DOI: https://doi.org/10.3329/medtoday.v37i1.79497

Review Article OPEN ACCESS

Infertility Due to Obesity in Women: Endocrine Pathways

Murshida Afruz Lubna*[1], Umme Sayeeda Bilkish[2]

Abstract

Infertility is a significant global health issue, with a negative impact on people's wellbeing and human rights. Despite the longstanding association between obesity and infertility, there remains uncertainty, about the precise mechanisms underpinning this association and best management strategies. In this article, we aimed to address these uncertainties by reviewing the recent literatures. We found that, obese women undergo perturbations of the 'hypothalamic pituitary ovarian axis', and frequently suffer of menstrual dysfunction leading to anovulation and infertility. Besides the hormone disorders and subfertility that are common in the polycystic ovary syndrome (PCOS), in obesity the adipocytes act as endocrine organ. The adipose tissue indeed, releases a number of bioactive molecules, namely adipokines that variably interact with multiple molecular pathways of insulin resistance, inflammation, hypertension, cardiovascular risk, coagulation, and oocyte differentiation and maturation.

Keyword: *Obesity, Infertility, hypothalamic-pituitary-ovarian axis.*

Number of References: 36; Number of Correspondences: 04.

***1. Corresponding Author:**
Dr. Murshida Afruz Lubna
MBBS, DGO (OBGYN)
Assistant Professor
Department of Obstetrics and Gynaecology
Sylhet Womens Medical College & Hospital
Sylhet, Bangladesh.
email: afruzmurshida@gmail.com
Contact: 01711954202

2. Dr. Umme Sayeeda Bilkish
FCPS (Obs & Gynae)
Assistant Professor
Department of Obstetrics and Gynaecology
North East Medical College & Hospital (NEMC)
Sylhet, Bangladesh.

Introduction:

Obesity is an abnormal or excessive build-up of body fat, which is a common metabolic disturbance. A body mass index (BMI) of more than 25 kg/m^2, 30 kg/m^2, 40 kg/m^2 are considered as overweight, obese and severely obese respectively according to the Center for Disease Control and Prevention (CDC) and World Health Organization (WHO) guidelines[1]. Obesity is linked to a slew of negative consequences. Metabolic problems, cardiovascular events, malignancies, gastrointestinal diseases, and arthritis are just a few of them[2]. Aside from the cardiometabolic effects of obesity, there is strong confirmation that both female and male obesity increases the chance of subfecundity and infertility. According to previous studies, more than 40% of females with menstruation abnormalities, infertility, and recurrent abortion are obese or overweight. Anovulatory periods, oligoamenorrhea, hirsutism, infertility, and/or sexual disorders are all more common in women with obesity than in normal weight women[3]. Obesity interferes with normal endocrine function, resulting in ovulation, endometrial growth, and embryo developmental abnormalities. According to the American Society of Reproductive Medicine Practice Committee[4], infertility is a disease generally defined as failure to conceive after twelve or more months of attempts of natural fertilization and is a rising problem in our society today. The WHO worldwide estimation suggests that this pathology currently affects up to 50–80 millions of women, with a variable incidence that in several instances may raise up to about 50% of all women[5]. Infertility is a major worldwide health concern, having severe consequences for people's well-being and human rights. Despite the ongoing relationship between obesity and infertility, there is still ambiguity about the specific processes behind this association and the optimal therapeutic techniques. Obese women undergo perturbations of the 'hypothalamic pituitary ovarian (HPO) axis', and frequently suffer of menstrual dysfunction leading to anovulation and infertility[6]. Obesity is now well recognised as a risk factor for type 2 diabetes, hypertension, vascular disease, tumours, and reproductive issues. Obese women had lower levels of gonadotropin hormones (GH), decreased fecundity, greater miscarriage rates, and inferior in vitro fertilisation results, indicating that obesity has an impact on female reproductive system. Moreover, adipose tissue features unique immune cells and obesity-induced inflammation is a chronic, low-grade inflammatory response[7]. Up to date, few single studies been done to determine the types and causative factors behind infertility. The current study will summarize some recent reviews on how obesity is affecting the female infertility. Pathophysiology of infertility in females: Several differential conditions concur to affect the woman fertility. These conditions mainly related to the pathophysiology of reproductive organs. Below are some of the major causes of infertility

Received: 16 September 2024 *Accepted revised version:* 20 November 2024

belonging to both pathogenic conditions.

