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ORIGINAL RESEARCH PAPER

Underweight and obese women – results of in vitro fertilization

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Abstract

Background: Both obese and underweight women with fertility problems often seek help from infertility treatment clinics using the in vitro fertilization (IVF) procedure. The aim of our study was to analyze the results of IVF in obese patients (BMI ≥ 30 kg/m2) and underweight patients (BMI < 18.5 kg/m2) in comparison to patients of normal weight.

Material and methods: This was a retrospective study of underweight (BMI < 18.5 kg/m2) and obese (BMI ≥ 30 kg/m2) women who underwent intracytoplasmic sperm injection (ICSI). The control group consisted of patients of normal weight. In order to exclude the influence of age on the results of IVF, patients in all groups were <38 years old.

Results: Significantly fewer oocytes were obtained from obese patients compared to normal weight patients (8.4±2 vs. 11.3±3). In addition, the lowest numbers of mature oocytes at the metaphase II stage and of blastocysts were obtained from these patients (2.8±0.2 vs. 3.7±0.4a, 4±0.3), and the blastocysts were of worse morphological quality than in the other groups. In obese patients, 17% of cycles were cancelled due to a lack of oocytes or embryos for transfer. There was no difference in the implantation rate in underweight patients compared to those of normal weight (47% vs. 51%), but a lower implantation rate was noted in obese patients (38%).

Conclusions: Obese patients cannot rely on the same effectiveness of IVF as patients of normal weight. However, it seems that underweight patients are in a much better situation, for whom most stages of the in vitro procedure are as effective as in patients of normal weight.

Keywords: obesity, underweight, IVF, implantaion rate, blastocysts

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Introduction

Obesity is recognized by World Health Organization (WHO) as a noncommunicable disease that constitutes a serious health problem worldwide, especially in highly developed countries. According to WHO, obesity occurs when the BMI exceeds 30 kg/m^2, and a person is considered overweight when the BMI exceeds 25 kg/m^2. The effects of obesity include, above all, an increased risk of cancer, diabetes and circulatory system disorders.

Another problem that is common in highly developed countries is infertility, which is also classified by WHO as a noncommunicable disease. Recently, a strong correlation has been demonstrated between these two diseases, i.e. obesity and infertility. Obese women (BMI ≥ 30) experience infertility three times as often as women with a normal BMI [1]. Obesity leads to infertility, among other things, by adversely affecting the functioning of the hypothalamus-pituitary-ovary axis [2]. Increased insulin levels and a tendency towards insulin resistance in obese women are often associated with the occurrence of polycystic ovary syndrome (PCOS) [3]. Obesity also leads to infertility through a direct impact on the quality and metabolism of oocytes [4,5]. The accumulation of lipids in oocytes and surrounding granulosa cells disrupts their functioning and leads to lipotoxicity [6]. Metabolic and endocrine disorders that accompany obesity negatively affect uterine receptivity and embryo implantation. They lead to endometrial disorders and increase the rate of pregnancy complications and miscarriages [6]. The risk of miscarriage increases by 25–37% in obese women [1]. On the other side of the global obesity problem, there is the fashion for a slim figure, and consequently eating disorders and new trends in weight loss leading to rapid reduction in weight and patients remaining underweight (BMI < 18.5 kg/m^2). Being underweight leads to such fertility disorders as impairments to the hypothalamic-pituitary-gonadal (HPG) axis and hormonal imbalances, irregular ovulation, or complete cessation of ovulation and complete cessation of menstruation [7].

Both obese and underweight women with fertility problems often seek help from infertility treatment clinics using the in vitro fertilization (IVF) procedure.

The aim of our study was to analyze the results of IVF in obese patients (BMI ≥ 30 kg/m^2) and underweight patients (BMI < 18.5 kg/m^2) in comparison to patients of normal weight.

Materials and methods

This was a retrospective study of underweight (BMI < 18.5 kg/m^2) and obese (BMI ≥ 30 kg/m^2) women who underwent intracytoplasmic sperm injection (ICSI) in the KrakOvi Clinic in Kraków (Poland) between 2021 and 2024. The control group consisted of patients of normal weight. In order to exclude the influence of age on the results of IVF, patients in all groups were <38 years old patients with PCOS and endometriosis were excluded from the study.

Couples with severe male factor infertility were also excluded. The research was carried out in accordance with the guidelines of the local bioethics committee.

Clinical protocols

Patients were treated using either the long agonist protocol or short antagonist protocol. The type of protocol used depended on the level of AMH and the overall risk of hyperstimulation.

