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Literature Review

Enhancing ART success in overweight and obese women: Current strategies and novel evidence-based approaches

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Background

Female obesity is frequently associated with suboptimal reproductive outcomes in patients undergoing assisted reproductive technologies (ART). This scoping review evaluated traditional and emerging strategies, protocol modifications, and biomarkers aimed at improving ART outcomes in overweight and obese women.

Methods

A comprehensive PubMed literature search (January 1, 2015–April 23, 2025) identified studies focusing on overweight and obese women undergoing ART. Studies evaluating underweight women or paternal obesity were excluded.

Results

A total of 50 studies (33 observational and 17 randomized controlled trials) were included. The impact of weight loss interventions was evaluated in 14 studies. Weight loss ⩾10% or >5 kg or that achieved after bariatric surgery was associated with improved ART outcomes. Adjunct therapies (N=5) such as micronutrient supplementation (e.g., folate, vitamin B12) demonstrated potential benefits with respect to ovulation, pregnancy, and live birth rates. While overweight or obese women required higher gonadotropin dosages and longer stimulation cycles (N=10), weight loss was associated with decreased gonadotropin consumption and improved ART outcomes. The use of letrozole (N=6), alone or in combination with other stimulation protocols, appeared to increase live birth rates and reduce the risk of miscarriages. Finally, biomarker analyses (N=15) suggested that lipid profiles, reproductive hormones, and inflammatory markers may serve as predictors of ART outcomes.

Conclusion

Interventions achieving greater degrees of weight loss, adjunct therapies, and letrozole-based protocols may improve ART outcomes, including pregnancy and live birth rates, in overweight and obese women. Personalized treatment protocols, biomarkers, and multidisciplinary approaches are essential for optimizing ART success in this population.

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TABLE OF ABBREVIATIONS

AFC, antral follicle count
AEs, adverse effects
ALA, alpha-lipoic acid
AMH, anti-Müllerian hormone
ApoB, apolipoprotein B
aRR, adjusted risk ratio
ART, assisted reproductive technologies
ASRM, American Society for Reproductive Medicine
BID, twice daily
BMI, body mass index
CC, clomiphene citrate
CFAS, Canadian Fertility and Andrology Society
CI, confidence interval
CLBR, cumulative live birth rate
COH, controlled ovarian hyperstimulation
COS, controlled ovarian stimulation
COMBI, combination treatment group
CPR, clinical pregnancy rate
DCI, d-chiro-inositol
DHR, dihydrorhodamine
DOR, diminished ovarian reserve
E2, estradiol
ET, embryo transfer
FET, frozen embryo transfer
FF, follicular fluid
FF-HDL, follicular fluid high-density lipoprotein
FSH, follicle-stimulating hormone
FSI, follicular sensitivity index
GC, granulosa cell
GDM, gestational diabetes mellitus
GnRH, gonadotropin-releasing hormone
hCG, human chorionic gonadotropin
HCY, homocysteine
HDL, high-density lipoprotein HMG, human menopausal gonadotropin
HOMA-IR, homeostatic model assessment for insulin resistance
HRT, hormone replacement therapy
ICSI, intracytoplasmic sperm injection
IL-8, interleukin-8
IL-18, interleukin-18
IL-18BP, interleukin-18 binding protein
IU, international units
IVF, *in vitro* fertilization
kg/m^2, kilogram per meter square
LA, linoleic acid
LBR, live birth rate
LDL, low-density lipoprotein
LDL-C, low-density lipoprotein cholesterol
LGI, low glycemic index
LH, luteinizing hormone
MET, metformin
MetS, metabolic syndrome
MII, metaphase II
MPA, medroxyprogesterone acetate
MPV, mean platelet volume
mSTC, mildly stimulated cycles
mtDNA, mitochondrial DNA
N, number of patients
NLR, neutrophil to lymphocyte ratio
NRF-2, nuclear factor erythroid 2–related factor 2
NS, not significant
NW, normal weight
OHSS, ovarian hyperstimulation syndrome
OR, odds ratio
PCOS, polycystic ovarian syndrome
PLR, platelet to lymphocyte ratio
PON1, paraoxonase 1
PUFA, polyunsaturated fatty acid
QD, once daily
qPCR, quantitative polymerase chain reaction
RCT, randomized controlled trial
r-hFSH-alfa, recombinant human follicle stimulating hormone alfa
rFSH, recombinant follicle-stimulating hormone
rLH, recombinant luteinizing hormone
RR, risk ratio
s.c., subcutaneous
SD, standard deviation
SDHA, succinate dehydrogenase complex flavoprotein subunit A
SGA, small for gestational age
SHBG, sex hormone binding globulin
SLR, systematic literature review
SoC, standard of care
TC, total cholesterol
TG, triglycerides
WCC, white cell count
ZYP, Zishen Yutai Pill

BACKGROUND

The prevalence of obesity has increased exponentially over the past 4 decades, and it is now widely considered a global health crisis.[1] According to the World Health Organization (WHO), as of 2022, 2.5 billion adults were overweight (body mass index [BMI] ⩾25 kg/m^2), of whom 890 million were living with obesity (BMI ⩾30 kg/m^2) worldwide. Among adults, obesity is more prevalent in women (504 million vs. 374 million men in 2022),[2] and its increasing incidence has been observed among women of reproductive age (18–40 years).[3,4] While obesity negatively impacts reproductive health in both sexes, in women, it can affect menstruation and fertility, and maternal obesity may influence pregnancy and the long-term health of both the mother and the child.[5,6]

Assisted reproductive technologies (ART) are strategies involving the manipulation of eggs or embryos to manage female infertility, among which *in vitro* fertilization (IVF) is the most frequently utilized.[7] Elevated BMI in women has been commonly linked to adverse reproductive function and ART outcomes.[6,8,9] The mechanisms by which obesity affects fertility and ART outcomes are complex and multifaceted.[5,6,10] These include hormonal dysregulation (e.g., insulin resistance, increased leptin, and altered adipokine levels), dyslipidemia, dysregulation of biogenic amines

(e.g., serotonin, dopamine), chronic inflammation and oxidative stress, mitochondrial dysfunction, and epigenetic alterations. Taken together, these cellular, molecular, and physiological mechanisms result in menstrual disturbances, reduced ovarian reserve, impaired ovulation, reduced follicular quality, endometrial dysfunction, impaired embryo implantation, as well as an increased risk of pregnancy-related complications.[5,6,8,10] Additionally, the presence of comorbidities such as metabolic syndrome or polycystic ovary syndrome (PCOS) is also associated with suboptimal reproductive and IVF outcomes.[11-14]

Given the significant burden associated with female obesity, reproduction, and infertility, clinical societies and health funding organizations across countries have published policies, guidelines, and recommendations for achieving successful pregnancies among obese women.[6,15-17] To avoid potential complications associated with ART in overweight/obese women, in some countries, women with obesity may face restrictions in accessing government-funded IVF services, with eligibility often contingent on meeting specific BMI thresholds, as outlined in local health authority guidelines.[18-20] In the United Kingdom (UK), specific boards recommend that a woman's BMI must be between 19–30 kg/m^2, and sometimes even more restrictive (18–25 kg/m^2), to be able to access government-funded IVF treatments.[19] Similarly, in the US, most fertility programs set a BMI threshold of 35–45 kg/m^2, above which women must delay their IVF treatment until weight loss is achieved.[20] While some guidelines recommend prioritizing weight loss or reduction in BMI through lifestyle modifications, medication, or surgery before starting fertility treatments,[16,17] others, such as the American Society for Reproductive Medicine, mention that the evidence is unclear with regard to pre-pregnancy weight loss interventions and successful IVF outcomes, such as live birth rate; however, it may improve the chances of pregnancy following natural conception.[15] In addition to varying BMI thresholds across countries, there appears to be a lack of uniform guidelines for treatment or protocol modifications for successful IVF outcomes in overweight and obese patients.

This scoping review examines traditional and emerging strategies as well as modifications to IVF protocols to enhance reproductive success in this population. In addition, the review aims to identify preconception and periconception biomarkers in overweight and obese women to aid in identifying those at risk of adverse IVF outcomes.

METHODS

A comprehensive literature search was conducted utilizing the keywords and medical subject headings (MeSH), including "Fertilization in Vitro"[MeSH], "Sperm Injections, Intracytoplasmic"[MeSH], "Reproductive Techniques, Assisted"[MeSH]), "IVF", "in vitro fertil*", "intracytoplasmic morphologically selected sperm injection", "obesity", "overweight", "adiposity", "dyslipidemia", "body mass index"[MeSH], "pregnancy in obesity", "anti-obesity agents", "weight loss", "bariatric surgery"[MeSH]. The search was performed in the PubMed database and retrieved studies published over the last decade, from January 1, 2015, to April 23, 2025. Additionally, relevant articles identified through cross-referencing were included.

The search was focused on overweight or obese women undergoing ART, including IVF and intracytoplasmic sperm injection (ICSI). PubMed indexing filters were utilized to identify primary studies (i.e., observational studies and controlled trials) conducted in humans and published in English. Studies focusing on low BMI (<18.5 kg/m^2) in women or the impact of paternal obesity on IVF outcomes were not in the scope of this review.

Titles and abstracts were screened based on the above criteria. If they met the requirements, full-text articles were retrieved for further analysis. Finally, the following information was extracted for each study: first author, year of publication, study type and population, interventions, IVF-related outcomes (e.g., oocyte retrieval, fertilization rate, clinical pregnancy rate, live birth rate, maternal complications, and neonatal outcomes), modifications to IVF treatment protocols, and study results.

RESULTS

We screened 282 studies and included 50 studies (N=33 observational studies and N=17 randomized controlled trials [RCTs]) relevant to the objectives of this review.

EXPERIMENTAL INTERVENTIONS AIMING TO IMPROVE IVF OUTCOMES

WEIGHT LOSS INTERVENTIONS

Fourteen studies (6 observational studies and 8 RCTs) assessed whether traditional strategies, such as weight loss interventions, influence IVF outcomes (**Table 1**).[21-34]

Three studies conducted in overweight/obese infertile women (BMI ranging from >25 to >45 kg/m^2) suggest that short-term lifestyle modifications (8 to 12 weeks), including dietary changes and physical exercise, may positively affect fertility and lead to better IVF outcomes.[28,33,34] Twelve weeks of a hypocaloric diet with a low glycemic index and glycemic load (N=14) was associated with significant weight loss and reduction in the percentage of body fat (P<0.05 each), which may have led to better reproductive outcomes, including more oocytes retrieved (P=0.039) and higher pregnancy rates vs. the control group.[34] Espinós et al.[28] demonstrated that a 12-week structured diet and exercise program resulted in significant weight loss (P<0.001), reduction in waist circumference (P=0.032), and significantly higher cumulative live birth rate (61.9% vs. 30.0% in the control group; P=0.045). Similarly, in comparison with the group receiving counseling on lifestyle modifications, an approximately 8-week intervention with physical activity combined with a reduced energy diet led to improved pregnancy rates in those with a higher intake of polyunsaturated fatty acid, particularly omega-6 and linoleic acid.[33] Moreover, an RCT showed that health-promoting lifestyle education alone significantly reduced the total number of risk factors 3 months post-intervention and improved clin-

Table 1. Experimental weight loss targeted interventions and their impact on ART outcomes in overweight/obese women

