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An android body fat distribution in females impairs the pregnancy rate of in-vitro fertilization–embryo transfer

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To assess if the waist:hip ratio (WHR) is associated with the pregnancy rate (PR) in in-vitro fertilization (IVF) and embryo transfer, waist and hip girths, in addition to height, weight, body mass index (BMI), indications for IVF, PR and other related variables, were measured in 220 women undergoing IVF–embryo transfer. Three variables were significantly negatively associated with PR; high age, smoking and WHR >0.80. Women with WHR between 0.70–0.79 had a PR of 29.9% as compared to 15.9% in women with WHR >0.80 [odds ratio 0.42, 95% confidence interval (CI) 0.2–0.9, $P = 0.03$]. There were no correlations between BMI and PR, nor were there any significant differences for the indications for IVF–embryo transfer, number of oocytes or oocyte fertilization rate, cleavage rate and number of embryos transferred. The association between a low PR and WHR >0.80 remained unchanged after adjustment for age, BMI, smoking, indication for IVF, parity and number of embryos transferred. In IVF–embryo transfer, fertilization is a laboratory and clinically controlled process, until the embryo is transferred to the uterus. Possible reasons for our finding of a decreased PR in women with an android body fat distribution include a different endocrinological and biochemical milieu for the oocyte in the growing follicle, oocytes of poor quality, or endometrial changes due to hormonal dysfunction.

Key words: body mass index/IVF–embryo transfer/waist:hip ratio

Introduction

Obesity in women is associated with a number of negative health consequences. In the Western world a body mass index (BMI) >25 has been associated with poor education, low income and low socio–economic status (Noppa and Bengtsson, 1980). An increased prevalence of metabolic diseases such as diabetes mellitus, gall-bladder disease, atherosclerosis, myocardial infarction and stroke has also been observed in obese individuals (Kissebah *et al.*, 1982), as well as negative psycho–social attitudes from other persons (Singh, 1993).

Obesity, in addition to hirsutism, oligo–amenorrhoea, elevated testosterone concentrations and infertility, is a component of the polycystic ovary syndrome (PCOS) (Holte *et al.*, 1994a,b). Women with PCOS are also characterized by an increased frequency of an android body fat distribution. Thus, upper-body fatness, defined as a waist:hip ratio (WHR) >0.80, is found more often in women with PCOS, as well as other endocrinological and metabolic changes; increased concentrations of free and total testosterone, androstenedione, oestradiol, insulin, LDL-cholesterol, triglyceride and blood glucose, but decreased concentrations of serum hormone-binding globulin (SHBG). Data on the correlation between WHR and dehydroepiandrosterone sulphate (DHEAS) have been conflicting (Kirschner *et al.*, 1990; De Pergola *et al.*, 1995; Pedersen *et al.*, 1995; Bernasconi *et al.*, 1996).

Little is known regarding whether an android body fat distribution as such, independent of obesity or anovulation, is related to fecundity. No clinical studies are available, where pregnancy rates in ovulating women with upper body obesity, independent of BMI, have been compared with females with a gynoid body composition. In women undergoing in-vitro fertilization (IVF) and embryo transfer, it is possible to measure pregnancy rates/cycle (PR) under strictly medically controlled conditions. Therefore we studied PR, and its relationship to WHR and BMI, in women undergoing IVF–embryo transfer.

Material and methods

A total of 220 women, referred for IVF–embryo transfer to the IVF unit of the Department of Obstetrics and Gynaecology, Falun Hospital, were included in this study. Before entering the study, they had had an infertility investigation, including sperm count, hysterosalpingography, laparoscopy, serum progesterone in the luteal phase, details taken about the menstrual pattern, duration of infertility and, in selected cases, additional investigations. All women who were accepted for IVF–embryo transfer were asked to participate in the study, when treatment was initiated. The upper age limit was 43 years. All women had given informed consent and there were no refusals. All IVF–embryo transfer cycles were down-regulated and stimulated, and only fresh pre-embryos were used.

