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Impact of Obesity on Live Birth among Women Undergoing IVF/ICSI: A Meta-Analysis

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In the past few decades a worldwide increase is observed in obesity prevalence among women of reproductive age group which may be linked with poor repriductive health outcomes moreover there is contradictory evidence about the effect of obesity on the live-birth following assisted reproducitve technology. To determine the pooled estimate of the association of female obesity with the probability of live birth outcome following in-vitro fertilzation/itractoplasmic sperm injection (IVF/ICSI). To evaluate the pooled effect of BMI on live birth as outcome following IVF/ICSI we carried this review. Platform PubMed, Google Scholar, Cochrane libraray and clinicaltrial.gov were used for literature searching since inception till March, 2020 to identify all the relevant studies. Differences in live births among underweight, normal weight, and overweight women incomparison to the obese group (BMI >30) were determined. For heterogenity >50% raandom-effects otherwise fixed-effects model was used to determine the pooled Risk ratio with 95% CI or pooled Odds Ratio with CI. Joanna Briggs Institute checklist (JBI) was used for methodological quality of the studies. Software STATA version 13, was used to conduct the statistical analysis p-value <0.05 was considered as degree of siginificant association. In the present meta-analysis thirty-two studies were included. Our finding suggests that women with obesity had 26% less live births as compared to women with normal BMI (OR, 0.74, 95% CI 0.69 to 0.78), 17% less live births compared to women with underweight (OR 0.83, 95% CI 0.80 to 0.85) and 14% less live births as compared to women with overweight (OR 0.86, 95% CI 0.83 to 0.88). The findings of present updated meta-analysis precisely demonstrated that female obesity is negatively associated with live birth rate following IVF/ICSI.

Keywords: IVF, BMI, obesity, infertility

Fertility is necessary part of reproduction and infertility condition is documented as a public health problem by world health organization (WHO). The 'failure to attain a pregnancy after 12 or >12 months of regular unprotected sexual intercourse' is defined as infertility (Zegers-Hochschild, 2019). According to WHO, every fourth couple in a developing country is affected with infertility whereas the prevalence of primary infertility in India varies from 3.9 and 16.8% (WHO, 2004).

Female cause of infertility is about 35% of couples in which they are unable to conceive, the remaining cause of infertility is male factor infertility in 30%, combination of both male and female factors in is 20%, and unexplained in around 15% (Healy, 1994). Despite its various social implications, the care and management of infertility remain highly neglected, especially in low- and middle-income countries. In recent years awareness has been increased for the prevention of infertility and its treatment.

Body mass index (BMI) is an important anthropometric and

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fact that it is a worlwide epidemic with high morbidity and mortality rates (NG, 2014). The impact of high BMI in women is evident throughout the period of reproductive age. It has been noted in the literature that overweight and obesity are associated with negative impact on the reproductive health outcome via manifestation of ovulatory disorders, impaired conception rates, dysfunctional uterine bleeding, higher early miscarriage rates, pregnancy complications (Practice Committee, 2015).

As per the WHO classification, BMI of "18.5 to 24.9 kg/m2 and 25 to 29.9 kg/m2" and ≥ 30 kg/m2 is considered as normal, overweight and obese respectively (Michael, 2003). Recent studies have shown that increased production of oxidative reactive oxygen species is an important factor for female reproduction. Reactive oxygen species may damage the oocyte and may impair the implantation and found to be associated with numerous developmental abnormalities and regarded as the one of the important reason for the spontaneous recurrent abortion. Success of IVF treatment is also impaired due to overproduction of the oxidative reactive oxygen species.

Many studies have shown the association of obesity with a higher risk of pregnancy complications (Linne, 2004; Catalano, 2006; Shirazian, 2009) and some have reported no adverse effect of raised BMI on the ART outcomes (Lashen, 1999; Martinuzzi, 2008; Dechaud, 2006). Due to the scarcity of robust evidence, weight reduction measures are not being rigorously practiced in many fertility centers across the globe. The present systematic review and meta-analysis aim to determine the relationship of High BMI with the likelyhood of live birth outcome after IVF/ICSI.

Hypothesis of the study

Hypothesis: High BMI is negatively associated with a live birth in women undergoing IVF/ICSI treatment

Research question

Patient: Patients with Infertility undergoing IVF/ICSI

Exposure: BMI categories per WHO classification

Comparison: Women with obesity (BMI>30) considered as the reference category

Outcome: Live births

Method

Search strategy

Search engines including Medline, PubMed, Google Scholar, Cochrane Library, clincialtrial.gov from inception till March 2020 were used to identify all relevant studies. The following keywords were applied"Obesity" OR "body mass index" OR "overweight" OR "BMI" AND "live births" OR "IVF" OR "in-vitro fertilization". Manual searches of the references list of the retrieved articles and pertinent reviews were also conducted. Our search and article review were restricted to articles reported in English language.

Inclusion criteria

- Studies investigating the effect of BMI on pregnancy outcome as live birth, among women undergoing IVF treatment with or without ICSI.
- Studies reporting the event and total cases of live birth.

Exclusion criteria

- Review, Meta-analysis, case report, or case series.
- Studies conducted on animals.
- Multiple reports from the same study in which earlier reports were excluded.
- Studies involving surrogacy.
- Articles published in language other than English

Instrument

JBI Scale was used for the quality assessment of the studies. This tool considers "(Q1Were the criteria for inclusion in the sample clearly defined?" "Q2Were the study subjects and the setting described in detail?" "Q3Was the exposure measured in a valid and reliable way?" "Q4Were objective standard criteria used for measurement of the condition?" "Q5Were confounding factors identified?" "Q6Were strategies to deal with confounding factors stated?" "Q7Were the outcomes measured in a valid and reliable way?" "Q8Was appropriate statistical analysis used?);"

Data were extracted by two independent authors (DR & SG) about the study selection, screening, data extraction in standardized data extraction form. The risk of bias level was recorded for each critical appraisal question instead of using a cut off to determine methodological quality. The influence of each type of risk of bias for the same outcome was explored during the meta-analysis. Any disagreement or inconsistencies were resolved after discussion with another review (AK).

