by measuring hemodynamic parameters and hormonal profile.

Methods: Twenty patients with PCOS represented the study group, and 22 patients with normal menstrual cycle (NMC) the reference group. The resistance index (RI) of uteroovarian arterial blood flow and serum level of LH and androstenedione were measured on days 4, 13, and 22 of the cycle and after 14 days of GnRHa administration.

Results: On day 22 of the cycle the RI in the uterine artery was 0.86 in the PCOS and 0.82 in the NMC group. Throughout the cycle the ovarian arterial blood flow in both ovaries in the PCOS group was similar to that in inactive ovaries in the NMC group. After the 14-day GnRHa administration the RI of uteroovarian blood flow and the serum level of androstenedione remained unchanged in the PCOS group.

Conclusions: RI in the uteroovarian blood flow and serum androstenedione level in the PCOS group are not affected by 14-day GnRHa administration.

KEY WORDS: androstenedione; luteinizing hormone; polycystic ovary syndrome; uteroovarian arterial blood flow.

INTRODUCTION

In stimulated as well as in unstimulated cycles the uteroovarian arterial blood flow during the preovulatory period is increased. Likewise, the blood flow remains high throughout the luteal phase on account of the increased diastolic flow (1–4). In patients with polycystic ovary syndrome (PCOS) the uteroovarian

arterial blood flow remains unchanged throughout the cycle (3,5).

Through the empirical evidence showing that ovulation induction is more successful in patients with hypothalamic amenorrhea than in patients with PCOS, coadministration of GnRH analogue (GnRHa) has become the treatment of choice considering the knowledge that pituitary desensitization causes a condition similar to hypogonadotrophic hypogonadism. The beneficial effect of GnRHa on synchronous follicle development and oocyte quality by lowering the serum level of LH has also been confirmed (6).

The purpose of this study was to evaluate the ovarian response to 14 days of GnRHa administration in patients with PCOS by measuring hemodynamic parameters and hormonal profile.

MATERIALS AND METHODS

Forty-two patients undergoing in vitro fertilization–embryo transfer (IVF-ET) were included in the prospective controlled study: 20 patients with PCOS represented the study group, and 22 patients with NMCs the reference group.

The inclusion criteria for the study group were an improper luteinizing hormone (LH): follicle stimulating hormone (FSH) ratio greater than 2 (for baseline values), oligomenorrhea (10 of the 20 patients had sporadic ovulation registered and confirmed by ultrasound), and at least 10 follicles sized less than 8 mm in diameter in the subcapsular region around hyper-echogenic central stroma found by the ultrasound scan in each ovary. The inclusion criteria for the control group were tubal infertility and regular ovulatory menstrual cycle.

In all patients ovarian stimulation was performed using GnRHa (Superfact; Hoechst AG, Frankfurt/

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Main, Germany) applied on day 22 of the cycle at a daily dose of 0.6 ml (600 pg) s.c. for 14 consecutive days.

Vascular impedance expressed in terms of the resistance index (RI) of the uteroovarian arterial blood flow was measured on days 4, 13, and 22 of the cycle, when GnRHa administration was introduced, and after 14 days of GnRHa administration. The Doppler ultrasound, in both color and spectral mode, had a frequency of 6.5 MHz (Brüel & Kjaer Colour Doppler 3535, Gentofte, Denmark). The system operates at a power output of less than 100 mW/cm² spatial peak temporal average in both imaging and Doppler modes. A high-pass filter of 125 Hz was used.

Serum levels of LH and androstenedione were determined synchronously.

LH was assayed by chemoluminescence with Byk-Sangtec LIA kits (Byk-Sangtec, Konstanz, Germany) on an LIA-mat System 300 (Byk-Sangtec, Konstanz, Germany). The sensitivity of the assay for LIA determination of LH was 0.5 IU/L. The intraassay coefficients of variation (CV) were 4.8, 5.9 and 6.5% for pool sera at 28.8, 53.9, and 164 IU/L, respectively. The interassay CV were 10.6, 8.1, and 10% for pool sera at 62, 30, and 60 IU/L, respectively.

Androstenedione was measured with a commercially available RIA kit (Immunotech International, Marseille, France). The sensitivity of the assay for RIA determination of androstenedione in serum was 0.14 nM, and the intrassay CV were 7.1, 7.1 and 5.6% for pool sera at 2.8, 9.6, and 30.4 nM, respectively. The interassay CV were 11.9, 9.3, and 6.0% for pool sera at 3.2, 9.6, and 31.6 nM, respectively.

Statistical Evaluation

The data in the PCOS and NMC groups were compared at given time points by an unpaired Student's *t* test. The significance was defined as *P* less than 0.05. All values are given as mean $\pm$ SD.

