

The Effects of Overweight and Obesity on Assisted Reproduction Technology Outcomes

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ABSTRACT

The aim of the present study was to assess the impact of professional nutrition assistance on assisted reproduction technology (ART) outcomes in overweight or obese patients with polycystic ovarian syndrome (PCOS). The study represents a retrospective analysis of fertilization rates, embryo quality and gestations after ART in seven PCOS patients, five obese and two overweight. The women attended a private Fertility Center in Brazil between the years 2010 and 2016. Out of the seven patients, the three that reached a successful gestation were the ones that underwent comprehensive lifestyle changes, taking care of their diet for a more prolonged period of time and reached an ideal weight loss during the nutrition counseling period.

Keywords: obesity, overweight, polycystic ovarian syndrome

INTRODUCTION

Overweight and obesity are public health problems that are getting increasingly worse and have become a global epidemic according to the World Health Organization (WHO, 2011). Obesity is characterized by abnormal or excessive body fat accumulation to the point at which it becomes harmful to one's health (WHO, 2016; Pinheiro *et al.*, 2004). The energy imbalance between "energy intake" (food calories taken) and "energy output" (calories being used for body energy requirements), due to the intake of food that are low in nutrients and high in calories together with a sedentary lifestyle, is the leading cause of obesity (WHO, 2016). Endocrine disorders may take place due to an individual's genetic background and due to a fattening environment, where low-nutrient, energy-dense food and drinks are frequently advertised influencing their consumption (Cruz Sanchez *et al.*, 2013). The worldwide prevalence of obesity has more than doubled between 1980 e 2014.

According to the WHO (2016), in 2014, 1.9 billion adults aged 18 years or older were overweight, out of which, 600 millions were obese. The body mass index (BMI) is the worldwide index used to identify overweight and obesity in adults. Overweight is defined as a BMI equal to or greater than 25kg/m², and obesity is when the BMI reaches 30kg/m² or above (WHO, 2016). The higher the weight gain, the higher becomes the BMI and the likelihood of developing associated diseases, such as chronic non-transmissible diseases (CNTD), among which are breathing and cardiac problems, type II diabetes, hypertension and some types of cancer. In addition to the chronic diseases, weight excess may harm fertility due to hormonal disorders that affect the reproductive system (Becker *et al.*, 2015). Overweight affects the reproductive physiology at different levels, including the hypothalamus (Tortoriello *et al.*, 2004), the ovary and the ovarian follicle (Woodruff & Shea, 2011), the oocyte (Robker *et al.*, 2009), the embryo (Jungheim *et al.*, 2010) and the endometrium (Bellver *et al.*, 2011). Considering that overweight is a frequent condition among women at reproductive age, it has already been associated with

several fertility problems, such as anovulation, irregular menses, infertility, spontaneous abortions and gestational complications (Jungheim *et al.*, 2013).

Obese women that seek assisted reproduction technologies for infertility treatment need higher doses of gonadotropins than normal weight patients to obtain adequate follicular development during ovarian stimulation cycles (Jungheim & Moley, 2010). Obese women present relatively poor oocyte quality and lower fertilization rates (Shah *et al.*, 2011), they are less likely to achieve clinical pregnancy after IVF and embryo transfer (Jungheim *et al.*, 2009), they have an increased risk of spontaneous abortion (Rittenberg *et al.*, 2011) and are less likely to have a baby born after IVF (Luke *et al.*, 2011). These situations may be caused by the poor oocyte and embryo quality found in obese patients (Metwally *et al.*, 2007), and/or are due to an abnormal endometrial growth and embryo implantation (Jungheim & Moley, 2010).