Author, Year (Study Type)	Study Population	Interventions	Outcomes	Results	Overall Conclusion
Shen et al., 2023[21] (Observational)	• Region: China • N=197 women with BMI ≥30 kg/m^2 who underwent their first IVF/ICSI cycle	• **Intervention group A:** (weight loss goal ≥5%) with 2–6-month weight management; n=98 • **Control group A:** (weight loss goal <5%); n=99 • **Intervention group B:** (weight loss goal ≥10%); n=56 • **Control B group:** (weight loss goal <10%); n=141	• CPR • LBR	• Significant ↓ in BMI after weight loss in the Intervention groups (**P<0.001** vs. Controls). • In Groups A, NS - no. of oocytes retrieved, fertilization rate, high-quality embryos, CPR, miscarriage rate, and LBR. • In Group B, the Intervention group had significantly ↑ CPR and LBR (**P=0.002** and **P=0.004** vs. Control, respectively).	Weight loss reaching 10% can significantly improve CPR and LBR.
Nilsson-Condori et al. 2022[22] (Observational)	• Region: Sweden • N=897 women undergoing IVF	• **Bariatric surgery**; n=153 • **Control:** matched for age, parity, and BMI at treatment; n=744	**Primary** - cumulative LBR **Secondary** - cancellation rate - no. of oocytes retrieved - no. of frozen embryos - pregnancy loss rate - neonatal outcomes	• Significantly ↓ no. of oocytes retrieved (**P=0.005**) and frozen embryos (**P=0.041**) in the surgery group. - Birth weight was significantly ↓ in neonates born to mothers in the surgery group (**P=0.037**). - *NS* – cumulative LBR, cancellation rate.	CLBR following IVF treatment after bariatric surgery was comparable to controls, despite a lower mean birth weight.
Wu et al. 2022[23] (Observational)	• Region: China • N=75 women for IVF-ET due to tubal factors • N=352 obese, infertile women with PCOS	• **Group A:** controls; n=75 • **Groups B-E:** Weight management 6 months prior to IVF-ET. Subgroups stratified by weight loss before IVF (0, 1–5, 5–10, and >10 kg); n=352	• clinical pregnancy outcomes - neuronal-reproductive-metabolic hormones	• After weight loss, the levels of LH and testosterone in Groups B-E were still ↑ than that in Group A (**P<0.05** or **P=0.01**) and significantly ↓ in Group E vs. Groups B and C (**P<0.05**). - In Group B the E2 level on trigger day and no. of oocytes obtained was significantly ↓ (**P<0.05** or **P=0.01** vs. Group E). - In Groups A, D, and E, embryo implantation rate, CPR, and LBR were ↑ and miscarriage rate was ↓ (**P<0.05** or **P=0.01** vs. Group B). - Significant differences among the control vs. PCOS groups in some genes that are involved in neuronal-reproductive-metabolic endocrine, transcriptional regulation, cell proliferation and differentiation, etc. (**P<0.05**).	Weight loss >5 kg improved the clinical performance of infertile patients with PCOS, but only a weight loss >10 kg resulted in significant changes in gene expression of follicular granulosa cells.
Wang et al., 2021[24] (RCT)	• Region: China • N=877 infertile women scheduled for IVF • BMI ≥25 kg/m^2	• **Placebo group;** n=438 - **Orlistat group;** n=439	**Primary:** - LBR **Secondary:** • pregnancy-related - IVF-related - weight-related	• Significant ↓ weight with Orlistat (**P=0.005**). • *NS* - live birth rate, conception rate, clinical pregnancy, pregnancy loss, IVF-related outcome. - Significant ↑ in singleton birth weight with Orlistat (**P=0.039**).	Orlistat treatment prior to IVF-ET, can produce modest weight loss in overweight/obese women; however, this did not improve the live birth rate.

Author, Year (Study Type)	Study Population	Interventions	Outcomes	Results	Overall Conclusion
Grzegorczyk-Martin et al., 2020[25] (Observational)	• Region: France • N=332 women (10,287 IVF/ICSI cycles)	• **Group 1:** bariatric surgery and overweight; n=83 • **Group 2:** no bariatric surgery and overweight; n=166 • **Group 3:** no bariatric surgery and severely obese; n=83	**Primary**: • CLBR **Secondary:** - no. of mature oocytes retrieved and embryos obtained • implantation rate • miscarriage rate • LBR per transfer • birthweight	• CLBR significantly higher in Group 2 vs. 3 (**P=0.042**) and *NS* between Groups 1 and 3. - *NS* – no. of mature oocytes or embryos retrieved, implantation and miscarriage rates. • Significant difference in LBR per transfer (**P=0.0167**); worst result in obese patients. - Mean birthweight significantly lower in Group 1 vs. 3 (**P=0.044**).	IVF success rates are similar for overweight women exposed or unexposed to bariatric surgery; however, overall higher BMI negatively impacts LBR.
Einarsson et al., 2019[26] (RCT)	• Region: Nordic countries • N=317 obese women scheduled for IVF • BMI between ≥30.0 and <35 kg/m^2	• **Weight intervention and IVF:** 12-week low-calorie diet, followed by a 3- to 5-week period of a normal healthy diet; n=160 • **IVF only;** n=157	**Primary:** - mean birthweight • mean deviation from the expected birthweight **Secondary:** - perinatal and maternal outcomes	• *NS* - mean birthweight and deviation from expected birthweight. • *NS* - perinatal or maternal outcomes between groups when stratified by BMI.	Weight intervention before IVF in obese women does not negatively affect birthweight or weight deviation at birth.
Salamun et al., 2018[27] (RCT)	• Region: Slovenia • N=28 infertile obese PCOS patients • BMI: 36.7±3.5 kg/m^2	Lifestyle intervention + 12-week treatment • **MET group**: metformin 1000 mg BID; n=14 • **COMBI group:** MET 1000 mg BID + liraglutide 1.2 mg QD s.c.; n=13	**Primary:** • pregnancy rate **Secondary:** • Stimulation dose - oocyte and embryo quality - weight loss	• Significant weight loss post-treatment in both groups (**P<0.001**). • Significantly ↑ pregnancy rate in the COMBI group (**P=0.03**). • Higher CPR in 12 months in the COMBI group: 69.2% vs. 35.7%. - *NS* - dose of stimulation, and the no. and quality of oocytes and embryos.	Preconception intervention with low dose liraglutide + metformin is superior to metformin alone in increasing pregnancy rate per embryo transfer and CPR in infertile obese women with PCOS, despite comparable weight reduction in both groups.
Espinós et al., 2017[28] (RCT)	• Region: Spain • N=41 women with a BMI of 30–40 kg/m^2 presenting for their first IVF cycle	• **Intervention group:** individualized diet and physical exercise program supervised by a dietician for 12 weeks; n=21 • **Control group:** started IVF with no previous intervention; n=20	**Primary:** - CPR **Secondary:** - LBR • weight-related - IVF-related • others	• Significant ↓ waist circumference (**P=0.032**) and fat mass (**P<0.001**) with intervention. • CLBR significantly higher in the intervention group (**P=0.045**). - Higher CPR and LBR in the intervention group but *NS*. - Both groups had similar total FSH consumption, no. of oocytes and embryos obtained, and no. and quality of embryos transferred.	A 12-week weight loss intervention significantly improved weight-related outcomes and increased CLBR in obese women.

Author, Year (Study Type)	Study Population	Interventions	Outcomes	Results	Overall Conclusion
Einarsson et al., 2017[29] (RCT)	• Region: Nordic countries • N=317 obese women schedule for IVF • BMI between ≥30.0 and <35 kg/m^2	• **Weight intervention and IVF:** 12-week low-calorie diet, followed by a 3- to 5-week period of a normal healthy diet; n=160 • **IVF only;** n=157	**Primary:** - LBR **Secondary:** • CPR • miscarriage rate • LBR via spontaneous pregnancy • gonadotropin dose • no. of oocytes retrieved • others	• Significant ↓ weight with intervention (**P<0.0001**). • LBR via spontaneous pregnancy significantly higher in the intervention group (**P=0.009**). • *NS* – LBR, CPR, miscarriage rates, gonadotropin dose, and no. of oocytes retrieved. • *NS* – LBR when stratified by PCOS and BMI subgroups.	Significant weight loss with intervention did not affect LBR in obese women scheduled for IVF; however, a significantly higher no. of spontaneous conceptions occurred.
Milone et al. 2017[30] (Observational)	• Region: Italy • N=40 obese women with idiopathic infertility who underwent ART after an initial failure	**Bariatric surgery**	• BMI • no. of follicles • no. of oocytes • no. of embryos • CPR • LBR • Miscarriage rate	• Post-surgery, significant ↓ weight and BMI (**P<0.001**), ↑ in no. of follicles ≥15 mm (**P=0.005**), no. of oocyte retrieved (**P=0.004**), top-quality oocytes (**P=0.001**), MII oocytes (**P=0.008**), fertilized oocytes (**P=0.02**), top-quality embryos (**P=0.003**), CPR (**P<0.001**), and LBR (**P<0.001**). Miscarriage rate was low (1 of 40). - BMI was significantly ↓ in patients who got pregnant after surgery (**P<0.001**).	Results are encouraging to suggest the use of bariatric surgery in obese infertile women seeking an ART treatment.
Kaya et al., 2016[31] (RCT)	• Region: Turkey • N=73 women with unexplained infertility scheduled for ART treatment	• **Education group:** health-promoting lifestyle education; n=33 • **Control group:** n=40	• CPR • BMI • stress • caffeine consumption • exercise • alcohol consumption	• Post-education, there was a significant improvement in average BMI, stress, caffeine consumption, and exercise levels (all **P<0.001**). • CPR was significantly higher in the Education group (**P=0.02**).	Health-promoting lifestyle education reduces infertility risk factors and improves CPR.

Author, Year (Study Type)	Study Population	Interventions	Outcomes	Results	Overall Conclusion
Mutsaerts et al., 2016[32] (RCT)	• Region: Netherlands • N=577 infertile women scheduled for IVF/ICSI • BMI: ≥29 kg/m^2	• **Intervention group:** 6-month lifestyle intervention 18 months prior to infertility treatment; n= 290 • **Control group:** Immediate infertility treatment for 24 months; n=287	**Primary**: • vaginal birth of a healthy singleton at term **Secondary:** • weight-loss related • LBR • ongoing pregnancy • CPR • time to pregnancy • complications • gestational age at delivery	• Significant greater weight loss (**P<0.001**) and change in waist circumference in the intervention group. • Significantly lower no. of vaginal births of healthy singletons at term and LBR in the intervention group. - The median time to pregnancy resulting in a live birth was significantly greater in the intervention group (**P=0.04**). • Significantly more women in the intervention group had ongoing pregnancies that resulted from natural conception. - The no. of treatment cycles was lower in the intervention group. - *NS* - ongoing pregnancy, CPR, frequency of maternal and neonatal complications, neonatal outcomes, mean birth weight, or the no. of SGA infants.	In obese infertile women, a 6-month lifestyle intervention preceding infertility treatment vs. immediate treatment did not result in higher rates of a vaginal birth of a healthy singleton at term within 24 months after randomization.
Moran et al., 2016[33] (Observational)	• Region: Australia • N=46 overweight and obese women undergoing IVF • BMI: ≥28 or >45 kg/m^2	• **Intervention group:** reduced energy diet and physical activity; n=18 • **Control group:** counseling for diet and lifestyle factors influencing fertility; n=20	• pregnancy rate - LBR - pre-study dietary intake	• *NS* – pregnancy rate and LBR. • Women who became pregnant had elevated intake of PUFA, specifically omega-6 PUFA with a trend for an elevated intake of omega-3 PUFA. With regards to specific fatty acids, this occurred for linoleic acid (**P=0.045** adjusted). - No dietary differences for women who did or did not have a live birth.	Maternal preconception PUFA, and specifically omega-6 and LA intake, were associated with improved pregnancy rates in overweight/obese women undergoing IVF.
Becker et al., 2015[34] (RCT)	• Region: Brazil • N=26 overweight or obese infertile women • BMI between >25 and <30 kg/m^2 and waist circumferences >80 cm	• **LGI group:** hypocaloric diet with low glycemic index and load for 12 weeks; n=14 • **Control group;** n=12	• weight-loss related • glucose • insulin • serum lipids • reproductive hormones • leptin • acylated ghrelin • no. of oocytes retrieved • pregnancy rate • LBR	• Greater weight-related improvements in the LGI group (**P<0.05**). • *NS* – change in glucose, insulin, lipids, reproductive hormones, and acylated ghrelin. • Significant ↓ in leptin levels in the LGI group (**P=0.013**) • The LGI group had significantly more oocytes retrieved (**P=0.039**), with a moderate negative correlation between the no. of oocytes retrieved and BMI (**P=0.020**), body fat percentage (**P=0.040**), and leptin concentration (**P=0.024**). • CPR=21.4% spontaneous pregnancy in 3/14 patients) in the LGI group, so LBR=100%. No pregnancies in the control group.	The hypocaloric LGI diet, despite the relative short intervention time and having started immediately before the IVF cycle, promoted a decrease in BMI, bodyfat percentage, and leptin concentrations. It is possible that these effects improved the oocyte development and pregnancy rate in the intervention group.

