

Correlation Among Obesity, Oocyte Characteristics, Embryo Characteristics and Maternal Plasma Folate Level in a Sample of Iraqi Women Undergoing Intracytoplasmic Sperm Injection (ICSI)

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ABSTRACT

The effect of maternal body mass index (BMI) on fertility outcomes in women undergoing in vitro fertilization/intracytoplasmic sperm injection cycles has been extensively evaluated and the results of these studies have shown a lot of controversial issues. Folate is a naturally occurring type of vitamin B9 crucial for reproductive health. 65 infertile couples were subjected to intracytoplasmic sperm injection cycles. Both primary and secondary types of infertility were involved, with different causes. The mean plasma folate of all infertile women was 12.71 ± 6.52 , with pregnant 11.60 ± 5.57 and non-pregnant 11.74 ± 8.80 ; with no significant difference in mean plasma folate between them. Moreover, the means of follicular fluid folate of all infertile women, pregnant women, and non-pregnant women were 8.00 ± 5.39 , 7.84 ± 4.68 , and 8.39 ± 6.19 respectively. There was no significant statistical difference in mean follicular fluid folate between pregnant and non-pregnant women ($p=0.719$). Also, both plasma folate and follicular fluid folate were not significantly correlated to oocyte and embryo characteristics. Although plasma folate was higher in obese than normal and overweight women, the difference did not reach statistical significance. It appears that the correlation among maternal BMI, folate level and fertility outcomes in women undergoing intracytoplasmic sperm injection cycles are still controversial and much research work is needed to figure out such complex interaction among these variables.

Keywords: Obesity; Oocyte characteristics; Plasma folate; ICSI.

1. Introduction

It has been shown that abnormal body mass index plays a key role in several health problems affecting humans including the cardiac system, respiratory system, nervous system, metabolic disorders, and others (*Arabipoor, et al. [1]*). The impact of this problem is increasing in developed as well as developing countries (*Bakos, et al. [2]*). The effect of maternal body mass index on fertility outcomes in women undergoing IVF/ICSI cycles has been extensively evaluated (*Le, et al. [3]*; *Merhi, et al. [4]*; *Umul, et al. [5]*; *Thomsen, et al. [6]*) and the results of these studies have shown a lot of controversial issues (*Arabipoor, et al. [1]*). Despite the richness of information about maternal obesity and associated fertility outcomes, Koning. et al. has concluded that data about such association are still less than optimum to reach a hard implication about adverse fertility outcomes in association with maternal obesity and that much research work is still needed (*Koning, et al. [7]*). Till the time the

current study was planned, there was no solid proof that maternal obesity may hamper pregnancy occurrence following ICSI despite the existence of several previous reports that have claimed so (*Arabipoor, et al. [1]*; *Koning, et al. [7]*). In one review article, however, poor ICSI outcomes have been linked to maternal overweight and obesity (*Rittenberg, et al. [8]*). To be clearer, the later review has shown a significant reduction in the number of live births in association with women obesity (*Rittenberg, et al. [8]*). One of the exciting results has come from the paper published by Luke et al. is “obesity had a negative impact on clinical pregnancy and live birth rates along with ART cycles with autologous oocytes” (*Luke, et al. [9]*). Actually, causes of infertility are numerous, however, they are categorized into 4 basic groups by specialists dealing with infertility issues: female factors, malefactors, combined female, and malefactors, and unexplained infertility (*Öztekin, et al. [10]*). Causes may be related to some genetic predisposition

(*Venkatesh, et al.* ^[11]; *Zorrilla and Yatsenko* ^[12]) or could be related to environmental factors (*Gaskins and Chavarro* ^[13]; *Hruska, et al.* ^[14]). With respect to the environmental causes, diet is receiving much attention and this is reflected by a huge amount of data that refer to a substantial and significant role for dietary items, in particular, micronutrient in the pathophysiology of fertility (*Gaskins and Chavarro* ^[13]). One of the main deities' items that have been recently discussed thoroughly is dietary folate (*Gaskins, et al.* ^[15]). Folate is required for the DNA synthesis, transfer RNA, methionine, and cysteine, for that reason, the need for folate is greatly increased at the time of rapid cell growth, including the peri-conceptual period (*Ebisch, et al.* ^[16]). The association among obesity, oocyte characteristics, embryo characteristics, and maternal plasma folate has been recently evaluated by several authors, but a clear conclusion is yet to be established. Therefore, the planning and conduction of the current study are aiming

at evaluating the correlation among obesity, oocyte characteristics, embryo characteristics, and maternal plasma folate level in a sample of Iraqi women undergoing intracytoplasmic sperm injection (ICSI).

