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INFLUENCE OF BODY MASS INDEX ON *IN VITRO* FERTILIZATION OUTCOME IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

UTICAJ INDEKSA TELESNE MASE NA ISHOD VANTELESNOG OPLOĐENJA KOD PACIJENTKINJA SA SINDROMOM POLICISTIČNIH JAJNIKA

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Summary

Introduction. The purpose of this study was to investigate the influence of the body mass index on the outcome of in vitro fertilization in patients with polycystic ovary syndrome. **Material and Methods.** The study sample consisted of 123 patients with polycystic ovary syndrome who completed their *in vitro* fertilization treatment at the Department of Gynecology and Obstetrics, Clinical Center Nis, Republic of Serbia, and they were retrospectively analyzed. The patients were divided by body mass index into two groups for the comparison of the findings. One group (normal weight) consisted of women with body mass index ≤ 25 kg/m^2 (mean 22.08±1.90), and the other group (overweight) included women with body mass index > 25 kg/m^2 (mean 27.65±1.47). The patients underwent either the standard long gonadotrophin-releasing hormone agonist protocol or flexible multidose gonadotrophin-releasing hormone antagonist protocol. **Results**. The normal-weight patients had a higher number of mature oocytes, significantly higher fertilization rate ($p<0.001$) and significantly higher number of the obtained embryos class I ($p<0.01$) than the overweight patients. However, the implantation rate and clinical pregnancy rate were the same in both groups. **Conclusion**. In the group of overweight women the numbers of mature oocytes and good quality embryos were lower. However, since this study dealt with the patients with polycystic ovary syndrome who generally had a higher number of the obtained oocytes and embryos, this shortfall did not affect clinical pregnancy rates, which were the same in both groups. Certainly, before starting the in vitro fertilization, each infertile patient should be informed about the possible negative effect of her high body mass index on the treatment outcome.

Key words: Body Mass Index; Fertilization *in Vitro*; Treatment Outcome; Polycystic Ovary Syndrome; Embryonic Development; Overweight; Infertility, Female

Sažetak

Uvod. Cilj ove studije bio je da se ispita uticaj indeksa telesne mase na ishod vantelesnog oplođenja kod pacijentkinja sa sindromom policističnih jajnika. **Materijal i metode.** Retrospektivno su analizirane 123 pacijentkinje sa sindromom policističnih jajnika koje su završile postupak vantelesnog oplođenja na Klinici za ginekologiju i akušerstvo Kliničkog centra u Nišu, Republika Srbija. Pacijentkinje su bile podeljene po indeksu telesne mase u dve grupe. Jednu grupu (normalno uhranjene) činile su žene sa indeksom telesne mase ≤ 25 kg/m^2 (prosečan 22,08 ± 1,90), a drugu grupu (prekomerno uhranjene) činile su žene sa indeksom telesne mase > 25 kg/m^2 (prosečan 27,65 ± 1,47). Pacijentkinje su bile tretirane standardnim dugim protokolom agonistima oslobađajućeg hormona za gonadotropine ili fleksibilnim, višedoznim protokolom antagonistima oslobađajućeg hormona za gonadotropine. **Rezultati.** Normalno uhranjene pacijentkinje su imale veći broj zrelih jajnih ćelija, značajno veću stopu oplodnje ($p < 0,001$) i značajno veći broj dobijenih embriona klase I ($p < 0,01$) u odnosu na prekomerno uhranjene pacijentkinje. Međutim, stope implantacije i stope kliničkih trudnoća bile su iste u obe grupe. **Zaključak.** U grupi prekomerno uhranjenih žena, broj zrelih jajnih ćelija i broj kvalitetnih embriona bio je niži. Međutim, kako je ova studija rađena kod žena sa sindromom policističnih jajnika koje generalno imaju veći broj jajnih ćelija i embriona, ova razlika nije uticala na stopu kliničkih trudnoća, koje su bile iste u obe grupe. Svakako, pre početka vantelesnog oplođenja, svaka infertilna pacijentkinja treba da bude informisana o mogućem negativnom uticaju njenog visokog indeksa telesne mase na ishod lečenja.

