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The BMI of men and not sperm parameters impact on embryo quality and the IVF outcome

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ABSTRACT

It has been reported that increased body mass index (BMI) of men influences fecundity but it is not clear if it impacts on sperm parameters. Whether or not BMI of men influence sperm parameters and subsequently *in vitro* fertilization (IVF) result remains to be clarified. The aim of the present study was primarily to investigate the relationship between the BMI of men and sperm parameters (volume, concentration and motility) and whether or not it impacts on embryo quality and IVF outcome. Secondly, to investigate the impact of BMI of both men and women, in combination with their age, on IVF result. Three hundred and one couples were categorized according to their BMI. Group 1 (n = 64, both men and women had BMI l $\leq$ 25 kg/m^2), group 2 (n = 79, both men and women had BMI > 25 kg/m^2), group 3 (n = 142, men had BMI > 25 kg/m^{2}and their wives had BMI $\leq$ 25 kg/m^2) and group 4 (n = 16, men had BMI $\leq$ 25 kg/m^2 and their wives had BMI > 25 kg/m^2). Overall (n = 301) BMI and age of men did not correlate with sperm parameters. Group 1 and group 4, regardless of the BMI of their women, demonstrated the highest quality of embryos and consequently the highest percentage of pregnancy. Furthermore, the score of the combination of both BMI and age of both men and women resulted in a threshold level of less than 800 with a relative high per cent of pregnancy. BMI of men does not correlate with sperm parameters, but influences the quality of produced embryos in such a way that impacts on pregnancy rate.

INTRODUCTION

Although successful embryo development depends upon genetic and epigenetic contributions from both male and female, the male impact on embryo quality and subsequently development has been underestimated. Even if most genetic contributing factors are closely associated with age, body mass index (BMI) may also account as a major factor contributing to the development of produced embryos.

Being overweight or obese has been associated with adverse effects on the reproductive ability of both men (Nguyen *et al.*, 2007) and women (Pasquali *et al.*, 2003). It has been shown that the elevated BMI of men results in decreased fecundity (Sallmen *et al.*, 2006; Ramlau-Hansen *et al.*, 2007). To interpret the reduced fertility of obese men, studies have investigated the relationship between obesity and semen quality (Fejes *et al.*, 2005; Levitas *et al.*, 2007; Hammoud *et al.*, 2008; Pauli *et al.*, 2008; Martini *et al.*, 2010; McDonald *et al.*, 2010). The results are conflicting. Some studies observed diminished gonadal function as increasing BMI (Hammoud *et al.*, 2008; Pauli *et al.*, 2008) and other researchers documented that there is no correlation between increased BMI and sperm parameters (Martini *et al.*, 2010; McDonald *et al.*, 2010). A study in male partners of subfertile couples showed that the increased BMI of men was associated with abnormalities in serum levels of hormones but to a lesser extent with abnormalities to semen quality (Chavarro *et al.*, 2010).

The relationship between the BMI of men and the sperm parameters (volume, concentration and motility) has not been extensively elucidated during IVF-ET treatments. Studies regarding the association of obesity with semen parameters, embryo quality and *in vitro* fertilization (IVF) outcome do not exist. The aim of this study was first to investigate further the relationship between BMI and the sperm parameters and secondly to investigate the impact of BMI and age of both men and women on embryo quality and IVF result.

MATERIALS AND METHODS

This retrospective study was performed during 2010–2011 and 301 cases were enrolled in this study, while semen samples were obtained from the male partner of couples being investigated for infertility in our IVF centre. The study was approved by the local ethics committee and written informed consent was obtained

from all participants. Among the 301 cases only 267 cases resulted in the embryo – transfer (ET) procedure. When semen sample was processed, the patients' height and weight was measured to obtain BMI.

