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Assessing the role of endometrial alteration among obese patients undergoing ART

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Abstract

Obesity seems to exert a small but important extra-ovarian effect that may influence cycle outcome during ART. Future investigation should focus on elucidating whether the endometrium is truly responsible for this deficit and, if present, determining the mechanisms involved.

Bellver and colleagues report in this issue of *Fertility and Sterility* a retrospective analysis of a large cohort of first time oocyte donation cycles to investigate the effect of recipient body weight on reproductive performance (1). By restricting their study to oocytes donated by normal weight women, the effect of obesity on oocyte development was eliminated thus permitting an assessment of the extra-ovarian effect of excess body weight on successful pregnancy outcomes.

To date, this is the largest study to examine this issue. The cohort included 2,656 first oocyte donation cycles with standardized stimulation and endometrial preparation protocols, using good quality embryos and excluding recipients with uterine defects or history of recurrent miscarriage. The recipients were stratified according to BMI: lean (<20 kg/m²), normal (20-24.9 kg/m²), overweight (25-29.9 kg/m²) and obese (≥30 kg/m²). Of the study subjects, 4.5% were obese and 17 % overweight. The authors conclude that 1) factors other than the ovary contribute to the observed reduced reproductive performance among overweight and

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obese patients; 2) the reproductive performance of lean women was not poorer and suggests that the accepted “inverted U shape theory” applies only to native oocyte conceptions.

Despite the size of the cohort, the retrospective study design makes it difficult to fully evaluate the authors’ stated study objective “to ascertain whether obesity can impair reproductive outcome through extra-ovarian effect”. The results should be taken cautiously; there appears to be an association; however, the authors are unable to make any further claims. The group was stratified by body mass index obtained within one year of the treatment cycle leaving doubt as to the accuracy of the measurement particularly in the overweight category. When the defined groups (lean, normal, overweight and obese) were compared, similar implantation, overall pregnancy, ectopic pregnancy and miscarriage rates were found. The authors observed a non-significant trend toward a reduced implantation rate with increasing BMI. It was only when the on-going pregnancy rates of normal and underweight recipients were compared to overweight and obese recipients that a statistically significant difference was seen. Yet when examining the overweight and obese groups there were large 95% CI due to relatively few recipients in the groups. This makes interpretation difficult as there is imprecision in the measurement and this finding may not be true in larger studies. This point is highlighted by the previous work in this area; three manuscripts on this topic have been published with differing conclusions. (Table)

The present study has addressed some of the design problems affecting previous reports. However it seems that all, including the current work, lack sufficient numbers of obese patients to provide appropriate power to draw solid conclusions; only 4.5% of the study population was obese. Furthermore the reduced on-going pregnancy rate, defined as gestations surpassing 20 weeks, seen in this study would be the result of cumulative effects of reduced implantation and increased miscarriage, both of which were not significantly different among groups. The effect of obesity and its associated aberrations may not impact implantation at all, but rather impart its effect on embryonic development. Yet neither conclusion can be made on the basis of this or previous studies.

It is known that obesity has profound effects on sex hormone secretion and metabolism leading to modification of bioavailable estrogen and androgens. This and other endocrine disruptions contribute to the infertile phenotype (5). Moreover, it has become increasingly clear that the overall abnormalities in the endocrine milieu may lead to impaired folliculogenesis and follicular atresia as a result of hypersecretion of leutinizing hormone (6), hyperinsulinemia (7), increased IGF-1 production (8) and an increased androgen ratio (9).

Attempts to eliminate the ovarian effect to identify extra-ovarian factors responsible for the poor reproductive outcome among obese patients remains an important undertaking. Several studies of fresh cycle assisted reproductive technology (ART) have shown that obesity is associated with worse reproductive outcomes including an increase in cycle cancellation (10), decreased implantation and clinical pregnancy rates (11), increased spontaneous abortion rates (12-14), lower on-going pregnancy rates (11), and lower live birth rates (13). While all point toward poorer results, these studies, too, have failed to be consistent in their findings. The current study lacks important maternal health information that could provide further insight into mechanisms of these outcomes. The impact of obesity, insulin resistance, hypertension and hyperlipidemia, components of the metabolic syndrome, on endometrial function have yet to be elucidated.

