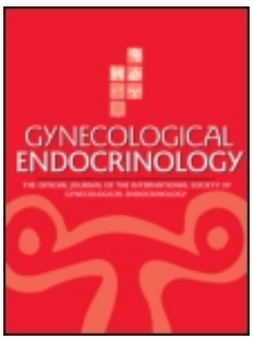

Gynecological Endocrinology

ISSN: 0951-3590 (Print) 1473-0766 (Online) Journal homepage: http://www.tandfonline.com/loi/igye20

# Superovulation with urinary human follicle-stimulating hormone: correlations with body mass index and body fat distribution

F. Zullo, C. Di Carlo, M. Pellicano, C. Catizone, P. Mastrantonio & C. Nappi

**To cite this article:** F. Zullo, C. Di Carlo, M. Pellicano, C. Catizone, P. Mastrantonio & C. Nappi (1996) Superovulation with urinary human follicle-stimulating hormone: correlations with body mass index and body fat distribution, Gynecological Endocrinology, 10:1, 17-21, DOI: 10.3109/09513599609041265

**To link to this article:** http://dx.doi.org/10.3109/09513599609041265

Gynecol. Endocrinol. 10 (1996) 17–21

# Superovulation with urinary human follicle-stimulating hormone: correlations with body mass index and body fat distribution

F. Zullo, C. Di Carlo*, M. Pellicano*, C. Catizone, P. Mastrantonio and C. Nappi*

Department of Gynecologic and Pediatric Sciences, Medical School of Catanzaro, University of Reggio Calabria Ospedale 'A. Pugliese', Catanzaro; and *Department of Gynecology and Obstetrics, University 'Federico II' of Napoli, Naples, Italy

Key words: BODY FAT DISTRIBUTION, CONTROLLED OVARIAN HYPERSTIMULATION, POLYCYSTIC OVARIAN SYNDROME, FOLLICLE-STIMULATING HORMONE, OBESITY



## ABSTRACT

*Our objective was to investigate the relationship between body mass index (BMI), waist/hip ratio (WHR), follicle-stimulating hormone (FSH) dose, length of stimulation and clinical outcome in infertile women with and without polycystic ovary syndrome (PCOS) undergoing controlled ovarian hyperstimulation.*

*Controlled ovarian hyperstimulation was induced in 60 women for a total of 111 cycles (48% in PCOS patients) with urinary human FSH (u-hFSH).*

*A significant correlation between BMI, u-hFSH dose and duration of stimulation was found in PCOS and non-PCOS patients with WHR < 0.8. These correlations were not present in PCOS patients with WHR > 0.8. Pregnant patients received significantly less ampules of u-hFSH.*

*From our data we suggest a controlled ovarian hyperstimulation protocol, for obese non-PCOS patients and obese PCOS patients with WHR < 0.8, starting with a double dose of u-FSH.*

## INTRODUCTION

The use of carefully controlled ovarian hyperstimulation, either in combination with artificial insemination with the partner's semen or not, has been employed with good results in infertile couples with anovulatory, mild endometriosis and unexplained infertility[1–3].

The production of two to four follicles by gonadotropin stimulation plays a key role in increasing the rate of single or twin pregnancies without dangerously raising the rate of multiple pregnancies (more than twins) and ovarian hyperstimulation syndrome (OHSS)[3]. Therefore, to this aim, it would be extremely useful to assess which are the factors influencing the ovarian response to induction of multiple follicular development in terms of gonadotropin requirement, starting dose and length of stimulation. Among these variables, body weight and body-fat distribution represent two important and easily assessed parameters for consideration.

Correspondence: Dr F. Zullo, via Michetti 10, 80127 Napoli, Italy

Indeed, it has been shown that obese women require higher doses of gonadotropin or clomiphene citrate to achieve an optimal ovarian response to stimulation[4–6] and, recently, increasing waist/hip ratio has been shown to be relatively associated with the probability of conception per cycle[7]. Moreover, a direct correlation was found between gonadotropin requirement and body weight in the induction of multiple follicular development[8,9]. However, other authors have failed to confirm these data[10].

