Physical activity, obesity and eating habits can influence assisted reproduction outcomes

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Objective: to determine if eating habits, physical activity and BMI can influence assisted reproduction outcomes. **Material and Methods:** this study analyzed 436 patients undergoing intracytoplasmic sperm injection cycles. Patients answered a questionnaire and regression analysis examined the relationship between lifestyle and BMI with the intracytoplasmic sperm injection cycles outcomes. **Results:** no influence of lifestyle and obesity was observed on the number of oocytes recovered. Obesity reduced the normal fertilization rate (coefficient [Coef.]: -16.0; p = 0.01) and increased the risk of miscarriage (OR: 14.3; p = 0.03). Physical activity positively affected implantation (Coef.: 9.4; p = 0.009), increased the chance of pregnancy (OR: 1.83; p = 0.013) and tended to decrease the risk of miscarriage (OR: 0.30; p = 0.068). In addition, an inverse correlation was found between physical activity and BMI, and a direct correlation was found between soft-drink consumption and BMI. **Conclusions:** eating habits, physical activity and obesity could affect clinical outcomes of assisted reproduction.

Lifestyle factors are known to affect fertility in both men and women, and there is increasing interest in investigating such factors. A combination of reduced exercise, changes of dietary composition and increased energy intake have been contributing to a growing worldwide epidemic of obesity, with serious impacts on several aspects of health [1].

Overweight and obesity are the result of a chronic imbalance between energy intake and energy expenditure, and despite the fact that energy intake has become more caloric, a parallel decline in the level of physical activity also exists, contributing to the obesity epidemic [2].

The deleterious effects of obesity on reproductive health include menstrual disorders and infertility [3]. Such disorders are probably related to multiple factors such as endocrine and metabolic functions, including the balance of sex steroids, insulin and leptin, which, in turn, may directly or indirectly affect ovarian function, follicular growth, implantation and development of a clinical pregnancy [4,5].

Although no consensus can be found on previous studies, the consumption of specific food and drinks and some habits can impair reproductive outcomes. Alcohol and caffeine intake, as well as tobacco smoking could be important factors in the failure of assisted reproduction (AR). A powerful influence of caffeine intake by females can be found on miscarriage, gestational age at delivery and on embryotoxic effect after AR treatment [6]. Furthermore, previous studies indicate that a high caffeine intake by a women during pregnancy is accompanied by a higher incidence of smoking and higher alcohol consumption [7].

Women who consume high amounts of alcohol may take longer to fall pregnant [8], have increased rates of spontaneous miscarriages and worse pregnancy outcomes [9]. In contrast, women who are wine consumers present a shorter waiting time to pregnancy in comparison to nonwine drinkers [8].

The effects of BMI on AR cycle's outcomes were recently reviewed. Although overweight, women required higher doses of gonadotrophins, and showed lower likelihoods of pregnancy and an increased risk of miscarriage after IVF; the live birth rates are still controversial [10].

The aim of the present study was to evaluate the potential effect of women's lifestyle (eating habits and physical activity) and obesity on AR treatment outcomes.

Materials & methods

Experimental design

This cohort study included 436 patients undergoing their first cycle of intracytoplasmic sperm injection (ICSI) between January 2005 and

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October 2007, in a private assisted reproduction center. This study was approved by the local Institutional Review Board, and written informed consents were obtained from all patients, in which they agreed to share the outcomes of their ICSI cycles for research purposes.

The causes of infertility were male factors (35.6%), ovarian disorders (17.2%), idiopathic cause (13.0%), endometriosis (11.0%), tubal-uterine factors (8.0%), polycystic ovarian syndrome (5.0%) and a combination of various other causes (10.2%). The study included couples undergoing controlled ovarian stimulation and ICSI, who had completed the lifestyle questionnaire.

The validated lifestyle questionnaire [11], containing multiple choice questions, was completed by the patients at the start of treatment. The women reported their (i) physical activity practices, and nutritional habits in terms of their consumption of (ii) caffeine-containing soft drinks, (iii) coffee, (iv) alcohol and (v) chocolate. The questionnaire was prepared by a nutritionist and based on the main nutritional habits observed on clinical routine of patients undergoing ICSI cycles in our center.