2. Materials and Methods

The current study was carried out in the High Institute of Infertility Diagnosis and Assisted Reproductive Technologies, Al Nahrain University, Baghdad, Iraq, between the period from September 2019 until February 2020. The study was approved officially by the Medical Ethical Committee of the High Institute of Infertility Diagnosis and Assisted Reproductive Technologies, Al Nahrain University, and informed written consent was obtained from every enrolled participant. The study included 65 infertile couples who were chosen from the pool of patients visiting the High Institute of Infertility Diagnosis and Assisted Reproductive Technologies and they were subjected to an intracytoplasmic sperm injection (ICSI) cycle. The range of age of

participants was from 18-38 years. Both secondary and primary infertility types were enrolled, with a variety of causes. Calculation of body mass index (BMI) is as follows:

$$\text{BMI} = \text{Weight (kg)} / \text{Height (m}^2\text{)}$$

The inclusion criteria included: a body mass index between $18.5 \leq 40 \text{ kg/m}^2$, all patients receiving the same GnRH antagonist protocol, fasting for at least 6 hours on the day of blood sampling, absence of co-existing endocrine disorders (hyperprolactinemia, diabetes mellitus, thyroid dysfunction, Cushing syndrome), Couples with unexplained infertility, patients with normal ovarian reserve. Women who were excluded from the study were: patients with coeliac disease, malabsorption syndrome and other chronic diseases, and severe endometriosis (confirmed laparoscopically), male partners with azoospermia, chronic smoker (passive and active), uterine anomaly confirmed either by hysterosalpingography, hysteroscopy. All

women were received folic acid supplements with different doses ranging from (0.4-0.8 mg) for 1-2 months. All patients were subjected to antagonist protocol, all enrolled women were started stimulation by (rFSH) from the second day of the cycle by daily subcutaneous injection in a dose of 150-225 IU till the day of the trigger by hCG injection while the GnRH antagonist injection (Cetrorelix) was started in a dose of 0.25 mg daily, once the developing follicles $\geq 14 \text{ mm}$ in mean diameter which was visualized by transvaginal ultrasound until triggering with recombinant hCG (rhCG 6500 IU, Ovitrelle®; Merck, Italy) subcutaneously (when leading follicle was with a mean diameter $\geq 18 \text{ mm}$). The oocyte retrieval under general anesthesia was done with the guidance of transvaginal ultrasound 34-36 hours following the hCG injection with sperm collection from the female partner on oocyte retrieval day then subjected to ICSI. A fertilization check was performed 18 hours after insemination by ICSI. Follicular fluid was collected on

the day of oocytes retrieval and centrifuged at a rate of 3000 rpm for ten minutes, plasma was obtained from blood samples after centrifugation at 5000 rpm for 10 minutes at room temperature and then both samples were stored at -20°C for later one run assessment of the concentration of folate using ELISA technique, oocyte denudation, oocyte maturation evaluation, intracytoplasmic sperm injection of mature (MII) oocytes, evaluation of fertilization and cleavage and embryo grading, embryo selection and embryo transfer, luteal phase support, beta hCG determination (to document biochemical pregnancy). Statistical analysis was carried out using a statistical package for social sciences (SPSS) (IBM, Chicago, USA, version 23). Categorical variables were expressed as number and percentage, while, quantitative variables were expressed as number and percentage. Independent samples t-test was used to compare means between any two groups; whereas, Chi-square and Yates correction tests were used to study the association

between any two categorical variables. Correlations were evaluated using the Spearman correlation test. The level of significance was set at $p \leq 0.05$, and the level of high significance was set at $p \leq 0.01$.