Polycystic ovarian syndrome (PCOS) represents one of the most common endocrine disorders among women at reproductive age that may need assisted reproduction treatment to conceive (Dumesic *et al.*, 2015). The prevalence of obesity among PCOS women ranges between 30 and 70% and it represents one of the several phenotypes associated with the syndrome (Pandey *et al.*, 2010), together with risks related to the metabolic syndrome (Moran *et al.*, 2010), to the non-alcoholic fatty liver disease (Baranova *et al.*, 2011), to endocrine disruptors, particularly bisphenol A (Diamanti-Kandarakis *et al.*, 2009), to cardiovascular diseases (Taponen *et al.*, 2004), to insulin resistance (Norman *et al.*, 2001) and to dyslipidemia (Valkenburg *et al.*, 2008).

The metabolic alterations associated with PCOS, such as obesity, hyperinsulinemia, insulin resistance and a low-grade chronic inflammation, may all be important factors affecting oocyte competence and reproductive potential in this group of patients (Dumesic *et al.*, 2015; Moran *et al.*, 2015). Finally, it is important to mention that maternal obesity, regardless of PCOS status, may represent a risk factor to several congenital diseases in the offspring such as neural tube defects (Shaw *et al.*, 1996), cardiac pathologies (Cai *et al.*, 2014) and an increased likelihood of fetal death (Aune *et al.*, 2014).

The objective of the present study was to evaluate the impact of professional nutrition assistance on assisted reproduction treatments, in terms of fertilization rates, embryo quality and gestations, for overweight-obese PCOS women.

MATERIAL AND METHODS

This study is a retrospective analysis of seven cases of PCOS, of which five were obese and two were overweight with borderline BMI (almost obese). The patients came to the Nilo Frantz Human Reproduction Center between the years 2010 and 2016.

The patients' records were obtained from the Clinic database and from their nutrition records. The women were diagnosed with PCOS according to the criteria established

by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine, ESHRE-ASRM 2003 PCOS criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004).

Assisted Reproduction Technologies (ART)

The patients underwent controlled ovarian stimulation for ICSI. We employed the classical ART protocols for superovulation, oocyte collection, fertilization, embryo culture and transfer for ICSI cycles. Surplus, good quality embryos (not transferred) were cryopreserved. The parameters analyzed were total number of oocytes, day-2 and day-3 embryo quality (% of embryos grade 1 and 2 at day 2 or 3), day 5 or 6 blastocyst rate, biochemical gestations, abortions and live births.

Nutritional follow-up

All seven patients were seen by the dietitian. The treatment was geared to the patients' weight loss, lifestyle improvement, identification of their dietary pattern and promotion of changes in it to benefit the ART outcomes.

Initially weight and height were measured to calculate the BMI. Their weight was subsequently measured once a month. A nutritional anamnesis was performed to identify the pattern of food consumption, the need of possible changes and the introduction of new foods and eating habits.

Patients' reports demonstrated that all seven women had similar eating patterns. They preferred carbohydrates, mainly refined, such as sugars, sweets and sugary drinks. The women reported continuous consumption, almost daily, of white bread, biscuits, cereal bars, pasta, pizza, margarine, ready-made fruit juices, soft drinks and yogurts containing sugar.

Based on this information, nutritional guidance was the same for all seven patients. They were recommended daily intake of vegetables, fruits, nuts and chestnuts, extra-virgin olive oil and fish. At the same time, it was suggested they decreased the consumption of red meat and the amount of carbohydrates, favoring the use of whole grain, refrain from refined carbs and soft drinks and keeping hydrated by drinking water. In addition, it was recommended they did not consume hot drinks in plastic cups or put plastic containers in the freezer, take Omega-3 supplements and get started or keep physical activities.

RESULTS

The assisted reproduction centre where the study was performed registered a linear increase in overweight, obese I and obese II patients from 17% to 25%, from 5.5% to 6.5% and from 0.98% to 1.30%, respectively, between 2012 and 2016.

Only three out of the seven women that underwent ART had a pregnancy and live births. One of the pregnancies was a spontaneous gestation. The remaining four patients did not have a successful outcome from their ART treatments (Table 1). The three patients that achieved gestation and live birth were patients who adhered to the behavioral changes recommended by the dietitian.

