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Effect of Bisphenol A Level In Serum and Follicular Fluid On ICSI Outcome.

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ABSTRACT

Infertility is the disability of a couple to obtain pregnancy after one year of sexual intercourse that is unprotected and regular. Bisphenol A is an industrial chemical spread worldwide, that is a raw material utilized in multiple industries. Bisphenol A is assorted as an endocrine-disrupting chemical, which can interfere with hormone activity. This study aimed to assess the effect of BPA levels in serum on ICSI outcomes. The study was conducted at the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies / Al-Nahrain University during the period from October 2021 to April 2022. sixty infertile women enrolled in this study. BPA levels were analyzed through an enzyme-linked immunosorbent assay (ELISA) technique. Mean serum BPA was not significantly higher in non-pregnant women in comparison with that of pregnant women. Serum BPA was positively correlated to immature oocytes (MI) and abnormal oocytes. Also, BPA inversely correlated to Grade1 embryos and positively correlated to Grade 3 embryos. Bisphenol A can be detected in sera of infertile female undergoing ICSI. High BPA level in serum may impact oocyte quality and embryo grading

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KEYWORD

Bisphenol A (BPA), Infertility, ICSI Cycle

1. Introduction

When a couple is unsuccessful to obtain a pregnancy after one year of sexual intercourse without contraceptive barriers, such a case is defined as infertility, which is a worldwide problem that impacts millions of couples globally **(World Health Organization's (WHO) Fertility, 2021 [1])**

It has been noticed there was an elevation in the infertility rate during the last decades **(Vasilopoulos et al. 2019 [2])**, which may be related to the Industrial Revolution and growing environmental contamination **(Tsatsakis et al. 2019 [3]).**

One of these interested contaminants is Bisphenol A. It is an organic synthetic compound that was made for the first time in 1891 by Alexander P. Dianin. BPA is widely used as stuff in multiple industries, like the internal coating of food cans and water bottles **(Ohore & Zhang, 2019 [4])**. BPA has estrogenic features, so it is categorized as an endocrine-disrupting chemical (EDC) **(Husain &Qayyum, 2013 [5])**

About 7.7 million metric tons of BPA had been consummated annually worldwide in 2015, and this consumption is estimated to grow at a rate of 4.8% from 2016 to 2022 **(Altmäe and Aghajanova, 2019 [6]).** Over time and with recurrent exposure to heat, these products can leach BPA into food and liquids **(Brede et al. 2003 [7])**. Food ingestion is the main source of human exposure to BPA **(Chen et al. 2016 [8]).** The accurate pathways of BPA-mediated effects on reproduction are not completely known. BPA can cumulate in reproductive organs and work as an endocrine disruptor due to its structural similarity to estrogen **(Vandenberg et al. 2007 [9])**

Through different pathways, BPA can adversely affect female fertility. Recently, it was demonstrated that BPA has many potential biological activities in addition to its estrogenic effect **(Hao et al. 2015 [10])**

Additionally, BPA can also bind to other reproductive hormone receptors (androgen and progesterone receptors), which play cardinal roles in female genital tract development and pregnancy maintenance **(Asencio-Hernandez et al. 2016 [11])**.

BPA interferes with the steroidogenesis process by reduction of StAR (Steroid Acute Regulatory Protein), which regulates the initial step of adrenal steroid genesis and P450 aromatase, by which the production of Estradiol (E2) is interrupted and follicular atresia is increased. These changes are seen in human diseases that lead to infertility, polycystic ovary syndrome, and endometriosis **(Santangeli et al. 2017 [12])**. Furthermore, BPA has multiple effects on the ovary. For example, BPA exposure is associated with lower antral follicle counts **(Souter et al. 2013 [13]).**

2. Patients and Methods

A total of 60 infertile women enrolled in the study. This study was conducted at the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University, during the period from October 2012 to April 2022. They are selected according to certain criteria.

The age of participants was from 20 to 42 years, and with period of infertility extending from one to 19 years. The cause of infertility was either male factor, female factor, combined cause, or unexplained cause .

Infertile females with primary or secondary type of infertility and with normal ovarian reserve (depending on FSH, AFC, and AMH) were contributed in the study. Whereas Patients who had uterine abnormality (congenital and acquired), or who's partner had sever male factor, or who had testicular biopsy were excluded. Also, the study excluded the frozen

embryos. All participants were received written informed consent after an explanation of the study procedure.