Positive answers to the questionnaire were considered when patients reported: (i) practice of physical activity: at least 1 h of activity three-times a week, (ii) daily consumption of at least one glass of caffeine-containing soft drink, (iii) daily consumption of more than one cup of coffee, (iv) consumption of alcohol more than five-times a week, and (v) consumption of chocolate bars more than five-times a week.

Patients were considered as obese with a BMI of ≥30.0 kg/m^2, overweight with a BMI of ≥25.0 and <30.0 kg/m^2, or nonoverweight with a BMI of <25.0 kg/m^2. The outcomes of ICSI cycles were retrospectively reviewed from the clinical database and correlated to the questionnaire answers regarding lifestyles and obesity.

Controlled ovarian stimulation & laboratory procedures

Women were submitted to pituitary down-regulation using a gonadotropin-releasing hormone agonist (Lupron Kit™, Abbott S.A Societé Française des Laboratoires, Paris, France) followed by ovarian stimulation with recombinant follicle-stimulating hormone ([FSH]; Gonal-F®, Merck Serono, Geneve, Switzerland).

Follicular dynamics was followed by ultrasound and dose adjustments were performed if necessary. When at least one follicle of 18 mm diameter or larger or two follicles of 16mm diameter or larger were observed, recombinant human chorionic gonadotropin (r-hCG) (250 µg; Ovidrel™, Merck Serono, Geneve, Switzerland) was administered to induce final follicular maturation. A total of 35 h after r-hCG administration, oocytes were collected by transvaginal ultrasound. The recovered oocytes were assessed for their nuclear status, and those in metaphase II (MII) were submitted to ICSI following routine procedures [12].

Normal fertilization, indicated by the presence of two clearly distinct pronuclei, was assessed 18 h after ICSI (it excludes abnormal fertilizations such as the presence of only one, or more than two pronuclei). Embryo quality was evaluated under an inverted microscope (Eclipse TE 300; Nikon®, Tokyo, Japan) and the following parameters were recorded: number and symmetry of blastomeres, fragmentation percentage, presence of multinucleation and defects in the zona pellucida and cytoplasm. One to three high-quality embryos, when available, were transferred per patient on the second or third day of development. When no high-quality embryos were available the cycle was cancelled.

Implantation rate was defined as the number of gestational sacs divided by the number of embryos transferred per patient. Clinical pregnancy was defined as the presence of a gestational sac with heartbeat visualized by ultrasound 4–6 weeks after embryo transfer. Miscarriage was considered when spontaneous loss of a pregnancy before 24 weeks' gestation occurred.

Data analysis

The ICSI outcomes analyzed in this study were specifically chosen to engage all aspects of treatment, including the number of oocytes recovered (representing the response to ovarian stimulation), the fertilization and implantation rates (reflecting oocyte and embryo quality respectively), and the clinical outcomes, which included clinical pregnancy and miscarriage.

The general characteristics of the groups were expressed as the mean ± standard deviation (SD) for numerical variables, and proportions (%) were used for categorical variables.

Prior to the multivariate analyses, univariate analyses were performed to identify which variable would affect the ICSI outcomes. For this analyses the predicted variables were BMI, eating habits and social habits

Multiple linear or logistic regression analysis were conducted to assess the influence of obesity, eating habits and physical activity on the outcomes of ICSI cycles. Regression analysis was adjusted for variables considered potential

confounders of the association between the factors evaluated and ICSI outcomes (women's age, dose of FSH administered, number of transferred embryos, cause of infertility for all analyses and endometrium thickness for clinical outcomes analysis).

A Pearson correlation coefficient was also calculated to establish the association between variables.

The power test was performed according to the sample size, standard deviation and difference between groups taking into account the implantation rate. The result was higher than 0.8.

Results were considered to be significant at the 5% critical level ($p \leq 0.05$). Data analysis was carried out using SPSS (version 15) statistical software.