All seven patients presented a reasonable good number of MII oocytes collected, fertilization rates and embryo quality, regardless of their overweight/obese status. However, in the case of Patient 4 a significant improvement in embryo quality was detected in her second ICSI cycle, after she had started the nutrition therapy and changed her lifestyle.

DISCUSSION

The three PCOS overweight or obese patients that reached gestation and live births were women that adhered to the diet and lifestyle changes recommended by the dietitian. These patients underwent lifestyle behavioral changes for a longer period and they presented a higher weight loss percentage during the period of nutritional follow up, than the patients who did not achieve gestation and live births. Patient 1 got pregnant naturally after she had an unsuccessful ART cycle and 18 months after she adhered to the treatment diet. It is likely that the new lifestyle and diet she adopted helped her to conceive. Unfortunately, this is a single case in the present study, and it is difficult to draw any conclusion from it. However, a study performed in Spain presented at the annual meeting of the European Society of Human Reproduction and Embryology (ESHRE) in Barcelona (2008), showed that natural conception may occur in infertile women who had previous ART cycle, because they maintain a healthy lifestyle. In addition, the study showed that excessive coffee and alcohol consumption and being significantly overweight reduces the likelihood of a subsequent natural conception.

On the other hand, patient 4, who underwent one ICSI cycle prior to the start of the nutrition therapy and another after adherence to the new routines and nutritional attitudes showed a remarkable improvement in embryo quality and achieved gestation and live birth. This observation is in accordance with previous reports that describe that embryo quality is associated with life style changes, which seem to influence term gestation and live birth (Metwally *et al.*, 2007; Shah *et al.*, 2011).

Endometrial growth, a key factor for successful term gestation did not seem to be affected by overweight or obesity. Except for one occasion, namely the second cycle of patient 7, all patients presented adequate endometrial thickness (>7mm) on the day of embryo transfer. On the other hand, there is controversy in the literature on whether obesity affects endometrial receptivity. A recent study by Coyne *et al.* (2016) on egg donation cycles for obese patients showed that embryos created using oocytes from healthy weight donors have implantation and pregnancy rates in obese recipients similar to those receipts with normal BMI. However, a previous study found opposite results (Bellver *et al.*, 2013), showing that obesity reduces pregnancy rates in egg donation cycles, possibly by affecting endometrial receptivity.

It is relevant to notice that out of the four patients that underwent a significant weight loss, between four and 14Kg, after the initial nutritional counseling on dietary habits and lifestyle changes, three achieved full term gestations. The observed weight loss achieved between five and 18 months corresponds to a weight reduction between five and 13% of their initial values, which are in accordance with the expected weight loss for obese patients to get pregnant (Jungheim *et al.*, 2009; 2013). In addition, the literature shows that obese women have an increased risk of having a spontaneous abortion, in addition to the fact that it takes longer to conceive when compared to women within the normal weight range (Rittenberg *et al.*, 2011). Despite controversies, the British Fertility Society published guidelines in 2007, stating that severely obese women should have their fertility treatment deferred until they have lost weight. The recommendations were based upon a comprehensive analysis of studies which establish the adverse impact of obesity on fertility. The report, published in the BFS Journal of Human Fertility, targets clinics and specialists providing care to obese women before and during pregnancy (Balen & Anderson, 2007).

Table 1. Physical characteristics and ART outcome of seven overweight/obese patients

