Adverse effect of higher waist circumference in assisted reproductive technology outcomes

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ABSTRACT

Background and purpose: Studies on the influence of obesity on the outcomes of treatment with assisted reproductive technologies (ART) are contradictory, although most have demonstrated a negative impact. The contribution of abdominal obesity, an effective marker of dysfunctional adipose tissue, has been poorly investigated.

Methods: Observational cohort study. All women (N=578) who underwent ART treatment at the fertility centre of a Portuguese University Hospital during the study period were included. The women's body mass index (BMI) and waist circumference (WC) were evaluated at the beginning of the stimulation cycle. They underwent controlled ovarian hyperstimulation with long agonist or short antagonist/agonist protocols. Data were stratified in two groups, according to the women's WC-based metabolic risk (defined according to Portuguese national guidelines): lower metabolic risk (WC < 88 cm) and higher metabolic risk (WC ≥ 88 cm).

Results: The women with a WC < 88 cm had a higher number of oocytes collected (≈ 8% more, p=0.049), a higher number of mature oocytes (≈ 20% more, p=0.010), a higher number of fertilized oocytes (≈ 28 more, p=0.017) and a lower gonadotropin requirement (≈ 10% less, p=0.042) than the women with a WC ≥ 88 cm. The chance of fertilization occurring was two times higher in women with a WC < 88 cm (OR [95% CI]:2.04 [1.04-4.00]). No significant associations were observed between WC group and pregnancy, live birth, cycle cancellation and miscarriage rates.

Conclusions: Women with a higher WC have poorer ART treatment outcomes, namely a lower number of oocytes collected, a lower number of mature oocytes, and a lower number of fertilized oocytes. This study highlights the importance of considering fat distribution in the quest to clarify the impact of obesity on ART treatment outcomes. According to our results, women with a WC ≥ 88 cm have poorer outcomes. It would be important to consider women's fat distribution when counseling and predicting ART treatment outcomes, particularly in terms of ovarian stimulation and oocyte quality.

KEYWORDS

Abdominal obesity, body mass index, assisted reproductive technologies, *in vitro* fertilization.

Introduction

Obesity is a worldwide epidemic and has more than doubled since 1980. In 2014, 39% of adults were overweight and 13% were obese [1]. Adipose tissue produces bioactive proteins, known as adipokines, which are involved in the coordination of several biological processes, including reproductive functions [2]. Excess adipose tissue is associated with ovulatory dysfunction [3], reduced conception rates and longer time to conception [4-6].

Studies on the influence of obesity on the outcomes of treatment with assisted reproductive technologies (ART treatment) are contradictory. Most studies have shown that body mass index (BMI) is directly associated with a higher gonadotropin requirement [7-9]; however, some studies have reported that obese women did not require significantly higher doses of gonadotropins [10-12]. Similarly, the number of oocytes collected and the number of mature oocytes were lower in the presence of raised BMI in some studies, [9-12] but not found to be affected by BMI in others [13,14]. Two meta-analyses evaluated the outcomes of ART treatment in obese and overweight women; both showed lower pregnancy rates among these women, although reached different conclusions regarding live birth rates: while Rittenberg *et al*. [15] found a relative risk of 0.84 for obese and overweight women, Maheshwari *et al*. [16] reported insufficient evidence on the effect of BMI on live birth. Another meta-analysis that assessed the effect of obesity and overweight on complications concluded that excess adipose tissue had an only slightly negative effect on ART outcomes, since there were no significant differences in complications, including ovarian hyperstimulation syndrome, ectopic and multiple pregnancy [17]. Metwally *et al*., in their meta-analysis, reported that there is insufficient evidence to describe the effect of obesity on miscarriage rates after ART treatment [18]. Because of these conflicting results, the need to study other adiposity measurements

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has been suggested.

The importance of adipose tissue distribution is emphasized in the definition criteria of metabolic syndrome. According to the joint statement released in 2009 by WHO, obesity is diagnosed using waist circumference (WC) and not BMI, as WC has been shown to better correlate with visceral adiposity and insulin resistance [19]. WC, after a certain threshold, increases the risk of cardiovascular disease and type 2 diabetes mellitus. The cut-off point for this threshold is population-specific and country-specific. Portuguese national guidelines state that women with a WC ≥ 88 cm have a very high metabolic risk [20].