Ključne reči: indeks telesne mase; *in vitro* fertilizacija; ishod lečenja; sindrom policističnih jajnika; razvoj embriona; gojaznost; ženska neplodnost

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects approximately 5–10% of women of reproductive age [1, 2]. Certain metabolic changes including obesity, insulin resistance, and type 2 diabetes have been associated with this syndrome [3–5]. PCOS is the most commonly en-

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Abbreviations

BMI – body mass index
PCOS – polycystic ovary syndrome
IVF – *in vitro* fertilization
GnRH – gonadotrophin-releasing hormone
FSH – follicle stimulating hormone
ET – embryo transfer
ICSI – intracytoplasmic sperm injection
hCG – human chorionic gonadotropin
OHSS – ovarian hyperstimulation syndrome

countered cause of anovulatory infertility in patients seeking fertility treatment [6]. For women diagnosed with PCOS and refractory to conventional infertility treatment or having coexisting infertility factors, *in vitro* fertilization (IVF) and embryo transfer (ET) are considered to be an effective treatment modality [7, 8]. Obesity and overweight are commonly linked to PCOS. Moreover, obesity increases the risk of pregnancy complications [9–11].

More than half of reproductive-aged women are overweight, their body mass index (BMI) being 25–29.9 kg/m^2 or obese, having the BMI >30 kg/m^2 [12, 13]. Women with an increased BMI in comparison to those with normal BMI (18.5–24.9 kg/m^2) are at a three times higher risk of infertility caused by disorders of the hypothalamic–pituitary axis, menstrual cycle irregularities and anovulation [14, 15].

However, there are conflicting reports about the influence of an increased BMI rate on the quality of oocytes, lower number of mature oocytes, embryo development and lower implantation and pregnancy rates in assisted reproduction [16, 17]. The effects of BMI on IVF outcomes are also known in the non-PCOS population [18, 19]. Although the improvement of fertility due to weight loss has been demonstrated in PCOS patients attempting spontaneous conception [20–22], the research studies performed on PCOS so far have not yet completely assessed the effect of BMI on the outcomes of IVF [16, 23–26].

In their review from 2007, Maheshwari et al. [16] reported lower pregnancy rates after IVF, along with the requirements for higher doses of gonadotropins for achieving a sufficient ovarian response, as well as higher miscarriage rates among obese and overweight women having a BMI of 25 kg/m^2 or higher. However, they concluded that there was not sufficient evidence for drawing a reliable conclusion on the influence of BMI on cycle cancellation, oocyte recovery, and live birth. In a systematic review on the influence of BMI and IVF-ET outcomes, Rittenberg et al. [27] stated that clinical pregnancy and live birth rates were lower, whereas miscarriage rates were higher in women with BMI ≥ 25 kg/m^2 undergoing IVF/intracytoplasmic sperm injection (ICSI). On the other hand, certain reports suggested that there were no significant differences in the IVF/ICSI outcomes between obese and non-obese PCOS patients [1, 25]. This could be caused by different cut-off points for BMI and by the differences between inclusion criteria used in the studies and/or varying focus of outcome measures.

Clinical outcomes such as pregnancy or implantation rate, rather than the quality of oocytes and embryos, have been the main point of interest of most of the studies dealing with the influence of obesity on infertility. The aim of this study was to examine the influence of BMI in women with PCOS on the outcomes of IVF under the assumption that a poorer oocyte and embryo quality in women undergoing IVF are associated with increased BMI.