ical pregnancy rates in women with unexplained infertility with mean BMI 25.5 kg/m^2 (46.15% vs. 19.24% in the control group; P=0.02).[31] Among women who underwent a lifestyle intervention consisting of a hypocaloric diet with a low glycemic index and physical activity of moderate intensity, combining low-dose liraglutide with metformin significantly improved pregnancy rates (85.7% vs. 28.6% with metformin alone; P=0.03) despite a significant weight loss in both groups (P<0.001).[27]

Three studies assessed the effect of bariatric surgery on ART outcomes.[22,25,30] In the study by Nilsson-Condori et al.,[22] despite a lower number of oocytes retrieved, frozen embryos, and mean birth weight in the surgery group (N=153), the cumulative live birth rate was comparable to the age-, parity-, and BMI-matched controls (N=744) at the time of IVF treatment. This is consistent with the findings of Grzegorczyk-Martin et al.[25] where the success of IVF outcomes was similar for BMI-matched overweight women (mean BMI: 28.8–28.9 kg/m^2) who had previously undergone bariatric surgery and those that were non-operated; however, the live birth rate was the worst in severely obese non-operated women (mean BMI: 37.7 kg/m^2). Milone et al.[30] assessed the impact of bariatric surgery in obese women who had initially experienced failure with ART. Post-surgery, there was a significant increase in various ART-related outcomes including increased number of follicles >15 mm, number of top-quality and mature oocytes, number of top-quality embryos, as well as clinical pregnancy and live birth rates (P<0.05 for all).

Multiple large RCTs (N=317–877) have shown that short-term weight loss interventions alone, such as physical activity with or without lifestyle modifications, or pharmacotherapies such as orlistat, result in significant weight loss or reduction in BMI but do not always improve IVF outcomes.[24,29,32] Einarsson et al.[26] further showed that weight intervention had no impact on other outcomes such as birth weight, preterm birth rate, gestational age, and neonatal complications.

Two studies stratified groups based on the amount of weight loss post-intervention.[21,23] Shen et al.[21] observed that in the weight management group with a weight loss goal of ⩾10% (N=56), there was a significant improvement in clinical pregnancy (P=0.002) and live birth rate (P=0.004) vs. controls (N=141). Similarly, Wu et al.[23] observed that IVF outcomes were significantly improved in those who lost 5–10 kg or >10 kg of body weight vs. those who lost 1–5 kgs.

ADJUNCT THERAPIES

Five studies (3 observational studies and 2 RCTs) evaluated the impact of adjunct therapies, alone or in combination with weight loss interventions, aimed at improving ART outcomes (**Table 2**).[35-39]

In 3 studies, micronutrient supplementation demonstrated promising results for various IVF outcomes.[36,37,39] In overweight/obese women with PCOS and who had a family history of diabetes, the combined low-dose use of d-chiro-inositol (500 mg) and α-lipoic acid (300 mg) twice daily for at least 1 month before controlled ovarian hyperstimulation improved insulin sensitivity and showed trends toward better oocyte and embryo quality.[36] Similarly, when compared with obese women using folic acid supplementation alone (OB-F), the combined supplementation of α-lipoic acid, myo-inositol, and folic acid (OB-S) improved antioxidant capacity in the follicular fluid which may have contributed to a trend towards an increase in pregnancy rates (OB-S: 33.3% vs. OB-F: 11.1%; not significant); however, the levels of mitochondrial DNA was negatively correlated to the number of total and MII oocytes.[37] Pre-treatment intake of folate and vitamin B12, resulting in high serum concentrations of both folate and vitamin B12, was positively associated with clinical pregnancy and live birth rates, while high serum vitamin B12 was also associated with improved implantation.[39]

The Zishen Yutai Pill (ZYP), a traditional Chinese medicine consisting of 15 natural medicines, significantly improved implantation, biochemical and clinical pregnancy, and live birth rates, particularly in women with BMI >24 kg/m^2.[35]

Short-term treatment with metformin (1000 mg per day) in overweight/obese women with PCOS significantly reduced the number of retrieved and fertilized oocytes (P<0.01 each) and did not improve fertilization, implantation, clinical pregnancy, and live birth rates (not significant vs. placebo).[38]

MODIFICATIONS TO ART PROTOCOLS IN OVERWEIGHT/OBESE WOMEN AND WOMEN WITH COMORBIDITIES

Dose adjustments to gonadotropins (including follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) or supplementation of gonadotropins during ovarian stimulation/ovulation induction were required in obese women and women with comorbidities such as diminished ovarian reserve, PCOS, and metabolic syndrome, as observed in 16 studies (13 observational studies and 3 RCTs) (**Table 3**).[21,23,25,28,30,36,40-49]

Mahony et al.[42] reported that dose adjustments (increased or decreased) of gonadotropins were frequent in younger patients, those with higher ovarian reserve, and women with ovulation disorders or PCOS. Several clinical studies showed that overweight/obese infertile women or those with comorbidities often require higher doses of gonadotropins and longer stimulation durations while undergoing ART.[21,23,25,36,40,43-45,47,48] Despite these modifications to the ovarian stimulation/ovulation induction protocols, in some of these studies there appeared to be no positive impact on ART outcomes such as oocyte yield, embryo quality, and pregnancy rates.[40,43-45,47,48]

Of note, while 1 study showed that weight loss did not alter the total rFSH dose used,[28] several other studies have shown that reduced weight can lower gonadotropin consumption.[21,23,25,30,46] The gonadotropin dose and stimulation duration required was significantly lower post-bariatric surgery.[30] In the study by Akpinar et al.[46] among women with PCOS, those resistant to clomiphene citrate (CC) received CC at a dose of 150 mg/d, while those responsive to CC received 50 mg/d. Of the parameters examined, BMI (P<0.001), LH (P<0.001), and LH/FSH ratio (P=0.01) were significantly higher in the CC-resistant group than that in

Table 2. Adjunct therapies alone or in combination with weight loss interventions and their impact on ART outcomes in overweight/obese women

Author, Year (Study Type)	Study Population	Interventions	Outcomes	Results	Overall Conclusion
Chen et al., 2023[35] (RCT)	Region: China N=2,265 infertile women undergoing fresh ET • BMI: <30 kg/m^2	• **ZYP group:** Zishen Yutai Pill 5 g oral 3 times/day; n=1,131 • **Placebo group;** n=1,134	• CPR • implantation rate • LBR • pregnancy loss • cycle cancellation • complications • neonatal weight	• In patients with BMI >24 - ZYP treatment had a ↑ implantation rate (RR 1.29; 95% CI 1.02, 1.64), CPR (RR 1.38; 95% CI 1.04, 1.83), and LBR (RR 1.41; 95% CI 1.03, 1.95). • *NS* – other outcomes.	Overweight/obese women could experience clinical benefits when treated with ZYP in their fresh ET cycles.
Artini et al., 2020[36] (Observational)	Region: Italy N=20 overweight (BMI ≥25 kg/m^2)/obese (BMI ≥30 kg/m^2), non-diabetic women with PCOS	• **Diabetic relatives;** n=10 • **No diabetic relatives;** n=10 DCI 500 mg + ALA 300 mg, twice a day, initiated at least 1 month before COH, until the beta-hCG blood test.	• Basal insulin • Stimulation duration - Peak serum E2 level and endometrial thickness on trigger day - no. and quality of oocytes - no. and quality of embryos	• Patients with diabetic relatives had ↑ basal insulin (**P=0.0010**), glucose levels (**P=0.0003**). - *NS* - differences in BMI and other parameters. • Patients with diabetic relatives had a trend towards ↑ no. of MII oocytes (P=0.1386), mean no. of quality embryos (P=0.1999), and blastocyst (P=0.3694).	Low-dose DCI + ALA may improve reproductive outcomes in overweight PCOS patients with familial diabetes by enhancing insulin sensitivity. Thorough patient history is essential to tailor effective integrative therapies and optimize ART success.
Novielli et al., 2020[37] (Observational)	• Region: Italy • N=42 infertile women with normal ovarian reserve who were normal weight (BMI:18–25 kg/m^2) or obese (BMI: >28 kg/m^2)	• **Normal-weight with folic acid (NW-F)**; n=19 • **Obese with folic acid (OB-F)**; n=9 • **Obese with folic acid, myo-inositol, and α-lipoic acid (OB-S)**; n=15 for 2 months before ovarian stimulation	• pregnancy rate - no. of oocytes - no. of MII oocytes - total antioxidant capacity in follicular fluid - mtDNA content and gene expression of respiratory chain complexes in granulosa cells	• Pregnancy rate was similar in NW-F women and OB-S patients, while it was lower in OB-F patients; although *NS*. • *NS* - total no. of oocytes retrieved and MII oocytes number. • Significantly ↑ antioxidant levels in OB-S group vs. NW-F and OB-F groups (**P=0.031**). • mtDNA levels in granulosa cells significantly and negatively correlated to the no. of both total and MII oocytes (**P=0.007** and **P=0.037**, respectively). • mRNA levels of SDHA and COX4I1 subunits were reduced (*NS*) in granulosa cells of OB-F vs. NW-F; supplementation with α-lipoic acid and myo-inositol seemed to restore both transcript levels.	The combined supplementation of α-lipoic acid, myo-inositol, and folic acid in infertile obese women showed a possible amelioration in the oxidative status of oocyte environment. This possibly contributed to ovarian improvement, which might have led to higher pregnancy rates.
Abdalmageed et al., 2019[38] (RCT)	• Region: Egypt • N=102 overweight and obese women with PCOS - BMI: >24 kg/m^2	• **Metformin group:** 2×500 mg/day; n=51 • **Placebo group**; n=51	**Primary:** - total no. of oocytes **Secondary:** - fertilization rate • no. of embryos • implantation rate • CPR • miscarriage rate • LBR	**Metformin vs. the placebo group:** - Significantly ↓ no. of retrieved oocytes (**P<0.01**), no. of fertilized oocytes (**P<0.01**) - *NS* – all other outcomes	Short-term administration of metformin to overweight or obese women with PCOS undergoing IVF decreased the number of the retrieved oocytes and did not improve the LBR.