1. Deregulated ovarian function – Ovulation is the result of a complex balance and interaction of hormones; any alteration of these mechanisms may influence its physiology. The most common cause of ovulation failure includes the polycystic ovary syndrome (PCOS)[8]. Other cause includes malfunctions of the hypothalamus or pituitary gland leading to the production of immature eggs.

2. Tubal infections and Endometriosis – pelvic inflammatory disease is a major etiologic event of anatomic and functional disorders of tubae and is predominantly associated to infections by Chlamydia Trachomatis and Neisseria Gonorrhoea which can ultimately lead to tubal related infertility. Tubal damage can occur as a result of the chronic inflammation associated to the growing endometrioid tissue and approximately 20–30% of women with endometriosis suffer of subfertility[9].

3. Cervical Factor - Any conditions modifying the mucosal film of the cervix may concur to prevent the progression of sperms toward the tubae, as provides the passageway for sperms, allowing them to access into the uterine cavity and ultimately into the fallopian tubes.

4. Uterine factors – Dysfunction in uterus such as defect of adhesion molecules, polyps, submucous fibroids, asymptomatic tumors and recurrent miscarriages as well as other endometrial pathologies and infections, may dramatically affect the blastocyst engraftment. Molecular and Endocrinological influence of obesity on woman fertility: Obesity Effect on Hypothalamic–Pituitary–Ovarian (HPO) Axis- The HPO axis in women is disturbed by excess body fat via central and peripheral pathways[10]. Clinical investigations show that extreme leanness is linked to delay of puberty whereas overweight or obesity is linked to early puberty. The alterations in the levels of hormone and some substrates cause the HPO axis to deteriorate. Obese females have high luteinizing hormone (LH), androstenedione, estrone, insulin, triglycerides, and very low-density lipoprotein levels and lower lipoprotein of high density[11]. The HPO axis deteriorates because of these changes, and various gynecological effects occur. The impact of obesity on reproductive function, especially ovulatory disorders, are mainly attributable to endocrine mechanisms , which interfere with neuroendocrine and ovarian functions, and reduce the ovulation omeostatic[12]. In obese women, gonadotropin secretion is affected as an effect of the increased peripheral aromatization of androgens to estrogens while the insulin resistance and hyperinsulinemia lead to hyperandrogenemia. Furthermore, the sex hormone-binding globulin (SHBG), growth hormone (GwH), and insulin-like growth factor binding proteins (IGFBP) are decreased and leptin levels are increased. Thus, the neuro-regulation of the HPO axis might severely deranged while the obese condition also increases the risk of miscarriage, poor pregnancy outcomes, and impaired foetal well-being [13]. Obesity Effect on Sex Steroid and Insulin: Obesity is linked to a rise in estrogens (17-estradiol (E2) and estrone (E1)) as well as androgens (testosterone (T), dihydrotestosterone (DHT), androstenedione, and de-hydroepiandrosterone (DHEA)) because of adipose tissue produces androgens directly and converts them to estrogens[14]. Obesity is also linked to lower levels of circulating sex hormone-binding globulin (SHBG), resulting in greater availability of androgens and estrogens to target tissues. These connections can be seen as early as adolescence and are more prominent in central obesity; they all contribute to a disorder known as "relative functional hyperandrogenism," which might compromise ovarian function and contribute to obesity related infertility[15, 16]. Obesity notably central obesity is distinguished by resistance to insulin and hyperinsulinemia, which promotes the production of androgens in the ovaries both directly and indirectly by raising the local sensitivity to LH. An excess of intra-ovarian androgen production may cause premature follicular atresia, which favours anovulation[17]. Furthermore, hyperinsulinemia causes a decrease in hepatic SHBG synthesis, resulting in an increase in the availability of free androgens[18], exacerbating peripheral hyperandrogenism, which causes an overproduction of acyclic E1 and, as a result, an excessive production of LH . Increased LH secretion can cause follicular growth to be arrested earlier, granulose cell luteinization to be accelerated, and oocyte quality to be compromised[19]. Insulin resistance and compensatory hyperinsulinemia, through all these mechanisms, may contribute to menstrual, ovulatory, and fertility disturbances[20]. Obesity effect through Adipokines on fertility: The dysfunction of the adipose tissue has been implicated in the pathophysiology of infertility based on recently discovered effects of adipokines. Their normal levels are critical to maintain the integrity of hypothalamus-pituitary-gonadal (HPG) axis. Also, to regulate ovulatory processes, successful embryo implantation, and in general the physiologic pregnancy, as adipose tissue is considered an endocrine organ that plays important roles in the regulation of many physiological events such as reproduction, immune response, glucose and lipid metabolism, through the secretion of a variety of bioactive adipokines[6]. Adipokines or adipocytokines, notably leptin been studied for their role in the body due to their stimulatory influence on gonadotropin releasing hormone (GnRH) pulses. Leptin is proven as a critical gatekeeper of puberty and future fertility in cellular and animal models[21, 22]. The quantity of body fat is directly connected to peripheral leptin levels[2]. Obese women have higher level of leptin, an adipokine that is produced by fatty tissue, than normal weight[21]. Women with high leptin levels in their blood and high leptin-to-BMI ratios have a reduced success rate with in-vitro fertilization (IVF)[15]. In the human ovaries, leptin suppresses the steroidogenesis in both granulosa and thecal cells and disrupts the ovulation process having a direct effect on fertility[2]. Finally, an obesity-related central insulin resistance condition could be involved, the infertility mechanisms identified in obesity through the influence on LH (Lutenizing hormone) secretion pulses' frequency and amplitude[23].