Material and Methods

A retrospective analysis included data from the computer database of the Department of Gynecology and Obstetrics, Clinical Center Nis, Republic of Serbia on PCOS patients undergoing IVF treatment in the period between June 2013 and December 2014. An ethics committee approval was granted for the study. All of the patients gave their written informed consent for the participation. The study included exclusively the patients with PCOS who fulfilled the criteria established by the recent ESHRE/ASRM Consensus (2004), i.e. who met any two of the three criteria after exclusion of other causes: oligoovulation and/or anovulation, clinical or biochemical hyperandrogenism, and polycystic ovaries detected by ultrasound [28]. The study sample consisted of 123 patients diagnosed with PCOS. The additional criteria for the inclusion were: age 18-39 years, BMI of 18-30 kg/m², the value of basal hormonal follicle stimulating hormone (FSH) levels in the early follicular phase <12 IU/L. The exclusion criteria were the following: abnormalities of the uterine cavity, the presence of an uncontrolled thyroid disease, surgically diagnosed endometrioses, submucosal myoma, ovarian cysts discovered on transvaginal ultrasound and the existence of severe spermatogenetic disturbances in the patients' partners that required ICSI technique. The patients were divided into two groups according to their BMI. The normal weight group included women with BMI ≤ 25 kg/m^2 while women with BMI >25 kg/m^2 formed the overweight group. Each patient could participate in the study only once.

The patients were treated by either standard long gonadotropin-releasing hormone (GnRH) agonist protocol or flexible multidose GnRH antagonist protocol. The GnRH agonist long protocol treatment included daily administration of 0.1 mg triptorelin (Diphereline, Ipsen Pharma Biotech, France), started on day 21 of the previous menstrual cycle and continued until the administration of human chorionic gonadotropin (hCG). Following the confirmation of down-regulation after 13-15 days (assessed by the serum estradiol levels <20 pg/mL, serum luteinizing hormone (LH) <2.0 mIU/mL, and no ovarian cysts present), gonadotropin stimulation was performed. The antagonist protocol, consisting of daily gonadotropin stimulation, was started on day 2 or 3 of menstruation. When the leading follicle reached the size of 14 mm and/or the levels of estradiol reached the value >300 pg/mL, a daily injection of cetrorelix

0.25 mg (Cetrotide; Merc Serono, Switzerland) was included. The treatment was continued until the day of hCG injection. A recombinant FSH (Gonal F, Merc Serono, Switzerland) was used in both protocols for gonadotrophin stimulation. The decision on the protocol used for ovarian stimulation was made on the basis of patients' characteristics and previous response in the IVF cycles.

The starting FSH dose, injected subcutaneously, was individually adjusted according to the ovarian response evaluated by transvaginal ultrasound assessment and measuring the serum estradiol levels. The moment when three follicles reached the mean diameter of ≥17 mm or when the dominant follicle measured ≥18 mm and the following two ≥16 mm, a dose of 10.000 IU hCG (Pregnyl, Organon, Holland) was administered intramuscularly in both protocols. At 34-36 h after the hCG administration, transvaginal ultrasound-guided oocyte retrieval was performed.

The retrieved oocytes that reached the metaphase II were classified as mature (MII), whereas those that reached metaphase I (MI) or germinal vesicle (GV) stage were considered as immature. Using a conventional IVF method, insemination was performed 38-40 hours after the hCG administration. Two pronuclei (PN) appearing 16-18 hours following the insemination confirmed normal fertilization. The fertilization rate was expressed as the number of zygotes with two pronuclei over the total number of inseminated oocytes. The embryo transfer was performed under transabdominal ultrasound guidance. The embryos were transferred on day 3. A daily dose of vaginal progesterone (Utrogestan 600 mg/day; Laboratories Besins-International S.A., France) was used for the luteal phase support and a serum pregnancy test was performed 12 days after the embryo transfer. The intrauterine gestational sac and fetal cardiac activity visualized by transvaginal ultrasound at 6-7 weeks of gestation confirmed clinical pregnancy. A clinical pregnancy loss prior to the 20 weeks of gestation was considered a miscarriage.

The embryo scoring was performed in accordance with the internal laboratory embryo score standards. Morphological features such as equal or unequal size of blastomeres and the presence or absence of fragmentation of cytoplasm, as well as the dynamics of embryo development, were used as parameters for the evaluation of the embryo quality. The dynamics of embryo development was performed by monitoring the number of blastomeres every 24 hours until the day of ET and by comparison of the actual number of blastomeres with their expected number. According to the above parameters, the embryo grading system consisting of four classes of embryos was created. The embryos assigned to the class I on day 3 or 68±1h after the insemination satisfied all of the following three criteria: 1. the embryos had 6 to 8 blastomeres; 2. the blastomeres were equal; 3. the blastomeres had no fragmentation. The class II embryos did not meet one of the above three criteria – they either had less than 6 blastomeres or had 6-8 blastomeres but of an unequal size, or there was fragmentation of the blastomeres. The embryos of the class III did not fulfill two of the criteria and the embryos belonging to the class IV did not satisfy any of the stated criteria.