All couples studied were categorized according to their BMI in four groups. Group 1 ($n = 64$) where both men and women had BMI $\leq$ 25 kg/m^2 (lean or normal), group 2 ($n = 79$) where both men and women had BMI > 25 kg/m^2 (overweight or obese), group 3 ($n = 142$) where men had BMI > 25 kg/m^2 and their wives had BMI $\leq$ 25 kg/m^2 (overweight-obese men and lean-normal women) and group 4 ($n = 16$) where men had BMI $\leq$ 25 kg/m^2 and their wives had BMI > 25 kg/m^2 (lean-normal men and overweight-obese women). The small sample size of the last group is justified from the fact that in Greece, it is uncommon that the BMI of husbands is smaller than that of their wives. The biological rationale for this categorization was to investigate the impact of the BMI of men on embryo quality and on the IVF result in combination with the BMI of their wives.

Semen specimens were collected after a period of 3–5 days of sexual abstinence and were allowed to liquefy for at least 20 min at 37 °C. After liquefaction, semen volume, sperm concentration and per cent of motility was evaluated according to the World Health Organization guidelines (World Health Organization, 2010). For each specimen, 200 spermatozoa were analysed manually by two different practitioners in order to avoid bias. The mean sperm concentration and motility from the two practitioners were calculated and were used in the statistical analyses. Following semen analysis, each specimen was treated with the SupraSperm System method (Origio, Medicult Media, Måløv, Denmark) as described in a previous work (Anifandis *et al.*, 2010).

The whole procedure of IVF or Intracytoplasmatic Sperm Injection that took place and embryo evaluation have been reported in previous work (Anifandis *et al.*, 2010). Briefly, embryo evaluation was performed on day 2 or 3 post-insemination, during Embryo Transfer (ET). Each embryo was scored according to the number of blastomeres, the degree of fragmentation and the regularity of blastomeres. Cumulative embryo Score (CES) was estimated by adding the score of each embryo produced and Mean Score of Embryo Transfer (MSET) was evaluated according to CES of embryos transferred divided by the number of embryos transferred. Serum β-hCG levels were assessed 12–13 days post-ET and a value above 15 IU/mL was considered positive. An intrauterine sac seen by ultrasound 3–4 weeks post-hCG was defined as clinical pregnancy. Implantation rate was defined as the number of intrauterine sacs seen by ultrasound divided by the number of transferred embryos.

Numeric data were normally distributed (one sample Kolmogorov–Smirnov test). Comparison of numeric variables between groups was performed using one way analysis of variance followed by Bonferroni post hoc testing. Bivariate correlation between numeric variables was tested with Pearson's correlation. Partial correlation between two numeric variables while controlling for the effects of one or more additional variables was also performed. Percentages were compared with chi-squared test. The statistical package used was SPSS version 15.0. Data were expressed as mean ± standard error of the mean. *P*-value less than 0.05 was considered statistically significant.

The primary end point was to investigate the relationship between the BMI of men and sperm parameters and secondary to investigate the impact of combination of both age and BMI of men and women on embryo quality and IVF outcome.

RESULTS

The causes of infertility in all couples studied were tubal factor (16%), anovulatory infertility (33.2%), endometriosis (18.7%), male factor (11.6%) and unexplained (20.5%). The prevalence of these causes was similar in the four groups ($\chi^2 = 6.484$, df = 12, $P = 0.889$). There was no correlation between the BMI of all men studied ($n = 301$) and semen volume or concentration. A negative correlation between concentration and volume was observed ($r = -0.12$, $P < 0.05$), while an expected correlation between concentration and PRM ($r = 0.41$, $P < 0.001$) and immotility (IM) ($r = -0.28$, $P < 0.001$) was found. Semen volume was positively correlated to PRM ($r = 0.11$, $P < 0.05$) and negatively correlated to non-progressive motility (NPM) ($r = -0.15$, $P < 0.05$). A weak negative association between BMI of men and non-progressive motility ($r = -0.13$, $P < 0.05$) was found. As expected, a negative correlation was found between RPM and NPM ($r = -0.13$, $P < 0.05$) and IM ($r = -0.76$, $P < 0.001$). There was no correlation between age of men and all sperm parameters. A positive relationship was observed between age and BMI of men ($r = 0.18$, $P < 0.001$).