Author, Year (Study Type)	Study Population	Interventions	Outcomes	Results	Overall Conclusion
Gaskins et al., 2015[39] (Observational)	• Region: USA • N=100 women (154 ART cycles) who underwent IVF/ICSI	• Pretreatment intake of folate and vitamin B-12 • 1 of 3 stimulation protocols as clinically indicated.	• oocytes - fertilization rate - implantation - CPR • LBR	• Women in the highest quartile of serum vitamin B-12 had significantly ↓ BMIs vs. women in the lowest quartile. - Women with higher serum folate concentrations had significantly ↑ CPR and LBR (P-trend=**0.04** and **0.01**, respectively). - Women with higher serum vitamin B-12 concentrations had significantly ↑ implantation, CPR, and LBR (P-trend=**0.03**, **0.01**, and **0.008**, respectively). - Serum folate was marginally associated with higher fertilization rates (P-trend=**0.07**). - Among women with pregnancy loss among cycles with a successful implantation (n=87), the adjusted % cycles lost after implantation was significantly ↓ in women with high folate and high vitamin B-12 vs. low folate and low vitamin B-12 (**P=0.05**).	High concentrations of folate and vitamin B-12 in serum are associated with an increased chance of live birth after ART.

Table 3. Modifications to ART protocols in overweight/obese women and those with comorbidities

Author, Year (Study Type)	Study Population	Ovarian Stimulation/ Ovulation Induction Protocol	Protocol Modification(s) and Related Outcomes
Devranoğlu et al., 2024[40] (Observational)	• Region: Turkey • N=833 women with DOR undergoing ICSI • **Non-obese:** BMI <30 kg/m^2; n=564 • **Obese:** BMI ≥30 kg/m^2; n=269	Standardized GnRH antagonist protocol	Obese patients required ↑ total gonadotropin dose (**P=0.043**), ↑ days of stimulation (**P=0.023**), and ↓ no. of MII oocytes (**P=0.032**) vs. non-obese patients; however, the CPR was similar across groups (P=0.427).
Lin et al., 2024[41] (Observational)	• Region: China • N=704 overweight infertile women who underwent IVF/ICSI and fresh embryo transfer • **GnRH antagonist**; n=585 • **GnRH antagonist + letrozole**; n=119	GnRH antagonist with or without letrozole	• Letrozole co-treatment significantly ↓ estrogen on trigger day, ↓ FSH, ↑ LH, and ↓ gonadotropin consumption and stimulation duration (**P≤0.001**).
Shen et al., 2023[21] (Observational)	• Region: China • N=197 women with BMI ≥30 kg/m^2 who underwent their first IVF/ICSI cycle • **Intervention groups:** (weight loss goal ≥5% or ≥10%) with 2–6-month weight management; n=98 or n=56 • **Control groups:** (weight loss goal <5% or <10%); n=99 or n=141	Short-acting GnRH agonist long protocol	• Significantly ↓ gonadotropin consumption in the Intervention groups (**P=0.001** or **P=0.004** vs. Controls). • In Group B, the Intervention group had significantly ↑ CPR and LBR (**P=0.002** and **P=0.004** vs. Control, respectively).
Wu et al., 2022[23] (Observational)	• Region: China • N=75 women for IVF-ET due to tubal factors • N=352 obese women with PCOS • **Group A:** controls; n=75 • **Groups B-E:** Weight management 6 months prior to IVF-ET. Subgroups stratified by weight loss before IVF (0, 1–5, 5–10, and >10 kg); n=352	GnRH antagonist protocol	• Groups B and C showed ↑ total gonadotropin dose and stimulation duration (**P<0.05** vs. Groups A and E). - The duration of stimulation was significantly ↑ in Group B (**P<0.05** vs. Groups A and E). • *NS* - difference in gonadotropin dose and duration in Group A vs. E.
Mahony et al., 2021[42] (Observational)	• Region: USA • N=33,962 ART cycles in patients receiving r-hFSH-alfa with or without LH	Patients received either a r-hFSH-alfa preparation with or without added LH-like product (hMG, micro-dose hCG, rhLH)	• LH-like products were used in most cycles (>90%), with no difference in the no. of cycles with or without dose adjustments. • Patients receiving dose adjustments had a lower BMI (**P<0.0001**). • Patients receiving ≥1 dose increase had no difference for BMI (*NS*) vs. those who had a constant dose. • ↑ women with dose adjustment vs. constant dose had ovulation disorders/PCOS.
Artini et al., 2020[36] (Observational)	Region: Italy N=20 overweight (BMI ≥25 kg/m^2)/obese (BMI ≥30 kg/m^2), non-diabetic women with PCOS • **Diabetic relatives;** n=10 • **No diabetic relatives;** n=10	Controlled ovarian hyperstimulation with GnRH antagonist protocol - DCI 500 mg + ALA 300 mg, twice a day, initiated ≥1 month before COH, until the beta-hCG blood test.	Those with no diabetic relatives had a trend for a ↑ dose of gonadotropins vs. with diabetic relatives (P=0.1239) and longer days of stimulation (P=0.1493).
Grzegorczyk-Martin et al., 2020[25] (Observational)	• Region: France • N=332 women (10,287 IVF/ICSI cycles) • **Group 1:** bariatric surgery and overweight; n=83 • **Group 2:** no bariatric surgery and overweight; n=166 • **Group 3:** no bariatric surgery and severely obese; n=83	Controlled ovarian stimulation with either long GnRH agonist or antagonist protocol	Significant ↑ in total gonadotrophin dose (**P=0.0005**) and longer stimulation duration (**P=0.0016**) in Group 3 vs. Groups 1 and 2.
Orvieto et al., 2020[43] (Observational)	• Region: Israel • N=189 women • **Obese group:** BMI: 34.3±4.2 kg/m^2; n=32 • **Non-obese group:** BMI: 23.1±3 kg/m^2; n=157	Ovarian stimulation using multiple-dose GnRH antagonist protocol	Trend for a higher total gonadotropin dose in obese patients (P=0.1; *NS*).

Author, Year (Study Type)	Study Population	Ovarian Stimulation/ Ovulation Induction Protocol	Protocol Modification(s) and Related Outcomes
Lainas et al., 2020[44] (Observational)	• Region: Greece • N=113 women at high risk for severe OHSS • **Low BMI group:** <25 kg/m^2; n=72 • **High BMI group:** ≥25 kg/m^2; n=41	A starting dose of 150 IU/day of rFSH was used for ovarian stimulation. Dose adjusted after Day 5, depending on ovarian response.	A significantly higher dose of rFSH was required for patients with high BMI compared with patients with low BMI (1875 [1650–2150] IU vs. 1650 [1600–1750] IU, P=0.003).
He et al., 2019[45] (RCT)	• Region: China • N=1,508 women with PCOS • **Metabolic syndrome (MetS) group**; n=410 • **Non-MetS group**; n=1,098	rFSH at a daily dose of 112.5 IU for patients weighing ≤60 kg and 150 IU for those weighing >60 kg was started on Day 2 or 3 of the menstrual cycle and adjusted according to ovarian response.	During ovarian stimulation, MetS group required significantly higher doses of gonadotropin, longer duration of stimulation, and had lower peak estradiol level, fewer retrieved oocytes, available embryos, a lower oocyte utilization rate, and OHSS than the non-MetS group.
Milone et al., 2017[30] (Observational)	• Region: Italy • N=40 obese women with idiopathic infertility who underwent ART after an initial failure • **Bariatric surgery**	GnRH antagonist protocol	• Post-surgery, significantly ↓ weight and BMI (**P<0.001**), ↓ in the dose and duration of gonadotropins (**P=0.001).**
Akpinar et al., 2016[46] (Observational)	• Region: Turkey • N=426 women with PCOS and infertility • **CC-resistant group:** women resistant to CC treatment at a dose of 150 mg/day; n=84 • **CC-responsive group (control)**: women who responded with growth of at least one graafian follicle at a dose of 50 mg/day; n=342	Ovulation induction with CC	• Mean BMI: CC-resistant group: 26.8 ± 3.2 kg/m^2 CC-responsive group: 24.3 ± 3.1 kg/m^2 - Of the parameters examined, BMI (**P<0.001**), LH (**P<0.001**), and LH/FSH ratio (**P=0.01**) was significantly higher in the CC-resistant vs. the CC-responsive group.
Espinós et al., 2017[28] (RCT)	• Region: Spain • N=41 women with a BMI of 30–40 kg/m^2 presenting for their first IVF cycle • **Intervention group:** individualized diet and physical exercise program supervised by a dietician for 12 weeks; n=21 • **Control group:** IVF started with no previous intervention; n=20	Controlled ovarian hyperstimulation was performed using a short protocol with GnRH antagonist and rFSH	• rFSH was initiated with 225 IU/day. When the antral follicle count in one of the two ovaries was >13, the initial dose was 150 IU/day (N=4 each group). • Eleven women required a dose adjustment during stimulation. • *NS* - total rFSH dose or for duration of stimulation.
Martinez et al., 2017[47] (Observational)	• Region: Spain • N=2,722 donor oocyte IVF cycles • **Q1:** BMI ≤19.9 kg/m^2 • **Q2:** BMI 19.91–21.5 kg/m^2 • **Q3:** BMI 21.51–23.50 kg/m^2 • **Q4:** BMI ≥23.51 kg/m^2	Protocol with GnRH antagonist with 0.25 mg of garnirelix combined with 150–200 IU of rFSH.	A statistically significant ↑ in the total dose of FSH and days of stimulation, and ↓in the total no. of oocytes retrieved and metaphase II oocytes, with increased donor BMI (all **P<0.05**).
Sheng et al., 2017[48] (Observational)	• Region: China • N=774 women with PCOS • **Underweight:** BMI <18.5 kg/m^2; n=51 • **Normal:** BMI 19–23.9 kg/m^2; n=449 • **Overweight:** BMI 24–27.9 kg/m^2; n=211 • **Obese:** BMI ≥28 kg/m^2; n=63	Not available	Significant difference among groups for the total dose of rFSH used (**P<0.001**); rFSH dose was higher in obese vs. underweight.