Results

The causes of infertility were equally distributed among the groups (Table 1). The general characteristics of patients and their classification according to BMI are shown in Table 2. Our data demonstrated the influence of age on both BMI (coefficient [Coef.]: 0.107; $p = 0.002$) and dose of FSH administered (Coef.: 50.15; $p < 0.001$). Of the patients, five were over 44 years of age. One alternative would be to exclude these patients from the analysis; however, instead all the regression analyses were maternal-age adjusted.

Regarding the patients eating habits, we observed that 31.5% of the patients consume coffee, 17.6% consume caffeine-containing soft drinks, 9.2% consume chocolate and 5.1% consume alcohol. On the other hand, 36.3% of the patients practice physical activity. Even though there were no correlations between BMI and coffee (Coef.: = 0.011; $p = 0.813$), caffeine-containing soft drinks (Coef.: = 0.058; $p = 0.231$), alcohol (Coef.: = -0.051; $p = 0.290$), or chocolate (Coef.: = -0.010; $p = 0.830$) consumptions, we observed that patients that practiced physical activity had lower BMI (Pearson correlation: r =-0.118; $p = 0.014$), and those who consumed caffeine-containing soft drinks had a higher probability for obesity (logistic regression analysis: OR: 2.67, CI 95%: 1.0–7.0; $p = 0.045$). The cycle's characteristics are shown in Table 3.

In a further analysis, we evaluated the influence of obesity, eating habits and physical activity on ICSI outcomes. The number of oocytes recovered was not influenced by any variable included in the model. However, obesity adversely influenced the normal fertilization rate and positively influenced the chance of miscarriage. In addition, physical activity had a positive effect on implantation rate, increasing the chance of pregnancy in nearly 80% of patients, and decreasing the chance of miscarriage (Table 4).

Discussion

The impact of obesity on the outcomes of AR cycles has been supported by many studies and has also been recently reviewed [10]. Several studies verified an adverse effect of obesity on IVF outcomes [5,13,14]. However, other studies have found no significant differences on clinical pregnancy between obese and nonoverweight women [15–17].

It is well known that BMI is closely related to lifestyle factors, such as eating habits and physical activity. In this study we aimed to investigate the influences of caffeine, caffeine-containing soft drinks, chocolate and alcohol consumptions, physical activity and obesity on ICSI cycles outcome.

Recent estimates in the USA highlight the prevalence of obesity (overweight or obese) in 61.8% of women [18]. However, considering the population evaluated in this study, only 22.2% of women were in such categories.

The difference between the prevalence of American and Brazilian or Spanish overweight-obese women is likely due to the different eating

Table 1. Distribution of the causes of infertility among the weight groups.

Cause of infertility	Normal (%)	Overweight (%)	Obese (%)
Endometriosis	6.5	4.7	7.9
Unexplained infertility	12.9	4.7	10.5
Male factor	35.1	38.1	36.1
Ovarian factor	16.8	4.7	13.1
Tubal factor	7.0	14.3	9.2
Polycystic ovarian syndrome	4.1	14.3	3.5
Associated factors	17.6	19.0	19.7

$p > 0.05$.

Table 2. General characteristics of patients regarding age, BMI and BMI categories.			
		Mean ± SD	**Range**
General characteristics			
Maternal age (years)		35.3 ± 4.8	23–48
BMI (kg/m^2)		23.0 ± 3.5	18.0–46.0
BMI categories	***Number (%)***	***Mean ± SD***	***Range***
Normal (BMI 18.0–24.5 kg/m^2)	339 (77.8)	21.6 ± 1.8	18.0–24.9
Overweight (BMI ≥25.0 and <30.0 kg/m^2)	76 (17.4)	26.9 ± 1.5	25.0–29.8
Obese (BMI ≥30.0 kg/m^2)	21 (4.8)	33.0 ± 3.6	30.1–46.1

habits. The low percentage of women who consumed caffeine-containing soft drinks, chocolate and alcohol in our study supports this hypothesis.

In our study, no influence of unhealthy eating habits was observed on clinical outcomes of ICSI cycles. However, patients who consumed caffeine-containing soft drinks had a higher probability of being obese, which supports the relationship of eating habits and obesity.

