## **Original Article**

## Economic perspective of evaluating fertility treatment in obese and overweight infertile women

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## **ABSTRACT**

الأهداف: لتقييم التكلفة المباشرة لدورة الإخصاب في المختبر/ حقن النطفة داخل الهيولي (IVF/ICSI) ونتائج الإنجاب بين النساء المصابات بالعقم مع مؤشر كتلة الجسم المختلفة (BMI).

النتائج: لم يكن هناك فرق ذو دلالة إحصائية لمعدل المواليد الأحياء ( LBR ) بين مجموعات مؤشر كتلة الجسم، مع حدوث LBR في 22 امرأة مع مؤشر كتلة الجسم الطبيعي ( 13.1%)، في 48 ( 14.2%) النساء اللائي يعانين من زيادة الوزن، في 48 ( 14.2%) عند النساء المصابات بالسمنة ( 14.2%). لم تختلف التكلفة المتوسطة لدورة علاج أطفال الأنابيب / الحقن المجهري عبر مجموعات مؤشر كتلة الجسم؛ كانت التكلفة 10.3%0 ريال سعودي للنساء ذوات الوزن الطبيعي، 10.4%0 ريال سعودي للنساء ذوات الوزن الوائد والسمنة ( 10.4%0).

الخلاصة: تشير نتائجنا إلى أن تكاليف التلقيح الاصطناعي / الحقن المجهري لا تتأثر بشكل كبير لدى النساء اللواتي يعانين من زيادة الوزن أو السمنة.

Objectives: To evaluate direct cost of in-vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) cycle and reproductive outcomes among infertile women with different body mass index (BMI).

Methods: A retrospective study of 826 subfertility patients who had IVF or IVF-ICSI in 2017 to 2018 were reviewed. The patients were divided into 4 groups bestowing to BMI to normal weight (18.5-24.9 kg/m²), underweight (<18.5 kg/m²), overweight(25-29.9 kg/m²), and obese(≥30 kg/m²). Data on treatment costs of IVF/ICSI and reproductive outcomes were collected and analyzed. A total of 338 patients (40.9%) were overweight, and 300 (36.3%) patients were obese. A bottom-up methodology was used to measure the resource utilization. The

capital inputs needed for individual procedures were defined and calculated by consulting with appropriate clinicians and priced using market prices for 2017-2018.

Results: There was no statistical significant difference for live birth rate (LBR) among the BMI groups, with the occurrence of LBR in 23 women with normal BMI (13.1%), in 48 (14.2%) women who were overweight, in 48 (16%) in women who were obese (p=0.7). The median cost for IVF/ICSI treatment cycle did not differ across BMI groups; the cost was 10,380 SAR for women of normal weight, 10,440 SAR for women who are overweight and obese (p=0.6).

Conclusion: Our results suggest that costs of IVF/IVF-ICSI is not significantly affected in women who are overweight or obese.

Keywords: overweight, obesity, cost, BMI, IVF

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Excess body weight is related to adverse effects on survival, disability free life years, quality of life, and productivity. The higher the percentage of population that is overweight and obese, the higher the demand for health care, and the higher medical costs for obesity-related diseases. A statistical analysis of the direct healthcare effects of obesity found that it accounts for



2.8% of healthcare spending accounted and infertility related increase in cost burden.<sup>2-4</sup> Recent US data, reported that obese patients pay 46% higher hospital costs, 27% higher doctor visits and the outpatient costs, and 80% amplified spending on prescription of the drugs compared to people with normal body weight.5 Globally, the prevalence of obesity is increasing from 5% in the developing nations to 30% in the developed nations. In the Kingdom of Saudi Arabia, prevalence of obesity is 35.5%.7 Given its global influence, it is a need to have a common universal norm. Although there are recommendations that one's waist-hip ratio corresponds better than the body mass index (BMI), with fitness and fertility, the latter is more commonly used. The World Health Organization (WHO) concept were followed in this study; people with BMI ≥25 kg/m<sup>2</sup> are overweight; those with BMI  $\geq 30 \text{ kg/m}^2$  are obese.<sup>8</sup>