3. Results

This study included 65 infertile couples of whom 21 got positive biochemical pregnancy results at the end of the study making the overall rate of pregnancy (32.3%). The demographic characteristics of infertile women participating in this study are shown in **Table 1**. None of these demographic characteristics has predicted positive biochemical pregnancy in a significant way ($p > 0.05$). It is worth to mention that in the present study, the mean body mass index (BMI) in all participants was $29.20 \pm 4.76 \text{ kg/m}^2$ and there was no significant difference in mean BMI between pregnant and non-pregnant women ($p = 0.373$), $28.43 \pm 5.61 \text{ kg/m}^2$ versus $29.57 \pm 4.32 \text{ kg/m}^2$, respectively; the distribution of women according to

BMI was also outlined in *Table 1*. The oocyte characteristics of infertile women according to pregnancy outcomes are demonstrated in *Table 2*. There was no significant difference in total oocytes, abnormal oocytes, germinal vesicles oocytes, mature metaphase II (MII), immature metaphase I (MI) oocytes, maturation index, and fertilized (2PN) oocytes between pregnant and non-pregnant women ($p > 0.05$). The embryo characteristics of infertile women according to pregnancy outcomes are shown in *Table 3*. There was no significant difference in grade I, II, III, and IV embryos % as well as selected embryos between pregnant and non-pregnant women ($p > 0.05$). The plasma folate and follicular fluid folate of infertile women according to pregnancy outcome are shown in *Table 4*. The mean plasma folate of all infertile women was 12.71 ± 6.52 , that of pregnant women was 11.60 ± 5.57 and that of non-pregnant women was 11.74 ± 8.80 . There was no significant difference in mean plasma folate between

pregnant and non-pregnant women ($p = 0.950$). Moreover, the mean follicular fluid folate of all infertile women was 8.00 ± 5.39 , that of pregnant women was 7.84 ± 4.68 and that of non-pregnant women was 8.39 ± 6.19 . There was also no significant difference in mean follicular fluid folate between pregnant and non-pregnant women ($p = 0.719$). In addition, both plasma folate and follicular fluid folate were not significantly correlated to oocyte and embryo characteristics ($p > 0.05$), as shown in *Table 5* and *Table 6*. The mean plasma folate of obese women ($\text{BMI} \geq 30 \text{ kg/m}^2$) was 12.25 ± 7.91 and that of normal and overweight weight women ($\text{BMI} < 30 \text{ kg/m}^2$) was 9.48 ± 7.53 . Although plasma folate was higher in obese than overweight women, the difference did not reach statistical significance ($p = 0.260$), as shown in *Figure 1*.

4. Discussion

In this study, none of the included demographic

Table (1): Demographic characteristics of infertile women according to pregnancy outcome

Characteristic	Total n = 65	Positive pregnancy n = 21	Negative pregnancy n = 44	P
Age (years)				
Mean ±SD	30.82±5.83	30.05±6.38	31.18±5.59	0.467 † NS
Range	19-38	19-38	19-38	
< 35, n (%)	48 (73.8 %)	15 (71.4 %)	33 (75.0 %)	0.579 Y NS
≥ 35, n (%)	17 (26.2 %)	6 (28.6 %)	11 (25.0 %)	
BMI (kg/m ²)				
Mean ±SD	29.20±4.76	28.43±5.61	29.57±4.32	0.373 † NS
Range	18-42.01	18-42.01	22.03-41.74	
Underweight (<18.5 kg/m ²), n (%)	1 (1.5 %)	1 (4.8 %)	0 (0.0 %)	
Normal (18.5-24.9 kg/m ²), n (%)	12 (18.5 %)	5 (23.8 %)	7 (15.9 %)	
Overweight (25-29.5 kg/m ²), n (%)	26 (40.0 %)	8 (38.1%)	18 (40.9 %)	
Class I obesity (30-34.5 kg/m ²), n (%)	18 (27.7 %)	4 (19.0 %)	14 (31.8 %)	
Class II obesity (35-39.5 kg/m ²), n (%)	5 (7.7 %)	2 (9.5 %)	3 (6.8 %)	
Class III obesity (≥ 40 kg/m ² , n (%)	3 (4.6 %)	1 (4.8 %)	2 (4.5 %)	
Duration of infertility (years)				
Mean ±SD	7.03±3.58	6.95±3.84	7.07±3.50	0.907 † NS
Range	2-19	2-17	2-19	
Type of infertility				
Primary, n (%)	42 (64.6 %)	16 (76.2 %)	26 (59.1 %)	0.178 ¥ NS
Secondary, n (%)	23 (35.4 %)	5 (23.8 %)	18 (40.9 %)	
Causes of infertility				
Male, n (%)	32 (49.2 %)	9 (42.9 %)	23 (52.3 %)	0.311 ¥ NS
Female, n (%)	17 (26.2 %)	8 (38.1 %)	9 (20.5 %)	
Unexplained, n (%)	16 (24.6 %)	4 (19.0 %)	12 (27.3 %)	

n: number of cases; SD: standard deviation; BMI: body mass index; ART: assisted reproductive technologies; †: Independent samples t-test; ¥: Chi-square test; Y: Yates correction; NS: not significant at $P > 0.05$