Author, Year (Study Type)	Study Population	Ovarian Stimulation/ Ovulation Induction Protocol	Protocol Modification(s) and Related Outcomes
Gizzo et al., 2015[49] (RCT)	• Region: Italy • N=40 Estimated poor responders undergoing IVF and GnRH antagonist treatment, with rLH supplementation during ovarian stimulation - BMI <30 kg/m^2 • **Group A:** 75 IU/day rLH; n=20 • **Group B:** 150 IU/day rLH; n=20 • **Subgroups A1/B1**: rLH administered at rFSH administration; n=10 each • **Subgroups A2/B2:** rLH administered at GnRH antagonist administration; n=10 each	GnRH antagonist flexible short-regimen stimulation	• In the 1st cycle, significant differences were identified between subgroups A1 and B1 vs. A2 and B2 regarding the no. of follicles measuring >10 mm at GnRH-ant administration (**P<0.001**) and the number of follicles >16 mm at hCG administration (**P<0.001**). • During hCG administration, B1 exhibited the highest mean serum E2 (**P<0.001**), while B2 exhibited the highest mean serum progesterone (**P<0.001**). • On the day of retrieval, B2 exhibited ↑ endometrial thickness vs. A1 (**P<0.001**). • ↑ no. of retrieved oocytes and MII oocytes B1 vs. other subgroups. A higher number of total oocytes and MII oocytes were identified in A1 vs. A2 and B2 (**P<0.01**). • *NS* – no. of embryos. • Following the 1 st treatment cycle, n=5 in subgroup B1 produced >3 embryos and n=7 in the 2 nd treatment cycle in B1. • Of 35 patients who underwent a 2 nd IVF cycle N=2 in B1 and N=1 each in A1 and B2 became pregnant. • Regarding total number of follicles and number of follicles >16 mm, B1 exhibited the optimal results, and the results in B1 and A1 were better than those in B2 and A2. • Stratified data of the endometrial thickness at retrieval revealed a statistically significant difference between the three cohorts, with the optimum results obtained in cohort 3 and the poorest results obtained in cohort 1 (**P<0.001**).

the CC-responsive group, suggesting that losing weight before treatment may reduce the need for more intensive gonadotropin-based protocols as well as reduce the risk of OHSS. Consistent with these findings, Grzegorczyk-Martin et al.[25] observed that gonadotropin dose and stimulation duration was lower while the cumulative live birth rate was significantly higher (P=0.042) in the overweight vs. severely obese women. Similarly, 2 observational studies found that patients who lost more weight (⩾10% or >5 kg) required lower doses of gonadotropin and shorter duration of stimulation and also had improved IVF outcomes including clinical pregnancy and live birth rates compared to those who lost less weight (<10% or <5 kg).[21,23] Additionally, co-treatment with letrozole while using the GnRH antagonist protocol in overweight infertile women was associated with significantly reduced gonadotropin consumption and stimulation duration when compared with GnRH antagonist alone (P<0.001).[41]

Gizzo et al.[49] evaluated rLH supplementation with 2 doses (75 and 150 IU/day) at 2 separate timings (starting from GnRH antagonist or rFSH administration). It was found that rather than the total dose of LH, the timing of administration affects the ovarian responses, with the optimal window being the mid-to-late follicular phase.

STUDIES COMPARING ART PROTOCOLS

A head-to-head comparison of ART protocols, particularly protocols used for ovarian stimulation and ovulation induction, was conducted in 8 studies (7 observational studies and 1 RCT) (**Table 4**).[41,50-56]

Four studies demonstrated that the use of letrozole alone or as an adjuvant appeared to be beneficial in improving ART outcomes in overweight or obese women when compared with other stimulation protocols.[41,51,52,54] Letrozole users had more live births vs. CC users across all BMI subgroups; however, among letrozole users, pregnancy complications were higher in those with metabolic syndrome vs. those without metabolic syndrome.[52] While combining letrozole with CC significantly increased ovulation rates (77% vs. 43% with letrozole alone; P=0.0068), no significant differences were found in clinical pregnancy or live birth outcomes in women with PCOS (mean BMI ~33–34 kg/m^2).[54] Liu et al.[51] observed that the addition of letrozole to medroxyprogesterone acetate (MPA) + hMG increased the number of follicles >16 mm and the follicular output rate vs. MPA + hMG alone; however, the number of mature oocytes, viable embryos, cycle cancellation rate, and implantation rate were comparable between groups. In another study, letrozole co-treatment with the GnRH antagonist protocol significantly improved several ART outcomes including the number of follicles >16 mm, oocyte retrieval rate, usable embryo rate, and live birth rate.[41]

Jiang et al.[55] assessed the addition of CC to MPA + human menopausal gonadotropin (hMG) in IVF cycles among obese women with PCOS. Compared with MPA + hMG alone, the combination with CC reduced the total hMG dose required but resulted in fewer oocytes and top-quality embryos. Zhang et al.[56] compared conventional IVF (long GnRH antagonist protocol + 150–300 IU/d gonadotropin injections) to minimal stimulation IVF (mini-IVF; 50 mg/d of CC orally + 75–150 IU/d gonadotropin injections) in 439 women and observed that while BMI negatively impacted the number of oocytes retrieved and MII oocytes in conventional IVF, this effect was not seen with mini-IVF.

Endometrial preparation with a letrozole mild cycle (2.5 mg/d of letrozole, before using hMG) or natural cycle (no medication until trigger day) reduced the risk of late miscarriages vs. hormone replacement (25 µg twice per day of oral ethinyl estradiol) or hMG late stimulation cycles (i.e., hMG at small doses).[50] Similarly, mildly stimulated cycles with letrozole plus hMG resulted in a significantly thicker endometrium, higher live birth rate, and lower miscarriage rates when compared with artificial cycles (estradiol + progesterone).[53]

DIFFERENTIAL LEVELS OF BIOMARKERS IN NORMAL WEIGHT VS. OVERWEIGHT/OBESE WOMEN UNDERGOING IVF TREATMENTS

In total, 15 studies (10 observational studies and 5 RCTs) assessed the multifactorial influences of preconception or periconception hormonal, metabolic, and inflammatory factors on ART success and their utility in predicting ART outcomes in overweight and obese women (**Table 5**).[34,57-70]

The differential levels of lipid parameters were assessed for their impact on reproductive success and ART outcomes. Some studies noted that increased BMI and elevated serum lipids, particularly low-density lipoprotein (LDL), total cholesterol (TC), triglycerides (TG), and apolipoprotein-B, negatively impacted various ART outcomes, including ovulation, fertilization, embryo quality, pregnancy, and live birth rates, and increased miscarriage risk.[62-64] In contrast, Bollig et al.[57] found no link between dyslipidemia and live birth unless both partners who are planning IVF had elevated LDL or TC. High-density lipoprotein (HDL) levels were positively associated with the number of oocytes, normal fertilized oocytes, and cleavage embryos (P<0.05),[64] and Bacchetti et al.[66] further highlighted that follicular fluid HDL function reflects oocyte quality more than HDL concentration. Becker et al.[34] suggested that dietary interventions promoted a decrease in BMI, percentage of body fat, and leptin concentrations, which in turn improved the oocyte yield (85.4% more oocytes retrieved vs. control; P=0.039) and spontaneous pregnancy rate (21.4% vs. 0% in the control group) in the intervention group. Consistent with this finding, compared with women of normal weight, overweight/obese women have high levels of leptin in the follicular fluid, which were negatively correlated with embryo quality.[69] Liu et al.[60] showed that pre-pregnancy LDL/HDL and TC/HDL ratios predicted GDM occurrence in women undergoing their first IVF/ICSI treatment, and those who developed GDM had higher BMI (21.91 vs. 21.23 kg/m^2 in the non-GDM group, P=0.005).

Some studies evaluated the levels of fertility- and reproduction-related hormones and their impact on ART outcomes. Hokmabadi et al.[58] identified that elevated serum progesterone (>1.54 ng/ml; initial cutoff considered was 1.2 ng/ml) on the human chorionic gonadotropin (hCG) trigger

Table 4. Studies comparing ART protocols

Author, Year (Study Type)	Study Population	Interventions	Outcomes	Results	Overall Conclusion
Lin et al. 2024[41] (Observational)	• Region: China • N=704 overweight infertile women who underwent IVF/ICSI and fresh embryo transfer	• **GnRH antagonist**; n=585 • **GnRH antagonist + letrozole**; n=119	**Primary** • LBR **Secondary** • hormone parameters • ovarian stimulation outcomes • pregnancy outcomes	• Letrozole co-treatment significantly ↓ estrogen on trigger day, ↓ FSH, ↑ LH, and ↓ gonadotropin consumption and stimulation duration (**P≤0.001**). - Significantly ↓ no. of total follicles (**P<0.001**), but ↑ no. of follicles >16 mm (**P<0.001**), ↓ no. of oocytes retrieved (**P=0.009**), ↑ oocyte retrieval rate (**P=0.016**), and usable embryo rate (**P=0.002**). - Significantly ↑ LBR with letrozole co-treatment (**P=0.026**). - *NS* - fertilization rate, no. of embryos transferred, endometrial thickness, obstetric and neonatal outcomes. • In the letrozole group, CPR was higher and miscarriage rate was lower, although *NS*.	Letrozole could serve as an adjuvant treatment in the antagonist protocol to improve the LBR following fresh ET in overweight patients.
Shen et al., 2024[50] (Observational)	• Region: China • N=22,392 undergoing their first FET cycle - Subgroups stratified by BMI	PPOS protocol with endometrial preparation using: • **Natural cycle** • **Hormone replacement cycle** • **hMG late stimulation cycle** • **Letrozole mild stimulation cycle**	• oocyte outcomes • embryo outcomes • CPR • LBR • miscarriage rate	• Significantly ↑ hMG doses used in overweight/obese patients (**P<0.001**). • ↑ application rate of hormone replacement cycle and letrozole stimulation cycle in the high BMI groups. • Higher BMI subgroups had ↑ miscarriage rates (especially late-term) and ↓ LBR. • Endometrial preparation with natural or letrozole stimulation cycle had ↓ risk of late miscarriage vs. hormone replacement or hMG late stimulation protocol.	Proper endometrial preparation with natural and letrozole stimulation cycles may decrease the incidence of late miscarriages.
Liu et al., 2023[51] (Observational)	• Region: China • N=1,508 overweight women with PCOS who were candidates for ART	• **Study group:** PPOS + letrozole; n=134 • **Control group:** PPOS; n=1,374	**Primary** • follicular output rate **Secondary** • no. of retrieved oocytes and viable embryos • oocyte retrieval rate • oocyte maturity • fertilization rates • hMG dose and duration • implantation rate	• Significantly ↑ follicular output rate (**P<0.001**), ↓ no. of follicles 14–16 mm but ↑ no. of follicles >16 mm (**P<0.05**), ↓ mature oocyte rate (**P<0.05**) in the Study group. - *NS* - no. of mature oocyte and viable embryos, average hMG dose and duration, cycle cancellation rate, and implantation rate - In the Study group, during COS, LH was significantly ↑ at MC8, MC9-11, and trigger day (**P<0.01**), ↑ P4 at MC9-11 (**P<0.01**). Letrozole use was associated with reduced estrogen (**P<0.01**). No differences in FSH levels between groups.	The addition of letrozole to the PPOS regimen increased follicular output rate in patient with PCOS with high BMI (>25 kg/m2); however, it did not improve cycle parameters of COS, including hMG consumption, or pregnancy outcomes.