Infertility which is defined as inability to get pregnant after more than 12 months of unprotected sexual activity, affects 1 in 7 couples worldwide. Obesity leads to disturbances in the hypothalamic pituitary ovarian axis leading to anovulation and infertility. Unexplained infertility and ovulatory defects account for >50% of infertile causes; a large percentage of which are directly or indirectly related to obesity. Decifically, obesity is associated with anovulation, infertility, miscarriage, poor pregnancy and neonatal outcomes. Thus, short and long-term management of such patients is challenging because of the synergistic adverse effects of infertility and obesity.

In-vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) is a well-established therapeutic choice, representing major economic and health effects for individuals, society and healthcare providers that can be primary costs and indirect costs.<sup>13</sup> Direct expenses include medical sessions, medications for ovulation stimulation, testing, embryology services, ultrasound screening, treatments such as oocyte pick up, embryo transfer, hospital bills, and administrative and overhead bills for nursing and therapy services. Therefore, relative to multiple groups of obesity and its effect on pregnancy and live birth rates, we decided to quantify the cost of the IVF/ICSI cycle. The main objective of the analysis is to compare between various BMI groups the cost of IVF/ICSI, and reproductive outcomes.

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**Methods.** After the conceptualization of idea, the literature search was carried out by using MeSH terms involving the search engines that include Pubmed, Medline, google scholar and open literature. Related research work was then analyzed to find out extent of research carried out on this topic. Relevant papers were screened and added for discussion. A retrospective chart review was conducted between January 2017 and December 2018 at the infertility center of King Fahad Medical City (KFMC) after taking institutional review board approval and according to principles of Helsinki Declaration. The inclusion criteria were all infertile women below the age of 42 who underwent first stimulated IVF cycle. We excluded the male infertility cases, patients with comorbid conditions, those who had freeze-all embryos and cancelled cycles, and those with incomplete data. Within 3 months of the start of the new IVF cycle, BMI was registered and patients were divided into 4 BMI categories; group 1-underweight (<18.5 kg/m<sup>2</sup>), group 2-average weight  $(18.5-24.9 \text{ kg/m}^2)$ , group 3-overweight  $(25-29.9 \text{ kg/m}^2)$ , and group 4-obese >30 kg/m<sup>2</sup>).

Data extracted include BMI, age of the female patients, infertility duration, infertility cause, total dosage and duration of gonadotropins utilized for the ovarian stimulation, and direct cost for blood tests and ultrasound scans for monitoring. The findings considered in the study were: day 15 human chronic gonadotr opin (ß-hCG) serum pregnancy hormone test once embryo is transferred, confirming the clinical pregnancy by transvaginal ultrasound 2-4 weeks later to check for fetal heartbeat, transvaginal ultrasound for miscarriage by confirming absent fetal heart. Continuing pregnancy is described as any positive fetal heart pregnancy, visualized on ultrasound at >11 weeks. All women had their details linked electronically with the obstetric outcomes; in case the information was not found, patients were contacted by phone.

The initial stimulatory dose of gonadotropins was started depending on day 2 level of follicle-stimulating hormone (FSH), patient's age, BMI, and antral follicle count (150 IU of gonadotropins was given in women younger than 37 years of age, 225 IU in women aged 37-39, in addition 300 IU for women aged 40 years or older). The patients were monitored using ultrasound reports and serum estradiol levels. A human chorionic gonadotrophin (HCG) trigger was given if minimum of 3 follicles that size greater than 17-18 mm in diameter were visualized by ultrasound. In all females, 2 embryos have been transferred in.

All categorical variables such as BMI, parity, miscarriage presented as numbers and percentages.