They were subjected to routine fertility workups before ovarian stimulation to know their fitness to share in the study .

Flexible GnRH antagonist protocol for controlled ovarian hyperstimulation (COH) were applied for all participants, in which recombinant FSH (Gonal F, 75IU) was initiated on day 2 of the cycle. When the largest follicle reached a diameter of 12- 14 mm, the GnRH antagonist (Cetrotide) was administered in a dose of 0.25 mg daily until three or more follicles attained a 17mm diameter or more. At this time, the ovulation is provoked by the administration of 250 µg human chorionic gonadotropin (hCG) (Ovitrelle®) subcutaneously .

Then, all participants were undergone oocyte pickup, ICSI, morphological assessment of oocytes and embryos, and embryo transfer. The end of the study period was defined as a positive or negative pregnancy test according to routine clinical practice.

1- Measurement of Bisphenol A in serum: On the day of oocyte retrieval, 5 ml of venous blood were sampled from women. The blood samples were centrifuged, and serum samples were stored in -20℃ to be used later for measurement of bisphenol A (BPA). Bisphenol A levels were analyzed through an enzyme-linked immunosorbent assay (ELISA) technique. The kit was purchased from My Bio Source® and labeled as a human Bisphenol ELISA kit.

2- Statistical analysis: Data were collected, summarized, analyzed, and presented using the statistical package for social sciences (SPSS) version 26 and Microsoft Office Excel 2016. Qualitative (categorical) variables were expressed as numbers and percentages, whereas quantitative (numeric) variables were expressed as means and standard Error of Mean (SEM) for continuous measurements. The t-test was done for the comparison between

pregnant and non-pregnant ladies regarding the mean age, mean BMI, oocyte characteristics, fertilization rate, embryo quality, and the levels of Bisphenol A. On the other hand, the comparison between pregnant and non-pregnant ladies regarding (different categories of type and causes of infertility, residency, educational level, occupation, and use of canned food) was done using chi-square. The probability value (P value) less than or equal to 0.05 was set as statistically significant. In order to detect the cutoff value that predicts a positive finding, receiver operator characteristic (ROC) curve analysis was used with its corresponding area under the curve (AUC), accuracy level, sensitivity, specificity, and level of significance (P).

3. Results

1- Demographic characteristics of pregnant and non-pregnant women: Sixty women accepted to participate in this study; twenty-two of them were pregnant, and the rest thirty-eight were non-pregnant. The mean age of pregnant women was 34.27±1.12years and that of women who failed to get pregnant was 32.32±0.85 years; there was no significant difference in mean age between pregnant and non-pregnant women (P = 0.16). The mean BMI of pregnant ladies was 28.5±3.67 kg/m2, and that of non-pregnant was 27.37±3.53 kg/m2; there was no significant difference in mean BMI between the two groups (P = 0.40). There was no significant difference between the two groups in the proportions of women according to their residency (rural or urban) (P=0.87), the educational level (primary, secondary, or high education) (P=0.25), their occupation (employee or housewife) (P=0.29), and their usage of canned food (P=0.22). Also, there was no significant difference in the proportions of women with primary or secondary infertility in either group,19 (86.4%) versus 31 (81.6%) and 3

(13.6%) versus 7 (18.4%), respectively (P = 0.63).

2- Serum Bisphenol A in pregnant and non-pregnant groups:

The mean level of the serum Bisphenol A of pregnant and non-pregnant women showed no significant statistical differences. Mean serum BPA was not significantly higher in non-pregnant women in comparison with that of pregnant women, 35.91±3.18 ng/ml versus 35.47±3.10 ng/ml, respectively (P = 0.92)

3- Predictive role of serum Bisphenol A (BPA); pregnancy outcome following assisted reproduction:

To obtain a cutoff value for the level of serum bisphenol A that predicts a positive pregnancy outcome with a certain level of accuracy, a receiver operator characteristic (ROC) curve analysis was carried out. The cutoff value of serum bisphenol A was >42.8ng/ml with sensitivity and specificity levels of 36.36% and 89.47%, respectively; the cutoff value had a non-significant level (P = 0.667).