No study has evaluated the role of insulin sensitivity on the endometrium among overweight and obese participants. Insulin resistance has been shown to be an independent risk factor for spontaneous abortion (15). Furthermore, hyperinsulinemia has been associated with disruptions in at least two key proteins in the endometrium; reduced glycodelin which has been

associated with recurrent pregnancy loss and decreased insulin-like growth factor binding protein which facilitates adhesion at the maternal-fetal interface (16).

Visceral adipose is a key regulator of the interrelated network of factors that increase insulin resistance, inflammation, coagulation and fibrinolysis (17). Increased levels of acute phase proteins (18) and adipose tissue-derived proinflammatory cytokines (19) are found in obese subjects such as interleukin-6 (IL-6), plasminogen activator inhibitor type-1 (PAI-1), and tumor necrosis factor- α (TNF- α). These inflammatory markers are thought to exert a negative effect on implantation and early embryonic development (20). Finally, the peripheral role of the adipocyte derived hormone leptin in implantation is being elucidated (21). Leptin resistance at the level of the hypothalamus is well recognized; could peripheral tissue demonstrate resistance as well (22)? We agree with the authors that extra-ovarian factors are likely at work and result in a subtle impact on ART outcome. Yet despite valiant attempts to gather evidence, the true magnitude and mechanism of the deficit remain to be determined.

In summary, the impact of obesity on extra-ovarian factors and its influence on ART outcome continues to be a provocative issue. Obesity is an important health concern especially in Western cultures and its impact on reproductive outcome during ART has been the subject of debate. The controversy continues with a recent National Health Service and British Fertility Society statement limiting ART services to those women with a BMI $<36 \text{ kg/m}^2$ due, in part, to poorer ART outcome (23). The long-term implications of obesity on fetal development have been well documented, including hypertension, gestational diabetes, pre-eclampsia and macrosomia (24). But what remains to be fully determined is the precise impact of obesity on the endometrium and the influence that it may have on implantation. Based on the current study, this impact seems to be small but likely important. Prospective evaluation is truly needed to adequately assess this question. Conceivably a study could be designed to examine obese oocyte donors who at the time of donation have an assessment of their endometrium to determine if molecular deficits are present. However, it is unlikely that this study will ever be performed as the great majority of oocyte donors are within the normal weight range. Until that time, we should continue to explore the biological alterations present within the endometrium among obese patients. Most importantly we should continue to counsel our patients on the health consequences of obesity and its potential negative impact on pregnancy outcomes and further encourage our patients to aggressively pursue weight reduction.

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Table 1
Summary of studies examining oocyte donation cycles in obese recipients

Study authors	Overall sample size (obese)	Implantation Rate controls/obese (p-value)	Pregnancy rate controls/obese (p-value)	Biochemical pregnancy rate controls/obese (p-value)	Ectopic Pregnancy rate controls/obese (p-value)	Miscarriage rate controls/obese (p-value)	On-going pregnancy rate controls/obese (p-value)
Bellver <i>et al.</i> (1)	2,656 (122)	34.6%/29.0% (NS)	60.1%/49.2% (NS)	8.0%/5.0% (NS)	0.9%/3.3% (NS)	15.9%/18.3% (NS)	45.2/36.1 (0.046)
Bellver <i>et al.</i> (2)	712 (50)	27.8%/18.8% (NS)	53.0%/42.0 (NS)	NR	NR	14.5%/38.1% (0.009)	NR
Watanakumtornkul <i>et al.</i> (3)	96 (12)	27%/29 (NS)	NR	NR	NR	NR	43%/42% (NS)
Styne-Gross <i>et al.</i> (4)	536 (77)	53.8%/54.8% (NS)	73.2%/74% (NS)	NR	NR	25%/29.8% (NS)	NR

NR=Not reported, NS=Not significant