Obesity Effect on Oocyte and Embryo: Obesity has been shown to affect the oocyte in a number of studies. Changes in numerous hormones, particularly those that trigger oocyte maturation, may impact oocyte competence and maturation in obese people[24]. Because adipose tissue is a key site for production of steroid hormones and metabolism, its overproduction in obesity can change steroid hormone levels[23]. Increased BMI in women was linked with lower SHBG and higher insulin, glucose, lactate, triglycerides, and C-reactive protein, an inflammatory marker in follicular fluid[24,25]. Insulin provokes steroidogenesis in ovaries and increases expression of LH receptor in the theca and granulosa cells. Obesity disrupts the ovulation and maturation of oocytes in women due to LH hyper-secretion and alteration of LH:follicular stimulating hormone (FSH) ratio[23]. In addition, greater levels of free fatty acids (FFAs) in circulation lead to an increase in reactive oxygen species (ROS) which causes apoptosis and damage of mitochondria and endoplasmic reticulum[26]. Furthermore, obese women have greater levels of leptin in their serum and follicular fluid, and as a result of in vitro investigations, leptin reduces estrogen and progesterone synthesis in granulosa cells in a dose dependent manner[15]. The effects of obesity on the oocytes might have ramifications for receptivity of endometrium and implantation of embryo. Moreover, obese infertile women who are treated with assisted reproductive technology confront some challenges. Several studies have found that obese women undergoing IVF have a poor ovarian response to regulated ovarian stimulation, reduced oocyte number and quality, bad embryo quality, decrease the number of transferred embryos, decreased intra-follicular human chorionic gonadotrophins and estrogen levels[27]. Obesity also affects the preimplantation embryo; obese women are expected to produce low-quality embryos in IVF cycles using autologous oocytes[28]. Increased leptin levels in obese women may have a direct detrimental effect on the developing embryo in addition to acting centrally. Leptin stimulates the formation of human trophoblastic stem cells in vitro, whereas inhibiting it reduces proliferation and drastically increases apoptosis[29]. In obesity, tonically increased levels of leptin may reduce the trophoblast's susceptibility to its effects [15]. **Obesity Effect on Endometrium:** Obese women with polycystic ovary syndrome (PCOS) have an inferior endometrial genetic profile and unsatisfactory decidualization when compared to normal-weighted women, according to gene expression investigations performed during the implantation window[30]. Endometrial decidualization is hindered in mice with diet-induced obesity; these findings were validated in human investigations conducted in vitro and in vivo, where stromal decidualization was found to be reduced in obese women[31]. The pathogenesis of this phenomenon could be traced back to proinflammatory cytokines and ROS that cause endothelial dysfunction[32], as well as obese women with recurrent miscarriages had greater endometrial levels of expression of haptoglobulin, an inflammatory marker . Furthermore, the ERK(extracellular signal-regulated kinase) signaling pathway, which is part of the MAPK/ER(mitogen-activated protein kinase) and is required for invasion of trophoplast into endometrial lining of uterus was demonstrated to be downregulated in obese women during implantation period[33]. It has also been proposed that obesity reduce endometrial receptivity due to a variety of reasons including; relative hyperestrogenemia, low level of glycodelin and insulin growth factor binding protein 1 (IGFBP1) that occurs as a result of insulin resistance and hyper-insulinemia, and dysregulation of leptin level[34]. Leptin has a regulatory role in modifying the uterine epithelium and activating proliferative and apoptotic cell pathways, in addition to influencing endometrial receptivity[35]. Furthermore, leukemia inhibitory factor (LIF) has been linked to the regulation of implantation, with a strong negative relationship found between endometrial LIF and BMI. Women with high BMI have been proven to demonstrate elevated pro-inflammatory cytokines interleukin 6 (IL 6) and tumor necrosis factor (TNF) levels, which are likely to have a deleterious impact on implantation[36]. All these phenomena could be contributing factors to low implantation and increased miscarriage rates in obese women.