Table (2): Oocyte characteristics of infertile women according to pregnancy outcome

Characteristic	Total n = 65	Positive pregnancy n = 21	Negative pregnancy n = 44	P
Number of oocytes				
Mean ±SD	9.71 ± 5.93	10.14 ± 5.79	9.50 ± 6.06	0.686 † NS
Germinal vesicle %				
Mean ±SD	6.38 ± 10.00	7.72 ± 9.64	5.73 ± 10.22	0.354 † NS
MI %				
Mean ±SD	10.75 ± 14.43	15.69 ± 18.23	8.39 ± 11.74	0.056 † NS
MII %				
Mean ±SD	62.98 ± 21.86	64.80 ± 16.75	62.11 ± 24.05	0.645 † NS
Maturity index %				
Mean ±SD	62.98 ± 21.86	64.80 ± 16.75	62.11 ± 24.05	0.646 † NS
Fertilized oocyte (2 PN)				
Mean ±SD	4.25 ± 3.18	4.05 ± 2.92	4.34 ± 3.33	0.731 † NS

n: number of cases; SD: standard deviation; MI: metaphase I (immature) oocytes; MII: metaphase II (mature) oocytes; PN: pro-nuclei; †: independent samples t-test; NS: not significant at $P > 0.05$

Table (3): Embryo characteristics of infertile women according to pregnancy outcome

Characteristic	Total n = 65	Positive pregnancy n = 18	Negative pregnancy n = 47	P
Grade I %				
Mean ± SD	61.17 ± 34.46	69.01 ± 28.99	57.43 ± 36.51	0.208 † NS
Grade II %				
Mean ± SD	19.02 ± 24.32	17.40 ± 19.02	19.79 ± 26.65	0.713 † NS
Grade III and IV %				
Mean ± SD	6.94 ± 15.48	8.69 ± 16.82	6.10 ± 14.92	0.533 † NS

n: number of cases; SD: standard deviation; †: Independent samples t-test; NS: not significant at $P > 0.05$

Table (4): Plasma folate and follicular fluid folate of infertile women according to pregnancy outcome

<i>Characteristic</i>	<i>Total n = 65</i>	<i>Positive pregnancy n = 18</i>	<i>Negative pregnancy n = 47</i>	<i>P</i>
<i>Plasma folate</i>				
<i>Mean ±SD</i>	12.71 ± 6.52	11.60 ± 5.57	11.74 ± 8.80	0.950 † NS
<i>Range</i>	2.30 - 25.10	2.3 - 22.1	2.3 - 25.1	
<i>Follicular fluid folate</i>				
<i>Mean ±SD</i>	8.00 ± 5.39	7.84 ± 4.68	8.39 ± 6.19	0.719 † NS
<i>Range</i>	0.60 - 23.20	0.6 - 18.5	1.1 - 23.2	

n: number of cases; SD: standard deviation; †: Independent samples t-test; NS: not significant at $P > 0.05$

Table (5): Correlation of plasma folate and follicular fluid folate to oocyte and embryo characteristics

Characteristic	Plasma folate		FF folate	
	r	P	r	P
Number of oocytes	0.056	0.655	0.108	0.392
Abnormal %	0.182	0.146	0.127	0.313
Germinal vesicle %	-0.008	0.953	0.066	0.600
MI %	-0.200	0.110	-0.157	0.212
MII %	0.037	0.769	-0.005	0.969
Grade I %	-0.015	0.907	0.131	0.299
Grade II %	0.056	0.656	-0.014	0.912
Grade III and IV %	-0.129	0.307	-0.098	0.437