Statistical analyses

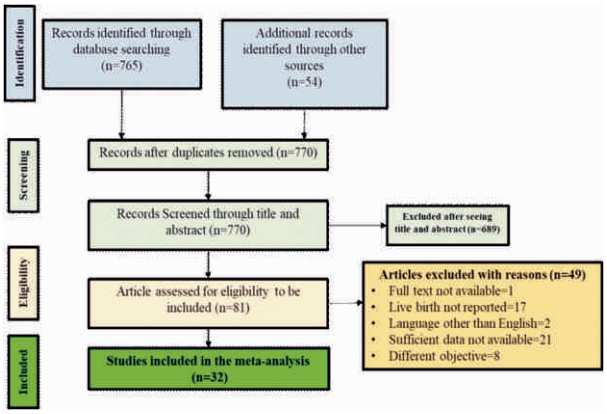
For heterogenity >50% random-effects otherwise fixed-effects model was used to determine the pooled Risk ratio with 95% CI or pooled Odds Ratio with CI. P value of less than 0.05 was considered statistically significant. Publication bias was assessed using a funnel plot, Begg, and egger's tests. All the statistical analyses were done using software STATA version 13.

Results

The flowchart for the selection of relevant studies is explained in Figure 1. A total of 765 articles were identified initially in addition of 54 via manual searching. After screening of title and abstracts followed by full text assessment (n=81), a total of 32 articles were included in the present meta-analysis (Figure 1).

Figure 1

Study flow diagram



Characteristics of included studies

Thirty-two studies were included in the meta-analysis. Among all included studies fourteen were from the USA (Bailey, 2014; Chavarro, 2012; Insogna, 2017; Kawwass, 2016; McCormick, 2008;

Pinborg, 2011; Provost, 2016; Provosot, 2016; Russo, 2017; Schliep, 2015; Sneed, 2008; Coyne, 2016; Jungheim, 2009; Zhang, 2015); three from China (Cai, 2017; Qiu, 2019; Zhang, 2010); two from Spain (Bellver, 2013; Bellver, 2010); two from Norway (Fedorcsak, 2000; Fedorcsak, 2004); two from France (Caillon, 2015; Sifer, 2014); one from Australia (Zander-Fox, 2012); one from theUK (Rittenberg 2011), one from Thailand (Wattanakumtornkul, 2003); one from Brazil (Vilarino, 2011); two from Israel (Friedler, 2017; Frahi, 2010); one from Turkey (Ding, 2019); one from Lithuania (Amsiejiene, 2017) and one from India (Sharma, 2014) (Table 1).

Table 1
Characteristics of study included in the meta-analysis

First Author and Year	Country	Sample Size	Study Design	Intervention (IVF/ICSI/ Both)	Cycle Rank	Oocyte cycle (Autologous/ Donor)	PCOS/ Non-PCOS	Embryo transfer type
Fedorcsak (2004)	Norway	2660	Cross-sectional	Both	All	Autologous	Both	Fresh
Bailey (2014)	USA	79	Retrospective cohort	Both	All	Autologous	PCOS	Fresh
Bellver (2010)	Spain	4227	Cross-sectional	Both	All	Autologous	Not Specified	Fresh
Bellver (2013)	Spain	9587	Retrospective cohort	Both	First	Donor	Not Specified	Both
Chavarro (2012)	USA	170	Prospective Cohort	Both	All	Autologous	Both	Fresh
Insogna (2017)	USA	461	Retrospective cohort	Both	First	Both	Both	Frozen thawed
Kawwass (2016)	USA	494097	Retrospective cohort	IVF	All	Autologous	Not Specified	Fresh
McCormick (2008)	USA	86	Cross-sectional	Both	All	Autologous	PCOS	Fresh
Pinborg (2011)	USA	487	Prospective Cohort	Both	All	Both	Not Specified	Both
Provost (2016a)	USA	Not Specified	Retrospective cohort	IVF	All	Donor	Not Specified	Fresh
Provost (2016b)	USA	Not Specified	Retrospective cohort	IVF	All	Autologous	Both	Fresh
Russo (2017)	USA	520	Cross-sectional	IVF	First	Autologous	Both	Both
Schliep (2014)	USA	721	Prospective Cohort	Both	First	Not Specified	Not Specified	Fresh
Sharma (2014)	India	500	Prospective Cohort	Both	Not Specified	Autologous	Not Specified	Fresh
Sneed (2008)	USA	1273	Cross-sectional	IVF	First	Autologous	Both	Fresh
Sifer (2014)	France	409	Cross-sectional	Both	All	Not Specified	Not Specified	Fresh
Zander-FOX (2012)	Australia	Not Specified	Cross-sectional	Both	All	Autologous	Not Specified	Fresh
Zhang (2010)	China	2628	Retrospective cohort	Both	First	Not Specified	Both	Fresh
Zhang (2015)	USA	439	Prospective Cohort	Both	First	Autologous	Not Specified	Fresh
Fedorcsak (2000)	Norway	383	Retrospective cohort	Both	First	Not Specified	Not Specified	Not Specified
Wattanakumtornkul (2003)	Thailand	96	Retrospective cohort	Both	First	Donor	Not Specified	Frozen
Vilarino (2011)	Brazil	191	Cross-sectional	Both	All	Autologous	Not Specified	Fresh
Farhi (2010)	Israel	233	Prospective Cohort	IVF	First	Not Specified	Both	not specified
Rittenberg (2011)	UK	413	Prospective Cohort	Both	All	Autologous	Both	Fresh and cryo thawed
Cai (2016)	China	4401	Retrospective cohort	Both	All	Autologous	Both	Fresh
Caillon (2015)	France	582	Cross-sectional	IVF	Not Specified	Not Specified	Both	Not Specified
Qiu (2019)	China	2587	Retrospective cohort	Both	First	Autologous	PCOS	Frozen
Ding (2019)	Turkey	9772	Cross-sectional	Both	First	Autologous	Both	Fresh
Amsiejiene (2017)	Lithuania	1133	Cross-sectional	Both	first	Autologous	Not Specified	Fresh
Friedler (2017)	Israel	Not Specified	Cross-sectional	Both	All	Autologous	Not Specified	Fresh
Coyne (2015)	USA	163	Cross-sectional	IVF	All	Both	Non PCOS	Fresh
Jungheim (2009)	USA	72	Retrospective cohort	Both	First	Autologous	PCOS	Fresh