Abbreviations:

BMI: Body mass index; CDC: Center for Disease Control and Prevention; DHEA: Dehidro-epiandrosterone; DHT: Dihydrotestosterone; E2: 17-estradiol; E1: Estrone; ERK: extracellular signal-regulated kinase; FT: Free testosterone; FFA: Free fatty acid; FSH: Follicular stimulating hormone; GH: Gonadotropin hormone; GwH: Growth hormone; GnRH: Gonadotropin releasing hormone; HPO: Hypothalamic-pituitary-ovarian; IVF: In-vitro fertilization; IGFBP: Insulin-like growth factor binding proteins; IGF-I: Insulin-like growth factor; LH: Lutenizing hormone; LIF: leukemia inhibitory factor; MAPK: mitogen-activated protein kinase; PKA: Protein kinase A; PCOS: polycystic ovary syndrome; ROS: Reactive oxygen species; SHBG: Sex hormone-binding globulin; T: Testosterone; T2DM: Type 2 diabetes mellitus; TNF: Tumor necrosis factor; WHO: World health Organization.

Conflict of Interest: None.

Conclusion:

There is an increase in obesity worldwide, and its detrimental influence on reproductive function, fertility state, and pregnancy rate is severe for both men and women. Obesity influences the quality and number of oocyte and embryo, receptivity of endometrium and implantation process in both natural and assisted conception. Overweight and obese women need longer time to conceive and undoubtedly are at higher risk of infertility.

References:

1. Chooi YC, Ding C, Magkos F. The epidemiology of obesity. Metabolism. 2019; 92:6-10.
https://doi.org/10.1016/j.metabol.2018.09.005
PMid:30253139

2. Gambineri A, Laudisio D, Marocco C, Radellini S, Colao A, Savastano S. On behalf of the Obesity Programs of nutrition ER, Assessment g: Female infertility: which role for obesity? International Journal of Obesity Supplements. 2019; 9:65-72.
https://doi.org/10.1038/s41367-019-0009-1
PMid:31391925 PMCid:PMC6683114

3. Slopien R, Horst N, Jaremek JD, Chinniah D, Spaczynski R. The impact of surgical treatment of obesity on the female fertility. Gynecol Endocrinol. 2019; 35:100-102.
https://doi.org/10.1080/09513590.2018.1500536
PMid:30599791

4. Habbema JD, Collins J, Leridon H, Evers JL, Lunenfeld B, Te Velde ER. Towards less confusing terminology in reproductive medicine: a proposal. Hum Reprod. 2004: 19:1497-1501.
https://doi.org/10.1093/humrep/deh303
PMid:15220305

5. Ombelet W, Cooke I, Dyer S, Serour G, Devroey P. Infertility and the provision of infertility medical services in developing countries. Hum Reprod Update. 2008; 14:605-621.
https://doi.org/10.1093/humupd/dmn042
PMid:18820005 PMCid:PMC2569858

6. Silvestris E, De Pergola G, Rosania R, Loverro G. Obesity as disruptor of the female fertility. Reprod Biol Endocrinol. 2018; 16:22.
https://doi.org/10.1186/s12958-018-0336-z
PMid:29523133 PMCid:PMC5845358

7. Yong W, Wang J, Leng Y, Li L, Wang H. Role of Obesity in Female Reproduction. Int J Med Sci. 2023; 20:366-375.
https://doi.org/10.7150/ijms.80189
PMid:36860674 PMCid:PMC9969507