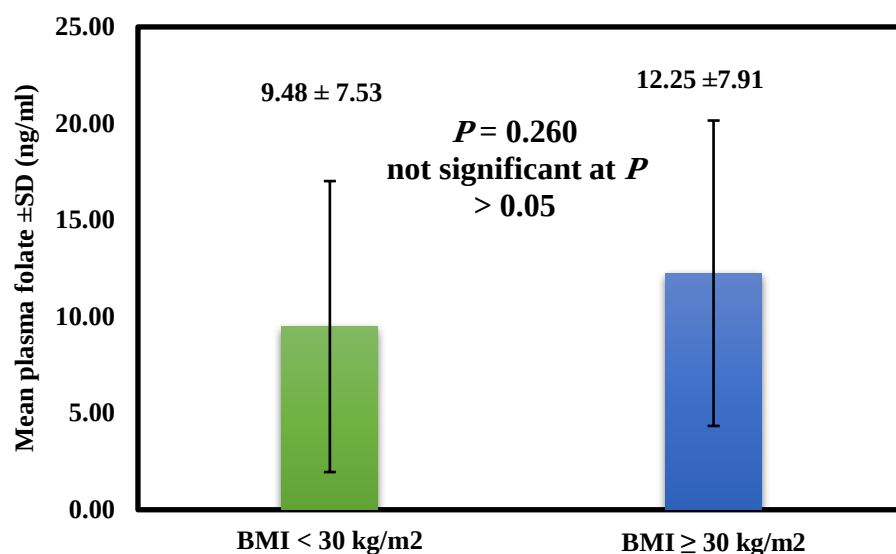


Figure (1): Comparison of mean plasma folate according to BMI ($\geq 30 \text{ kg/m}^2$ versus $< 30 \text{ kg/m}^2$)

characteristics offered significant association with positive biochemical pregnancy outcome, including age, BMI, duration of infertility, type of infertility, cause of infertility, parity, and the number of previous IVF cycles. This finding is in accordance with the finding of previous studies, that demographic characteristics have no significant impact on biochemical pregnancy outcome in women subjected to assisted reproductive techniques (*Choi, et al.* ^[17]). Moreover, in the current study, women's BMI appeared with no adverse

effect on pregnancy outcome. Indeed, there is an agreement between the present study finding “no association between biochemical pregnancy outcome and BMI” and the findings of previous authors (*Banker, et al.* ^[18]; *MacKenna, et al.* ^[19]; *Esinler, et al.* ^[20]); however, it is contradicted the findings of other studies (*Sampo, et al.* ^[21]; *Kumbak, et al.* ^[22]). Actually, it has been shown that both underweight and overweight have affected adversely the pregnancy outcome in infertile women undergoing ICSI. It has been shown that irregular menstruation,

lack of ovulation, and disturbances in endocrine and metabolic functions are the main players in low fertility in women with abnormal BMI, nevertheless, modern standard assisted reproduction may overcome these obstacles (*Tziomalos and Dinas* ^[23]). It has been shown that obesity and overweight have an affect fertility outcome adversely in women undergoing ART (*Tziomalos and Dinas* ^[23]; *Silvestris, et al.* ^[24]); however, there is still controversy about the effect of women BMI on ART outcome (*Oliveira JB.* ^[25]). It has been suggested that the relatively young age of participating women may have reduced the significant impact of maternal BMI on pregnancy outcome. In the present study, there were no significant differences in total oocytes, abnormal oocytes, germinal vesicles oocytes, mature metaphase II (MII), metaphase I (MI) oocytes, maturation index, and fertilized (2PN) oocytes between pregnant and non-pregnant women ($p>0.05$). Previous studies have shown similar results (*Pongsuthirak and*

Vutyavanich ^[26]); however, other authors have shown different results (*Vitale, et al.* ^[27]; *Lazzaroni-Tealdi, et al.* ^[28]; *Ingilizova, et al.* ^[29]; *Shi, et al.* ^[30]). For that reason, the sole dependence on light microscopical morphological criteria for the assessment of oocyte quality can be inadequate because oocyte may have variable ultra-structural and metabolic features which need more sophisticated techniques to be evaluated other than the conventional light microscope examination (*Rienzi, et al.* ^[31]). The use of polarized microscopy by previous authors has shown that the oocyte may still be immature even in the presence of a polar body (*Hoshino Y.* ^[32]). Therefore, the use of the polarized light microscope technique can help to select mature oocyte (those having specific criteria of the meiotic spindle (MS)) and thereby increasing the rate of subsequent fertilization, cleavage, and implantation (*Asa, et al.* ^[33]). In this study, there was no significant difference in grade I, II, III, and IV embryo percent between pregnant and