Note: IVF-In-vitro fertilization; PCOS-Polycystic ovary syndrome

Among all studies, twenty had autologous oocyte cycle (Bailey, 2014; Chavarro, 2012; Kawwass, 2016; McCormick, 2008; Provost, 2016; Russo, 2017; Schliep, 2015; Sneed, 2008; Jungheim, 2009; Zhang, 2015; Qui, 2019; Bellver, 2010; Fedorcsak, 2000; Zander-Fox, 2012; Rittenberg, 2011; Vilarino, 2011; Friedler, 2017; Ding, 2019; Amsiejiene, 2017; Sharma, 2014); three had donor oocyte cycle (Provost, 2016; Bellver, 2013; Wattanakumtornkul, 2003); three had both (Insogna, 2017; Pinborg, 2011; Coyne, 2016); however, for rest it was not specified in the respective study. Sixteen studies were done among all cycle rank (Bailey, 2014; Chavarro, 2012; Kawwass, 2016; McCormick, 2008; Pinborg, 2011; Provos,t 2016; Provost, 2016; Coyne, 2016; Cai, 2017; Bellver, 2010, Fedorcsak, 2004; Sifer, 2014; Zander-fox, 2012; Rittenberg, 2011; Vilarino, 2011; Friedler, 2017), fourteen from first cycle (Insogna 2017; Russo 2017; Schliep 2015; Sneed, 2008; Jungheim, 2009; Jhang, 2015; Qiu, 2019; Zhang, 2010; Bellver, 2013; Fedorcsak, 2000; Wattanakumtornkul, 2003; Farhi, 2010; Ding, 2019; Amsiejiene, 2017) and two were not specified (Caillon, 2015; Sharma, 2014) (Table 1).

Twenty-two studies were done using fresh embryo transfer (bailey, 2014; Chavarro, 2012; Kawwass, 2016; McCormick, 2008; Provost, 2016; Provost, 2016; Schliep, 2015; Sneed, 2008; Coyne, 2016; Jungheim, 2009; Zhang, 2015; Cai, 2017; Zhang, 2010; Bellver ,

2010; Fedorcsak, 2004; Sifer, 2014; Zander-Fox, 2012; Vilarino, 2011; Friedler, 2017; Ding, 2019; Amsiejiene, 2017; Sahrma, 2014); two using frozen embryo transfer (Qui, 2019; Wattanakumtornkul, 2003); one from frozen thawed (Insogna, 2017); one from frozen cryo-thawed (Rittenberg, 2011); three among both (Pinborg, 2011; Russo, 2017; Bellver, 2013) (Table 1).

Among all thirty-two studies four were done among PCOS (Bailey, 2014; McCormick, 2008; Jungheim, 2009; Qiu, 2019); one in Non-PCOS (Coyne, 2016); twelve among both (PCOS/Non-PCOS) (Chavarro, 2012; Insogna, 2017; Provost, 2016; Russo, 2017; Sneed, 2008; Cai, 2017; Zhang, 2010; Fedorcsak, 2004; Caillon, 2015; Rittenberg, 2011; Farhi, 2010; Ding, 2019) and rest 15 were not specified.

Meta-analysis findings

Our finding suggests that women with obesity had 26% less live births as compared to women with normal BMI (OR, 0.74, 95% CI 0.69 to 0.78) figure: 2, 17% less live births compared to women with underweight (OR 0.83, 95% CI 0.80 to 0.85) figure:3 and 10% less live births as compared to women with overweight (OR 0.86, 95% CI 0.83 to 0.88) figure:4.