A recent study demonstrated a marked interaction between BMI and age, and a significant influence of BMI on oocyte recovery, fertilization, implantation, pregnancy and live birth rates of IVF cycles [19]. In the present study, no influence of obesity was found on oocyte recovery rates, likely owing to the adjustments performed on dose of FSH administered.

The relationship between oocyte quality and obesity remains a matter of debate. Attention has been given to the cause of poor fertility outcomes in obese women, seeking to determine whether impaired outcomes are due to an ovarian effect, endometrial effect or a combined effect. While some studies demonstrated that obese women have a higher risk of nonrecurrent miscarriages, which points to oocyte quality as the main factor for poor reproductive performance [15,20,21]; others did not find an association between the quality of oocytes and obesity [14,22,23].

In the present study, the relationship between BMI, eating habits and physical activity on the outcomes of ICSI was evaluated. Oocyte dimorphisms were not evaluated. However, it is well known that intracytoplasmic and extracytoplasmic anomalies developing during the maturation process may lead to fertilization failure [24,25] and developmental impairment of the embryo despite normal fertilization [24,26,27].

The interaction between obesity and pregnancy loss is probably not caused by the IVF procedure itself, since obesity also increases the miscarriage rate in ovodonation cycles [13]. In addition, previous studies have shown that obesity is an independent cause of miscarriage in spontaneous pregnancies [21]. The mechanism underlying obesity-related pregnancy loss may involve endocrine and biochemical factors that may affect ovarian function and endometrial receptivity [22,28].

Indeed, a recent study showed that a BMI of >30 is an independent factor for poor pregnancy outcome. Therefore, the evidence of endometrial compromise is evident in obese women [29].

By contrast, in a previous report, 6500 IVF cycles and more than 80,000 oocytes were analyzed. Implantation, pregnancy and live birth rates were significantly lower as BMI increased. In addition, FSH dose was also adjusted and

Table 3. General characteristics of intracytoplasmic sperm injection cycles.	
General characteristics	
Follicle-stimulating hormone (total dose administered [IU])	2376.9 ± 691.3
Number of follicles aspirated	17.7 ± 14.2
Number of oocytes recovered	11.5 ± 9.0
Fertilization rate (%)	74.9 ± 7.5
Implantation rate (%)	20.9 ± .17.0
Pregnancy rate (%)	31.4
Endometrial thickness (mm)	11.8 ± 2.5
Number of embryos transferred per patient	2.0 ± 0.9

Table 4. Effect of obesity and practicing physical activity on the intracytoplasmic sperm injection cycles outcomes.

Linear regression analysis†		Obesity		Practicing physical activity	
	Mean value (%)	*Coefficient*	*p-value*	*Coefficient*	*p-value*
Normal fertilization rate	68.8	-16.0	0.010	1.6	0.553
Implantation rate	20.3	1.6	0.852	9.4	0.009

Logistic regression analysis†		Obesity			Practicing physical activity		
	Mean value (%)	*95% CI*	*OR*	*p-value*	*95% CI*	*OR*	*p-value*
Clinical pregnancy	31.4	0.3 – 3.2	1.02	0.976	1.1–2.9	1.83	0.013
Miscarriage	14.8	1.3–157.0	14.3	0.030	0.08–1.1	0.30	0.068

†*Regression analyses maternal age-adjusted.*

no differences appeared in number of retrieved oocytes among the BMI groups, although more FSH was needed in the obese group to obtain this result. Moreover, mean age was similar among BMI groups [30].

A significant poorer outcome was observed in surrogate mothers who received donated ova and nonseverely altered sperm samples when BMI was higher than 35 [31].

A higher rate of early pregnancy loss in obese women had been described [22,28]. It is important to note that miscarriage, as a consequence of obesity in women undergoing IVF, is an additional potential complication. This emphasizes the necessity of weight reduction before the beginning of fertility treatments [28,32], especially in younger patients who are not at risk of an age-related decline in fertility [19].