RESULTS

The patients in the PCOS group were further divided into anovulatory (*n* = 10) and ovulatory (*n* = 10) PCOS patients, whereas in the NMC group only one patient was anovulatory.

The dynamics of vascular impedance in the uterine artery in PCOS patients was constant regarding various phases of unstimulated cycle. On day 22, the RI was lower in the NMC group (*n* = 21) compared to anovu-

Fig. 1. Vascular impedance expressed as the resistance index (RI) in the uterine artery in patients with PCOS and anovulatory cycles (○) and in patients with NMCs (●), considering the day of the cycle (4, 13, and 22) and after 14 days of GnRHa administration. Data are means $\pm$ 2 SE. The asterisk denotes a statistically significant difference.

latory PCOS cycles (*n* = 10) (0.82 ± 0.04 vs 0.86 ± 0.04 ; *P* < 0.05) (Fig. 1).

After 14 days of GnRH administration, the RI remained unchanged in the anovulatory PCOS cycles (*P* = NS), whereas in ovulatory NMC cycles (*n* = 21) it increased from 0.83 ± 0.04 to 0.87 ± 0.05 (*P* < 0.05) (Fig. 1).

By measuring vascular impedance in the hilum of the left ovary (LO) and the right ovary (RO) in different parts of studied cycles, no differences were noted in the anovulatory PCOS group (*P* = NS) (Fig. 2). In

Fig. 2. Vascular impedance expressed as the resistance index (RI) in the hilum of the active ovary (○) and the inactive ovary (●) in patients with normal menstrual cycles (NMCs; top) and the RI in the hilum of the right ovary (○) and left ovary (●) in patients with PCOS and anovulatory cycles (PCOS; bottom), considering the day of the cycle (4, 13, and 22) and after 14 days of GnRHa administration. Data are means $\pm$ 2 SE. Asterisks denote statistically significant differences.

contrast, the situation was different in the NMC group, in which vascular impedance in the hilum of the active ovary (AO) was found to be lower compared to the inactive one (IO) on days 4, 13, and 22 and after 14 days of GnRHa administration (Fig. 2).

Serum LH levels were higher in the PCOS ($n = 20$) than in the NMC group ($n = 22$) on day 22 (9.40 ± 9.72 IU/L vs 2.08 ± 3.45 IU/L; $P < 0.05$) and after 14 days of GnRHa administration (0.87 ± 0.77 IU/L vs 0.41 ± 0.27 IU/L; $P < 0.05$) (Fig. 3). Serum androstenedione levels were higher throughout the cycle in the PCOS group compared to the NMC group ($P < 0.05$) (Fig. 3).

DISCUSSION

Vascular Impedance in the Uterine Artery

Vascular impedance in the uterine artery is decreased by the end of the follicular phase, being the lowest just before ovulation. Considering the cycle as a whole, the blood flow is highest in the luteal phase on account of the diastolic flow (1–3). These observations were also confirmed in this study.

In PCOS patients vascular impedance remained unchanged throughout the cycle. On day 22 of the cycle, vascular impedance and serum LH levels were significantly higher than in the NMC group, whereas serum levels of androstenedione in the PCOS group

were significantly higher throughout the cycle. The relation between high serum LH and androstenedione levels, on the one hand, and vasoactive substances, on the other, has not been defined so far. Nevertheless, we know that at the time of ovulation, when the LH surge coincides with the $\text{PgF}_{2\alpha}$ and oxytocin surges, vascular impedance in the uterine artery is increased (7–9). The aforementioned consideration is suggestive for a similar explanation in PCOS patients.

The difference in hemodynamic parameters between the PCOS and the NMC group was also detected after 14 days of GnRHa administration. Vascular impedance in the uterine artery of patients with PCOS was high on day 22, and GnRHa administration did not change it, probably because it was already maximal at the beginning of the studied cycles. In the NMC group the measurement of the uterine blood flow reflects the suppressive effect of GnRHa administration.

Vascular Impedance in the Hilum of the Ovary

In this study, the topographic locations of ovaries and their vessels were changed in most of the patients, because of previous surgical adnexal procedures. We overcome these problems by measuring the lowest vascular impedance in the hilum of the ovary. In this way the vessels nourishing the follicles and corpus luteum were selected (10). The sonograms of ovarian hila were similar to those of the uterine artery, thus we presumed that the uterine part of the ovarian arterial blood flow was measured. The dynamics of vascular impedance in the hilum of the ovary was comparable with vascular impedance in the ovarian artery in the NMC group (1,3).