Patient	IMC	Classif.	(% lost)	ART procedure	Age (years)	Oocytes MII (n)	Fert. rate (%)	Embryo Quality rate (%)	D5-6 Blast +/-	ET (+/-)/Day/BI	Endo (mm)	Outcome
1	37.85	Obesity II	13.6%	ICSI	36	10	100	60	-	+/D3	10	Abortion
												Natural pregnancy/ Birth
2	37.28	Obesity II	9.22%	ICSI FET	39 39	12 -----	83.3 -----	40 -----	+ -----	+/D2 +/BI	11 10	β-HCG (-)
												Abortion
3	32.82	Obesity I	3.47%	ICSI (1) FET (1) ICSI (2) FET (2)	37 38 38 39	7 ----- 13 -----	71.4 ----- 84.6 -----	60 ----- 58.3 -----	+ ----- + -----	+/D2 +/BI - +/BI	8 7.3 N/A 7.7	Abortion
												Abortion
												β-HCG (-)
												N/A
4	31.60	Obesity I	5%	ICSI (1) ICSI (2)	31 31	11 5	36.8 100	28.6 100	- +	+/D3 +/D3	----- -----	Biochem. gestation
												Biochem. gestation
5	30.23	Obesity I	13.53%	ICSI	30	17	76.5	61.5	+	+/D3	9.5	Birth/Twins
												β-HCG (-)
6	29.82	Overweight	1.17%	IUI (6) ICSI (1)	38 36	----- 9	----- 88	----- 62.5	----- +	----- +/D3	----- 7.8	Abortion
												Abortion
7	29.50	Overweight	2.9%	FET (1) ICSI (2) FET (2) ICSI (3) FET (3)	37 38 38 39 39	----- 11 ----- 10 -----	----- 72.7 ----- 70 -----	----- 62.5 ----- 75 -----	----- + ----- + -----	+/BI +/D3 +/BI +/D3 +/BI	6 8 7.5 7.5 8	β-HCG (-)
												β-HCG (-)
												β-HCG (-)
												β-HCG (-)

The negative effect of high BMI on the chances of PCOS patients becoming pregnant has been previously reported by Kulmann *et al.* (2016) on the same group of women investigated in the present study. The authors described lower positive beta-hCG and ongoing pregnancy rates among women with high BMI (>25), when compared to normal-weight women.

Overall, the present study shows that bad eating habits seem to be related to poor assisted reproduction outcomes, in terms of ongoing and full term gestations. On the other hand, positive ART outcomes may be achieved by women that adhere to the recommended nutritional and lifestyle changes and maintain the new habits for a period long enough to conceive and sustain a pregnancy.

It is important to point out that quick and short-term changes in weight loss may have negative effects on ART outcomes (Becker *et al.*, 2015; Sim *et al.*, 2014). It has been established that dietary and lifestyle changes need a minimum of three to five months to be effective for women to improve their odds of getting pregnant (Domecq *et al.*, 2013; Moran *et al.*, 2011; Islam *et al.*, 2016; Juanol-Falgarona *et al.*, 2014). Also, for example, the effects of one commonly used dietary supplement recommended to decrease inflammation in obese and overweight patients, occur at medium-long term consumption (Skulas-Ray *et al.*, 2011).

The finding that no overweight or obese patient got pregnant after frozen embryo transfer may be explained by the hypothesis of putative higher lipid content in the blastomers of their embryos, which decreases post-thawing embryonic viability. It is well known among cattle breeders that donor cows, which are overweight or have a high-fat and high-calorie feed, present low quality oocytes and generate embryos with low post-cryopreservation survival rates, when compared with embryos from cows fed standard diets (Santos *et al.*, 2008).

Despite the findings described in the present study and data from the literature, there is a lack of consensus on the negative effects of obesity on the female reproductive potential in ART cycles. Whereas some authors describe a decrease in conception likelihood due to obesity (Bellver *et al.*, 2013), others did not find a relationship between BMI and pregnancy rates after ART (Shah *et al.*, 2011). Thus, further studies involving a larger population of PCOS patients undergoing ART cycles are necessary to clarify the effects of obesity on conception and birth rates.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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REFERENCES