The characteristics and semen parameters of each group are presented in Table 1. Age of men of group 2 was significantly higher than that of men from group 1. Age of women of group 2 was significantly higher than that of women from group 3. As expected, by definition, there were significant differences in Age × BMI of men and women among the four groups. Embryological data of the four groups are demonstrated in Table 2. It is noteworthy to mention that the embryo quality of groups 2, 3 was significantly lower as compared to that from groups 1, 4. Despite the comparable cumulative embryo score between the groups, it seems that the quality of embryos produced by each

Table 1 Mean (± SEM) values of all parameters among the groups studied

	BMI groups				
	Group 1	Group 2	Group 3	Group 4	*P*-value
No of cases	64	79	142	16	
Age of men (y)	35.7 ± 0.5	38.7 ± 0.6	37.8 ± 0.5	37.2 ± 1	<0.05
Age × BMI (men)	853.1 ± 12.6	1177 ± 23.7	1083.6 ± 17.6	892.1 ± 33	<0.05
Age of women (y)	33.9 ± 0.6	36.1 ± 0.5	33.8 ± 0.5	33.8 ± 0.7	<0.05
Age × BMI (women)	776.2 ± 19.6	869.8 ± 26.5	823.3 ± 16.8	847.2 ± 55.8	<0.05
Semen volume (mL)	3.1 ± 0.2	3.5 ± 0.2	3 ± 0.1	2.9 ± 0.4	NS
Sperm concentration (10^6/mL)	41.3 ± 4.4	47.6 ± 5.2	45.5 ± 3.5	48.5 ± 11.3	NS
Sperm motion (%)					
PRM	45.7 ± 2.9	48.5 ± 2.6	46 ± 2	46.1 ± 7.2	NS
NPM	10.9 ± 1.1	9.4 ± 0.7	10.1 ± 0.6	8.8 ± 1.9	<0.05
IM	39.4 ± 2.7	38.9 ± 2.6	40.7 ± 2	45.1 ± 7.7	NS

PRM, progressive motility; NPR, non-progressive motility; IM, immotility.

Table 2 Embryological data among the four groups

	BMI groups				
	Group 1	Group 2	Group 3	Group 4	*P*-value
No of cases	64	79	142	16	
No of ETs	60	69	124	14	
CES	23.4 ± 5	16.6 ± 5.5	16.8 ± 6.4	33.3 ± 3	NS
MSET[a]	9.1 ± 1	8.1 ± 0.6	8.1 ± 0.8	9.6 ± 0.5	<0.05
Implantation rate (IR)%[c]	17.4% (23/132)	11.1% (20/180)	8.6% (30/348)	18.9% (7/37)	<0.05
Pregnancy (%)[b]					
Positive hCG	30.5% (18)	29% (20)	23.4% (29)	42.9% (6)	<0.05
Clinical	26.7% (16)	24.6% (17)	18.5% (23)	28.6% (4)	<0.05
On going	25% (15)	21.7% (15)	16.1% (20)	22.2% (2)	<0.05
Live birth rate	25% (15)	21.7% (15)	16.1% (20)	22.2% (2)	<0.05

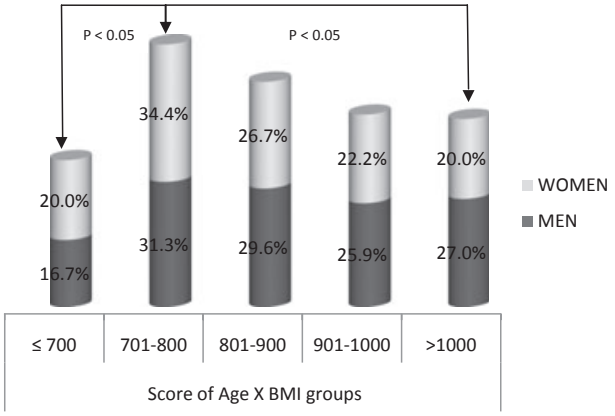
[a,b]Group 4 demonstrated the best embryo quality and the highest pregnancy per cent when compared to group 2 and 3 (for MSET: group 4 vs. group 2, $P = 0.03$ and group 4 vs. group 3, $P = 0.01$ and for pregnancy: group 4 vs. group 2, $P = 0.002$ and group 4 vs. group 3, $P = 0.001$), but comparable to group 1 (both embryo quality and pregnancy: group 4 vs. group 1, P = NS). [c]In all groups, in some women was observed more than one intrauterine sac and that is why the number of implanted embryos is different from the number indicated in parenthesis in the clinical pregnancy rate. These numbers (in the clinical pregnancy row) are the numbers of cases and not the numbers of intrauterine sacs. ETs, embryo transfers; CES, cumulative embryo score; MSET, mean score of embryo transfer.