A modified classification system based on combined criteria reported by Golan et al. [29] was used to determine the grades of severity of ovarian hyperstimulation syndrome (OHSS). The patients having the symptoms of mild OHSS such as abdominal distension and discomfort were classified as Grade I. Other symptoms of mild OHSS included nausea, vomiting, diarrhea, as well as an ovarian enlargement of 5-12 cm. The features of mild OHSS in combination with the ascites detected by ultrasound were considered as moderate OHSS or Grade II. The patients requiring hospitalization due to the development of a severe or critical OHSS, or because of their medical condition fulfilled one or more of the hospital admission criteria, were included in Grade III or severe OHSS. The hospital admission criteria required the presence of one of the following features: ascites, hydrothorax, hematocrit ≥45%, oliguria, elevated liver enzymes, dyspnoea, anasarca or acute renal failure.

The primary outcome measures included the number of mature oocytes, fertilization rate, and quality of embryos. The secondary outcome measures consisted of the total gonadotropin dose requirements, clinical pregnancy rate, implantation rate, miscarriage rate, and the incidence of OHSS.

The continuous variables were described by means±standard deviations and by medians. For the categorical variables, absolute numbers and percentages were given. The distributions of the continuous variables were assessed for normality by the Shapiro-Wilk test. The differences between independent groups were analyzed by an unpaired t-test in case of a normal distribution or by Mann-Whitney test if the distribution of data was not normal. A chi-square test was used to compare proportions of categorical variables between groups. The level of significance was set at 0.05. The calculations were carried out using the SPSS statistical package version 15.0.

Results

A total of 123 patients with PCOS who fulfilled the specified inclusion criteria were analyzed. The patients were divided into two groups: 96 women in the group with normal weight, with a BMI ≤ 25 kg/m^2 and 27 in the overweight group, with the BMI >25 kg /m^2. The average age of the patients, the average BMI in the groups, the number of cycles, and the rate of the applied protocols are given in **Table 1**.

The total amount of gonadotropins used for ovarian stimulation, as well as the duration of stimulation did not differ between the two groups. The proportion of mature oocytes in the total number of aspirated oocytes was statistically higher in the women with normal weight (70.89% vs. 64.84%). In addition, the fertilization rate was statistically higher in the pati-

Table 1. Patients' characteristics and treatment regimen
Tabela 1. *Karakteristike pacijentkinja i vrsta primenjenog protokola stimulacije*

Variable/*Promenjive*	BMI ≤25 kg/m^2	BMI >25 kg/m^2
No. of patients/*Br. pacijentkinja*	96	27
Mean BMI (kg/m^2)/*Prosečan BMI (kg/m^2)*	22.08±1.90 (22.00)	27.65±1.47 *** (28.00)
Patients' age (years)/*Starost pacijentkinje (godine*)	31.65±3.99 (32.00)	31.59±4.35 (31.00)
No. of cycles/*Br. ciklusa*	96	27
Protocol type/*Tip protokola*		
Long GnRH agonist/*Dugi GnRH- agonisti*	60 (62.50%)	18 (66.67%)
Flexible GnRH antagonist/*Flexibilni GnRH- antagonisti*	36 (37.50%)	9 (33.33%)

*** – p<0.001 Mann-Whitney test, Unpaired Student t-test/Chi square tests,
GnRH - gonadotropin-rilizing hormon, BMI - indeks telesne mase

Table 2. Ovarian stimulation characteristics
Tabela 2. *Karakteristike ovarijalne stimulacije*