The standard treatment protocol was initial down-regulation of the pituitary and ovarian function with buserelin acetate [gonadotrophin releasing hormone (GnRH)] nasal spray (Suprecur^{R}, Hoechst, Stockholm, Sweden), 0.30 mg×4, from day 21 of the menstrual cycle. GnRH treatment continued until induction of ovulation. Serum oestradiol was measured after 3 weeks, and, if <150 pmol/l, ovarian follicle stimulation was started with purified follicle stimulating hormone (FSH) (Fertinorm^{R}; Serono, Solna, Sweden). After standard monitoring of the follicles by ultrasonography and measurement of serum oestradiol, ovulation was induced with human chorionic gonadotrophin (HCG; Pregnyl^{R}; Organon, Gothenberg, Sweden) when there were at least two follicles measuring >18 mm diameter. Oocyte aspiration was performed 36–38 h after induction of ovulation. Conventional fertilization or intracytoplasmic sperm injection (ICSI),

Table I. Anthropometric variables in the whole study population (n = 220)

	Mean	SD	Range
Weight (kg)	66.3	11.7	38–108
Height (m)	1.67	0.06	1.5–1.8
Body mass index (kg/m^2)	23.9	4.2	15.2–40.6
Waist girth (cm)	78.7	10.4	60–120
Hip girth (cm)	101.5	9.1	73–142
Waist:hip ratio (cm/cm)	0.78	0.07	0.66–1.26

embryo culture and embryo transfer were performed: eggs and embryos were fertilized and cultured in M2-medium (Medicult, Copenhagen, Denmark). Embryo transfer was performed with a TDT-catheter (SPS, Gothenburg, Sweden). One embryo was transferred in 19 cases, three in one case and two embryos were transferred in the remaining 200 cases. Pregnancy was defined as a positive pregnancy test and visible intrauterine heart beats by sonography 4–5 weeks after embryo transfer. Pregnancy rate was defined as pregnancy per started cycle. In a few cases, where the sperm quality was extremely poor, ICSI, which at this unit gives the same PR as conventional fertilization, was used.

Height (m), weight (kg), waist girth (the minimum measurement between the xyphoid process and the umbilicus) (cm) and hip girth (at the most protruding points of the greater trochanters) (cm) were measured before ovulation induction was induced with HCG. All measurements were made during 1 year by one of the investigators at the IVF unit (between March 1994 and March 1995). BMI was calculated as weight/height^2 (kg/m^2). WHR was calculated as waist:hip (cm/cm).

Other variables included in the study were indications for IVF–embryo transfer treatment [tubal occlusion, male factor, endometriosis, PCOS (diagnostic criteria were menstrual history, habitus and ultrasound scanning), and unexplained infertility], smoking habits, number of previous unsuccessful IVF–embryo transfer treatments, number of previous pregnancies, childbirths and miscarriages, and outcome of the IVF–embryo transfer cycle [cancelled cycle, no fertilization, chemical pregnancy (pregnant only according to pregnancy test, with no subsequent viable fetus)] and pregnancy (positive pregnancy test and visible heart beats on ultrasonography). Pregnancy as defined above was the end-point of the study.

Approval from the Ethics Committee was not obtained, as the study included no invasive procedures and otherwise only procedures that are normal in the registration of couples attending for IVF–embryo transfer. In addition, no individual couple could be identified when the study results were analysed and presented

The results were calculated on the JMP statistical program (SAS Institute, 1994). For crude comparisons, a χ^2 test (likelihood ratio) was used for nominal variables and *t*-test for continuous variables. Multifactorial analyses, by logistic regression (log likelihood test) were used when adjustment for possible confounding factors was made, and for estimation of odds ratios (OR) and 95% confidence intervals (CI).

Results

The mean age of the 220 women was 33.5 years [±4.1 (SD), range 24–44]. Anthropometric variables for the whole study group are shown in Table I.

The indications for IVF–embryo transfer were: 100 (46.3%) women with tubal dysfunction, 37 (17.1%) with endometriosis and in 48 (22.2%) cases male infertility was regarded as the major indication for IVF–embryo transfer. Ten (4.6%) women with anovulation diagnosed as PCOS were included after they had undergone at least three unsuccessful attempts to achieve ovulation induction with no more than three mature follicles. In 21 (9.7%) couples there was no obvious explanation for the infertility and in four cases data were missing. For 137 women (62.8%) it was the first IVF cycle, and 172 (78.9%) of the women had no previous biological children. The overall PR per started IVF cycle was 25.9%.