group played a crucial role in the implantation rate, which was higher in groups 1, 4. Moreover, it is apparent that the BMI of men influences the quality of produced embryos which in turn influences the pregnancy rate. To further elucidate the effect the BMI of men might have on the quality of embryos, a partial correlation procedure was performed to compute the correlation between these two variables (BMI of men and embryo quality), while controlling for the effects of female factor, i.e. age of women and BMI of women. The correlation coefficient was −0.123 ($P = 0.047$). Even after adjustment for sperm parameters, this correlation was unchanged. We also performed a correlation analysis between the sperm parameters and embryo quality and no significant relationship was found. Furthermore, no significant differences were found in all sperm parameters between pregnancy and non-pregnancy.

The comparison of the pregnancy rates resulted in significant differences between groups 1, 4 and groups 2, 3.

In an attempt to evaluate the impact of both age and BMI in the IVF outcome we measured the Age × BMI score of both men and women. Figure 1 was resulted after the evaluation of the Age × BMI score. If this combination is over 1000 the possibility for achieving pregnancy is relatively low. The fluctuated values of BMI do not allow using this level as a threshold level, but it seems that as this level is decreasing the per cent for achieving pregnancy is also increasing.

Figure 1 The significantly low pregnancy rate when the score of the combination of Age and BMI of both men and women is over 900. The threshold level of less than 800 is just a suggestion attributable to the fluctuated values of BMIs, but it seems that when the couple has an Age × BMI score between 701 and 800 the possibility for achieving pregnancy is high. In women: 34.4 vs. 20% ($P < 0.05$). In both women and men: 34.4 vs. 20% and 31.3 vs. 16.7% respectively ($P < 0.05$)



DISCUSSION

Although the reproductive consequences of overweight or obese women during IVF treatments have received substantial attention, the reproductive consequences of excess body weight of men have been studied to a lesser extent. This retrospective study revealed that BMI of men and not semen parameters impact on embryo quality and IVF result. Furthermore, this study showed the consequences of both BMI and Age of the couples on the IVF outcome.

Studies investigating the impact of obesity on fertility (but not in relation to IVF) suggested that couples with overweight and obese BMI male partners were more likely for seeking infertility treatment referable to the low sperm count (Sermondade *et al.*, 2012). It has been proposed that BMI impacts on fertility in a dose-response manner (Hammoud *et al.*, 2008). As far as male obesity and IVF is concerned, associations of increased BMI of men and abnormalities in serum levels of almost all the reproductive hormones, but to a lesser extent with abnormalities of semen parameters were found (Chavarro *et al.*, 2010). Semen quality seems to be more closely associated with age rather than the BMI of men (Paasch *et al.*, 2010). In accordance with our results, most studies proposed that male BMI does not correlate with sperm parameters, semen volume, motility or morphology (Kort *et al.*, 2006; Pauli *et al.*, 2008). This study revealed an association of male BMI with embryo quality although male BMI does not seem to correlate to sperm parameters. Moreover, we showed that sperm parameters seem not to impact on the IVF outcome. This relationship was more profound even after adjustment with the BMI of women. Group 3 demonstrated the worst quality of embryos in comparison to the other groups ($P < 0.05$). It seems that the BMI of men via the alteration in hormonal parameters influences the sperm DNA integrity (Chavarro *et al.*, 2010) in such grade that this alteration has a direct impact on embryo quality. Although their wives had normal BMI (group

3), it seems that the decreased pregnancy rate of this group was related to the increased BMI of the men. The associate mechanism between the BMI of men and embryo quality has not yet been clarified. Whether the BMI of men or the deviation of hormonal parameters influence embryo quality remains to be further clarified. Furthermore, whether the increased BMI is derived by the hormonal alterations or the other way round is another issue, even if it has been proposed that reproductive hormones cannot explain the relation between BMI and sperm parameters (Qin *et al.*, 2007).