We observed an inverse correlation between BMI and physical activity. Furthermore, practicing physical activity had an independent effect on ICSI outcomes, as woman who practiced physical activity had higher implantation rates, increased chance of becoming pregnant and a lower probability of miscarriage. However, despite the fact that obesity did not influence the implantation and clinical pregnancy rates, whether or not the benefit of physical activity on implantation and pregnancy rates is mediated by BMI reduction is still to be elucidated.

The US Center for Disease Control and Prevention (CDC) recommends 30 min of physical activity on most days of the week [33]. Although exercise is known to improve several health aspects, the relationship between exercise and fertility is complex. Physical activity can impact reproductive function through its ability to regulate energy balance, influencing the hormonal milieu, which in turn may favorably or unfavorably affect assisted reproductive outcomes.

Previous studies have shown that intense physical activity practiced by female athletes is linked to anovulation and infertility due to lower levels of estrogen and progesterone, which suggest an absence of follicular development, ovulation and luteal function [34]. On the other hand, physical activity performed aiming to improve health, may promote changes on energy balance status, which in turn is tightly coupled with the reproductive system [35]. In addition, exercise leading to weight loss in obese women has been suggested to improve ovulation and subsequent fertility [36–38].

Studying the benefits of physical activity for nonathletes is complex due to the difficulty of quantifying physical activity in terms of frequency, intensity, modality and duration. Thus, studies evaluating the effect of exercise for health recommendations specifically on AR outcomes are scarce.

In a previous study evaluating the influence of exercise on AR treatment, no contribution of physical activity was found to influence IVF outcomes [39]. On the other hand, we found that regular physical activity increased implantation rates, improved the chance of becoming pregnant to 80%, and reduced the risk of miscarriage by 70%. In this study, physical activity was considered when performed at least three-times a week, independently of modality, duration or intensity.

In summary, our findings demonstrate that obesity impaired oocyte quality and clinical outcomes of women undergoing ICSI cycles. Furthermore, BMI is inversely related to physical activity, which in turn may independently lead to many benefits on clinical outcomes such as implantation, clinical pregnancy and miscarriage. Thus, patients should be encouraged to regularly practice physical activity aiming to decrease the BMI in obese patients, resulting in better clinical outcomes. This study also

supports the importance of lifestyle on ICSI outcomes and nutritional counseling during the treatment.

However, since in the present study, few patients were classified as obese, which is a limitation of the study, a larger trial with an increased number of patients recruited, would confirm our findings.

Future perspective

A combination of reduced exercise, changes on dietary composition and increased energy intake have been contributing to a growing worldwide obesity epidemic, with serious impacts on several aspects of human health, such as reproductive outcomes. Recent estimations in the USA highlight the prevalence of obesity (overweight or obese) in 61.8% of women. Less is known about the cause of poor fertility outcomes in obese women. There is a growing interest in determining whether these impaired outcomes are due to an ovarian effect, endometrial effect or a combined effect. On the other hand, it is well known that BMI is closely related to lifestyle factors, such as eating habits and physical activity. Another key point to discuss regards the relationship between exercise and fertility. Physical activity can impact reproductive function through its ability to regulate energy balance. However, it can be argued that by influencing the hormonal milieu, exercises could, in turn, favorably or unfavorably affect AR outcomes. Although there is an increasing interest in investigating this issue at present, only a small number of reports attempt to demonstrate that lifestyle factors can affect fertility. This is certainly a topic for further review and discussion emphasizing nutritional counseling during AR treatment. Futhermore, the increase in the number of large and randomized studies will allow for improved data collection and a more accurate indication of the effects of lifestyle and obesity factors on AR statistics.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