Figure 2

Comparsion with obesity vs normal weight

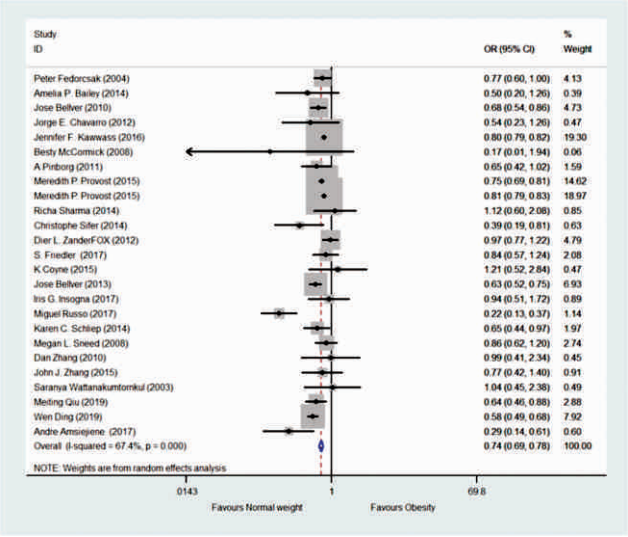


Figure 3

Comparsion with obesity vs underweight

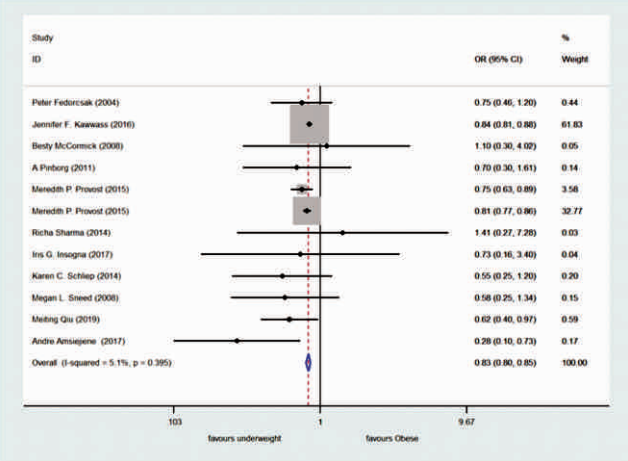


Figure 4

Comparsion between obsesity vs overweight

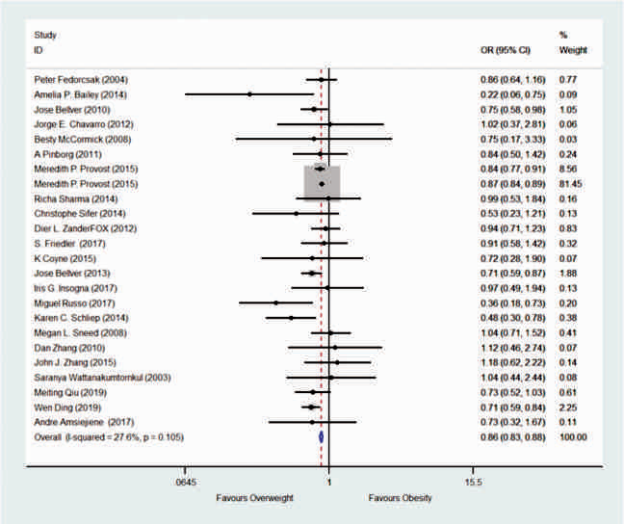


Figure 5

Stratified analysis for cross sectional studies for underweight BMI category

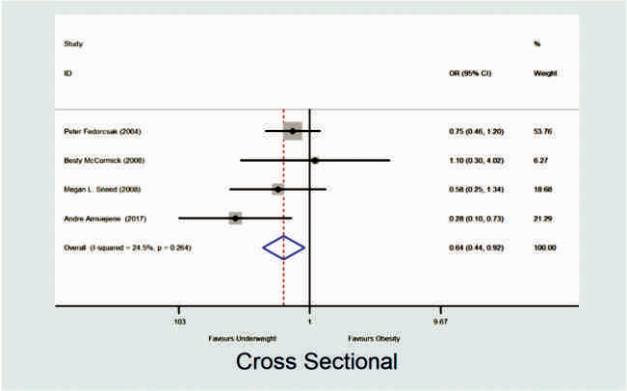
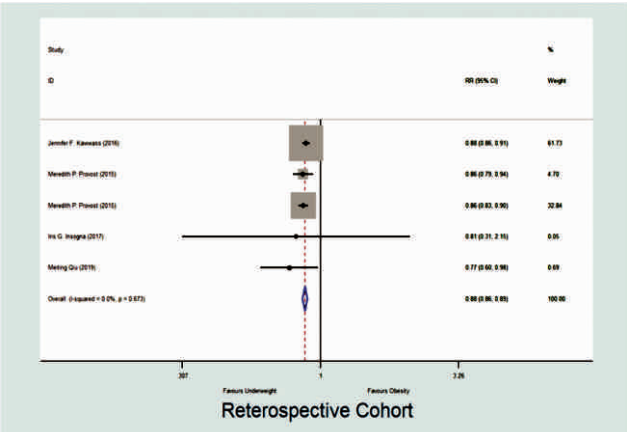


Figure 6

Stratified analysis for retrospective studies for underweight BMI category



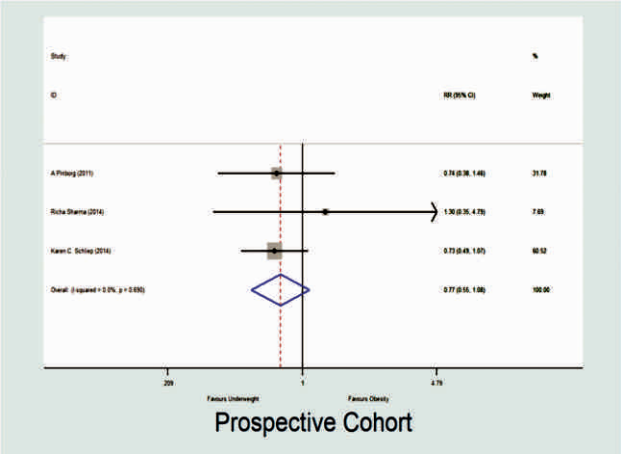
Stratified analysis as per study design: Our stratified data analysis according to study design suggested the following:

Underweight: We observed that four cross-sectional studies reported the data to compute the pooled effect size for comparison

underweight vs overweight. Our pooled analysis suggested that women with BMI>30 (Obese) are 36% less likely to give live births post ART as compared to underweight (OR 0.64, 95% CI: 0.44 to 0.92) (Fig:5). A meta-analysis based on retrospective cohort study design observed women with BMI >30 (Obese) are 12% (statistically significantly) less likely to give live births post ART as compared to underweight (RR 0.88, 95% CI: 0.86 to 0.89) (Fig:6). Pooled analysis including prospective cohort studies did not detect a statistically significant difference in live birth outcomes between obese and underweight women undergoing IVF/ICSI (RR 0.77, 95% CI: 0.55 to 1.08) (Fig:7).