4- Correlations of serum level of Bisphenol A with the number of oocytes and oocytes quality:

There was no significant correlation of serum Bisphenol A with the total number of oocytes, MII, GV oocytes, maturity index, and fertilization rate. Serum BPA is positively correlated with MI and abnormal oocytes.

5- Correlations of serum level of Bisphenol A with the embryo transfer and embryo quality:

There was no significant correlation between serum Bisphenol A with the number of the transferred embryo and G2 embryos. Serum BPA negatively correlated with the G1 embryo and positively correlated with the G3 embryo.

Table (1): Comparison of demographic features between pregnant and non-pregnant (Mean ± SEM)

Variable		pregnant (n=22)	non-pregnant (n=38)	P value
age (years)		34.27±1.12	32.32±0.85	0.16 NS
BMI (kg/m^2)		28.5±3.67	27.37±3.53	0.40NS
Residency n (%)	urban	17 (77.3%)	30 (78.9%)	0.87NS
	Rural	5 (22.7%)	8 (21.1%)	
Education n (%)	primary	4 (18.2%)	20 (52.6%)	0.25NS
	secondary	10 (45.5%)	8 (21.1%)	
	higher	8 (36.3%)	10 (26.3%)	
occupation n (%)	employee	11 (50%)	8 (21.1%)	0.02*
	housewife	11 (50%)	30 (78.9%)	
Use of Canned food, n (%)	Yes	14 (63.6%)	18 (47.4%)	0.22NS
	No	8 (36.4%)	20 (52.6%)	
type of infertility	primary	19 (86.4%)	31 (81.6%)	0.63
	secondary	3 (13.6%)	7 (18.4%)	
cause of infertility	female factor	3 (13.7%)	7 (18.4%)	0.63
	male factor	17 (77.3%)	23 (60.5%)	0.01*
	unexplained	2 (9%)	8 (21.1%)	0.23
history of IVF	first trail	18 (81.8%)	36 36 (94.7%)	0.10
	repeated trial	4 (18.2%)	2 (5.3%)	
Duration of infertility (Mean±SEM) Yr		6.6 ± 0.76	8.1± 0.85	0.25

*: signifiant (p≤0.05), NS : No-signifiant.

Table (2): Serum Bisphenol A; in pregnant and non-pregnant groups

Groups	Mean ± SEM of BPA in serum (ng/ml)
Pregnant	35.47±3.10
Non-pregnant	35.91±3.18
P-value	0.92
NS: Non-significant (p>0.05)	

Table (3): Characteristics of ROC curves

Characteristics	Serum Bisphenol A
Cut off value	>42.8
AUC (95 % CI)	0.537 (0.404 - 0.667)
Sensitivity	36.36
Specificity	89.47
P-value	0.667
NS: Non-significant (p>0.05)	