Continuous variable age, duration of infertility and total cost are expressed as Median (interqurtile range). We used non-parametric tests when data was skewed/ non-normal data and normality of the data checked by Kolmogorov Smirnov test. Kruskal-Wallis test applied to find out median differences between BMI classifications and clinical characteristics of patients. The exact test of Chi-square/Fisher was applied on the basis of whether the predicted cell frequency was lower than 5 and the significant relation between categorical variables was determined. Data was analyzed on direct costs of IVF in each cohort. For interventions like IVF and ICSI, the costs and clinical outcomes associated with each strategy were compared for different weight groups. The average cost for each cohort of clinical testing was calculated. Regression and correlation analysis was applied to find out significant correlation between total cost (SAR) of IVF and patient's BMI. A 2-tailed p-value less than 0.05 considered significant for all comparisons. All data was entered and evaluated via the IBM SPSS Statistics for Windows, version XX (IBM Corp., Armonk, N.Y., USA).

Cost calculations. A bottom-up methodology was used to measure the resource utilization parameters in the reproductive endocrine and infertility medicine department (REIMD); oocyte regeneration, ultrasound scans, blood testing, drug used, embryo transfer and IVF/ICSI. As outlined in REIMD budget, all capital inputs (for example, personnel, facilities, space, and consumables) needed for individual procedures were defined and calculated by consulting with appropriate clinicians and priced using market prices for 2017-2018. The cost of r-FSH (Gonal F) was calculated at a price of 49 Saudi Riyal (SAR) (13\$) per 75 units, the cost of human menopausal gonadotropin (Merional) was calculated at a cost 40 SAR (11\$) per 75 units, and the baseline cost for IVF/ICSI procedure was calculated at 9000 SAR (2400\$) based on market price cost. The cost of biochemical pregnancy; when the pregnancy fails before ultrasound detection of it after a positive pregnancy test; was estimated on the assumption that, on average, each would require one ß-HCG test and ultrasound.

**Results.** A total of 1157 women underwent IVF/ICSI between January 2017 and December 2018. However, 331 patients were excluded due to; freeze-all embryos (n=209), cancelled cycles (n=106), or cycles that were converted to intrauterine insemination (n=16). A total of 826 patients who fulfilled inclusion criteria were available for analysis; group 1 (n=12) patients (1.5%), group 2 (n=176) patients (21.3%),

group 3 (n=338) patients (40.9%) and group 4 (n=300) patients (40.9%) (**Table 1**).

**Table 2** displays the characteristics of women in each BMI group. There was a trend towards older age in obese women. The median age was 27.5 years in women

**Table 1 -** Descriptive analysis of variables (N=826).

Parameters	n (%)
BMI classifications	12 (1.5)
<18.5 (underweight)	176 (21.3)
18.5-24.9 (normal)	338 (40.9)
25 - 29.9 (overweight)	300 (36.3)
≥30 (obese)	
Parity	786 (95.2)
0	35 (4.2)
1	5 (0.6)
2	<i>y</i> (0.0)
Causes of infertility	
Anovulatory infertility	680 (82.3)
Ovulatory	146 (17.7)
Anovulatory	(-, ., ,
•	129 (15.6)
Polycystic ovarian syndrome Yes	129 (15.6) 697 (84.4)
No	097 (64.4)
	2= // 5
Tubal factor infertility	37 (4.5)
Yes	789 (95.5)
No	
Unexplained infertility	123 (14.9)
Yes	703 (85.1)
No	
Endometriosis	35 (4.2)
Yes	791 (95.8)
No	
Number of embryos transferred	807 (97.7)
Yes	19 (2.3)
No	1) (2.3)
	203 (24.6)
Number of frozen embryos Yes	623 (75.4)
No	023 (/ 3.4)
	57( ((0.7)
Treatment protocol	576 (69.7)
Antagonist	250 (30.3)
Long	
Assisted reproduction technique	811 (98.2)
IVF-ICSI	15 (1.8)
IVF	
Gonadotropins	413 (50.0)
HMG (merional)	413 (50.0)
r-FSH (gonal-F)	
Clinical pregnancy rate	347 (42.0)
Yes	479 (58.0)
No	(/
Miscarriage rate	110 (13.3)
Yes	716 (86.7)
No	( , )
Live birth rate	120 (14.5)
Yes	706 (85.5)
No	/ 00 (0).))
110	

HMG: human menopausal gonadotropins, r-FSH: recombinant follicle stimulating hormone

Table 2 - Impact and association of body mass index (BMI) with respect to clinical characteristics of the study.