Long agonist protocol

Starting 1 week before the expected menses (cycle day 18–23), patients received the GnRH agonist, triptorelin (Decapeptyl, Ferring Pharmaceuticals, 1 mg/d, sc). After successful pituitary downregulation (when the serum estradiol [E_2] levels were < 40 pg/mL), ovarian stimulation was begun with a fixed daily dose of 150–300 IU recombinant follitropin alfa (rFSH, sc) with or without an additional 75–150 IU menotropin (hMG).

Antagonist protocol

A GnRH antagonist Cetrorelix (Cetrotide, Merck Europe, 0.25 mg/d, sc or Ganirelix Gedeon Richter, 0.25 mg/d), was administered, commencing when the largest follicle reached a diameter of 14 mm. rFSH/hMG was initiated on day 2–4 of the cycle.

The agonist and antagonist protocols were continued up to and including the day of human chorionic gonadotropin (hCG) administration, which was when the leading follicle reached a diameter of 18 mm or more and at least three follicles reached a diameter of 17 mm or more. rFSH was then stopped, and a single sc bolus of 10,000 IU hCG (Eutrig, Samarth Life Sciences) or 6,500 IU rhCG (Ovitrelle, Merck) was administered 36h before the planned time of oocyte retrieval. When there was a risk of OHSS in an antagonist cycle, the trigger was a single sc bolus of triptorelin 2mg, and a freeze-all policy was applied. All follicles 12 mm or larger were aspirated.

Ovarian stimulation monitoring in ICSI

Baseline blood sampling and transvaginal sonography (TVS) were performed on day 2 or 3 of the treatment cycle for all patients. Monitoring of response during the treatment cycle consisted of TVS and blood sampling for hormonal analysis on cycle days: 2–3 (E_2, FSH, LH); 5–6 (E_2); 8–9 (E_2); and day of hCG administration (E_2, P_4). Additional TVS monitoring was performed as clinically indicated.

Frozen embryo transfer (FET)

Treatment with oral E_2 was started on the first, second or third day of the cycle to prime the endometrium and suppress spontaneous follicle growth. Oral estradiol was administered in an incremental fashion 2 mg/day during days 1–7, 4 mg/day during days 8–12 and 6 mg/day from day 13 until embryo transfer. Usually, after 12–14 days of E_2 administration, a vaginal ultrasound examination was performed to measure the endometrial thickness and to confirm the absence of a leading follicle. When the endometrial thickness was >7 mm, P_4 supplementation was commenced, and timing of FET was scheduled accordingly. For t-NC, TVS was performed on day 2 or 3 of menses to rule out any cyst or corpus luteum remaining from the previous cycle. Cycles were usually cancelled when serum P_4 exceeded 1.5 ng/ml on day 2 or 3 of menses. Transvaginal ultrasonographic monitoring was usually started on day 8–10, while endocrine parameters were monitored and serum E_2, LH and P_4 was measured when the leading follicle attained a mean diameter of approximately 15 mm in diameter. Following frequent endocrine and ultrasonographic monitoring, on alternate days or daily, the day of ovulation was precisely documented to schedule the timing of FET.

Clinical pregnancy was defined by the ultrasound confirmation of an intrauterine gestational sac after 8 weeks of gestation with visible foetal cardiac activity. Ongoing pregnancy was defined after over 12 weeks of gestation with visible foetal cardiac activity.

Laboratory protocols

Oocyte-cumulus complexes (COCs) were identified using a stereoscopic microscope and then washed, and after 3h of incubation (approx. 3h) the cumulus cells were removed using hyaluronidase (Gynemed, Germany) and mechanical pipetting. Only oocytes at metaphase II with a first polar body were used for further procedures. ICSI was performed following the standard technique. Embryos were cultured in SAGE® medium (Origio,

Denmark) under an atmosphere of 6.0% CO_2, 5.0% O_2 and balance nitrogen at 37°C. Embryo development was assessed every day. Blastocysts were graded according to the Gardner scoring criteria [8]. Fresh embryo transfer was carried out on day 3 or 5. Blastocysts were vitrified using Kitazato® media and the Cryotop device (Kitazato, Japan) according to the manufacturer's protocol. For FET, blastocysts were warmed in Kitazato media for a minimum of 1.5h before transfer and then placed in EmbryoGlue® medium (Vitrolife, Sweden) medium. The embryo glue was used for all embryo transfers (ET, FET).

Statistical analysis

Non-parametric data, such as differences in the percentage values between groups, were assessed using the chi-squared test. Parametric data were expressed as means ± SD and compared using two-way ANOVA. Differences were considered significant when the P-value was ≤0.05. The statistical analysis was performed using PQStat 1.6.2 (PQStat Soft, Poznan, Poland).