- A combination of reduced exercise, changes in dietary composition and increased energy intake have been contributing to a growing worldwide obesity epidemic, with serious impacts on several aspects of health.
- The deleterious effects of obesity on reproductive health include menstrual disorders and infertility.
- The consumption of specific food and drinks and some habits can impair reproductive outcomes. Alcohol and caffeine intake, as well as tobacco smoking could be important factors in the failure of assisted reproduction treatment.
- This cohort study included 436 patients undergoing their first cycle of intracytoplasmic sperm injection, who had completed the lifestyle questionnaire. The outcomes of intracytoplasmic sperm injection cycles were analyzed and correlated to the questionnaire answers regarding lifestyle and obesity.
- There was no relation between BMI and coffee intake (coefficient [Coef.]: 0,011; p = 0.813), caffeine-containing soft drinks (Coef.: 0.058; p = 0.231), alcohol (Coef.: -0.051; p = 0.290) or chocolate (Coef.: -0,010; p = 0.830) consumptions.
- We observed that patients undertaking physical activity have lower BMI (Pearson correlation: r = -0.118; p = 0.014), and those consuming caffeine-containing soft drinks have a higher probability for obesity (logistic regression analysis: OR: 2.67, 95% CI: 1.0–7.0; p = 0.045).
- Obesity adversely influenced the normal fertilization rate and positively influenced the chance of miscarriage.
- Physical activity had a positive effect on implantation rate, increasing the chance of pregnancy in nearly 80%, and decreasing the chance of miscarriage.

Bibliography

Papers of special note have been highlighted as:
• of interest

1. Bessesen DH: Update on obesity. *J. Clin. Endocrinol. Metab.* 93(6), 2027–2034 (2008).
2. Stubbs CO and Lee AJ: The obesity epidemic: both energy intake and physical activity contribute. *Med. J. Aust.* 181(9), 489–491 (2004).
3. ACOG: ACOG Committee Opinion number 315, September 2005. Obesity in pregnancy. *Obstet. Gynecol.* 106(3), 671–675 (2005).

• **Highlights that obese women are at an increased risk for several adverse outcomes, maternal and fetal complications during pregnancy. Moreover, it emphasizes that obstetricians should provide counseling and encourage obese patients to undertake a weight-reduction program before attempting pregnancy.**

4. Pasquali R, Pelusi C, Genghini S, Cacciari M, Gambineri A: Obesity and reproductive disorders in women. *Hum. Reprod. Update* 9(4), 359–372 (2003).

• **Suggests that obesity in women may favor resistance to clomiphene and gonadotrophin-induced ovulation and reduce outcomes of IVF procedures. The authors recommend that lifestyle intervention programmes should represent the first-line approach in the treatment of infertile obese women.**

5. Pasquali R and Gambineri A: Metabolic effects of obesity on reproduction. *Reprod. Biomed. Online* 12(5), 542–551 (2006).
6. Klonoff-Cohen H, Bleha J, Lam-Kruglick P: A prospective study of the effects of female and male caffeine consumption on the reproductive endpoints of IVF and gamete intra-Fallopian transfer. *Hum. Reprod.* 17(7), 1746–1754 (2002).
7. Olsen J: Cigarette smoking, tea and coffee drinking, subfecundity. *Am. J. Epidemiol.* 133(7), 734–739 (1991).
8. Juhl M, Olsen J, Andersen AM, Gronbaek M: Intake of wine, beer and spirits and waiting time to pregnancy. *Hum. Reprod.* 18(9), 1967–1971 (2003).
9. Klonoff-Cohen H, Lam-Kruglick P, Gonzalez C: Effects of maternal and paternal alcohol consumption on the success rates of *in vitro* fertilization and gamete intrafallopian transfer. *Fertil. Steril.* 79(2), 330–339 (2003).
10. Maheshwari A, Stofberg L, Bhattacharya S: Effect of overweight and obesity on assisted reproductive technology – a systematic review. *Hum. Reprod. Update* 13(5), 433–444 (2007).

• **Systematic review of the literature on the effects of overweight and obesity on assisted reproduction. The authors observed that women with a BMI of ≥25 kg/m² have a lower chance of pregnancy following IVF, require a higher dose of gonadotrophins and have an increased miscarriage rate, compared with women with a BMI of 25 kg/m² or less.**

11. Ribeiro AC, SávioII, KEO, Rodrigues MLCF, Costa THM, Schmitz BA: Validation of a food frequency questionnaire for the adult population. *Revista de Nutrição* 19(5), 10–16 (2006).
12. Palermo G, Joris H, Derde MP *et al.*: Sperm characteristics and outcome of human assisted fertilization by subzonal insemination and intracytoplasmic sperm injection. *Fertil. Steril.* 59(4), 826–835 (1993).
13. De Andres J, Valia JC, Olivares A, Bellver J: Continuous spinal anesthesia: a comparative study of standard microcatheter and Spinocath. *Reg. Anesth. Pain Med.* 24(2), 110–116 (1999).
14. Metwally M, Cutting R, Tipton A *et al.*: Effect of increased body mass index on oocyte and embryo quality in IVF patients. *Reprod. Biomed. Online* 15(5), 532–538 (2007).