Author, Year (Study Type)	Study Population	Interventions	Outcomes	Results	Overall Conclusion
Arya et al., 2022[52] (Observational)	• Region: USA • N=750 women with PCOS and infertility	• **CC** • **Letrozole** for ovulation induction for 1-5 cycles or until pregnancy	• LBR • CPR • complications	• LBR was ↑ in letrozole vs. CC users in all BMI subgroups. The detrimental effects of having MetS on LBR was observed in all BMI subgroups, but especially in those with BMI 25–35 kg/m^2 (**P=0.03**) and among CC users. - Incidence of complications was similar between groups. Among letrozole users, pregnancy complications was ↑ in MetS vs. non-MetS (**P=0.01**).	Although having MetS was associated with more pregnancy complications, overall letrozole users had more live births.
Guan et al., 2022[53] (Observational)	• Region: China • N=680 overweight/obese women with PCOS who underwent their first FET cycles	Endometrium preparation - • **mSTC group:** letrozole and hMG; n=173 • **Artificial cycle group:** estradiol valerate and progesterone; n=507	**Primary** • LBR **Secondary** • implantation rate • CPR • endometrial thickness • ectopic pregnancy • pregnancy loss rate	• Significantly thicker endometrium in the mSTC group (**P<0.05**). - The mSTC group had significantly ↑ LBR (**P<0.05**) and ↓ miscarriage rate (**P<0.001**). - *NS* - no. of embryos transferred, embryo grades and stages, implantation rate, CPR, and ectopic pregnancy.	Mildly stimulated cycles using letrozole plus hMG for endometrial preparation might result in superior pregnancy outcomes and be a potentially better alternative to artificial cycles for overweight or obese women with PCOS.
Meija et al., 2019[54] (RCT)	• Region: USA • N=70 infertile women infertility with PCOS	• **Letrozole alone** (2.5 mg); n=35 - **Letrozole** (2.5 mg) **+ CC** (50 mg); n=35 daily on cycle Days 3–7 for one treatment cycle • Stratified by age (<35 vs. ≥35 years) and BMI (<30 and ≥30 kg/m^2).	**Primary:** • ovulation **Secondary:** - conception - CPR - LBR - pregnancy loss • size and no. of follicles - endometrial thickness - adverse events	• Higher ovulation rate when combining letrozole with CC (77% vs. 43% with letrozole alone; **P=0.0068**); rate ratio for ovulation with combination treatment 1.80, 95% CI: 1.18, 2.75. - *NS* - secondary outcomes between the two groups.	Combining letrozole with CC leads to higher ovulation rates in women with PCOS-related infertility compared to letrozole alone; however, further trials are needed to confirm effects on pregnancy and live birth rates.
Jiang et al., 2017[55] (Observational)	• Region: China • N=174 obese women with PCOS undergoing IVF	• **Study group:** hMG + MPA + CC; n=90 - **Control group:** hMG + MPA; n=84	**Primary:** • no. of oocytes retrieved **Secondary:** • no. of embryos - maturation rate - fertilization rate - cleavage rate - OHSS	• The addition of CC ↓ total hMG dose (**P=2.038E−4**), but ↓ no. of oocytes retrieved (**P=6.333E−5**) and top-quality embryos (**P=0.003**). - *NS* - HMG duration, fertilization rate, and cleavage rate.	CC in combination with hMG in MPA-primed cycles reduces hMG use, but results in fewer retrieved oocytes and top-quality embryos.

Author, Year (Study Type)	Study Population	Interventions	Outcomes	Results	Overall Conclusion
Zhang et al., 2015[56] (Observational)	• Region: USA • Women undergoing 1 st autologous cycle of conventional IVF (N=219) or mini-IVF (N=220)	• **Conventional IVF;** n=219 ‣ Normal weight; n=121 ‣ Overweight; n=73 ‣ Obese; n=25 • **Mini-IVF;** n=220 ‣ Normal weight; n=124 ‣ Overweight; n=69 ‣ Obese; n=27	**Primary:** • no. of MII oocytes **Secondary:** • total no. of oocytes • fertilized oocytes • cleavage and blastocyst stage embryos • CPR • LBR	• Conventional IVF ‣ *NS* - CPR, LBR, no. of fertilized oocytes, or no. of embryos at the cleavage and blastocyst stages. ‣ Obese groups had significantly ↓ no. of oocytes retrieved (**P=0.005**) and no. of MII oocytes (**P=0.02**) vs. normal weight women. ‣ Day 3 FSH was significantly ↑ (although not clinically significant) in normal weight vs. overweight women (**P=0.04**), peak estradiol levels on day of hCG was significantly ↓ in overweight and obese vs. normal weight women (**P<0.0001**). ‣ In an adjusted multivariable linear regression, BMI is an independent predictor of the number of MII oocytes (**P=0.0004**). • Mini-IVF ‣ *NS* – no. of oocytes • BMI was negatively correlated with the no. of oocytes retrieved (r=-0.24, **P=0.0005**), no. of MII oocytes (r=-0.20, **P=0.004**), and no. of fertilized oocytes (r=-0.17, **P=0.02**) in the conventional IVF group, but not in the mini-IVF group.	Obese women might not have a worse ovarian response if they undergo minimal ovarian stimulation IVF. Female adiposity might impair oocyte number and maturity in conventional IVF but not in mini-IVF. As high doses of gonadotropins have been shown to be detrimental to human oocyte, minimal stimulation IVF might represent a potential alternative to conventional IVF in obese women with poor oocyte/embryo quality.

Table 5. Biomarkers in women undergoing ART procedures

Author, Year (Study Type)	Study Population	Biomarkers	Outcomes	Results	Overall Conclusion
Bollig et al., 2024[57] (RCT)	• Region: USA • N=2,126 females (with TC, HDL, and TG values) and N=2,094 females (with LDL values) seeking fertility treatment	Lipid parameters	**Primary:** • LBR	• 76.1% females had ≥1 abnormal lipid parameter with abnormal levels of LDL being the most common (51.1%). • Females with dyslipidemia had higher BMI and were more likely to have a diagnosis of infertility and pursue non-IVF fertility treatment. • Higher proportions of abnormal HDL and TG in females planning non-IVF methods to conceive. • In couples planning IVF where both partners had elevated TC or LDL, live birth was lower than in those with normal levels. • *NS* - LBR in females overall or in those planning non-IVF treatment across all 4 lipid parameters in fully adjusted models.	If both partners had elevated TC or LDL, live birth was lower than in those with normal levels.
Hokmabadi et al., 2024[58] (Observational)	• Region: Iran • N=496; infertile women undergoing IVF/ICSI cycles Grouped based on serum progesterone on the HCG trigger day • **Group A:** <1.2 ng/ml; n=260 • **Group B:** >1.2 ng/ml; n=236	Serum progesterone on the day of HCG trigger	Effect of serum progesterone levels on the day of hCG trigger on: • oocyte maturation • embryo quality • fertilization rate	• Initial progesterone cutoff of 1.2 ng/ml was considered; however, a more accurate cutoff of 1.54 ng/ml was identified, beyond which the mean no. of M1 oocytes significantly ↓. • On the day of hCG injection, progesterone levels were not linked to the age or BMI of patients. • Optimal fertilization rates noted among those with a BMI ranging from 25–30 kg/m^2. • Significant correlation between BMI and the incidence of quality B embryos (**P=0.006**), but not for quality A and C, and for four to six cell embryos (*NS*).	• Elevated progesterone level, particularly beyond the identified cutoff of 1.54 ng/ml, is a valuable clinical indicator of suboptimal IVF outcomes due to its negative impact on oocyte maturation. • BMI may influence embryo development to some extent.
Komorowski et al., 2024[59] (RCT)	• Region: USA • N=333 women with anovulatory infertility attributed to PCOS	AMH	Association between AMH and • ovulation • CPR • LBR	• Women who ovulated had significantly lower BMI. • NS - association between baseline AMH concentration and CPR or LBR. Treatment group was not a significant effect modifier (P=0.54). • BMI was a significant effect modifier of the association between baseline AMH concentration and ovulation, with women with higher BMI having a steeper decline in probability of ovulation with ↑ baseline AMH concentration vs. those with lower BMI (**P=0.009**). • BMI was a potential confounder for ovulation, CPR, and LBR.	In women with infertility and PCOS, a higher AMH concentration was associated with reduced odds of ovulation with OI with clomiphene, clomiphene + metformin, and metformin. This remained statistically significant when controlling for BMI and other confounders.
Liu et al., 2024[60] (Observational)	• Region: China • N=767 women who underwent their first IVF/ICSI treatment and were pregnant for the first time • Age: 18–40 years	Lipid parameters	• Baseline lipid parameters (before IVF/ICSI and pregnancy) • GDM development	• 30% had ≥1 dyslipidemia parameter. • Those who developed GDM had higher BMI (**P=0.005**), LDL (**P=0.004**), TG (**P=0.010**), and lower HDL (**P<0.001**). • LDL, HDL, and TG, show a significant difference between GDM vs. non-GDM (**P<0.05**). • Following multivariate logistic regression considering confounders, continuous LDL, HDL, LDL/HDL ratio, and TC/HDL ratio were still significantly different in GDM vs. non-GDM patients, while other lipid parameters, TC, TG, and TG/HDL ratio were not significantly associated with GDM. • Higher prevalence of GDM in women with high BMI (≥21.33 kg/m^2).	• Couples planning IVF where both partners had elevated TC or LDL and males planning IVF with elevated LDL had decreased probability of live birth. • Pre-pregnancy LDL/HDL and TC/HDL ratios were most significantly associated with GDM incidence.
Melado Vilades et al., 2023[61] (Observational)	• Region: UAE • N=1,660 euploid FET cycles with 2,439 euploid blastocysts	AMH	• CPR • miscarriage rate • LBR	• *NS* - in outcomes when groups were analyzed per four AMH categories (<0.5 ng/ml, 0.5–<1.3 ng/ml, 1.3–6.25 ng/ml, >6.25 ng/ml). • In patients with AMH >6.25 ng/ml, the HRT protocol was chosen for endometrial preparation in 86.8% of the cycles. • When a possible interactive effect was studied between high AMH concentrations (>6.25 ng/ml) and BMI, no differences were observed for CPR, but obese patients had higher risk for clinical miscarriage and pregnancy loss, and lower possibilities of a live birth at any AMH concentrations.	• Non-obese patients with AMH concentrations >6.25 or <6.25 ng/ml had no increased risk for miscarriage and similar chances for live birth rate; only obese patients had an increased risk of clinical miscarriage and pregnancy loss, hence decreased live birth rate. • For patients with high AMH (>6.25 ng/ml), FET was mainly prepared using an HRT protocol, which might have an impact on the outcomes.