Results

Table 1 presents the results of IVF in underweight, normal weight and obese patients. Underweight patients were the youngest compared to the age of normal weight and obese women (30.2±3 vs. 33.1±3, 32.5±4). Significantly fewer oocytes were obtained from obese patients compared to normal weight patients (8.4±2 vs. 11.3±3). Furthermore, the lowest number of mature oocytes at the met II stage was obtained from these patients. The next lowest indicator in obese patients was the number of blastocysts in comparison to underweight and normal weight patients (2.8±0.2 vs. 3.7±0.4[a], 4±0.3). Moreover, these blastocysts were of worse morphological quality than in the other groups (Fig. 1). In obese patients, 17% of cycles were cancelled due to a lack of oocytes or embryos for transfer. In patients of normal weight and underweight ones, the percentage of cycles cancelled was at a similar level (6% vs. 8.5%).

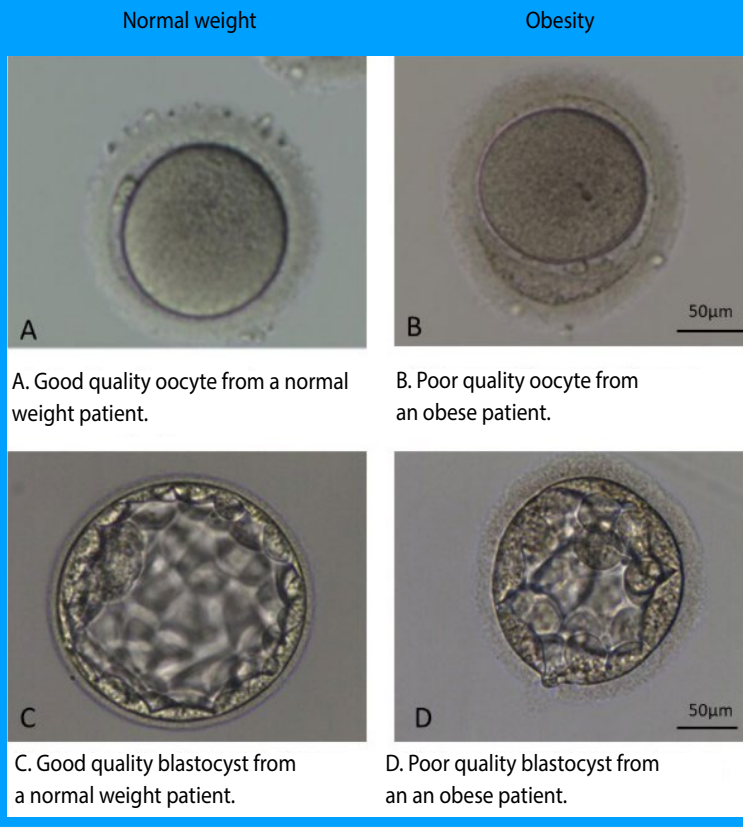
The most commonly used embryo transfer strategy in all groups was FET, but in obese women FET accounted for as many as 75% of all transfers. There was no difference in the implantation rate in underweight patients compared to normal weight (47% vs. 51%), but a lower implantation rate was noted in obese patients (38%).

Table 1. Results of in vitro fertilization depending on the patient's body weight

		Underweight	Normal weight	Obesity
No. of patients (cycle), *n*		35	35	35
BMI (range), mean±SD		(16.9–18.3) 17.9±0.6	(19–24) 22.3±1	(31–41) 35.8±3
Age (years), range, mean±SD		(28–35) 30.2±3	(28–37) 33.1±3	(28–37) 32.5±4
AMH (ng/ml), mean±SD		2.8±0.8	3.4±0.9	3.3±0.7
Oocytes recovery, *n* mean±SD		322 9.2±2	395 11.3±3[a]	294 8.4±2[b]
Ovarian stimulation protocol	Antagonist protocol *n* (%)	25/23 (72%)[a]	31/35 (89%)[b]	27/35 (78%)[a]
	Long agonist protocol *n* (%)	10/35 (28%)[a]	4/35 (11%)[b]	8/35 (22%)[a]
Oocytes at metaphase II stage, *n* mean±SD		248 7.1±1	353 10.1±2[a]	206 5.9±1[b]
Blastocyst, *n* mean±SD		129 3.7±0.4[a]	140 4.0±0.3[a]	98 2.8±0.2[b]
Blastocyst quality	No. of excellent quality *n* (%)	39/129 (30%)[a]	46/140 (33%)[a]	19 (19%)[b]
	No. of good quality *n* (%)	45/129 (35%)[a]	39/140 (28%)[a]	21 (21%)[b]
	No. of medium quality *n* (%)	45/129 (35%)[a]	55/140 (39%)[a]	58 (59%)[b]
Cycle cancelled due to lack of oocytes or blastocysts		3/35 (8.5%)[a]	2/35 (6%)[a]	6/35 (17%)[b]
Embryo transfer	Day 3	3/16 (19%)	3/17 (18%)	2/12 (17%)
	Day 5	2/16 (12%)[a]	4/17 (23%)[b]	1/12 (8%)[a]
	FET	11/16 (69%)	10/17 (59%)[a]	9/12 (75%)[b]
Total implantation rate		16/32 (50%)[a]	17/33 (51%)[a]	12/29 (41%)[b]
Ongoing pregnancy *n* (%)		15/32 (47%)[a]	17/33 (51%)[a]	11/29 (38%)[b]