Visceral fat is thought to contribute to a greater amount of free fatty acids (FFAs) in the hepatic circulation, which may impair liver metabolism and contribute to insulin resistance [2]. Although insulin resistance is not included as a diagnostic feature, it has been reported in up to 50% of obese women with polycystic ovary syndrome, a condition characterized by oligo/anovulation, hyperandrogenism and polycystic ovaries [21]. Moreover, in an animal model of glucocorticoid-induced insulin resistance, dexamethasone was responsible for decreased circulating levels of estradiol and anovulation [22]. The expression of adipokines also differs according to the site of fat deposition, with a higher secretion of inflammatory cytokines and lower secretion of leptin and adiponectin in visceral adipose tissue [2]. Both of these adipokines are involved in the regulation of reproductive functions, including gonadotropin secretion and steroidogenesis (leptin) [23], oocyte maturation and early embryo development [23,24].

Wise *et al*. observed that obese women have a longer time-to-pregnancy and this association became stronger after controlling for WC. Notwithstanding, the relationship of WC and waist-to-hip *ratio* (WHR) with fecundability rate was null or weakly positive [6]. The few studies that have assessed fat distribution on ART treatment outcomes have found that WHR was inversely associated with the probability of conception per *in vitro* fertilization (IVF) cycle [25] and that a WHR ≥ 0.8 reduced the pregnancy rate of embryo transfer [26].

Following the widespread clinical use of WC as a marker of abdominal obesity and metabolic risk, we searched for differences in ART treatment outcomes in women who, according to their WC measurement, presented different levels of metabolic risk.

Materials and Methods

1. Study population

All the women who underwent ART treatment – *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) – at the Human Reproduction Department of a Portuguese University Hospital between October 2012 and August 2014 were included in the study. The women's BMI and WC were evaluated at the beginning of the stimulation cycle. The WC measurement was taken midway between the lowest rib and the iliac crest. Other clinical information, such as the women's age, the duration and cause of infertility, smoking habits, number of previous IVF cycles, ovarian stimulation protocol, type of fertilization (IVF or ICSI), and semen characteristics were recorded.

2. Ovarian stimulation protocols, embryo transfer and follow-up

The women underwent controlled ovarian hyperstimulation (COH) with one of the following protocols: short antagonist protocol, long agonist protocol or short agonist protocol. A small percentage of women (5.2%) were stimulated with other combinations of drugs. The choice of protocol was made on a case-by-case basis according to patient clinical characteristics. COH was achieved by administration of recombinant follicle-stimulating hormone (FSHr) (Puregon®, Organon, Netherlands; or Gonal-F®, Merck Serono, Italy) or human menopausal gonadotropin (hMG) - Menopur®, Ferring, Germany. Doses ranged from 75 to 450 IU/day depending on the women's age, antral follicle count, FSH and anti-Müllerian hormone levels, and response to previous COH. From day 5 of stimulation, gonadotropin doses were adjusted according to serum oestradiol (E2) levels and ovarian response, assessed by vaginal ultrasound examination. In the short antagonist protocol, ovarian stimulation was initiated on day 2 of the menstrual cycle. Administration of a daily dose of 0.25 mg of gonadotropin releasing hormone antagonist (GnRHa) (Cetrotide®, Merck, Germany; or Orgalutran® Organon, Ireland) was initiated when the larger follicle reached a mean diameter of 14 mm. In the long agonist protocol, pituitary desensitization with daily subcutaneous administration of triptorelin 0.1 mg (Decapeptyl®, Ipsen Pharma Biotech, France) began in the midluteal phase of the previous menstrual cycle. This dose was continued until ovarian quiescence was confirmed by ultrasound examination and by E2 level (<50 pg/mL), at which point the dose of the GnRH was halved and maintained until ovulation induction in combination with FSHr or hMG. In the short agonist protocol, a daily dose of 0.1 mg of triptorelin (Decapeptyl®, Ipsen Pharma Biotech, France) was initiated at day 2 of the menstrual cycle in combination with gonadotropin administration. Ovulation and oocyte maturation were induced with intramuscular administration of 5000 or 10000 IU of human chorionic gonadotropin (hCG) (Pregnyl®, Organon, Netherlands) when at least three leading follicles reached a mean diameter of 17 mm. Transvaginal oocyte retrieval was scheduled 34 to 36 hours after hCG administration. Women were instructed to begin micronized intravaginal progesterone 200 mg every 8 hours (Progeffik®, EFIKK, France) from the day of the fertilization. Fertilization was assessed after 18 hours and fertilization rates were calculated. Embryo cleavage was assessed every 24 hours thereafter and transfer was performed 3 or 5 days after oocyte retrieval. Fourteen days after oocyte retrieval a quantitative serum value of β-hCG was obtained.