Figure 7

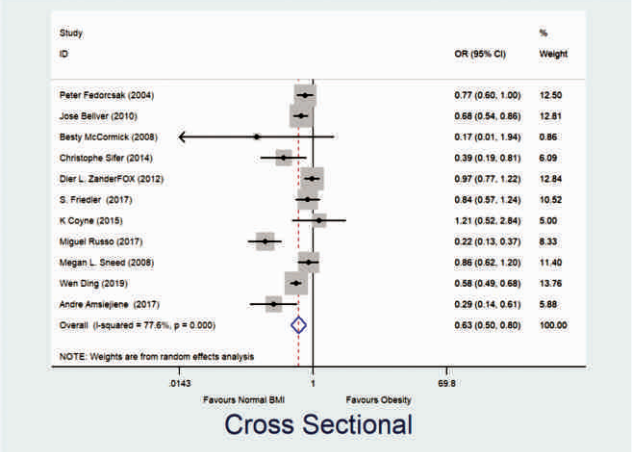
Stratified analysis for prospective studies for underweight BMI category



Normal BMI: A total of 11 cross-sectional studies reported sufficient data to determine the pooled effect size for comparison between Obesity and Normal BMI for outcome live births. We used the random-effect model due to the presence of significant heterogeneity. Our meta-analysis including cross-sectional studies suggested 37% less live birth outcomes in women with obesity compared to women with normal BMI (OR 0.63, 95% CI: 0.50 to 0.80) (Fig:8). A meta-analysis based on nine retrospective cohort study design observed 15% less live births in women with obese

Figure 8

Stratified analysis for cross sectional studies for Normal BMI category



compared to normal-weight women (RR 0.85, 95% CI: 0.85 to 0.86) (Fig. 9). Stratified analysis including five prospective cohort studies observed 19% (statistically significant) less live births in women with obesity compared to normal-weight women undergoing IVF/ICSI (RR 0.81, 95% CI: 0.69 to 0.94) (Fig:10).

Figure 9

Stratified analysis for retrospective cohort studies for Normal BMI category

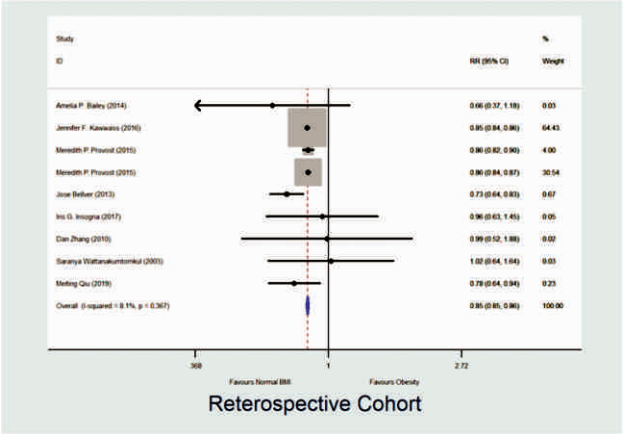


Figure 10

Stratified analysis for prospective studies for Normal BMI category

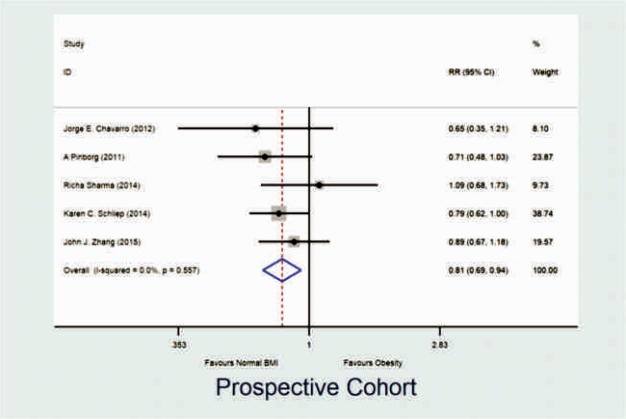
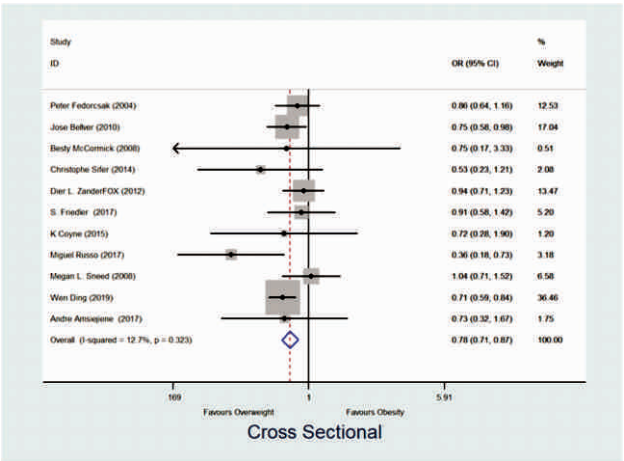


Figure 11

Stratified analysis for cross-sectional studies for overweight BMI category



Overweight: A total of 11 cross-sectional studies reported sufficient data to determine the pooled effect size for outcome live births for comparison between obese women and normal-weight women. Our meta-analysis noticed 22% (statistically significant) less live births in women with obesity compared to the overweight BMI category (OR 0.78, 95% CI 0.71 to 0.87) (Fig:11). A meta-analysis including eight retrospective cohort studies suggested that women in obese BMI category were 10% less likely to give live birth compared to women who were overweight (RR 0.90, 95% CI 0.89 to 0.92) (Fig:12), however, a meta-analysis including five prospective cohort studies did not observe a statistically significant difference in live births between obese women and overweight women for the outcome, live births (RR 0.86, 95% CI 0.73 to 1.01) (Fig:13).