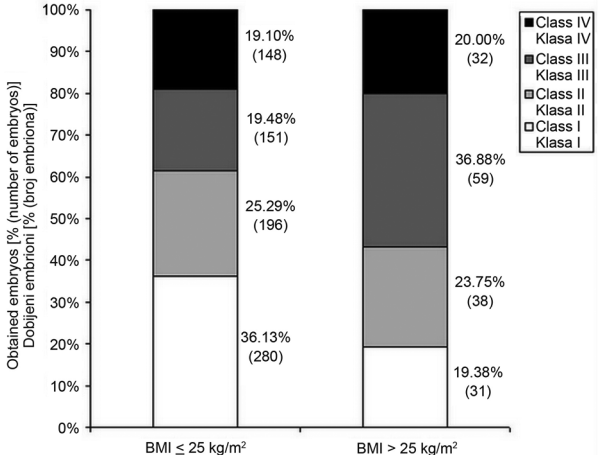
Variable/*Promenjive*	BMI ≤25 kg/m^2	BMI >25 kg/m^2
Total gonadotropin dose/*Ukupna doza gonadotropina (IU)*	1599.09 ± 474.09 (1550.00)	1759.72 ± 685.81 (1575.00)
Duration of stimulation (days)/*Dužina stimulacije (dani)*	10.29 ± 2.24 (10.00)	10.63 ± 2.20 (10.00)
The total number of oocytes retrieved *Ukupan broj preuzetih oocita*	1350	310
Mean number of retrieved oocytes *Srednji broj preuzetih oocita*	14.06 ± 7.89 (13.50)	11.48 ± 6.52 (11.00)
The total number of retrieved mature oocytes *Ukupan broj preuzetih zrelih oocita*	957 (70.89%) *	201 (64.84%)
Mean number of mature oocytes/*Srednji broj zrelih oocita*	10.07 ± 6.33 (9.00)	7.44 ± 4.86 (6.00)
Fertilization rate (%)/*Stopa oplodnje*	68.22% (921/1350)***	57.10% (177/310)
The total number of obtained embryos *Ukupan broj dobijenih embriona*	775	160
Mean number of obtained embryos *Srednji broj dobijenih embriona*	8.42 ± 4.90 (7.00)	6.40 ± 3.96 (5.00)
Total number of obtained embryos class I *Ukupan broj dobijenih embriona klase I*	280 (36.13%)***	31 (19.38%)
Mean number of obtained embryos class I *Srednji broj dobijenih embriona klase I*	3.04 ± 3.10 (2.00)**	1.24 ± 1.74 (1.00)
Endometrial thickness on hCG day (mm) *Debljina endometrijuma na dan davanja hCG-a (mm)*	10.39 ± 1.46 (10.10)	9.89 ± 1.57 (10.00)

* – p<0.05, ** – p<0.01, *** – p<0.001 Mann-Whitney test, Unpaired Student t-test, Chi square tests
hCG - humani horionski gonadotropin, BMI - indeks telesne mase

Table 3. Pregnancy outcome and complications
Tabela 3. *Ishod trudnoće i komplikacije*

Variable/*Promenjive*	BMI ≤25 kg/m^2	BMI >25 kg/m^2
No. of embryos transferred/*Broj transferiranih embriona*	2.70 ± 0.61 (3.00)	2.80 ± 0.50 (3.00)
Implantation rate/*Stopa implantacije*	24.19%	22.86%
No. of clinical pregnancies per ET/*Broj kliničkih trudnoća po ET*	45/92 (48.91%)	12/25 (48.00%)
No. of biochemical pregnancies per ET/*Broj biohemijskih trudnoća po ET*	3/92 (3.26%)	0/25 (0.00%)
No. of multiple pregnancies per ET/*Broj multifetalnih trudnoća po ET*	10/92 (10.87%)	1/12 (8.33%)
No. of miscarriages/*Broj pobačaja*	7/45 (15.56%)	1/12 (8.33%)
No. of cancelled cycles/*Broj otkazanih ciklusa*	4 (4.17%)	2 (7.41%)
OHSS	15 (15.63%)	2 (7.41%)
Grade I/*Gradus I*	14 (14.58%)	1 (3.70%)
Grade II/*Gradus II*	1 (1.04%)	1 (3.70%)