• **Effects of increased BMI on oocyte and embryo quality during IVF cycles were studied. Results demonstrated that obesity may adversely affect embryo quality in women undergoing IVF/ intracytoplasmic sperm injection (ICSI). However, obesity did not have any significant effect on markers of oocyte quality or clinical pregnancy rates.**

15. Wittemer C, Ohl J, Bailly M, Bettahar-Lebugle K, Nisand I: Does body mass index of infertile women have an impact on IVF procedure and outcome? *J. Assist. Reprod. Genet.* 17(10), 547–552 (2000).
16. Frattarelli JL and Kodama CL: Impact of body mass index on *in vitro* fertilization outcomes. *J. Assist. Reprod. Genet.* 21(6), 211–215 (2004).
17. Lashen H, Ledger W, Bernal AL, Barlow D: Extremes of body mass do not adversely affect the outcome of superovulation and in-vitro fertilization. *Hum. Reprod.* 14(3), 712–715 (1999).

• **Compared IVF outcome between obese patients (BMI >27.9) with control group, and underweight patients (BMI <19) with control group. Results demonstrated that the obese patients had lower peak estradiol concentrations than their normal controls despite receiving similar gonadotrophin doses. However, the extremes of BMI did not adversely affect IVF outcome.**

18. Ogden CL, Carroll MD, Curtin LR *et al.*: Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA* 295(13), 1549–1555 (2006).
19. Sneed ML, Uhler ML, Grotjan HE *et al.*: Body mass index: impact on IVF success appears age-related. *Hum. Reprod.* 23(8), 1835–1839 (2008).
20. Carrell DT, Jones KP, Peterson CM *et al.*: Body mass index is inversely related to intrafollicular HCG concentrations, embryo quality and IVF outcome. *Reprod. Biomed. Online* 3(2), 109–111 (2001).
21. Lashen H, Fear K, Sturdee DW: Obesity is associated with increased risk of first trimester and recurrent miscarriage: matched case-control study. *Hum. Reprod.* 19(7), 1644–1646 (2004).

• **Addressed the impact of obesity on the risk of miscarriage. Obese (BMI >30 kg/m²) women were compared with an age-matched control group with normal BMI (19–24.9 kg/m²). Results showed that obesity is associated with increased risk of first trimester and recurrent miscarriage.**

22. Fedorcsak P, Dale PO, Storeng R *et al.*: Impact of overweight and underweight on assisted reproduction treatment. *Hum. Reprod.* 19(11), 2523–2528 (2004).

• **Analyzed the effect of body weight on IVF outcome. The authors observed that obesity is associated with an increased risk of early pregnancy loss. Moreover, a positive correlation between BMI and gonadotrophin requirement during stimulation and a negative correlation between BMI and number of collected oocytes were observed.**

23. Wu J, Zhang L, Wang X: Maturation and apoptosis of human oocytes *in vitro* are age-related. *Fertil. Steril.* 74(6), 1137–1141 (2001).
24. Ebner T, Moser M, Tews G: Is oocyte morphology prognostic of embryo developmental potential after ICSI? *Reprod. Biomed. Online* 12(4), 507–512 (2006).
25. Rienzi L, Ubaldi FM, Iacobelli M *et al.*: Significance of metaphase II human oocyte morphology on ICSI outcome. *Fertil. Steril.* 90(5), 1692–1700 (2008).
26. Loutradis D, Drakakis P, Kallianidis K *et al.*: Oocyte morphology correlates with embryo quality and pregnancy rate after intracytoplasmic sperm injection. *Fertil. Steril.* 72(2), 240–244 (1999).
27. Ebner T, Yaman C, Moser M *et al.*: A prospective study on oocyte survival rate after ICSI: influence of injection technique and morphological features. *J. Assist. Reprod. Genet.* 18(12), 623–628 (2001).