Figure 12

Stratified analysis for retrospective cohortstudies for overweight BMI category

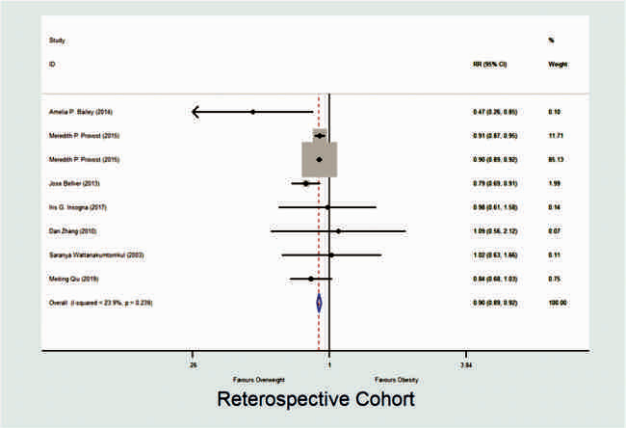
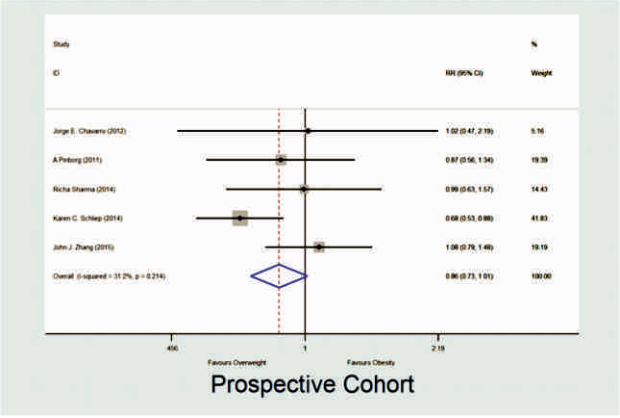


Figure 13

Stratified analysis for prospective studies for overweight BMI category



Significant publication bias was observed for comparison between underweight and obesity as evident by the asymmetry in the funnel plot (Figure 14), which further confirmed by (Egger test p-value = 0.041). Significant publication bias was also noticed for the pooled comparison of normal weight with obesity evident by the asymmetry in the funnel plot (Figure 15) which is confirmed by the (Egger's test p = 0.019). No statistically significant publication bias in the pooled analysis of the comparison between overweight and obsese group was noticed in the funnel plot (Figure 16) and also confirmed by the Egger's test p = 0.065.

Figure 14

Funnel plot showing publication bias in the study for BMI underweight category

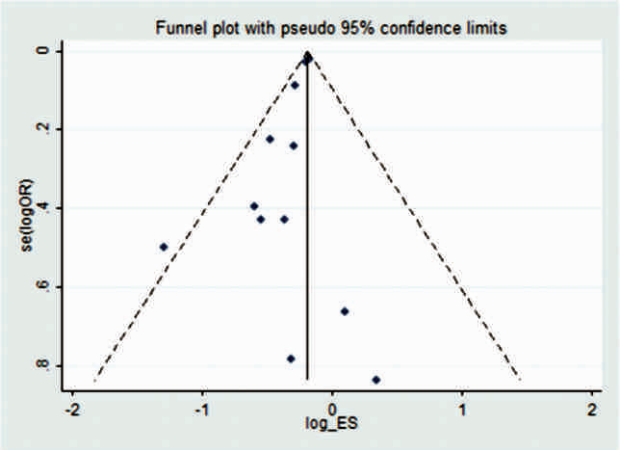


Figure 15

Funnel plot showing publication bias in the study for BMI Normal weight category

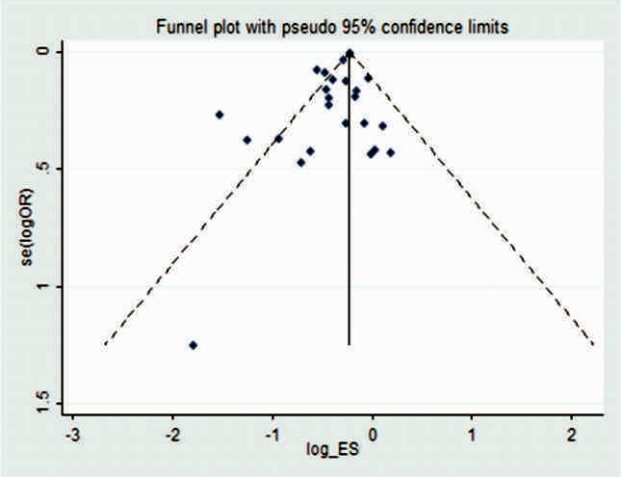


Figure 16

Funnel plot showing publication bias in the study for BMI overweight category

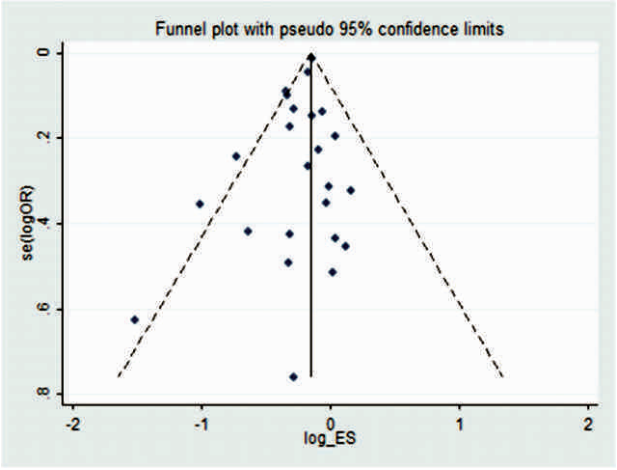


Table 2
Risk of bias of the selected studies by JBI-MAStARI for cross-sectional studies