Author, Year (Study Type)	Study Population	Biomarkers	Outcomes	Results	Overall Conclusion
Cai et al., 2022[62] (RCT)	• Region: China • N=1,000 women with PCOS	Serum lipid concentrations	• ovulation • conception • pregnancy • live birth • miscarriage	• Serum lipid concentrations per one unit increment were independently associated with reproductive outcomes after controlling for confounders. • ↑ LDL-C was independently associated with a ↓ chance of ovulation. • ↑ total cholesterol, LDL-C, triglycerides, and ApoB were independently associated with a ↓ chance of clinical pregnancy and live birth, and all except triglycerides ↑ higher chance of miscarriage.	Increased serum lipids were negatively associated with the reproductive outcomes of PCOS women undergoing ovulation induction with clomiphene with or without acupuncture.
Raviv et al., 2020[63] (Observational)	• Region: Israel • N=41 women <40 years • **High BMI:** >30 kg/m2; n=15 - **Low BMI:** <25 kg/m2; n=26	Lipid parameters	• no. of oocytes - fertilization rate - cleavage rate - blastulation rate - no. of embryos - CPR	• Significantly ↑ serum LDL level (**P=0.048**), ↓ embryo quality (**P=0.04**) and embryo quantity (**P=0.044**) in the high BMI group. - *NS* – no. of treatment days, dose of gonadotropins, final estradiol level on the day of hCG, endometrial thickness, no. and quality of oocytes collected, fertilization rate, and CPR.	Higher levels of LDL and lower embryo quality were found in the group with high BMI; however, there was no difference in pregnancy rates between groups.
Wang et al., 2020[64] (Observational)	• Region: China • N=488 patients undergoing conventional IVF - **Pregnant group;** n=286 - **Nonpregnant group;** n=202	Blood lipid levels	• no. of oocytes • no. of embryos • lipid parameters	• *NS* – no. of oocytes, normal fertilized oocytes, cleavage embryos, and good quality embryos between the 2 groups. • Pregnant group had significantly ↑ normal fertility rate and good quality embryo rate (**P<0.05** each). - Negative correlations between: BMI and no. of normal fertilized oocytes, no. of cleavage embryos, and no. of good quality embryos; serum TG, TC, and LDL and no. of normal fertilized oocytes; TG, TC, and lipoprotein(b) and no. of good quality embryos; TG and no. of oocytes and no. of cleavage embryos (**P<0.05** for all). - HDL and lipoprotein(a) were positively correlated with the no. of oocytes, no. of normal fertilized oocytes, and no. of cleavage embryos (**P<0.05**).	Blood lipid levels may provide certain reference for the prediction of IVF pregnancy outcome.
Zhang et al., 2020[65] (Observational)	• Region: China • N=120 women - **PCOS group;** n=60 - **Control group;** n=60 • Stratified by BMI	IL-18	**Primary**: • FF and serum IL-18 and IL-18BP levels in women with PCOS undergoing IVF **Secondary:** • effect of FF and serum IL-18 levels on obesity	• Significantly ↑ FF IL-18 levels and FF IL-18BP levels were observed in PCOS patients (**P=0.001** vs. controls). - Overweight PCOS patients had higher FF IL-18 levels (**P=0.027** vs. normal weight PCOS patients). - Positive correlation found between FF IL-18 levels and the no. of retrieved oocytes (r=0.78, **P=0.002**).	Elevated FF IL-18 levels in PCOS patients, especially those overweight, may reflect local inflammation impairing folliculogenesis and oocyte quality. This inflammation could contribute to anovulation, warranting further research on the role of IL-18 in PCOS and IVF outcomes.

Author, Year (Study Type)	Study Population	Biomarkers	Outcomes	Results	Overall Conclusion
Bacchetti et al., 2019[66] (Observational)	• Region: Italy • N=58 women - Groups based on BMI: - Normal weight (≥18.5–≤24.9 kg/m^2); n=38 - Overweight or obese (≥25–≤29.9 kg/m^2 or ≥30–<35 kg/m^2); n=20	FF-HDL functionality	**Biochemical parameters:** - FF-HDL oxidation rate - HDL-associated antioxidants - lipid hydroperoxide levels **Embryological outcomes:** • no. and quality of oocytes - fertilization rate - % of embryos • no. of embryos transferred	• *NS* - modifications in the FF levels of lipids and protein content. - Obese women showed a trend for ↑ FF levels of lipid hydroperoxides (NS). - The mean values of oxidation rate of DHR in FF-HDL from overweight or obese women were significantly ↑ vs. normal-weight subjects (**P<0.001**). - A significant correlation was observed between PON1 activity in FF and oxidation rate of DHR values of FF-HDL vs. the no. of oocytes retrieved or the no. of good quality oocytes.	The quality of FF-HDL is important determinant for oocyte quality. Therefore, targeting FF-HDL functionality, in addition to FF-HDL-C levels, may represent a promising and interesting biomarker for reproductive outcomes.
Chang et al., 2019[67] (RCT)	Region: China N=936 with PCOS and baseline HCY levels	HCY levels	• ovulation - conception - pregnancy - pregnancy loss - live birth	• The higher HCY tertile was associated with ↑ BMI and free testosterone levels and ↓ FSH, fasting glucose levels, and ovulation. - BMI, fasting glucose/insulin levels, HOMA-IR and hirsutism scores in HHCY group were similar to controls. - LH, LH/FSH ratio, and SHBG in the metabolic syndrome group were ↓ vs. control. - Subjects in HHCY group had ↓ estradiol and ↑ free testosterone. - In HHCY group, the ovulation rate ↓ and the pregnancy loss rate in second or third trimester ↑, whereas the ovulation rate lost difference after adjustment for treatment and hormone factors. - Reproductive outcomes including ovulation rate, conception rate, CPR, pregnancy loss rate and LBR were statistically ↓ in the metabolic syndrome group before or after adjusting treatment, and the pregnancy rate, pregnancy loss rate in second or third trimester, and live birth rate maintained statistical difference after adjusting for treatment and hormone factors.	• Elevated maternal serum levels of HCY might be a sensitive biomarker for the early prediction of adverse pregnancy outcomes, such as ovulation defects. • Elevated maternal serum HCY and metabolic syndrome are linked to adverse reproductive outcomes in PCOS patients, including ovulation defects and pregnancy loss. Since both can be modified, early interventions like folic acid, vitamin B, weight loss, and lifestyle changes are crucial.
Mizrachi et al., 2018[68] (Observational)	• Region: Israel • N=326 treatment cycles - **Above median hCG levels** (>91.35 IU/L); n=163 - **Below median hCG levels** (<91.35 IU/L); n=163	hCG levels	**Primary:** - LBR **Secondary:** - CPR - no. of oocytes retrieved - fertilization rate - metaphase II oocyte rate - implantation rate	• Serum hCG levels were inversely correlated with patient's BMI (r=−0.50, **P<0.001**). - Although statistically significant, the correlation between hCG levels and patient's age was weak (r=−0.15, **P=0.006**). - *NS* – no. of oocytes obtained, the rate of MII oocytes, fertilization rate, CPR, and LBR.	Serum hCG levels after ovulation trigger inversely correlate with age and BMI but do not predict clinical or lab outcomes. From a clinical point of view, neither routine testing for serum hCG levels after ovulation triggering nor hCG supplementation based on the testing results can be recommended at the moment.

Author, Year (Study Type)	Study Population	Biomarkers	Outcomes	Results	Overall Conclusion
Lin et al., 2017[69] (Observational)	• Region: China • N=189 women undergoing IVF - Groups based on BMI: **- Normal:** 18.5–23.9 kg/m^2; n=125 **- Overweight and obese:** ≥ 24 kg/m^2; n=64	Leptin levels	• positive serum hCG levels - implantation - miscarriage - ongoing pregnancy	• Significantly ↑ CPR (**P=0.002**), ongoing pregnancy (**P=0.004**), and LBR (**P=0.007**) in normal weight women vs overweight/obese group. - *NS* – no. of oocytes retrieved, cleavage rate, fertilization rate, available embryos rate, implantation, and miscarriage rates. - Serum and FF leptin levels were significantly ↑ in overweight/obese group. • FF leptin level was negatively correlated to the good quality embryo rate (r=−0.414, **P<0.05**).	A high FF leptin concentration could be a predictor of poor embryo development. Our results suggest that high leptin levels might inhibit proliferation and promote apoptosis, linking to attenuated embryo development, which is a novel mechanism that may contribute to the poor pregnancy outcomes in infertile women who are overweight or obese.
Çakıroğlu et al., 2016[70] (Observational)	• Region: Turkey • N=292 normal weight or obese women undergoing IVF/ICSI with or without PCOS • Groups - **NW-PCOS**; n=69 - **OB-PCOS**; n=77 - **NW-control**; n=69 - **OB-control**; n=77	Inflammatory markers	• inflammatory markers • total no. of oocytes and MII oocytes • fertilization rate • implantation rate • miscarriage • CPR	• AFC, LH, and AMH levels were significantly ↑ in the NW-PCOS group and AFC and AMH were ↑ in the OB-PCOS group vs. controls. • Total oocytes retrieved and MII oocyte counts were significantly ↑ in the OB-PCOS vs. OB-controls. • *NS* - fertilization, pregnancy, and miscarriage rates. • NLR and PLR were significantly ↑ in NW- PCOS even though the WCC did not rise. The WCC, NLR, PLR, and MPV were significantly ↑ in the OB-PCOS vs. OB-control (**P<0.05**). • OB-PCOS had significantly ↑ WCC, neutrophil, and lymphocyte levels, and a significantly ↓ PLR vs. NW-PCOS (**P<0.05**). • LH levels were negatively correlated with neutrophil (r=−0.198, **P<0.05**) and lymphocyte count (r=−0.189, **P<0.05**) and positively correlated with PLR (r=0.192, **P<0.05**). Prolactin levels were negatively correlated with NLR (r=−0.208, **P<0.05**). • BMI levels of PCOS were positively correlated with WCC (r=0.789, **P=0.00**), neutrophil (r=0.741, **P=0.00**), lymphocyte (r=0.486, **P=0.00**) and MPV (r=0.236, **P=0.005**). BMI levels (PCOS) were negatively correlated with NLR (r=−0.203, **P=0.01**), and PLR (r=−0.321, **P=0.00**). • Total oocyte numbers were negatively related WCC (r=−0.210, **P=0.01**), neutrophil (r=−0.180, **P=0.03**). MII oocyte counts were negatively related to WCC (r=−0.236, **P=0.005**), neutrophil (r=−0.214, **P=0.01**), lymphocytes (r=−0.179, **P=0.03**). PLR was significantly positively correlated with miscarriage rates (r=0.185, **P<0.05**). MPV was negatively correlated with CPR (r=−0.513, **P<0.001**) and implantation rates (r=−0.470, **P<0.001**). • BMI was one of several independent risk factors for pregnancy rates in women with PCOS and controls.	NLR and PLR were significantly increased in all PCOS subjects vs. controls. PLR was significantly increased in NW-PCOS vs. control and OB-PCOS. MPV negatively associated with CPR independent of age, BMI and HOMA-IR, suggesting that inflammation may have a negative impact on IVF outcomes.

Author, Year (Study Type)	Study Population	Biomarkers	Outcomes	Results	Overall Conclusion
Becker et al., 2015[34] (RCT)	• Region: Brazil • N=26 overweight or obese infertile women • BMI >25–<30 kg/m^2 were included in the study only when their waist circumferences were >80 cm	• Lipid parameters • Glucose • Insulin • Leptin • Ghrelin	• body weight • BMI • percentage of body fat • glucose • insulin • homeostasis model assessment of insulin resistance • serum lipids • reproductive hormones • leptin • acylated ghrelin • no. of oocytes retrieved • pregnancy rate	• Greater ↓ in body mass, BMI, percentage of body fat, waist:hip ratio, hip circumference, and leptin in patients in the LGI-diet group (**P<0.05**). • *NS* - acylated ghrelin concentrations despite an 18% change in mean values. • The LGI-diet group had 85.4% more oocytes retrieved (**P=0.039**). Moderate negative correlation between the number of oocytes retrieved with BMI (r^2=-0.542, P=**0.020**), % body fat (r^2=-0.475, **P=0.040**), and leptin concentration (r^2=-0.515, **P=0.024**). CPR=21.4% (spontaneous pregnancy in 3/14 patients) in the LGI group, so LBR=100%. No pregnancies in the control group. • Caloric intake lower in the LGI-diet group, vs. no change in diet composition in the control group.	The hypocaloric LGI diet, despite the relative short time of the intervention and having started immediately before the IVF cycle, promoted a decrease in BMI, percentage of bodyfat, and leptin concentrations. It is possible that these effects improved the oocyte development and pregnancy rate in the intervention group.

day was associated with reduced mature (M1) oocyte yield and that BMI further influenced embryo quality, particularly of 8-cell quality B embryos. However, Mizrachi et al.[68] showed that although hCG levels on the day after trigger were inversely correlated with BMI, they did not influence any laboratory or clinical outcomes, and thus testing hCG levels after ovulation induction was not recommended. The association between anti-Müllerian hormone (AMH) levels on reproductive outcomes was assessed in 2 studies.[59,61] Komorowski et al.[59] observed that in women with infertility and PCOS, higher AMH levels were associated with reduced ovulation, and this was further influenced by higher BMI; however, AMH levels were not associated with pregnancy and live birth rates. Similarly, Melado Vilades et al.[61] found no differences in pregnancy or live birth rates across different AMH categories (<0.5 ng/ml, 0.5 to <1.3 ng/ml, 1.3–6.25 ng/ml, >6.25 ng/ml). However, obese patients had higher miscarriage risks and lower live birth rates, irrespective of AMH levels, suggesting BMI plays a more decisive role than AMH alone.