- Aune D, Saugstad OD, Henriksen T, Tonstad S. Maternal body mass index and the risk of fetal death, stillbirth, and infant death: a systematic review and meta-analysis. *JAMA*. 2014;311:1536-46. PMID: 24737366 DOI: 10.1001/jama.2014.2269
- Balen AH, Anderson RA; Policy & Practice Committee of the BFS. Impact of obesity on female reproductive health: British Fertility Society, Policy and Practice Guidelines. *Hum Fertil (Camb)*. 2007;10:195-206. PMID: 18049955 DOI: 10.1080/14647270701731290
- Baranova A, Tran TP, Bireddinc A, Younossi ZM. Systematic review: association of polycystic ovary syndrome with metabolic syndrome and non-alcoholic fatty liver disease. *Aliment Pharmacol Ther*. 2011;33:801-14. PMID: 21251033 DOI: 10.1111/j.1365-2036.2011.04579.x
- Becker GF, Passos EP, Moulin CC. Short-term effects of a hypocaloric diet with low glycemic index and low glycemic load on body adiposity, metabolic variables, ghrelin, leptin, and pregnancy rate in overweight and obese infertile women: a randomized controlled trial. *Am J Clin Nutr*. 2015;102:1365-72. PMID: 26561614 DOI: 10.3945/ajcn.115.117200
- Bellver J, Martínez-Conejero JA, Labarta E, Alamá P, Melo MA, Remohí J, Pellicer A, Horcajadas JA. Endometrial gene expression in the window of implantation is altered in obese women especially in association with polycystic ovary syndrome. *Fertil Steril*. 2011;95:2335-41, 2341.e1-8. PMID: 21481376 DOI: 10.1016/j.fertnstert.2011.03.021
- Bellver J, Pellicer A, García-Velasco JA, Ballesteros A, Remohí J, Meseguer M. Obesity reduces uterine receptivity: clinical experience from 9,587 first cycles of ovum donation with normal weight donors. *Fertil Steril*. 2013;100:1050-8. PMID: 23830106 DOI: 10.1016/j.fertnstert.2013.06.001
- Cai GJ, Sun XX, Zhang L, Hong Q. Association between maternal body mass index and congenital heart defects in offspring: a systematic review. *Am J Obstet Gynecol*. 2014;211:91-117. PMID: 24631708 DOI: 10.1016/j.ajog.2014.03.028
- Coyne K, Whigham LD, O'Leary K, Yaklic JK, Maxwell RA, Lindheim SR. Gestational carrier BMI and reproductive, fetal and neonatal outcomes: are the risks the same with increasing obesity? *Int J Obes (Lond)*. 2016;40:171-5. PMID: 26290016 DOI: 10.1038/ijo.2015.159
- Cruz Sanchez MC, Tuñón Pablos ET, Villaseñor Farias M, Álvarez Gordillo GC, Nielsen RB. Sobrepeso y obesidad: una propuesta de abordaje desde la sociología. *Reg Soc*. 2013;25:165-202. DOI: 10.22198/rys.2013.57.a115
- Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, Zoeller RT, Gore AC. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocr Rev*. 2009;30:293-342. PMID: 19502515 DOI: 10.1210/er.2009-0002
- Domecq JP, Prutsky G, Mullan RJ, Hazem A, Sundaresh V, Elamin MB, Phung OJ, Wang A, Hoeger K, Pasquali R, Erwin P, Bodde A, Montori VM, Murad MH. Lifestyle modification programs in polycystic ovary syndrome: systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2013;98:4655-63. PMID: 24092832 DOI: http://dx.doi.org/10.1210/jc.2013-2385
- Dumesic DA, Oberfield SE, Stener-Victorin E, Marshall JC, Laven JS, Legro RS. Scientific Statement on the Diagnostic Criteria, Epidemiology, Pathophysiology, and Molecular Genetics of Polycystic Ovary Syndrome. *Endocr Rev*. 2015;36:487-525. PMID: 26426951 DOI: 10.1210/er.2015-1018
- Islam MA, Alam F, Solayman M, Khalil MI, Kamal MA, Gan SH. Dietary Phytochemicals: Natural Swords Combating Inflammation and Oxidation-Mediated Degenerative Diseases. *Oxid Med Cell Longev*. 2016;2016:5137431. DOI: 10.1155/2016/5137431