First Author	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Yes Score (_/8)
Fedorcsak	2004	N	Y	Y	Y	Y	Y	Y	Y	7/8
Bellver	2010	N	Y	U	Y	Y	N	Y	N	4/8
McCormick	2008	Y	Y	U	Y	N	N	Y	N	4/8
Russo	2017	Y	NA	U	Y	Y	Y	Y	N	5/8
Sneed	2008	Y	Y	N	Y	Y	Y	Y	Y	7/8
Sifer	2014	Y	Y	U	Y	Y	Y	Y	Y	7/8
Zander-FOX	2012	Y	Y	U	Y	Y	N	Y	N	5/8
Vilarino	2011	Y	Y	U	Y	N	N	Y	N	4/8
Caillon	2015	N	Y	U	Y	Y	N	Y	N	4/8
Ding	2019	Y	Y	U	Y	Y	Y	Y	Y	7/8
Amsiejiene	2017	N	N	U	Y	N	N	Y	N	2/8
Friedler	2017	N	Y	U	Y	Y	Y	Y	Y	6/8
Coyne	2015	N	Y	U	Y	Y	N	Y	N	4/8

Note: This tool considers (Q1-Were the criteria for inclusion in the sample clearly defined? Q2-Were the study subjects and the setting described in detail? Q3-Was the exposure measured in a valid and reliable way? Q4-Were objective standard criteria used for the measurement of the condition? Q5-Were confounding factors identified? Q6-Were strategies to deal with confounding factors stated? Q7-Were the outcomes measured in a valid and reliable way? Q8-Was appropriate statistical analysis used?); Code: Yes=Y; No.=N; Unclear=U; Not applicable=NA

The methodological quality of the study

Cross-sectional study

- *For inclusion of sample clearly defined:* Among all 13 studies we rated 46% (6/13) at high risk of bias and 54% (7/13) at low risk of bias.
- *For study settings and subjects:* we rated 85% (11/13) at low risk of bias as clear information about the study setting was described.
- For question exposure measured validly and reliably, we rated 85% (11/13) as insufficient information was available to judge.

Table 3
Risk of bias of the selected studies by JBI-MAStARI for cohort studies

First Author	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Yes Score (_/11)
Bailey	2014	U	Y	U	Y	Y	Y	Y	Y	Y	NA	Y	8/11
Bellver	2013	Y	Y	U	Y	N	Y	Y	Y	Y	NA	Y	8/11
Chavarro	2012	Y	Y	U	Y	Y	Y	Y	Y	Y	NA	Y	9/11
Insogna	2017	N	Y	U	Y	Y	Y	Y	Y	Y	NA	Y	8/11
Kawwass	2016	N	Y	N	Y	Y	Y	Y	Y	Y	NA	N	7/11
Pinborg	2011	Y	Y	U	Y	Y	Y	Y	Y	Y	NA	Y	9/11
Provost	2016a	Y	Y	U	Y	Y	Y	Y	Y	Y	NA	Y	9/11
Provost	2016b	N	Y	U	Y	Y	Y	Y	Y	Y	NA	Y	8/11
Schliep	2014	Y	Y	U	Y	Y	Y	Y	Y	Y	NA	Y	9/11
Sharma	2014	Y	Y	U	Y	Y	Y	Y	Y	Y	NA	N	8/11
Zhang	2010	Y	Y	U	Y	Y	Y	Y	Y	Y	NA	N	8/11
Zhang	2015	Y	Y	U	Y	Y	Y	Y	Y	Y	NA	Y	9/11
Fedorcsak	2000	Y	Y	U	Y	N	Y	Y	Y	Y	NA	Y	8/11
Wattanakumtornkul	2003	U	Y	U	Y	Y	Y	Y	Y	Y	NA	Y	8/11
Farhi	2010	N	Y	U	Y	Y	Y	Y	Y	Y	NA	Y	8/11
Rittenberg	2011	Y	Y	U	Y	Y	Y	Y	Y	Y	NA	Y	9/11
Cai	2016	Y	Y	U	Y	Y	Y	Y	Y	Y	NA	Y	9/11
Qiu	2019	Y	Y	U	Y	Y	Y	Y	Y	Y	NA	N	8/11
Jungheim	2009	N	Y	U	Y	N	Y	Y	Y	Y	NA	N	6/11

Note: This tool considers (Q1-Were the two groups similar and recruited from the same population? Q2-Were the exposures measured similarly to assign people to both exposed and unexposed groups? Q3- Was the exposure measured in a valid and reliable way? Q4-Were confounding factors identified? Q5-Were strategies to deal with confounding factors stated? Q6-Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? Q7-Were the outcomes measured in a valid and reliable way? Q8-Was the follow-up time reported and sufficient to be long enough for outcomes to occur? Q9-Was follow-up complete, and if not, were the reasons to loss to follow up described and explored? Q10-Were strategies to address incomplete follow up utilized? Q11-Was appropriate statistical analysis used?) Code: Yes=Y; No.=N; Unclear=U; Not applicable=NA

- We rated all 13 studies at low risk for bias they all have used the objective, standard criteria of the condition.
- For the item confounding factors were identified we rated 77% (10/13) at low risk and 23% (3/10) at high risk of bias.
- However, among all 54% (7/13) were rated at high risk of bias because strategies to deal with confounding factors were not stated.
- We rated all studies at low risk of bias for the question if the outcome was measured validly and reliably.
- For the question appropriate statistical analysis used 62% (8/13) were rated at high risk of bias and 38% (5/13) at low risk of bias due to appropriate statistical analysis was used.