BMI – the body-mass index is the weight in kilograms divided by the square of the height in metres; AMH – Anti-Mullerian hormone, excellent quality (Bl 4AA, Bl 5AA), good quality (Bl 4AB, 4BA, 5AB, 5BA), medium quality (Bl 4BB, Bl 5BB); FET– frozen embryo transfer; a:b – values with different superscripts within the same rows differ significantly ($p < 0.05$)

Figure 1. The effect of obesity on oocyte and embryo morphology



A. Good quality oocyte from a normal weight patient.

B. Poor quality oocyte from an obese patient.

C. Good quality blastocyst from a normal weight patient.

D. Poor quality blastocyst from an an obese patient.

Discussion

ESHRE (European Society of Human Reproduction and Embryology) and other health organizations generally recommend that women with obesity aiming for IVF/ICSI should be encouraged to lose weight before starting treatment [1,9,10]. ESHRE does not mandate a specific BMI cut-off for accessing treatment, but some fertility clinics consider BMI when assessing a patient's suitability for IVF/ICSI. A common threshold is a BMI between 19 and 30 [10]. However, a significant number of these patients are looking for a quick solution and a "shortcut", especially if they are under the pressure of reproductive aging. Therefore, these patients often decide to undergo the IVF procedure. There are also obese or underweight patients for whom IVF is the only chance to have a child due to, for example, blocked fallopian tubes or the partner's sperm being of poor quality. Our observations and

reports of other authors clearly show that obese patients cannot rely on the same effectiveness of IVF as patients of normal weight [11,12]. However, it seems that underweight patients, for whom most stages of the in vitro procedure are as effective as in patients of normal weight, are in a much better situation.

In obese patients, almost twice as many cycles are cancelled due to the lack of oocytes at metaphase II stage or embryos for embryo transfer compared to patients with normal weight or who are underweight. It can be assumed that the lack of embryos is due to the poor morphological quality of the oocytes. Oocytes collected from obese women are characterized by increased expression of transcripts associated with oxidative stress and lower activity of fat metabolism genes [13]. The formation of free radicals (ROS) damages mitochondria, which limits the maturation of oocytes, which are smaller in obese women and have a thinner *zona pellucida* compared to the oocytes of normal weight women [14]. Poor quality of oocytes and metabolic disorders lead to the arrest of embryonic development [15]. In our study, we also confirmed a significantly lower number of embryos at the blastocyst stage in obese women compared to both normal weight and obese women. Moreover, the blastocysts obtained were characterized by poorer morphological quality, which is probably the result of fertilization with poor quality oocytes. Metabolic and endocrine disorders that accompany obesity negatively affect uterine receptivity and embryo implantation. In our study, the implantation rate in obese women was 10% lower than in women with normal weight and who were underweight.

The main limitation of our research is the small size of the groups studied. The small size of the groups make it impossible to reliably analyze the impact of different stimulation protocols within the group. Another limitation is that the analysis of the results was limited to a comparison of the ongoing pregnancies rates rather than live birth rates. The advantage of our research is that it was conducted at a single centre using a single set of protocols, which ensured the repeatability of the procedures.

Conclusions

To sum up, obese patients undergoing IVF must be made aware that obesity also affects the outcome of this procedure. However, the success of IVF is only the first step towards the birth of a healthy child, and obesity leads to endometrial disorders and also increases the rate of pregnancy complications and miscarriages [16]. If these patients are young, and are not under the pressure of reproductive aging they should definitely consider losing weight before starting the IVF procedure.

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