- Juanola-Falgarona M, Salas-Salvadó J, Ibarrola-Jurado N, Rabassa-Soler A, Díaz-López A, Guasch-Ferré M, Hernández-Alonso P, Balanza R, Bulló M. Effect of the glycemic index of the diet on weight loss, modulation of satiety, inflammation, and other metabolic risk factors: a randomized controlled trial. *Am J Clin Nutr.* 2014;100:27-35. PMID: 24787494 DOI: 10.3945/ajcn.113.081216
- Jungheim ES, Lanzendorf SE, Odem RR, Moley KH, Chang AS, Ratts VS. Morbid obesity is associated with lower clinical pregnancy rates after in vitro fertilization in women with polycystic ovary syndrome. *Fertil Steril.* 2009;92:256-61. PMID: 18692801 DOI: 10.1016/j.fertnstert.2008.04.063
- Jungheim ES, Moley KH. Current knowledge of obesity's effects in the pre- and periconceptional periods and avenues for future research. *Am J Obstet Gynecol.* 2010;203:525-30. PMID: 20739012 DOI: 10.1016/j.ajog.2010.06.043
- Jungheim ES, Schoeller EL, Marquard KL, Louden ED, Schaffer JE, Moley KH. Diet-induced obesity model: abnormal oocytes and persistent growth abnormalities in the offspring. *Endocrinology.* 2010;151:4039-46. PMID: 20573727 DOI: http://dx.doi.org/10.1210/en.2010-0098
- Jungheim ES, Travieso JL, Hopeman MM. Weighing the impact of obesity on female reproductive function and fertility. *Nutr Rev.* 2013;71:S3-8. PMID: 24147921 DOI: 10.1111/nure.12056
- Kulmann MIR, Basso CG, de Oliveira NP, Frantz GN, Dutra CG, Chagas JC, Robin F, Frantz N. The effect of body mass index on the assisted reproductive outcomes for polycystic ovary patients. *JBRA Assist Reprod.* 2016;20:182. PMID: 27584612 DOI: 10.5935/1518-0557.20160036
- Luke B, Brown MB, Missmer SA, Bukulmez O, Leach R, Stern JE; Society for Assisted Reproductive Technology writing group. The effect of increasing obesity on the response to and outcome of assisted reproductive technology: a national study. *Fertil Steril.* 2011;96:820-5. PMID: 21821244 DOI: 10.1016/j.fertnstert.2011.07.1100
- Metwally M, Cutting R, Tipton A, Skull J, Ledger WL, Li TC. Effect of increased body mass index on oocyte and embryo quality in IVF patients. *Reprod Biomed.* 2007;15:532-8. PMID: 18044034 DOI: 10.1016/S1472-6483(10)60385-9
- Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update.* 2010;16:347-63. PMID: 20159883 DOI: 10.1093/humupd/dmq001
- Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database Syst Rev.* 2011;(7):CD007506. PMID: 21328294 DOI: 10.1002/14651858.CD007506.pub2
- Moran LJ, Norman RJ, Teede HJ. Metabolic risk in PCOS: phenotype and adiposity impact. *Trends Endocrinol Metab.* 2015;26:136-43. PMID: 25591984 DOI: 10.1016/j.tem.2014.12.003
- Norman RJ, Masters L, Milner CR, Wang JX, Davies MJ. Relative risk of conversion from normoglycaemia to impaired glucose tolerance or non-insulin dependent diabetes mellitus in polycystic ovarian syndrome. *Hum Reprod.* 2001;16:1995-8. PMID: 11527911 DOI: 10.1093/hum-rep/16.9.1995
- Pandey S, Pandey S, Maheshwari A, Bhattacharya S. The impact of the male obesity on the outcome of fertility treatment. *J Hum Reprod Sci.* 2010;3:62-7. PMID: 21209748 DOI: 10.4103/0974-1208.69332
- Pinheiro ARO, Freitas SFT, Corso ACT. Uma abordagem epidemiológica da obesidade. *Rev Nutr.* 2004;17:523-33. DOI: 10.1590/S1415-52732004000400012