non-pregnant women ($p>0.05$). One of the significant predictors of successful pregnancy following ICSI is a good quality embryo; however, previous studies have shown inconsistent results with respect to the association between embryo quality and pregnancy outcome. Some of these reports favored a significant role (*Spitzer, et al.* ^[34]; *Kim, et al.* ^[35]) and others denied such a significant role for embryo quality (*Wang, et al.* ^[36]) in determining the pregnancy outcome following ART. The possible explanation for the absence of significant association between embryo quality and pregnancy outcome in this study can be attributed to the fact that the mere morphological assessment of the quality of the embryo is not sufficient to choose the optimal embryos that can guarantee the best implantation outcome. Because of the inadequacy of morphological assessment of embryo quality, recent techniques for better assessment of embryo quality, whether invasive or non-invasive, have appeared in recent literature such as the

advances in the fields of genomics, metabolomics, transcriptomics, and proteomics technologies (*Uyar and Seli* ^[37]; *Krisher, et al.* ^[38]). So far, the above findings have highlighted the fact that selecting morphologically normal sperm and good quality oocyte may lead to successful fertilization, however, these gametes may lack the essential characteristics to produce healthy zygote and embryo required for fruitful pregnancy despite appearing morphologically normal. Therefore, the selection of good quality embryos should be based on more advanced techniques rather than depending on morphological assessment only, as a good quality embryo is one of the rate-limiting steps in determining pregnancy outcome besides endometrial receptivity, in a ratio of 1:2. In the present study, there was no significant difference in mean plasma folate and follicular fluid folate levels between pregnant and non-pregnant women. Experimental studies have shown that FA is essential in successful

implantation by providing a much more favorable receptive decidua environment to receive the implantation-competent blastocyst for a successful pregnancy (*Chandracharya, et al.* ^[39]). Defects in decidualization (induced by folate deficiency via bringing changes to the methylation patterns of genes involved in decidualization) will affect implantation and pregnancy outcomes. Folate is required for DNA synthesis, transfer RNA, methionine, and cysteine. For that reason, the need for folate is greatly increased at the time of rapid cell growth, including the peri-conceptual period (*Ebisch, et al.* ^[16]). The present study has shown that obesity has no significant impact on plasma folate levels. In 2004, the National Health and Nutrition Examination Survey (NHANES) data found that increased BMI of women of childbearing age was associated with a lower plasma folate level (*Mojtabai, R.* ^[40]). Another study in the UK obstetric cohort found that lower folate concentrations were associated with

higher BMI, independently from the diet, age, BMI, vitamin supplements, and parity (*Knight, et al.* ^[41]). It has been shown in previous reports that plasma folate levels are suboptimal in obese women (25.5%) (*de Luis, et al.* ^[42]) and overweight women (45%) (*Ortega, et al.* ^[43]); however, other authors have shown no significant association between maternal obesity and plasma folate level (*Ruiz-Tovar, et al.* ^[44]; *Stern, et al.* ^[45]). Moreover, with respect to the direct correlation between maternal body mass index and plasma folate levels, data are inconsistent: a number of studies found a positive correlation between BMI and folate levels (*de Luis, et al.* ^[42]; *Ortega, et al.* ^[43]); whereas, others found no such correlation (*Baltaci, et al.* ^[46]). So far, it appears that consensus about the role of BMI in affecting plasma folate in women is still lacking and further research work is needed to solve such controversy.

5. Conclusions

In conclusion, it appears that the correlation among maternal BMI, folate level, and fertility outcomes in women undergoing ICSI cycles is still controversial and much research work is needed to figure out such complex interaction among these variables.

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Author Contribution

Hasan, NA performed the study, examined and reviewed results, and manuscript writing with the help and supervision of Abdulhameed, WA, and Rahim, AI.

Conflict of Interest

The author declares no conflict of interest.

Ethical Clearance

The study was approved by the Ethical Approval Committee.

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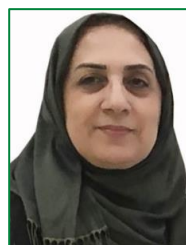
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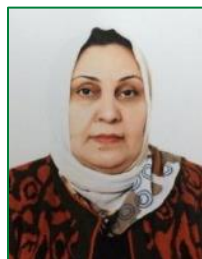
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