Cohort

- *Similarity among groups:* We rated 63% (12/19) studies at low risk of bias and 26% (5/19) studies at high risk of bias and 11% (2/19) studies were declared as unclear risk of bias due to insufficient information to judge.
- *Similarity of exposure assigned both the group:* We rated all the studies at low risk of bias.
- *Validity of exposure measurement:* Most of the studies that is 95% (18/19) were classified at an unclear risk of the bias due to insufficient information to judge regarding the validity of exposure measurement.
- *Confounder factor:* All studies were judged at low of bias, due to the identification of confounders in their study.
- Strategies to deal confounders: We rated 84% (16/19) studies at low risk of bias because the strategies to deal with the confounding effect was stated.
- *Outcome at the moment of exposure:* All studies were at low risk of bias because all were free from the exposure at the beginning of the exposure measurement.
- *Outcome measure:* All studies were at low risk of bias because all outcome was measured validly.
- *Follow up time:* All studies were classified at low risk of bias because sufficient time was mentioned for the outcome to occur.
- *Lost to follow up:* All studies were rated as low risk of bias because of lost to follow up was less than 10%,
- *Strategies for lost to follow up:* As there were no significant lost to follow up hence this item was classified as not applicable.
- *Statistical analysis:* 74% (14/19) studies were judged at low risk of bias and 26% (5/19) at high risk of bias, as the statistical analysis method was not mentioned.

Discussion

The present meta-analysis includes, a total of 32 studies with live birth as our main objective concluding that obese women had 20% less live birthrate as compared to normal BMI (Figure 2) and 17% less live birth ratecompared to women with underweight (Figure 3). When the women with obesity were compared to women with overweight BMI categories (Figure 4), we observed 10% less live birth in the obese women compared to overweight. A meta-analysis published by Sermondade et al. has also observed the similar association which included 21 studies considering live birth as their primary outcome. The review has shown decreased probability of live birth following IVF in obese women when compared to normal weight (RR= 0.85). Our updatd meta-analysis including a total of 32 studies strengthen the evidence associated with negative relationship of obesity with live births.

Previous meta-analyses also considered live birth as secondary outcome which also observed lower chance of clinical pregnancy and live birth in women who were obese (Jungheim, 2009).

Adipose tissue is an endocrine organ that is found to be associated with several adipokines, including leptin, tumor necrosis factor alpha and other proinflammatory markers (McGown, 2014). There are greater probability that obese women have lower level of anti-inflammatory protein adiponectin which promotes the hyperlipidemia and glucose intolerance (Ziemke, 2010) Obese women have higher level of leptin in the follicular fluid and Leptin has been found to be associated with dose dependent decrease in the estrogen and progesterone production thereby effecting the oocyte development and embryo quality (Lin, 2009; Greisen, 2000). High BMI has been found to be associated with delayed conception in a dose response gradient manner (Law, 2007). High BMI is associated with anovulation, which isfurther related to menstrual irregularity, impairment of oocyte development.

Obesity may be associated with impaired embryonic development and altered uterine environment, thereby explaining the poorer reproductive outcome in obese women. However, detailed information regarding the mechanism of association still remains unclear. The poposed mechanism for negative impact of obesity in disruption in fertility may be linked with poor Oocyte quality, disruption in pre-implantation embryo quality, improper placental or embryonic health. Evidence for involvement of increased reactive oxygen species in the obese women which may be associated with DNA damage in case of infertility. Oocyte quality is crucial for the proper conception and subsequent fertility outcome. The oocyte is surrounded by the follicular fluid and granulosa cells throughout oocyte maturation. A study showed that there is alteration of the follicular fluid composition in women with obesity, 51 thereby explaining the probable mechanism of poor oocyte development and oocyte quality in women with obesity. It has also been observed that blastocyst development is impaired in obese women.

Our study observed the dose-response relationship for the association of obesity with poor outcome in women with obesity strengthening the precise information about dose and effect relationship. Our updated meta-analysis has selected the live birthrate as an outcome as it represent the gold standard for assessment of IVF outcomes, by avoiding the variation in the definition used for the pregnancy rate. The uniform definition of BMI classified by the World Health Organization is used in our study further providing the homogeneity in the exposure measurement for the precise estimation of effect size.

The International fertility society has also recommended informing the obese women of their complications and decreasing the change of pregnancy following IVF. Some of the International society does not recommend IVF procedures in the condition of morbid obesity (BMI>35 kg/m3) Ranzcog, 2020). The evidence about the weight loss program along with fertility drugs to improve the pregnancy outcome is still not clear, however, studies have shown that there is clear evidence that weight loss program has been positively associated with improved natural fertility (Legro, 2016).

Limitations of the study

Many confounding factors that influence the fertility outcome

following IVF could not be included in the present study. Studies have shown that Age, types of embryo transfer, parity and obstetric history, and smoking status could be important confounders for the exposure and outcome relationship. There are a majority of papers included in the current meta-analysis with the autologous vs donor cycle being unknown; as maternal age often affects this decision and could also affect the live birth rates, it is important to further assess the impact of this unknown.

Conclusion

The findings of present updated meta-analysis precisely demonstrated that female obesity is negatively associated with live birth rate following IVF/ICSI. Future studies focusing on biological basis for these findings would be promising. The future research should focus on conducting randomized controlled trial to explore whether rigourous weight reduction program helps in improvement of fertility outcomes.

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