- Rittenberg V, Sobaleva S, Ahmad A, Oteng-Ntim E, Bolton V, Khalaf Y, Braude P, El-Toukhy T. Influence of BMI on risk of miscarriage after single blastocyst transfer. *Hum Reprod.* 2011;26:2642-50. PMID: 21813669 DOI: 10.1093/humrep/der254
- Robker RL, Akison LK, Bennett BD, Thrupp PN, Chura LR, Russell DL, Lane M, Norman RJ. Obese women exhibit differences in ovarian metabolites, hormones, and gene expression compared with moderate weight women. *J Clin Endocrinol Metab.* 2009;94:1533-40. PMID: 19223519 DOI: 10.1210/jc.2008-2648
- Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril.* 2004;81:19-25. PMID: 14711538 DOI: 10.1016/j.fertnstert.2003.10.004
- Santos JEP, Cerri RL, Sartori R. Nutritional management of the donor cow. *Theriogenology.* 2008;69:88-97. PMID: 17959235 DOI: 10.1016/j.theriogenology.2007.09.010
- Shah DK, Missmer SA, Berry KF, Racowsky C, Ginsburg ES. Effect of obesity on oocyte and embryo quality in women undergoing in vitro fertilization. *Obstet Gynecol.* 2011;118:63-70. PMID: 21691164 DOI: 10.1097/AOG.0b013e31821fd360
- Shaw GM, Velie EM, Schaffer D. Risk of neural tube defect-affected pregnancies among obese women. *JAMA.* 1996;275:1093-6. PMID: 8601928 DOI: 10.1001/jama.1996.03530380035028
- Sim KA, Partridge SR, Sainsbury A. Does weight loss in overweight or obese women improve fertility treatment outcomes? A systematic review. *Obes Rev.* 2014;15:839-50. PMID: 25132280 DOI: 10.1111/obr.12217
- Skulas-Ray AC, Kris-Etherton PM, Harris WS, Heuvel JP, Wagner PR, West SG. Dose-response effects of omega-3 fatty acids on triglycerides, inflammation, and endothelial function in healthy persons with moderate hypertriglyceridemia. *Am J Clin Nutr.* 2011;93:243-52. PMID: 21159789 DOI: 10.3945/ajcn.110.003871
- Taponen S, Martikainen H, Järvelin MR, Sovio U, Laitinen J, Pouta A, Hartikainen AL, McCarthy MI, Franks S, Paldanius M, Ruokonen A; Northern Finland Birth Cohort 1966 Study. Metabolic cardiovascular disease risk factors in women with self-reported symptoms of oligomenorrhea and/or hirsutism: Northern Finland Birth Cohort 1966 Study. *J Clin Endocrinol Metab.* 2004;89:2114-8. PMID: 15126528 DOI: 10.1210/jc.2003-031720
- Tortoriello DV, McMinn J, Chua SC. Dietary-induced obesity and hypothalamic infertility in female DBA/2J mice. *Endocrinology.* 2004;145:1238-47. PMID: 14670988 DOI: 10.1210/en.2003-1406

Valkenburg O, Steegers-Theunissen RP, Smedts HP, Dall'inga-Thie GM, Fauser BC, Westerveld EH, Laven JS. A more atherogenic serum lipoprotein profile is present in women with polycystic ovary syndrome: a case control study. *J Clin Endocrinol Metab.* 2008;93:470-6. PMID: 18056772 DOI: 10.1210/jc.2007-1756

WHO. World Health Organization. Obesity and Overweight factsheet from the WHO [Internet]; 2011. Available at: <http://www.thehealthwell.info/node/82914>. Accessed: 2/7/2018.

WHO. World Health Organization. Obesity and Overweight [Internet]; 2016. Available at: <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>. Accessed: 2/7/2018.

Woodruff TK, Shea LD. A new hypothesis regarding ovarian follicle development: ovarian rigidity as a regulator of selection and health. *J Assist Reprod Genet.* 2011;28:3-6. PMID: 20872066 DOI: 10.1007/s10815-010-9478-4