Parameters	Description	<18.5 (Underweight)	18.5-24.9 (Normal)	25-29.9 (Overweight)	≥30 (Obese)	P-value	
Age	Median (IQR)	27.5 (31.75 - 25.5)	31 (35 - 28)	33 (37 - 29)	33 (38 - 29.25)	<0.001*	
BMI	Median (IQR)	17.2 (18 - 16.25)	22.8 (23.88 - 21.2)	27.4 (28.7 - 26.3)	32.2 (33.9 - 31)	<0.001*	
Duration of infertility	ration of infertility Median (IQR)		5 (8 - 4)	6 (8 - 4)	7 (10 - 5)	0.022*	
FSH (IU/L) Median (IQ		7.2 (8.76 - 5.21)	6.5 (7.6 - 4.7)	5.9 (6.92 - 4.33)	6.3 (7.4 - 4.71)	0.112	
LH (IU/L)	Median (IQR)	7.65 (8.43 - 5.59)	5.6 (8.3 - 3.75)	5.1 (7.98 - 3.75)	6.2 (8.95 - 4.15)	0.030*	
E2 (pmol/L)	Median (IQR)	119 (259.5 - 87.25)	146.5 (250.5 - 86.78)	145.5 (213 - 56.69)	143 (220 - 49)	0.891	
Prolactin (mIU/L)	Median (IQR)	203 (306 - 19.8)	234 (409.75 - 16.2)	204 (378 - 14.25)	208 (370 - 16)	0.945	
TSH (mIU/L) Median (IQR)		1.2 (4.65 - 0.84)	2.6 (4.7 - 1.89)	2.52 (4.78 - 1.6)	2.54 (4.13 - 1.49)	0.329	
Number of eggs fertilized			2 (4 - 1.75)	3 (4 - 2)	3 (4 - 2)	0.113	
Number of aspirated follicles	Median (IQR)	8.5 (15 - 5.25)	6 (10.75 - 4)	7 (11 - 4)	7 (11 - 4)	0.873	
Dose of r-FSH (Gonal-F) (IU)	Median (IQR)	150 (150 - 112)	150 (206 - 112)	150 (225 - 150)	150 (225 - 150)	0.486	
Dose of HMG (Merional)(IU)	Median (IQR)	150 (375 - 150)	225 (300 - 150)	225 (300 - 150)	225 (300 - 150)	0.685	
Treatment days	Median (IQR)	10 (11 - 9)	10 (11 - 9)	11 (13 - 9)	11 (13 - 9)	0.562	
Patients with embryo	Yes	11 (91.7)	173 (98.3)	333 (98.5)	290 (96.7)	0.198	
transfer (%)	No	1 (8.3)	3 (1.7)	5 (1.5)	10 (3.3)		
Patients with frozen	Yes	4 (33.3)	36 (20.5)	86 (25.4)	77 (25.7)		
embryos (%)	No	8 (66.7)	140 (79.5)	252 (74.6)	223 (74.3)	0.486	
Miscarriages (%)	Yes	0 (0.0)	18 (10.2)	45 (13.3)	47 (15.7)		
	No	12 (100.0)	158 (89.8)	293 (86.7)	253 (84.3)	0.192	
Assisted reproduction technique	IVF-ICSI	12 (100.0)	173 (98.3)	332 (98.2)	294 (98.0)		
	IVF	0 (0.0)	3 (1.7)	6 (1.8)	6 (2.0)	0.961	
Gonadotropins	HMG (Merional)	5 (41.7)	95 (54.0)	161 (47.6)	152 (50.7)		
	r-FSH (Gonal-F)	7 (58.3)	81 (46.0)	177 (52.4)	148 (49.3)	0.521	
Clinical pregnancy	Yes	6 (50.0)	63 (35.8)	144 (42.6)	134 (44.7)	0.250	
	No	6 (50.0)	113 (64.2)	194 (57.4)	166 (55.3)	0.259	
Live birth rate	Yes	1 (8.3)	23 (13.1)	48 (14.2)	48 (16.0)		
	No	11 (91.7)	153 (86.9)	290 (85.8)	252 (84.0)	0.747	