Legend/*Legenda*: ET - embryo transfer/*embrio transfer;* OHSS - ovarian hyperstimulation syndrome/*sindrom ovarijalne hiperstimulacije*



Graph 1. The effect of BMI on embryo quality. Distribution of the obtained embryos by classes on day 3
Grafikon 1. *Uticaj indeksa telesne mase na kvalitet embriona. Distribucija dobijenih embriona po klasama trećeg dana*

ents with BMI ≤ 25 kg/m^2 (68.22% vs. 57.10%). The presence of class I embryos in the total number of the obtained embryos (36.13% vs. 19.38%), and their average number was statistically higher in the normal weight women group compared to the overweight ones. These data are shown in **Table 2**.

The proportions of the obtained embryos classified by the quality in relation to the BMI are shown in **Graph 1**.

Table 3 shows the pregnancy outcomes and complications. The implantation rate, the rate of clinical, biochemical and multifetal pregnancies were similar. However, the incidence of miscarriages and OHSS was higher in the normal weight women, but it was not statistically significant.

Discussion

There is a close relation between obesity and PCOS, as well as certain overlapping features [30]. In addition, the association between these two disorders is related to insulin resistance. The BMI is known to be in oppostie correlation with the response to some drugs and decrease in the body weight contribute to a better reproductive outcome [31]. It has been determined that less gonadotropin ampoules for stimulation as well as a higher number of the obtained oocytes and embryos are required for women with PCOS undergoing IVF. Furthermore, they are also more prone to OHSS. However, no agreement has yet been reached regarding the influence of BMI on the IVF outcome. Although a poorer IVF outcome has been reported by most of the studies, a certain number of them did not associate the poorer outcome with overweight (BMI: 25–29.9 kg/m^2), but only with obesity (BMI > 30 kg/m^2).

Our study did not show any statistically significant difference between the normal and the overweight group related to the total dose of gonadotropins. As it has been previously established, a larger amount of gonadotropins is required to stimulate obese patients. The association with the volume of distribution or peripheral metabolic clearance may be a possible reason for gonadotropin resistance in these patients [32]. This discrepancy can be explained by the fact that the median BMI among women of the overweight group was 28 kg/m^2 and that the women over BMI of 30 kg/m^2 could not undergo IVF before losing weight.

The same number of oocytes, but a lower total number of mature oocytes was obtained in the group of normal weight patients, as well as the same number of the obtained embryos, but a smaller number of those belonging to class I. Such a result could be only related to the BMI since the median age in both groups was 31.

The precise mechanism of how BMI influences the reproductive outcome is still unclear. A low embryo quality can be possibly caused by adverse follicular conditions related to insulin resistance, endocrine alterations, and possibly, by embryo toxic cytokines [23, 25, 33, 34]. The levels of estrogen and androgen are modified by obesity. The impairment of folliculogenesis and follicular atresia are caused by this endocrine disturbance due to an increased secretion of luteinizing hormone [35], an increased ratio of androgen [36], hyperinsulinemia [37] and an increased production of insulin-like growth factor (IGF-1) [38]. Another possible mechanism is a potential influence of adipokines leptin, adiponectin, ghrelin PYY3-36 and resistin on energy homeostasis, all of which can affect female fertility [39, 40].

In our study, there was no statistically significant difference in the IVF outcome between the groups. The number of the obtained mature oocytes and class I embryos was smaller in the group of overweight patents. However, the implantation rate and clinical pregnancy rate were the same. The mean number of aspirated oocytes was 11 in the overweight group and the mean number of obtained embryos was 5. Due to such a high number of embryos we were able to choose the best quality ones for transfer.

Conclusion

Female overweight is associated with a fewer number of mature oocytes and fewer good quality embryos; however, since the number of the obtained oocytes and embryos in polycystic ovary syndrome patients included in this study was generally higher, this shortfall did not affect pregnancy rates, which were the same in both groups. Certainly, before starting the *in vitro* fertilization, each infertile patient should be informed about the possible negative effect of the high body mass index on the treatment outcome. Furthermore, higher body mass index increases the risk of complications during pregnancy and at childbirth.

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