Increased body weight and hyperandrogenism are common features among anovulatory women with polycystic ovary syndrome (PCOS), and hyperandrogenism is known to be associated with altered ovarian responsiveness to gonadotropin stimulation[11].

Body fat distribution provides a reliable estimate of androgenization in women[12,13]. Therefore, considering the frequent association between obesity and androgenization in PCOS patients, we undertook a study to investigate whether there is a correlation between body mass index (BMI) and various parameters of controlled ovarian hyperstimulation as a function of body fat distribution.

## MATERIALS AND METHODS

Sixty infertile patients, aged 25–37 years (mean ± SD, 30.4 ± 5.3) were included in the study. The mean duration of infertility was 4.1 ± 2.4 years. Tubal infertility and male factor were excluded.

Patients were divided into two groups: normoovulatory and PCOS. Patients were defined as affected by PCOS when presenting an ultrasonographic pattern of polycystic ovaries (more than ten follicles ranging from 2 to 8 mm in diameter in the subcapsular region of the ovarian cortex; the ovarian stroma is expanded and echogenic; the whole volume is greater than 9 ml) together with one or more of the symptoms characteristic of the syndrome (oligo-amenorrhea, anovulation, hirsutism, acne, obesity)[14,15].

All patients underwent controlled ovarian hyperstimulation followed either by timed intercourse or by intrauterine and/or intraperitoneal insemination after semen preparation[16]. The controlled ovarian hyperstimulation protocol started with the administration of 75 IU of urinary human follicle-stimulating hormone (u-hFSH; Metrodin, Serono, Italy) daily for 7 days. The dose was doubled after 7 days in the absence of ovarian response and then every 3 days in step-up fashion.

Monitoring was performed by transvaginal ultrasonography using a 5-mHz transducer attached to an Aloka sector scanner, and by serum estradiol evaluation. Both ultrasound examinations and estradiol determinations were performed after the first 7 days of treatment and then every 3 days. Estradiol levels were measured by radioimmunoassay (RIA) using a commercial kit (Radim, Rome, Italy).

Human chorionic gonadotropin (hCG; Profasi, Serono, Italy) 10 000 units was administered when one to four (and no more than four) follicles reached a minimum diameter of 18 mm in the presence of serum estradiol levels of between 200 and 1500 pg/ml per follicle > 15 mm. Ovulation was assessed by ultrasonographic monitoring and serum progesterone evaluation.

In all cycles, the following parameters were evaluated: patient BMI, calculated by the ratio of body weight (kg) divided by the height$^2$ (m$^2$); patient waist/hip ratio (WHR), calculated by the ratio of waist circumference measured at the umbilicus divided by hip circumference (cm) measured at the largest measurement of the hips; number of ampules of u-hFSH administered; ovulation rate; and pregnancy rate.

Statistical analysis was performed by Pearson's test, $\chi^2$ and Student's test when appropriate.

## RESULTS

An overall summary of the clinical outcome is presented in Table 1. The total number of stimulated cycles was 111. The overall ovulation rate was 90.1% (100/111) and the pregnancy rate was 17.1% (19/111). Among the 19 pregnancies, three (15.8%) were twin. There were no higher multiples (triplets or above) or any cases of severe OHSS.

The mean BMI was 25.4 ± 3.6 (range 18.7–34.6), the mean number of u-hFSH ampules was 12.6 ± 4.1 (range 6.5–42.0), and the mean duration of stimulation was 12.4 days ± 2.5 (range 8–25). BMI was found to be significantly correlated with both the number of u-hFSH ampules administered and the length of stimulation ($r = 0.3863$, $p < 0.001$ and $r = 0.4561$, $p < 0.001$, respectively).