FSH: follicle-stimulating hormone, LH: luteinizing hormone, TSH: thyroid stimulating hormone, HMG: human menopausal gonadotropins, IQR: interquartile range IVF-ICSI: in-vitro fertilization/intracytoplasmic sperm injection, r-FSH: recombinant follicle stimulating hormone

**Table 3** - Comparative analysis of IVF cost and patient's body mass index.

Parameters	Description	<18.5	18.5 - 24.9	25 - 29.9	≥30	P-value
		(Underweight)	(Normal)	(Overweight)	(Obese)	
Total cost HMG (Merional)	Median (IQR)	10280 (11680 - 9760)	10560 (11160 - 10120)	10440 (10920 - 10040)	10560 (10920 - 10140)	0.712
Total cost r-FSH (Gonal-F)	Median (IQR)	10200(10320 - 10080)	10200(10590 - 10080)	10440 (10800 - 10080)	10320 (10605 - 10080)	0.254
Total cost of injections	Median (IQR)	1240 (1410 - 1080)	1380 (2055 - 1080)	1440 (1920 - 1080)	1440 (1800 - 1080)	0.598
Total cost of IVF/IVF-ICSI (SR)	Median (IQR)	10240 (10410 -10080)	10380 (11055 -10080)	10440 (10920 -10080)	10440 (10800 -10080)	0.598

HMG: human menopausal gonadotropins, r-FSH: recombinant follicle stimulating hormone, IQR: interquartile range, IVF-ICSI: in-vitro fertilization/intracytoplasmic sperm injection

who were underweight, 31 years in women with normal weight, 33 years in overweight women, and 33 years in obese women (p<0.001). The duration of infertility was similar across the groups except in the obese group where the duration of infertility was longer, a range of 5 to 10 years and a median of 7 years in the obese group.

There were no statistical significant differences in baseline serum FSH, TSH, prolactin and estradiol among the groups; however, there was statistical difference in the level of LH. The median was 7.65 IU/L in women who were underweight, 5.6 IU/L in women with normal weight, 5.1I U/L in women who were overweight, and 6.2 IU/L in those women who were obese (p=0.03), (**Table 2**). There were no statistical significant differences for number of days required for stimulation among groups; 10 days for women with underweight and normal weight and 11 days for women with overweight and obese group respectively (p=0.6). Majority of the patients had IVF-ICSI cycles (n=811, 98.2%) in comparison to IVF (n=15, 1.8%) (Table 2), and 576 patients (69.7%) had antagonist ovarian stimulation protocol, and 250 (30.3%) had day 21 long ovarian stimulation protocol (Table 2). Of the 826 patients, 347(42%) had a positive pregnancy test and 479 women (58%) had a negative pregnancy test. There was no statistical significant difference in the pregnancy rate among the different BMI groups, pregnancy occurred in 6 women in group 1 (50%), in 63 women in group 2 (35.8%), 144 (42.6%) women occurred in group 3, and 134 (44.7%) women occurred in group 4 (Table 2).

No statistical significant differences were seen in miscarriage rates between groups: 18 (10.2%), normal BMI; 45 (13.3%), overweight 47 (15.7%) and among obese women (p=0.2).

No statistical significant differences were seen with regard to frozen embryos among group; 86 (25.4%) in the overweight and 77 (25.7%) in the obese group verses 36 (20.5%) in the normal weight group.