3. Outcome measures

The outcome measures considered in this study were outcomes of assisted reproductive treatments, including dose of gonadotropin used for ovarian stimulation, number of oocytes collected, number of mature oocytes, number of cancelled cycles, embryo development, fertilization, implantation and miscarriage rates, and pregnancy and live birth rates.

Clinical pregnancy was ascertained by the presence of an intrauterine gestational sac on ultrasound examination and was expressed per cycle started as well as per embryo transfer. Live

birth was considered achieved when the fetus was born alive beyond the 24th week of gestation. Embryo morphology (number of cells and degree of fragmentation) was recorded daily. Blastocysts were graded according to the degree of expansion and quality of the inner cell mass and trophectoderm. Implantation rates were considered per embryo transfer. Miscarriage was defined as a pregnancy failing to reach the 24th week of gestation after detection of a gestational sac(s).

4. Statistical analysis

We performed a study of a cohort of 578 women who underwent ART treatment. Initially we conducted an exploratory data analysis using graphical techniques and quantitative analysis in order to characterize the sample, and detect possible extreme outliers and measurement errors. Data were stratified into two groups, according to the women's metabolic risk, as based on their WC [20]: lower metabolic risk (WC < 88 cm) and higher metabolic risk (WC ≥ 88 cm).

To investigate the existence of differences between women with a WC ≥ 88 cm and those with a WC < 88 cm, we conducted a one-way ANCOVA (analysis of covariance), assuming equal variances (Levene's test for equality of variances). To study the association between WC and ART treatment outcomes, we calculated Fisher's exact test and risk estimate (*odds ratio*). The assumptions of the statistical techniques used were validated.

Post-hoc power calculations demonstrated that the sample size achieved was sufficient to detect medium effects [f=.15, p<.05, power = .95, G*Power 3] in the ANCOVA [27].

Statistical analysis was performed with the support of IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp, with the level of significance fixed at 5%.

Results

A total of 610 couples was enrolled in the study. Of these, 24 were lost to follow-up and a further 8 couples were excluded from the study because they failed to initiate treatment due to personal reasons (n=6) or spontaneous pregnancy (n=2). The final sample consisted of 578 couples.

The women's mean age (years) was 35 ± 3 and almost all were Caucasian (99.5%). Primary infertility was present in 77% of the couples. A short antagonist protocol was used in 51.2% of cycles, a long agonist protocol in 37%, and a short agonist protocol in 6.6%. FSHr was used in 62.8% of cycles and hMG in 37.2%.

Most of the women were of normal weight (63%), 3.1% were underweight, 24% were overweight, and 9.9% were obese. According to their WC measurement, 82.5% of women had a lower metabolic risk (WC < 88 cm) and 17.5% a higher metabolic risk (WC ≥ 88 cm). The clinical characteristics of the cohort of patients are presented in Table I (A, B). It is interesting to note that not all the obese women had a higher metabolic risk (9 of these women had a WC < 88 cm). On the other hand, in the overweight and normal weight classes, there were 45 and 8 women, respectively, who had a higher metabolic risk

Table 1a Clinical characteristics of the cohort of patients (578 women).

	MEAN (± SD) / FREQUENCY	MIN-MAX / %
Age (years)	35 ± 3	21-40
WC (cm)	79.4 ± 8.8	60.0-114.0
BMI (Kg/m²)	24.0 ± 4.1	14.9-42.0
Duration of infertility (months)	58 ± 35	12-204
Previous IVF cycles (no.)	1 ± 1	0-5
Smoking	88	16.1
Main cause of female infertility		
Ovulatory dysfunction	63	16.1
Endometriosis	65	16.6
Tubal factor	95	24.3
Cervical factor	7	1.8
Unexplained infertility	121	30.9
Male factor	40	10.2
Weight class		
Underweight (BMI <18.5 Kg/m²)	18	3.1
Normal weight (18.5 Kg/m² ≤ BMI < 25.0 Kg/m²)	364	63.0
Overweight (BMI: 25.0 Kg/m² ≤ BMI < 30.0 Kg/m²)	139	24.0
Obese (BMI ≥30.0 Kg/m²)	57	9.9
WC group		
Lower metabolic risk (WC <88 cm)	477	82.5
Higher metabolic risk (WC ≥ 88 cm)	101	17.5

BMI: body mass index; **WC**; waist circumference; **SD**: standard deviation; **IVF**: *in vitro* fertilization

Table 1b Clinical characteristics of the cohort of patients (578 women).