Fifty-eight cycles (52.3%) were induced in non-PCOS patients. Among these patients the mean

**Table 1** Clinical outcome of 60 patients with induced controlled ovarian hyperstimulation

| | | | PCOS | |
|---|---|---|---|---|
| | *All patients* | *Non-PCOS* | *WHR < 0.8* | *WHR > 0.8* |
| Cycles | 111 | 58 | 19 | 34 |
| Ovulatory cycles | 100 (90.2%) | 58 (100%) | 17 (89.4%) | 25 (73.5%) |
| Peak estradiol (pg/ml) (mean ± SD) | 512 ± 194 | 419 ± 162 | 512 ± 172 | 632 ± 214 |
| Follicles > 18 mm at hCG administration (mean ± SD) | 1.6 ± 0.4 | 1.4 ± 0.3 | 2.0 ± 0.6 | 1.8 ± 0.5 |
| Pregnancies | 19 (17.1%) | 9 (15.5%) | 4 (21.1%) | 6 (17.6%) |
| u-hFSH ampules administered | 12.6 ± 4.1 | 12.7 ± 2.8 | 10.9 ± 2.7 | 13.9 ± 5.9 |
| Duration of stimulation (days) | 12.4 ± 2.5 * | 12.4 ± 2.0 * | 10.8 ± 2.0 * | 13.2 ± 3.2 |
| Body mass index (kg/m$^2$) | 25.4 ± 3.6 * | 24.1 ± 3.1 * | 24.7 ± 4.2 * | 28.1 ± 2.5 |

PCOS, polycystic ovarian syndrome; WHR, waist/hip ratio; hCG, human chorionic gonadotropin; u-hFSH, urinary human follicle-stimulating hormone; * variables significantly correlated ($p < 0.001$)

BMI was 24.1 ± 3.1 (range 18.7–30.0), the mean number of u-hFSH ampules was 12.7 ± 2.8 (range 9–21) and the mean duration of stimulation was 12.4 ± 2.0 (range 9.0–18.0). The ovulation rate was 100% (58/58) and the pregnancy rate was 15.5% (9/58). BMI was again found to be significantly correlated with both the number of u-hFSH ampules administered and the length of stimulation ($r = 0.5788$, $p < 0.001$ and $r = 0.5766$, $p < 0.001$, respectively).

Fifty-three cycles (47.7%) were induced in patients with PCOS. Among these, 19 cycles were induced in patients with a WHR < 0.8 and 34 cycles were induced in patients with a WHR > 0.8.

In the PCOS patients with WHR < 0.8, the ovulation rate was 89.4% (17/19) and the pregnancy rate was 21.1% (4/19). The mean BMI was 24.7 ± 4.2 (range 19–32.8), the mean number of u-hFSH ampules administered was 10.9 ± 2.7 (range 6.5–16) and the mean duration of stimulation was 10.8 ± 2.0 days (range 8.0–14.0). In this restricted group of patients, BMI was found to be significantly correlated with both number of u-hFSH ampules administered ($r = 0.8467$, $p < 0.001$) and length of stimulation ($r = 0.8668$, $p < 0.001$).

In the PCOS patients with WHR > 0.8 the ovulation rate was 73.5% (25/34) and the pregnancy rate was 17.6% (6/34). No significant difference was detected in the ovulation rate and pregnancy rate between PCOS patients with WHR < 0.8 and PCOS patients with WHR > 0.8. The mean BMI was 28.1 ± 2.5 (range 25–34.6), the mean number of u-hFSH ampules was 13.9 ± 5.9 (range 7–42) and the mean duration of stimulation was 13.2 ± 3.2 days (range 8–25). In this group of patients it was not possible to demonstrate any significant correlation of BMI either with the number of u-hFSH ampules administered ($r = 0.1343$), or with the length of stimulation ($r = 0.0913$).

No statistically significant difference was detected among non-PCOS women, PCOS women with WHR > 0.8 and PCOS patients with WHR < 0.8, in the number of u-hFSH ampules, in the length of stimulation, in the number of mature follicles at hCG administration and in the peak estradiol serum levels. However, we observed a mean number of u-hFSH ampules and days of stimulation significantly lower ($p < 0.05$) in cycles leading to pregnancy than in unsuccessful cycles.

## DISCUSSION

Weight and body mass are known to be important parameters in determining the potential of a woman's reproductive system[17] but their influence on ovarian response to exogenous gonadotropins is still controversial[4–6,9,10].

Our data confirm a significant inverse correlation between BMI and ovarian response to gonadotropin (expressed as u-hFSH ampules and length of stimulation) at least in normo-ovulatory patients and in women with PCOS and WHR < 0.8. This correlation was not found in PCOS patients with a central-type body fat distribution.