Studies performed by various authors have shown that in the active ovary of NMC patients, the diastolic flow gradually increases during the late follicular phase, whereas the blood flow in the luteal phase remains high due to vasodilatation. In the sonograms of the inactive NMC ovary, diastolic flow is absent, whereas a high vascular impedance persists throughout the cycle (1,3,11).

In their study of the normal menstrual cycle, Hata *et al.* (1) did not prove the difference in blood flow during the early follicular phase, whereas Taylor *et al.* (11) did. Our results are in agreement with those of Taylor *et al.* considering the fact that in normally cycling patients the ovarian blood flow on day 4 was significantly higher in the ovary that later proved to be active than in the inactive one. By measuring the ovarian blood flow during the early follicular phase, one can therefore establish which ovary is about to

Fig. 3. Serum levels of LH and androstenedione in the patients with PCOS (○) and in patients with NMCs (●), considering the day of the cycle (4, 13, and 22) and after 14 days of GnRHa administration. Data are means $\pm$ 2 SE. Asterisks denote statistically significant differences.

ovulate. This puts the aforesaid diagnostic method before the methods based on recognition of the dominant follicle and periovulatory endometrium with the B-mode US scan.

In NMC patients there was an increased vascular impedance in the inactive ovary in comparison to that in the active ovary, and it was the same as in polycystic ovaries. The explanation may be that in PCOS patients, although demonstrating serum E_2 levels similar to those of NMC patients, the increased vascular impedance may result from either decreased or inadequate local synthesis of estrogens in the ovary itself.

In PCOS patients 14-day GnRHa administration does not increase vascular impedance. The situation is different in the ovaries of normally cycling women, in whom the vascular impedance increases significantly in both the active and the inactive ovary. These results confirm the presumption that polycystic ovaries permanently secrete vasoactive substances and androgens, which may increase the vascular impedance to such an extent that the addition of GnRHa does not have any effect on the blood flow.

We conclude that in PCOS patients 14-day GnRHa administration does not affect the uteroovarian arterial blood and proved too short to suppress androstendione discharge.

REFERENCES

1. Hata K, Hata T, Senoh D, Makihara K, Aoki S, Takamiya O, Kitao M: Change in ovarian arterial compliance during the human menstrual cycle assessed by Doppler ultrasound. *Br J Obstet Gynaecol* 1990;97:163-166
2. Steer CV, Campbell S, Pampiglione JS, Kingsland CR, Mason BA, Collins WP: Transvaginal colour flow imaging of the uterine arteries during the ovarian and menstrual cycles. *Hum Reprod* 1990;5:391-395
3. Kurjak A, Kupesic-Urek S, Schulman H, Zalud I: Transvaginal color flow Doppler in the assessment of ovarian and uterine blood flow in infertile women. *Fertil Steril* 1991;56:870-874
4. Schurz B, Schon HJ, Wenzl R, Eppel W, Huber J, Reinold E: Endovaginal Doppler flow measurements of the ovarian artery in patients with a normal menstrual cycle and with polycystic ovary syndrome during in vitro fertilization. *J Clin Ultrasound* 1993;21:19-25
5. De Ziegler D, Bessis R, Fanchin R, Frydman R: Transvaginal pulsed and color Doppler in gynecology. *Contracept Fertil Sex* 1992;20:1155-1165
6. Homburg R, Berkowitz D, Levy T, Feldberg D, Ashkenazi J, Ben Rafael Z: In vitro fertilization and embryo transfer for the treatment of infertility associated with polycystic ovary syndrome. *Fertil Steril* 1993;60:858-863
7. Koullapis EN, Collins WP: The concentration of 13,14-dihydro-15-oxo-prostaglandin F₂α in peripheral venous plasma throughout the normal ovarian and menstrual cycle. *Acta Endocrinol* 1980;93:123-128
8. Mitchell MD, Haynes PJ, Andersson ABM, Turnbull AC: Oxytocin in human ovulation. *Lancet* 1980;2:704
9. Amico JA, Sief SM, Robinson AG: Elevation of oxytocin and the oxytocin-associated neurophysin in the plasma of normal women during midcycle. *J Clin Endocrinol Metab* 1981;53:1229-1232
10. Weiner Z, Thaler I, Levron J, Lewit N, Itskovitz-Eldor J: Assessment of ovarian and uterine blood flow by transvaginal color Doppler in ovarian-stimulated women: Correlation with the number of follicles and steroid hormone levels. *Fertil Steril* 1993;59:743-749
11. Taylor KJW, Wells PNT, Conway DI, Hull MGR: Ultrasound Doppler flow studies of the ovarian and uterine arteries. *Br J Obstet Gynaecol* 1985;92:240-246