There was no statistical significant difference for the LBR among the BMI groups, with the occurrence of LBR in 23 women with normal BMI (13.1%), in 48 (14.2%) women who were overweight, in 48 (16%) in women who were obese (p=0.7) (**Table 2**). Besides, the median cost of medications in different groups showed trend increase; however, it was not statistically significant. The cost was 1240 SAR for group 1, 1380 SAR for group 2, 1440 for group 3 and 4 (p=0.59) (**Table 3**). The median total cost for IVF/ICSI treatment cycle did not differ across BMI groups; the cost was 10,240 SAR for underweight women, 10,380 SAR for normal weight women, 10,440 SAR for overweight women, and 10,440 SAR for obese women (p=0.62) (**Table 3**).

**Discussion.** The management of infertility has been transformed by the use of assisted reproductive technologies (ART). These developments have a medical, reproductive and economic impact with the cost of a single new IVF in the United States as a proportion of an individual's annual disposable income was 50%; in the United Kingdom, Scandinavian countries, and

Australia, about 20%; and in Japan, 12%.<sup>14</sup> In women with anovulation, where clomiphene citrate is used for ovulation induction (OI) in overweight and obese cohort of women, resulted in lower ovulation and total live birth rates, but if OI is successful, no difference in pregnancy rates is seen in different weight categories.<sup>15</sup> Higher cancellation rates and substantially higher miscarriage rates are also correlated with obesity, resulting in decreased live birth rates. 16 The pregnancy rate and live birth rate decreases due to higher miscarriage rates among obese women such as those found in our study.<sup>17</sup> Lifestyle changes and weight loss programs for obese women have restored menstrual regularity, ovulation and improved the likelihood of conception.<sup>18</sup> A better awareness of the link between the cost, use, and healthy clinical practice of IVF therapy would not only promote equal access to care for patients with subfertility, but also enable children born from IVF get the best possible start in life.<sup>19</sup> Previous studies showed relationship between obesity and ovulatory dysfunction and thus need a higher dose of gonadotrophins; similarly, in our results there was slight increase in gonadotropin requirement in the overweight and obese group, but this did not achieve statistical significance. This is because protocols modify dosage based on the BMI for the IVF cycle.<sup>20</sup> Conflicting results about pregnancy and its outcomes have been found in previous studies, 15-19 but we found that the higher the BMI, the higher the likelihood of having a miscarriage.

The outcomes per IVF/ICSI may vary because of factors that can affect fertility like age, sperm quality, and comorbid conditions in both partners. In the literature, variable results were obtained for the outcomes in IVF/ ICSI for overweight and obese women. 17,18 We found no statistically significant differences in IVF/ICSI outcomes among women with different BMI categories. In addition, obesity was associated with pregnancy complications such as high risk of miscarriage, congenital defects, gestational diabetes, hypertensive diseases. It also leads to prolonged labor, fetal macrosomia and increased need for operative delivery, shoulder dystocia, and postpartum hemorrhage.<sup>19</sup> A system within which the effects of fertility therapy and the implications of the subsequent pregnancy can be measured concurrently for infertile women in various groups of body weight needs to be established. It will help reduce the indirect treatment cost for infertility patients by producing a provisional model of working on lifestyle modifications to increase the chances of natural conception. The estimated costs of IVF/ICSI will help us identify costeffective measures to avoid unnecessary interventions.

Study limitations. This study was conducted at a single center therefore, a large sample with multicenter study, can find statistical significance even when the differences or associations are small/weak. Additionally, researcher and clinicians sometimes misinterpret statistically significant result as being practically or clinically important. But cost significance is not the same as practical significance or importance. Additionally, women in this study were randomly selected on fulfilling the eligibility criteria after initial screening and many women with BMI greater than 35 kg/m<sup>2</sup> were not eligible for treatment, and thus might alter the true number of the obese women in this study. Consequently, our results are not generalizable for women with obesity of BMI more than 35 kg/m<sup>2</sup>.

In conclusion, our results suggest that being overweight or obese does not significantly increase the costs of IVF-ICSI. Women could get pregnant if they are overweight or obese but pregnancy might be high risk. Therefore, weight loss measures should be introduced before starting IVF treatment to improve pregnancy outcomes, and reduce obesity linked pregnancy complications.

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