8. Balen AH, Rutherford AJ. Managing anovulatory infertility and polycystic ovary syndrome. BMJ. 2007; 335:663-666.
https://doi.org/10.1136/bmj.39335.462303.80
PMid:17901517 PMCid:PMC1995495

9. Johnson N, Farquhar C. Endometriosis. BMJ Clin Evid. 2007.
https://doi.org/10.1136/bmj.39073.736829.BE
PMid:17272567 PMCid:PMC1790744

10. Michalakis K, Mintziori G, Kaprara A, Tarlatzis BC, Goulis DG. The complex interaction between obesity, metabolic syndrome and reproductive axis: a narrative review. Metabolism. 2013; 62:457-478.
https://doi.org/10.1016/j.metabol.2012.08.012
PMid:22999785

11. Castellano JM, Bentsen AH, Sánchez-Garrido MA, Ruiz-Pino F, Romero M, Garcia-Galiano D, et al. Early metabolic programming of puberty onset: impact of changes in postnatal feeding and rearing conditions on the timing of puberty and development of the hypothalamic kisspeptin system. Endocrinology 2011; 152:3396-3408.
https://doi.org/10.1210/en.2010-1415
PMid:21712362

12. Pasquali R, Pelusi C, Genghini S, Cacciari M, Gambineri A. Obesity and reproductive disorders in women. Hum Reprod Update. 2003; 9:359-372.
https://doi.org/10.1093/humupd/dmg024
PMid:12926529

13. Talmor A, Dunphy B. Female obesity and infertility. Best Pract Res Clin Obstet Gynaecol. 2015; 29:498-506.
https://doi.org/10.1016/j.bpobgyn.2014.10.014
PMid:25619586

14. Santoro N, Torrens J, Crawford S, Allsworth JE, Finkelstein JS, Gold EB, et al. Correlates of circulating androgens in mid-life women: the study of women's health across the nation. J Clin Endocrinol Metab. 2005; 90:4836-4845.
https://doi.org/10.1210/jc.2004-2063
PMid:15840738

15. Broughton DE, Moley KH. Obesity and female infertility: potential mediators of obesity's impact. Fertil Steril. 2017; 107:840-847.
https://doi.org/10.1016/j.fertnstert.2017.01.017
PMid:28292619

16. Pasquali R, Gambineri A. Metabolic effects of obesity on reproduction. Reprod Biomed Online. 2006; 12:542-551.
https://doi.org/10.1016/S1472-6483(10)61179-0
PMid:16790096

17. De Leo V, Musacchio MC, Cappelli V, Massaro MG, Morgante G, Petraglia F. Genetic, hormonal and metabolic aspects of PCOS: an update. Reprod Biol Endocrinol. 2016; 14:38.
https://doi.org/10.1186/s12958-016-0173-x
PMid:27423183 PMCid:PMC4947298

18. Toprak S, Yönem A, Cakir B, Güler S, Azal O, Ozata M, et al. Insulin resistance in nonobese patients with polycystic ovary syndrome. Horm Res. 2001; 55:65-70.
https://doi.org/10.1159/000049972
PMid:11509861

19. Liu N, Ma Y, Wang S, Zhang X, Zhang Q, Zhang X, et al. Association of the genetic variants of luteinizing hormone, luteinizing hormone receptor and polycystic ovary syndrome. Reprod Biol Endocrinol. 2012; 10:36.
https://doi.org/10.1186/1477-7827-10-36
PMid:22546001 PMCid:PMC3403896

20. Gambineri A, Laudisio D, Marocco C, Radellini S, Colao A, Savastano S. Female infertility: which role for obesity? Int J Obes Suppl. 2019; 9:65-72.
https://doi.org/10.1038/s41367-019-0009-1

PMid:31391925 PMCid:PMC6683114

21. Quennell JH, Mulligan AC, Tups A, Liu X, Phipps SJ, Kemp CJ, et al. Leptin indirectly regulates gonadotropin-releasing hormone neuronal function. Endocrinology. 2009;150:2805-2812.

https://doi.org/10.1210/en.2008-1693

PMid:19179437 PMCid:PMC2732287

22. Quennell JH, Howell CS, Roa J, Augustine RA, Grattan DR, Anderson GM. Leptin deficiency and diet-induced obesity reduce hypothalamic kisspeptin expression in mice. Endocrinology. 2011; 152:1541-1550.