Previous papers on this subject seem to show that reduced ovarian sensitivity to exogenous gonadotropins in obese patients is not related to different absorption and distribution of the drug[18],

but could be better explained by altered hypothalamic neuromodulation and/or peripheral steroid metabolism[19]. The lack of correlation in patients with PCOS and WHR > 0.8 is probably explained by the intraovarian interferences of the increased free androgen levels and insulin resistance. Indeed, it has been shown that both these conditions are present in this subpopulation of PCOS patients[20,21].

In PCOS women, hyperandrogenism has been claimed to be caused by a primitive insulin-resistance with secondary hyperinsulinism. The increased insulin levels, together with a reduction in the binding proteins for insulin-like growth factor I (IGFBP-I), might act on the ovarian theca IGF-I receptor, increasing the responsiveness of the follicle to luteinizing hormone (LH)[22].

From these considerations, we hypothesize that in our PCOS patients with WHR > 0.8, the metabolic disturbance characteristic of the syndrome, causes an increase in the follicular response to FSH which is masked, up to an as yet undetermined point, by the negative effect on folliculogenesis exerted by the increased androgen levels[23]. When follicular development is set in motion by exogenous FSH, the increased sensitivity is then unmasked causing an exaggerated response. Furthermore, we found in our series that a significantly lower number of u-hFSH ampules and a shorter duration of stimulation were needed in conceptional cycles than in non-conceptional cycles. This fact may be explained either by an increased chance of pregnancy in better responders or by a lower threshold level for follicular development in these patients. This point needs further observations in order to be clarified.

The correlation between BMI and ovarian response to u-hFSH, although needing confirmation on a larger scale, allows us to suggest a controlled ovarian hyperstimulation protocol with a higher starting dose of u-hFSH in obese normal or obese PCOS patients with WHR < 0.8 obese patients in order to achieve an optimal number of mature follicles (two to four)[3]. In obese PCOS patients with WHR > 0.8, because of the unpredictability of ovarian response, it is probably more appropriate to employ a low-dose, slow-increase protocol[24].

In conclusion, we can say that simple clinical data, such as BMI and body fat distribution, should be taken into account for a correct personalization of controlled ovarian hyperstimulation.

## REFERENCES


1. Aboulghar, A. M., Mansour, R. T., Serour, G. I., Amin, Y., Abbas, A. M. and Salah, I. M. (1993). Ovarian superstimulation and intrauterine insemination for the treatment of unexplained infertility. *Fertil. Steril.*, **60**, 303–6
2. Corsan, G. H. and Kemmann, E. (1991). The role of superovulation with menotropins in ovulatory infertility. *Fertil. Steril.*, **55**, 468–77
3. Mascarenhas, L., Khastgir, G., Davies, W. A. R. and Lee, S. (1994). Superovulation and timed intercourses: can it provide a reasonable alternative for those unable to afford assisted conception? *Hum. Reprod.*, **9**, 67–70
4. Chang, A. P., Rafael, R. W. and Forte, C. C. (1986). Influence of weight in the induction of ovulation with human menopausal gonadotropin and human chorionic gonadotropin. *Fertil. Steril.*, **46**, 599–602
5. McClure, N., McQuinn, B., McDonald, J., Kovacs, G. T., Healy, D. L. and Burger, H. G. (1992). Body weight, body mass index and age: predictors of menotropin dose and cycle outcome in polycystic ovarian syndrome. *Fertil. Steril.*, **58**, 622–4
6. Shepard, M. K., Balmaceda, J. P. and Leija, C. G. (1979). Relationship of weight to successful induction of ovulation with clomiphene citrate. *Fertil. Steril.*, **32**, 641–4
7. Zaadstra, B. M., Seidell, J. C., Van Noord, P. A., Velde, E. R., Habbema, J. D., Vrieswijk, B. and Karbaat, J. (1993). Fat and female fecundity: prospective study of effect of body fat distribution on conception rates. *Br. Med. J.*, **306**, 484–7
8. Halme, J., Hammond, M. G., Talbert, L. M., O'Rand, M., Bailey, L. and Sloan, C. (1986). Positive correlation between body weight, length of human menopausal gonadotropin stimulation, and oocyte fertilization rate. *Fertil. Steril.*, **45**, 372–6
9. Halme, J., Hammond, M. G., Bailey, L. and Talbert, L. M. (1988). Lower doses of human menopausal gonadotropin are associated with improved success with *in vitro* fertilization in women with low body weight. *Am. J. Obstet. Gynecol.*, **158**, 64–8