Table II. Anthropometric data in women with an established clinical pregnancy (n = 57) per IVF cycle[a]

	Pregnancy[b] rate of patients with BMI and WHR no. (%)	Pregnancy[b] rate of patients in normal range[c,d] no. (%)	*P*-value
Mean			
Body mass index <20 (%)	7 (22.6)[a]	37 (28.9)[c]	0.46
Body mass index ⩾25 (%)	13 (21.0)[a]	37 (28.9)[c]	0.24
Waist:hip ratio <0.7 (%)	4 (30.8)[a]	43 (29.9)[d]	0.94
Waist:hip ratio ⩾0.8 (%)	10 (15.9)[a]	43 (29.9)[d]	0.03

[a]Only one cycle/couple was measured.
[b]Defined as fetal heart beats visible by ultrasound.
[c]Body mass index (BMI) 20 to <25.
[d]Waist:hip ratio (WHR) 0.70 to <0.80.

A WHR ⩾0.80 was associated with a significantly decreased PR per IVF cycle, as compared to women with a WHR between 0.70 and 0.79 (Table II) (OR 0.44, 95% CI = 0.2–0.9, P = 0.03). Of the 10 women with PCOS, only three women had a WHR ⩾0.80. Analyses were made to evaluate possible associations between WHR ⩾0.80 and the other variables studied. After exclusion of other anthropometric variables, age (34.4 versus 33.1 years, P = 0.04) and smoking habits (32.1 versus 17.9%, P = 0.04) were the only variables that were significantly associated with WHR ⩾0.8. As these were also correlated with the PR, multifactorial analyses were made, adjusting for age and smoking habits. Number of embryos transferred was also included in this analysis, although it did not significantly differ between the two groups studied. Of the 19 women who had one embryo transferred the PR was 21.1% compared to 26.5% in those who had two embryos transferred. The women with a WHR between 0.70–0.79 (normal range) had on average 1.93 embryos transferred, as compared to 1.87 (not significant) in women with a WHR ⩾0.80. The adjustment for possible confounding factors had only minor effects on the PR (OR = 0.42, 95% CI 0.2–0.9, P = 0.03), for women with WHR ⩾0.80. When PCOS and parity were added into the analyses, the OR for successful IVF treatment remained essentially unaltered (OR = 0.44, 95% CI 0.2–0.9, P = 0.04).

To check if the decreased PR in women with a high WHR was due to an increased frequency of cancelled cycles, these cases (n = 14) were excluded from the analyses. Then PR/non-cancelled cycle was 32.1% in women with a WHR between 0.70–0.79 versus 16.7% in women with a WHR ⩾0.80 (OR = 0.42, 95% CI 0.2–0.9, P = 0.03). Adjusted OR was 0.41 (95% CI = 0.2–0.9, P = 0.04).

Table III. Clinical pregnancy rates/initiation of IVF distributed on body mass index (BMI) and waist:hip ratio (WHR) in 220 women. Numbers refer to number of pregnancies in each group, while percentages refer to pregnancy rates in each group

WHR	BMI		
	<20	20 to <25	⩾25
<0.70	1 (25.0)	3 (33.3)	–
0.70 to <0.80	6 (24.0)	34 (31.5)	3 (27.3)
⩾0.80	0 (0.0)	8 (20.5)	2 (8.7)

P (analysis of variance) = 0.04.

No other anthropometric measurement was significantly associated with PR. The average height was 1.67 m in both women becoming pregnant and in those who were non-pregnant. The average weight was 65.3 kg in the pregnant women versus 66.7 kg in those non-pregnant ($P = 0.43$). When different cut-off values were used for BMI, none showed any significant differences in PR between women with BMI in the normal range compared to those with high or low BMI (Table II). A cut-off value at BMI >28 was found to be most decisive when comparing pregnancy rates with women with lower BMI, and was therefore used in Table III.

When both BMI and WHR were included into a multifactorial analysis, WHR ⩾0.80, as compared to a WHR between 0.70–0.79 (OR = 0.42, 95% CI = 0.2–0.9), but not BMI ⩾25 as compared to a BMI between 20–25 (OR = 1.0, 95% CI = 0.4–2.3) was significantly correlated to a decreased PR.