https://doi.org/10.1210/en.2010-1100

PMid:21325051 PMCid:PMC3206710

23. Jain A, Polotsky AJ, Rochester D, Berga SL, Loucks T, Zeitlian G, et al. Pulsatile luteinizing hormone amplitude and progesterone metabolite excretion are reduced in obese women. J Clin Endocrinol Metab. 2007; 92:2468-2473.

https://doi.org/10.1210/jc.2006-2274

PMid:17440019

24. Purcell SH, Moley KH. The impact of obesity on egg quality. J Assist Reprod Genet. 2011; 28:517-524.

https://doi.org/10.1007/s10815-011-9592-y

PMid:21625966 PMCid:PMC3158259

25. Souter I, Baltagi LM, Kuleta D, Meeker JD, Petrozza JC. Women, weight, and fertility: the effect of body mass index on the outcome of superovulation/intrauterine insemination cycles. Fertil Steril. 2011; 95:1042-1047.

https://doi.org/10.1016/j.fertnstert.2010.11.062

PMid:21195401

26. Broughton DE, Jungheim ES. A Focused Look at Obesity and the Preimplantation Trophoblast. Semin Reprod Med. 2016; 34:5-10.

https://doi.org/10.1055/s-0035-1570032

PMid:26696274

27. Dağ Z, Dilbaz B. Impact of obesity on infertility in women. J Turk Ger Gynecol Assoc. 2015; 16:111-117.

https://doi.org/10.5152/jtgga.2015.15232

PMid:26097395 PMCid:PMC4456969

28. Carrell DT, Jones KP, Peterson CM, Aoki V, Emery BR, Campbell BR. Body mass index is inversely related to intrafollicular HCG concentrations, embryo quality and IVF outcome. Reprod Biomed Online. 2001; 3:109-111.

https://doi.org/10.1016/S1472-6483(10)61977-3

PMid:12513872

29. Magariños MP, Sánchez-Margalet V, Kotler M, Calvo JC, Varone CL. Leptin promotes cell proliferation and survival of trophoblastic cells. Biol Reprod. 2007; 76:203-210.

https://doi.org/10.1095/biolreprod.106.051391

PMid:17021346

30. Bellver J, Melo MA, Bosch E, Serra V, Remohí J, Pellicer A. Obesity and poor reproductive outcome: the potential role of the endometrium. Fertil Steril. 2007; 88:446-451.

https://doi.org/10.1016/j.fertnstert.2006.11.162

PMid:17418840

31. Rhee JS, Saben JL, Mayer AL, Schulte MB, Asghar Z, Stephens C, et al. Diet-induced obesity impairs endometrial stromal cell decidualization: a potential role for impaired autophagy. Hum Reprod. 2016; 31:1315-1326.

https://doi.org/10.1093/humrep/dew048

PMid:27052498 PMCid:PMC4871191

32. Palomba S, De Wilde MA, Falbo A, Koster MP, La Sala GB, Fauser BC. Pregnancy complications in women with polycystic ovary syndrome. Hum Reprod Update. 2015; 21:575-592.

https://doi.org/10.1093/humupd/dmv029

PMid:26117684

33. Knöfler M. Critical growth factors and signalling pathways controlling human trophoblast invasion. Int J Dev Biol. 2010; 54:269-280.

https://doi.org/10.1387/ijdb.082769mk

PMid:19876833 PMCid:PMC2974212

34. Carrington B, Sacks G, Regan L. Recurrent miscarriage: pathophysiology and outcome. Curr Opin Obstet Gynecol. 2005;17:591-597.

https://doi.org/10.1097/01.gco.0000194112.86051.26

PMid:16258340

35. Yang YJ, Cao YJ, Bo SM, Peng S, Liu WM, Duan EK. Leptin-directed embryo implantation: leptin regulates adhesion and outgrowth of mouse blastocysts and receptivity of endometrial epithelial cells. Anim Reprod Sci. 2006; 92:155-167.

https://doi.org/10.1016/j.anireprosci.2005.05.019

PMid:16023802

36. Esinler I, Bozdag G, Yarali H. Impact of isolated obesity on ICSI outcome. Reprod Biomed Online. 2008; 17:583-587.

https://doi.org/10.1016/S1472-6483(10)60249-0

PMid:18854116