	WC < 88	WC ≥ 88
	Frequency	
Underweight (BMI <18.5 Kg/m²)	18	0
Normal weight (18.5 Kg/m² ≤ BMI < 25.0 Kg/m²)	356	8
Overweight (BMI: 25.0 Kg/m² ≤ BMI < 30.0 Kg/m²)	94	45
Obese (BMI ≥30.0 Kg/m²)	9	48

BMI: body mass index; **WC**; waist circumference

(Table IB). The women with a smaller WC (< 88 cm) had a higher number of oocytes collected (≈ 8% more, p=0.049), a higher number of mature oocytes (≈ 20% more, p=0.010), a higher number of fertilized oocytes (≈ 22% more, p=0.017), and a lower gonadotropin requirement (≈ 10% less, p=0.042) than the women with a WC ≥ 88 cm. Figure 1 displays the outcomes related to oocytes retrieved and fertilization in both groups. Although the difference was not statistically significant, the women with a WC < 88 cm had a higher fertilization rate. The implantation rate was not different between groups. The comparison of ART outcomes according to WC group is presented in Table II.

There was a significant association between WC group and the occurrence of fertilization (p=0.033). The occurrence of fertilization was higher in the women with a WC < 88 cm (OR [95% CI]: 2.04 [1.04-4.00]). No significant associations were observed between WC group and pregnancy, live birth, cycle cancellation and miscarriage rates (Table III).

Figure 1 Comparison of the outcomes related to oocytes retrieved and fertilization between groups: WC < 88 cm (lower metabolic risk) and WC ≥ 88 cm (higher metabolic risk).

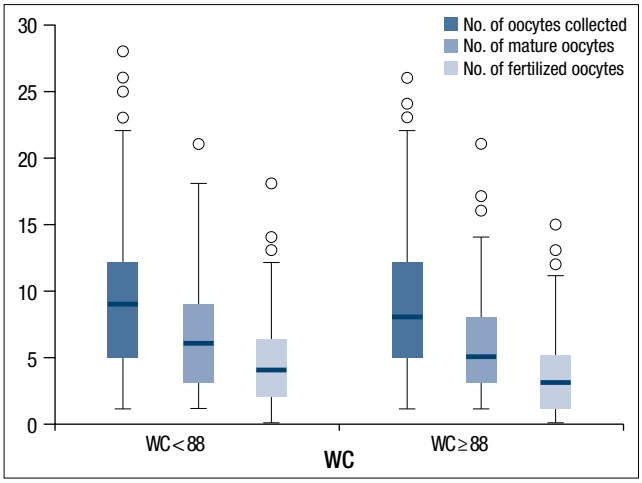

Table 2 Comparison of ART outcomes according to WC group.

	WC < 88 cm - NO.= 477	WC ≥ 88 cm - NO.= 101	ONE-WAY ANCOVA	
	Mean ± SD		F	*p*
Total dose of FSH (IU) - short antagonist protocol [a]	1793.1 ± 659.1	1989.1 ± 681.3	4.170	0.042*
No. of oocytes collected [a]	9.1 ± 5.3	8.4 ± 6.1	3.891	0.049*
No. of mature oocytes [a]	6.5 ± 4.1	5.4 ± 4.2	6.629	0.010*
No. of fertilized oocytes [a]	4.1 ± 3.0	3.2 ± 3.2	5.780	0.017*
Fertilization rate [a]	63.5 ± 30.8	60.1 ± 35.0	0.315	0.238
Implantation rate [a]	21.0 ± 33.4	21.1 ± 34.3	0.052	0.795

[a] mean adjusted for age (years), duration of infertility (months) and no. of previous IVF cycles; * difference is significant at 0.05 (2-tailed); **ART**: assisted reproductive technologies; **WC**: waist circumference; **BMI**: body mass index; **FSH**: follicle-stimulating hormone; **SD**: standard deviation

Table 3 Association of ART treatment outcomes according to class of WC.