The PR in women with different combinations of BMI and WHR was compared (Table III), and this confirmed that low PR were seen in the groups of women with WHR ⩾0.8, independent of BMI, but BMI seemed to have no independent effect on pregnancy rates.

Discussion

The results of this study showed that women with an android fat tissue distribution, defined as WHR ⩾0.80, had a PR during IVF–embryo transfer treatment which was less than half of those with a gynoid body shape. The reason for these results is unclear but several explanations are possible.

It has previously been shown that obesity as such has an impact on the steroid hormone concentrations in females (Kumar *et al.*, 1993). However, upper body fatness, rather than lower body fatness, is associated with increased serum concentrations of testosterone, free testosterone, oestradiol (Holte *et al.*, 1994b) and increased triglycerides, whereas SHBG concentrations are decreased (De Pergola *et al.*, 1994), although this is not uniformly found (Bernasconi *et al.*, 1996). Increased serum insulin concentrations (and insulin resistance) have been associated with BMI >25 (Barbieri *et al.*, 1986).

Weight reduction results in normalization or reduction of the testosterone, androstenedione, oestradiol, insulin and free cortisol concentrations and an increase in SHBG concentrations (Bates and Withworth, 1982; Harlass *et al.*, 1984; Crave *et al.*, 1995; Wabitsch *et al.*, 1995; Hollmann *et al.*, 1996), which is particularly evident in women with abdominal obesity. Also, weight reduction significantly lowers the WHR, in one study from 0.90 to 0.83 (Crave *et al.*, 1995). Another study on obese, infertile women found that weight reduction decreased the frequency of irregular menstruation, and that 29% of the women subsequently became pregnant (Hollmann *et al.*, 1996).

IVF–embryo transfer offers an opportunity to study fecundity under strictly controlled conditions. The pituitary–ovarian axis is down-regulated and the follicles are stimulated exclusively by exogenous hormones. Evaluation of oocyte maturation and oocyte and sperm quality are all rigorously controlled. Under these conditions, and despite adjustment for possible confounding factors, women with WHR ⩾0.80, in contrast to women with an increased BMI, regardless of cut-off value, exhibited a dramatically decreased fecundity, with ORs varying from 0.42 to 0.44 in crude and multifactorial analyses, as compared to women with a gynoid body shape. A previous study (Zaadstra *et al.*, 1993) on donor insemination showed that the cumulative PR for a maximum of 12 insemination cycles in women with WHR ⩾0.80 was 38.2%, as compared to 50.2% for women with a gynoid fat tissue distribution, irrespective of BMI, smoking, menstrual interval and reasons for insemination. However, in that study, there was no report of an infertility investigation, which might have been important, since 82% of those women had never been pregnant. Also, ovulation was not hormonally or otherwise established. Nine per cent of the women were stimulated by clomiphene because of long or irregular menstrual cycles. Our study was able to overcome the limitations of the former study (Zaadstra *et al.*, 1993). Oocyte maturation was controlled by down-regulation/ovarian stimulation with monitoring of the follicles and the endometrium, and fertilized oocytes was transferred. Our study strongly supports the conclusion that a high WHR, rather than obesity, might be an important factor for female fecundity.

There are findings, however, that women with a high BMI show a poorer response to ovulation induction than those with a low BMI (Crosignani *et al.*, 1994). We were unable to confirm these results, as only 14 women in our study population did not respond to induction.

The underlying mechanisms for the results of our study remain unclear. The excessive androgen production observed in women with a high WHR might influence the oocyte through all stages of development, resulting in oocytes of poor quality. Thus, the oocyte could already be negatively affected when the down-regulation starts. Also, androgen production may not be as influenced by down-regulation as the gonadotrophins and the female sexual steroids. Androgen effects on the endometrium are at present unknown.

We did not analyse differences in embryo score between the women with different WHR, nor the endometrium or the follicle fluid. If our results can be confirmed in other studies, this might be one of the pathways to investigate the biological/biochemical mechanisms by which WHR affects female fecundity. This study raises the question whether women with a high WHR should be recommended to undergo weight reduction before IVF–embryo transfer treatment. Such a strategy might have important health and economic consequences in improving the chances for a successful pregnancy.

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