28. Wang JX, Davies MJ, Norman RJ: Obesity increases the risk of spontaneous abortion during infertility treatment. *Obes. Res.* 10(6), 551–554 (2002).

29. Dessolle L, Darai E, Cornet D *et al.*: Determinants of pregnancy rate in the donor oocyte model: a multivariate analysis of 450 frozen-thawed embryo transfers. *Hum. Reprod.* 24(12), 3082–3089 (2009).

30. Bellver J, Ayllon Y, Ferrando M *et al.*: Female obesity impairs *in vitro* fertilization outcome without affecting embryo quality. *Fertil. Steril.* 93(2), 447–454 (2010).

- **Retrospective study aimed at comparing embryo quality and IVF outcome according to the women's BMI. The authors concluded that female obesity impairs IVF outcome, but embryo quality is not affected, pointing to a possible alteration in the uterine environment.**

31. DeUgarte DA, DeUgarte CM, Sahakian V: Surrogate obesity negatively impacts pregnancy rates in third-party reproduction. *Fertil. Steril.* 93(3), 1008–1010 (2010).

32. Dokras A, Baredziak L, Blaine J *et al.*: Obstetric outcomes after *in vitro* fertilization in obese and morbidly obese women. *Obstet. Gynecol.* 108(1), 61–69 (2006).

33. Patel M, Gutzwiller F, Paccaud F, Marazzi A: A meta-analysis of acupuncture for chronic pain. *Int. J. Epidemiol.* 18(4), 900–906 (1989).

34. Warren MP, Perlroth NE: The effects of intense exercise on the female reproductive system. *J. Endocrinol.* 170(1), 3–11 (2001).

- **Pointed out that despite the fact that exercise provides substantial health benefits, intensive exercise is also associated with a unique set of risks for women. The authors addressed the hypothalamic dysfunction associated with strenuous exercise, the resulting disturbance of gonadotropin-releasing hormone pulsatility, leading to delayed menarche and disruption of menstrual cyclicity. The study highlights that increasing caloric intake to offset high energy demand may be sufficient to reverse menstrual dysfunction, and may in fact prove more effective than that aimed at correcting estrogen deficiencies.**

35. Redman LM: Physical activity and its effects on reproduction. *Reprod. Biomed. Online* 12(5), 579–586 (2006).

36. Rich-Edwards JW, Spiegelman D, Garland M *et al.*: Physical activity, body mass index, ovulatory disorder infertility. *Epidemiology* 13(2), 184–190 (2002).

37. Clark AM, Ledger W, Galletly C *et al.*: Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. *Hum. Reprod.* 10(10), 2705–2712 (1995).

- **Prospective study that assessed a weight-loss programme in order to determine whether it could help infertile overweight anovulatory women to establish ovulation and assist in achieving pregnancy. The authors concluded that weight loss is the first therapeutic option for women who are infertile and overweight, leading to an improvement in ovulation, pregnancy outcome, self-esteem and endocrine parameters.**

38. Hollmann M, Runnebaum B, Gerhard I: Effects of weight loss on the hormonal profile in obese, infertile women. *Hum. Reprod.* 11(9), 1884–1891 (1996).

- **Designed to investigate the effects of weight loss in obese, infertile women. The results demonstrated that weight reduction is the appropriate treatment for women with obesity-related endocrine derangement, menstrual irregularity and infertility.**

39. Morris SN, Missmer SA, Cramer DW *et al.*: Effects of lifetime exercise on the outcome of *in vitro* fertilization. *Obstet. Gynecol.* 108(4), 938–945 (2006).

- **Attempted to estimate whether exercise before the first cycle of IVF affects cycle outcomes. The authors concluded that regular exercise before IVF may negatively affect outcomes, especially in women who exercised 4 or more hours per week for 1–9 years and those who participated in cardiovascular exercise.**