	WC < 88 cm - N = 477	WC ≥ 88 cm - N = 101	FISHER'S EXACT TEST	RISK ESTIMATE
Outcome	Frequency (%)		*p*	OR (95% CI)
Fertilization	387 (93.1)	72 (83.7)	0.033*	2.04 (1.04-4.00)
Pregnancy				
Per cycle	97 (20.3)	17 (16.8)	0.421	1.27 (0.71-2.22)
Per transfer	97 (32.3)	17 (32.1)	0.970	1.02 (0.54-1.89)
Live birth (per transfer)	72 (24.0)	15 (28.3)	0.210	0.38 (0.08-1.79)
Cancelled cycle	42 (8.8)	12 (11.9)	0.335	0.71 (0.36-1.43)
Miscarriage	26 (26.5)	2 (11.8)	0.184	2.70 (0.58-1.25)

* association is significant at the 0.05 level (2-tailed); **ART**: assisted reproductive technologies; **WC**: waist circumference; **OR**: *odds ratio*; **CI**: confidence interval

Discussion

This study aimed to examine whether women with different levels of metabolic risk, as based on their WC measurement, have different ART treatment outcomes. The results showed that women with a WC ≥ 88 cm have poorer outcomes and that the probability of fertilization was 2 times higher in women with a lower WC.

Obese women are prone to ovulatory dysfunction as a consequence of insulin resistance [22] and altered expression of adipokines (higher levels of leptin and lower levels of adiponectin) [23,24]. The associations of obesity with insulin resistance and with hyperinsulinemia are more striking in the presence of abdominal distribution of adiposity [2], which is in accordance with our results. Women with a WC ≥ 88 cm had a higher gonadotropin requirement and lower numbers of oocytes collected and of mature oocytes. Approximately half of the women with higher metabolic risk (WC ≥ 88 cm) were non-obese, a finding that underlines the importance of fat distribution.

Another effect of obesity is high FFA levels, which have been linked with insulin resistance (systemic levels), but also with apoptosis of human granulosa cells [28] and with poor cumulus oocyte complex morphology [29], the latter a consequence of high levels of FFA in the follicular fluid, which correlates with plasma levels [30]. Obese women have higher levels of pro-inflammatory cytokines, insulin, lactate and triglycerides in the follicular fluid [31]. Abdominal obesity is associated with markers of oxidative stress in follicular fluid [32], which has been associated with poor oocyte quality. The altered microenvironment of oocytes could explain our findings of impaired response to gonadotropins, as well as lower quality of oocytes in women with a WC ≥ 88 cm (lower number of mature and fertilized oocytes).

Despite the negative influence of abdominal obesity on ovulation and oocyte quality, the implantation and clinical pregnancy per transfer rates were not impaired in our study, suggesting that dysfunctional adipose tissue does not influence endometrial receptivity. Although there are no studies evaluating women with different WC measurements, this hypothesis is supported by a meta-analysis of IVF outcomes in obese donor oocyte recipients [33]. Moreover, a study concerning women who underwent ICSI has demonstrated that obesity has no impact on endometrial thickness, endometrial pattern and uterine blood flow. In fact, obese and overweight women who participated in the study by Zeng *et al*. had similar pregnancy and miscarriage rates to those recorded in normal weight women [34].

Our study has an important merit. To the best of our knowledge, it is the first study concerning the influence of WC (a marker of metabolic risk) on ART treatment outcomes. The association of android fat tissue distribution (defined as WHR ≥0.8) with lower pregnancy rate in IVF was previously evaluated by Wass *et al*. [26]. Our data was analyzed adjusting for the women's age in order to evaluate the value of abdominal obesity in itself. We believe this is an important issue, as there is robust evidence suggesting that female age should be considered one of the stronger predictors of successful pregnancy after IVF [35]. Alongside the aforementioned strength, this study has a limitation: we did not take into account the role of male obesity and semen quality, factors that may have influenced some of our study outcomes.

Although the mechanism is not totally understood, it is widely recognized that regional abdominal fat, irrespective of the total amount of body fat, leads to metabolic complications. Therefore, the contradictory results of studies concerning the influence of obesity on ART outcomes could be explained in part by differences in fat distribution. This hypothesis has already been addressed by Wise *et al*. in spontaneous pregnancy. In their study, they found that the overweight and obese women had a lower fecundability rate (FC), ranging from 0.55 to 0.83, in comparison with the normal weight women (FC=1.00). When adjusting for women's WC, the FC was even lower, ranging from 0.48 to 0.72 [6].

In conclusion, this study highlights the importance of considering women's fat distribution when predicting ART treatment outcomes and counseling on treatments, particularly ovarian stimulation and oocyte quality.

Authors' roles

AFF designed the study, analysed and interpreted the data and drafted the article. APS collected and analysed the data. MMR analysed and interpreted the data and edited and revised the manuscript. BRC performed the statistical treatment and analysis of the data. PC and ALC collected the data and revised the article. TAS designed the study, interpreted the data and revised the manuscript. All authors read and approved the final version of the manuscript to be published.

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