10. Lewis, C. G., Warnes, G. M., Wang, X. and Matthews, C. D. (1990). Failure of body mass index or body weight to influence markedly the response to ovarian hyperstimulation in normal cycling women. *Fertil. Steril.*, **53**, 1097–9
11. McClamrock, H. D., Bass, K. M. and Adashi, E. Y. (1991). Ovarian hyperandrogenism: the role of and sensitivity to gonadotropins. *Fertil. Steril.*, **55**, 73–9
12. Nestler, J. E., Barlascini, C. O., Matt, D. W., Steingold, K. A., Plymate, S. R. and Clore, J. N. (1989). Suppression of serum insulin by diazoxide reduces serum testosterone levels in obese women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.*, **68**, 1027–30
13. Pasquali, R., Casimirri, F. and Platè, L. (1990). Characterization of obese women with reduced sex-hormone-binding globulin concentrations. *Horm. Metab. Res.*, **22**, 303–6
14. Adams, J., Polson, D. W. and Franks, S. (1986). Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. *Br. Med. J.*, **293**, 355–9
15. Franks, S. (1989). Polycystic ovary syndrome: a change in perspective. *Clin. Endocrinol.*, **31**, 87–120
16. Sher, G., Knutzen, V. K., Stratton, C. J., Montakhab, M. M. and Allenson, S. G. (1984). *In vitro* sperm capacitation and transcervical intrauterine insemination for the treatment of refractory infertility: phase I. *Fertil. Steril.*, **41**, 260–4
17. Rich-Edwards, J. W., Goldman, M. B., Willet, W. C., Hunter, D. J., Stampfer, M. J., Colditz, G. A. and Manson, J. E. (1994). Adolescent body mass index and infertility caused by ovulatory disorder. *Am. J. Obstet. Gynecol.*, **171**, 171–7
18. Remorgida, V., Giordano, M., Lanera, P., Costantini, S. and de Cecco, L. (1993). The relationship between body composition and plasma concentrations of exogenously administered urinary follicle stimulating hormone. *Hum. Reprod.*, **8**, 1001–4
19. Reid, R. L. and Van Vugt, D. A. (1987). Weight-related changes in reproductive function. *Fertil. Steril.*, **48**, 905–13
20. Dale, P. O., Tanbo, T., Vaaler, S. and Abyholm, T. (1992). Body weight, hyperinsulinemia, and gonadotropin levels in the polycystic ovarian syndrome: evidence of two distinct populations. *Fertil. Steril.*, **58**, 487–91
21. Anttila, L., Ding, Y. Q., Ruutiainen, K., Erkkola, P., Irjala, K. and Huhtaniemi, I. (1991). Clinical features and circulating gonadotropin insulin and androgen interactions in women with polycystic ovarian disease. *Fertil. Steril.*, **55**, 1057–61
22. Nobels, F. and Dewailly, D. (1992). Puberty and polycystic ovarian syndrome: the insulin/insulin like growth factor I hypothesis. *Fertil. Steril.*, **58**, 655–66
23. Polson, D. W., Reed, M. J., Scanlon, M. J., Quiney, N. and Franks, S. (1988). Androstenedione concentrations following dexamethasone suppression: correlation with clomiphene responsiveness in women with polycystic ovary syndrome. *Gynecol. Endocrinol.*, **2**, 257–64
24. Shoham, Z., Patel, A. and Jacobs, H. S. (1992). Polycystic ovarian syndrome: safety and effectiveness of stepwise and low-dose administration of purified follicle-stimulating hormone. *Fertil. Steril.*, **55**, 1051–6