Two studies investigated the effect of inflammatory factors on ART outcomes in obese women, especially in those with PCOS. Zhang et al.[65] reported elevated levels of interleukin-18 (IL-18) in both follicular fluid and serum of obese and PCOS women, with positive correlations to oocyte count and negatively correlated to oocyte quality. Çakıroğlu et al.[70] observed that in women with PCOS, BMI was positively correlated with neutrophil and lymphocyte count, and mean platelet volume (MPV) while it was negatively correlated with platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR). Additionally, PLR correlated positively with miscarriage rate and MPV was negatively correlated with implantation and clinical pregnancy rates.

Chang et al.[67] reported that in maternal hyperhomocysteinemia, a metabolic disorder characterized by abnormally high homocysteine levels, the ovulation rate decreased, and the pregnancy loss rate in the second or third trimester increased, helping early prediction of adverse pregnancy outcomes.

DISCUSSION

To the best of our knowledge, this is the first comprehensive scoping review to consolidate findings published over the last decade regarding traditional and emerging treatment strategies and interventions for optimizing ART outcomes in overweight and obese women with fertility disorders and with or without comorbidities, including metabolic syndrome, PCOS, and GDM. This review of 50 studies evaluated various traditional weight loss strategies, adjunct therapies, and ART protocol modifications and assessed their impact on ART outcomes in overweight and obese women. In brief, bariatric surgery, weight management interventions with weight loss ⩾10% or >5 kg, micronutrient supplementation, especially in women with PCOS, and ovarian stimulation/ovulation induction and endometrial preparation with letrozole were associated with improved ART outcomes. During ovulation induction, obese women often required increased gonadotropin dosages and longer stimulation periods. Although these modifications did not necessarily lead to better outcomes, weight loss interventions reduced gonadotropin consumption and were associated with better ART outcomes. In addition, the review identified preconception and periconception biomarkers, such as differential levels of lipid parameters, reproductive hormones, and inflammatory markers in overweight and obese women versus women of normal weight, which may help predict the success of IVF treatment.

Based on recent systematic literature reviews and meta-analyses the impact of elevated BMI on ART outcomes in overweight/obese women remains unclear.[8,9,71,72] Recent evidence analyzed in this review demonstrates that short-term lifestyle interventions of 8 to 12 weeks improve ART outcomes, including the number of oocytes retrieved and clinical pregnancy and live birth rates.[28,33,34] Larger clinical studies (N=317–877) showed that weight-loss interventions resulted in significant weight loss, but did not necessarily improve ART outcomes.[24,29,32] However, it is important to highlight that 2 studies reported that a greater degree of weight loss (⩾10% or >5 kg) was associated with improved ART outcomes.[21,23] The study by Wu et al.[23] further demonstrated that a greater degree of weight loss (>5 kg vs. 0–5 kg) in obese women with PCOS was associated with significant changes in neuronal-reproductive-metabolic hormones, improved insulin sensitivity, and altered gene expression of follicular granulosa cells, thus providing mechanistic insights into the pathways through which greater weight loss improves fertility. Among women who underwent lifestyle intervention, pregnancy rates were significantly higher when patients were co-treated with a low-dose of liraglutide and metformin than in those treated with metformin alone.[27] Newer injectable glucagon-like peptide-1 receptor agonists (e.g., liraglutide and exenatide) show greater weight loss efficacy than older pharmacotherapies (e.g., orlistat), and also improve fertility outcomes in women[73]; however, these drugs must be used prior to IVF treatment initiation as they are contraindicated during pregnancy.[74] Consistent with the above findings, several clinical guidelines recommend weight loss before initiating IVF treatment[16,17] and guidelines and fertility programs in some countries state IVF treatment must be deferred until weight loss is achieved in patients whose BMI exceeds a certain threshold.[16,17,20] While long-term weight loss interventions involving bariatric surgery may improve pregnancy outcomes,[22,25,30,75] given the age-related decline in fertility and its impact on successful ART outcomes,[76] clinicians must weigh the benefits of a long-term weight loss intervention prior to IVF treatment versus immediate IVF treatment at an individual level, especially in older women.

Women who have undergone bariatric surgery may have long-term vitamin and mineral deficiencies and require additional preconception nutritional supplementation.[15,77] The current review demonstrated that in obese women, adjunct therapies such as micronutrient supplementation (e.g., vitamin B12, folate) helped improve insulin sensitivity and various IVF outcomes, including better oocyte

and embryo quality, and higher pregnancy and live birth rates.[36,37,39] In fact, per the best practice statement of the Royal Australian and New Zealand College of Obstetricians and Gynecologists, high-dose folate (5 mg) supplementation is recommended in obese women to decrease the risk of neural tube defects, while calcium and aspirin supplementation is recommended during early pregnancy through gestation to reduce the risk of pre-eclampsia.[77] These findings underscore the potential benefit of supplements in optimizing reproductive outcomes independent of weight loss.

Obesity in women is associated with lower ovarian responsiveness and technical difficulties during oocyte retrieval, including anesthesia- and procedure-related complications.[15,78] It is well known that during ovulation induction, obese women require a higher dose of gonadotropins and longer days of stimulation,[15] which was consistently observed across several studies[21,23,25,36,40,43-45,47,48]; however, these protocol modifications did not improve outcomes with respect to oocyte yield, embryo quality, and clinical pregnancy in some of these studies.[40,43-45,47,48] Furthermore, it must be noted that increasing gonadotropin dose and stimulation duration may increase the risk of OHSS in obese women and women with PCOS.[44,78] To minimize the risk of OHSS, Zeng et al.[78] recommended individualizing initial gonadotropin doses based on body weight. In addition, it was noted that weight lossamong overweight and obese women was associated with reduced gonadotropin consumption[21,23,25,30,46] and improved ART outcomes.[21,23,25] Furthermore, in a study evaluating rLH supplementation, it was observed that ovarian response was impacted more by the timing of rLH administration rather than the total dose, with the mid-to-late follicular phase considered the optimal window for administration.[49]

Among studies comparing ovarian stimulation and ovulation induction protocols, when compared with the conventional IVF stimulation protocol, findings by Zhang et al.[56] suggested that the mini-IVF protocol may result in more oocytes and MII oocytes in obese women. In addition, ovarian stimulation/ovulation induction or endometrial preparations with letrozole, alone or in combination with other stimulation protocols, appeared to be especially beneficial for improving several ART outcomes, including increasing follicular output, ovulation, and live birth rates, and reducing the risk of miscarriages.[41,50-54] Based on an abstract presentation at the 2005 Annual Meeting of the American Society for Reproductive Medicine, there were initial concerns regarding letrozole having an increased risk of congenital anomalies[79,80]; however, 2 large RCTs[81,82] and several observational studies[83-85] have since shown that there is no increased risk when compared with clomiphene or natural cycles. Letrozole, an aromatase inhibitor, is approved for the treatment of hormone receptor–positive breast cancer in postmenopausal women[86]; however, its use for ovulation induction in infertility treatment, remains off-label in many countries. Despite its increasing clinical application in ART, letrozole is not approved for infertility treatment and is contraindicated in premenopausal and pregnant women.[86] Therefore, its use in this context warrants careful ethical consideration, including informed patient consent and adherence to applicable regulatory and institutional guidelines. Any potential regulatory approval of letrozole for infertility indications would require robust clinical evidence demonstrating its safety, efficacy, and benefit–risk profile in this specific population.

Obese women and women with comorbidities, such as PCOS and metabolic syndrome, have dysregulated lipid parameters and reproductive hormones, and increased levels of inflammatory markers, which can influence IVF outcomes and the risk of GDM.[34,59-66,69,70] These findings not only provide mechanistic insights involved in obesity and reproduction but also act as preconception and periconception biomarkers that can help identify obese women at risk of adverse IVF outcomes.[87] In addition, Bollig et al.[57] observed that among couples planning to undergo IVF treatments, elevated LDL and TC levels in both partners and elevated LDL levels among males were associated with lower live birth rates. Although this review focuses on female obesity, emerging evidence highlights the need for couple-based approaches, as high male BMI can independently affect semen quality and IVF outcomes.[88-90] In addition, male obesity and diet can influence offspring health through transgenerational, molecular, and potential epigenetic mechanisms.[91] However, these adverse effects on sperm quality and ART success may improve with weight loss.[89] Therefore, it is recommended that clinicians consider assessing both partners when evaluating the risk of adverse IVF outcomes. Furthermore, future studies should evaluate and identify a panel of key biomarkers with clinical utility in aiding screening the likelihood of overweight/obese individuals having successful ART outcomes, as well as the predictive value of such biomarkers.

STRENGTHS AND LIMITATIONS

This scoping review synthesizes evidence from 50 studies published over the past decade, providing a comprehensive overview of current and emerging strategies aimed at achieving successful ART outcomes in overweight and obese women. Notably, the inclusion of a substantial number of observational studies (N=33) enhances the relevance of the findings to real-world clinical settings. However, several limitations should be acknowledged. The review was restricted to a single database, which may have limited the scope of the included literature. Additionally, some studies had small sample sizes, which may affect the robustness and generalizability of their findings. Considerable heterogeneity was observed across studies with respect to study populations, BMI classifications, ovarian stimulation or ovulation induction protocols utilized, and reported outcomes. Therefore, these aspects must be carefully considered when interpreting and comparing results across studies.

CONCLUSION

In conclusion, this review highlights the complex and multifaceted impact of obesity on ART outcomes, emphasizing that weight loss alone may not improve reproductive success. Adjunct therapies, including nutritional supplements, modifications to IVF protocols based on female BMI, and preconception and periconception biomarker-led approaches for early identification of at-risk women, show promise in optimizing IVF outcomes in overweight and obese women, particularly in those with comorbidities. Furthermore, the review underscores that given the lack of standardized guidelines, personalized medicine approaches during ART procedures are becoming increasingly important in this high-risk population.

COMPETING INTERESTS

GVD is the Chairman of Aksigen IVF Pvt. Ltd., India. SNP is a Consulting Clinical Director at Aksigen IVF Pvt. Ltd., India. All other authors declare no competing interests related to this article.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable

AI STATEMENT

We would like to confirm that we have not used any AI tools in preparing the manuscript. The literature search, screening, analyzing, writing, and formatting were all done manually.

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

AUTHORS' CONTRIBUTIONS

Conceptualization: GVD, GSD
Methodology/Search Strategy: GVD, NNP, AOM
Literature Review & Evidence Analysis: SNP, NNP
Writing – Original Draft Preparation: GVD, SNP, NNP
Writing – Review & Editing: GVD, SNP, GSD, NNP, AOM
Supervision & Strategic Direction: GSD, GVD, AOM
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