Another conclusion from the present results is that the BMI of men have higher impact on the embryo quality comparatively to the BMI of women. This conclusion can be deduced after the comparison of group 3 and 4. After adjustment for age (in both groups) embryo quality of group 4, in terms of MSET, was significantly higher when compared to group 3. If we take into account the fact that the increased BMI of women results in the production of immature oocytes (or degenerative oocytes), bad quality of embryos and early pregnancy loss and generally in decreased pregnancy rates, it is unexpected the clinical pregnancy rate of group 4 to be significantly higher when compared to group 3 ($P < 0.05$). The explanation of this phenomenon seems to lie in the fact that the BMI of men in group 3 is higher than the relative BMIs of group 4. Of course the small size of group 4 does not allow drawing solid conclusions, but according to our results we suggest that the increased BMI of men produces bad quality of embryos, which results in decreased pregnancy rates. How, now, BMI influence embryo quality because it appears that semen quality does not influence embryo quality? In the present study BMI affects somehow indirectly sperm DNA integrity, which cannot be documented either by motility or morphology but is reflected to the embryo development.

The well-known effect of BMI of women on embryo quality has been introduced years ago, while the influence of male on embryo quality has been described only recently(Chenoweth, 2007). In this study the influence of BMI of men on embryo quality, in terms of MSET has been observed. Specifically, when we compared groups 2, 3 to groups 1, 4, even after adjustment with the BMI of women, it was observed that the embryo quality of groups 2, 3 was significantly lower to groups 1, 4 ($P < 0.05$). The reduced live birth rate of group 2 depicts the profound effect of both BMIs (women and men) on pregnancy during IVF treatments. It has been proposed that a certain per cent of weight loss may improve semen quality and reproductive hormones (Hakonsen *et al.*, 2011), but with uncertainty relative to the IVF result. The results by Kupka *et al.* (2011) regarding the BMI of men and women in relation to IVF outcome showed that the highest success rate was found when the male partner was overweight or obese, but without significant differences to the other groups studied. In the present study, regardless of the small sample (relative to the study of Kupka and colleagues), sperm parameters, embryo quality and age were evaluated as co-factors for the IVF result.

A question that emerges is which parameter influences more embryo quality and consequently IVF result. One study revealed that semen parameters are more closely related to age of men than BMI (Paasch *et al.* 2010), suggesting that age is more related to IVF result, but other studies proposed that the influence of age on semen parameters is not always apparent (Jensen *et al.*, 2004). In this study we introduced the Age × BMI factor and according to the results it appears that when the score of Age and BMI is over 1000, the pregnancy rate is decreasing dramatically. We suggest that both factors impact on embryo quality and IVF outcome and each factor contributes to the IVF result proportionally, meaning that the combination of an increased BMI with young age impact in the same way on the IVF result as a man who has normal BMI, but older age. The production of a combined model between Age and BMI of men and Age and BMI of women is shown in Fig. 1, which depicts the reduction of pregnancy rate as the combination of Age and BMI of both men and women is increasing.

To sum up, it seems that BMI of men and not sperm parameters influences IVF outcome through the quality of transferred embryos. The quality of transferred embryos influenced the implantation rates, something which was reflected directly in the IVF result. Furthermore, the BMIs of both men and women in combination with their ages, expressed as a BMI X Age score, may influence the IVF outcome.

CONFLICT OF INTEREST STATEMENT

The Authors declare no conflicts of interest.

AUTHORS' CONTRIBUTION

GA performed the embryological part of the study and helped to draft the manuscript, KD participated in the clinical part, the design and statistical analysis of the study and helped to draft the manuscript, CIM helped to draft the manuscript, NP helped to draft the manuscript, and IEM conceived of the study, participated in the clinical part, the design and coordination of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

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