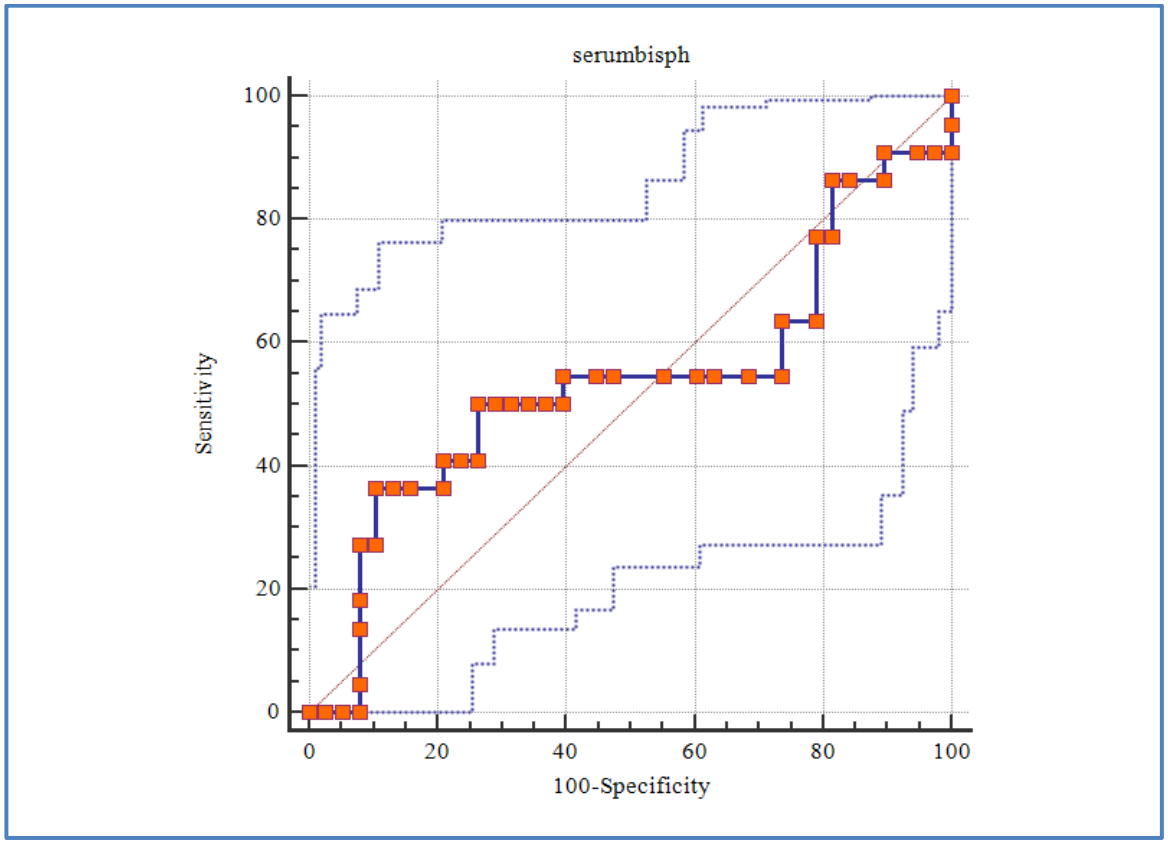
Table (4): Correlations of serum Bisphenol A with the number of oocytes and oocyte quality

Variable		Serum BPA
Total Oocytes	R	0.103
	P	0.432
Metaphase I	R	0.322*
	P	0.045
Metaphase II	R	0.112
	P	0.394
Germinal vesicles (GV)	R	0.073
	P	0.696
Abnormal	R	0.376*
	P	0.037
Maturity index	R	0.069
	P	0.600
Fertilization rate	R	0.218
	P	0.094
*: Significant at p-value < 0.05		

Table (5): Correlations of serum level of Bisphenol A with the embryo transfer and embryo quality

Variable		Serum BPA
Grade 1	r	-0.319*
	p	0.024
Grade 2	r	-0.134
	p	0.428
Grade 3	r	0.473*
	p	0.047
Embryo transfer	r	0.161
	p	0.220
*: Significant at p-value < 0.05		

Figure (1): ROC curve of serum BPA as a predictor of pregnancy



4. Discussion

The current study showed that there was no significant difference in mean age between pregnant and non-pregnant women, which is inconsistent with the result of another study, which noticed an acceptable low outcome in women aged 35-37 years during the first three ovarian stimulation cycles **(Zhang et al. 2018 [14])**. On the contrary, other studies concluded that the female age is the fundamental predictor of pregnancy after the assisted reproduction technique, and there is a negative relation between advancing female age and the success rate of ICSI **(Razi et al. 2014 [15]; Fahad et al. 2015 [16]).**

According to this study, bisphenol A can be detected in sera of all participants. This result is following that of previous studies **(Gao et al. 2021 [6]; Kahn et al. 2020 [17])**. However, it is disagreed with **(Bin et al. 2016 [18]),** who detected bisphenol A in only 43% of females undergoing IVF. These different results may be caused by the variability of the sample size of these studies, different durations of exposure to BPA, as well as the varying capacity of BPA metabolism among individuals and ethnic groups (enzyme polymorphisms).

Female fertility is highly affected by BPA via different pathways; recently, it was suggested that bisphenol A has multiple biological activities in addition to its role as a weak estrogen. **(Hao et al. 2015 [19]).** The suggested effect of BPA in IVF/ ICSI has been investigated in several observational studies, which reported a negative correlation between BPA levels and IVF/ICSI outcomes **(Pivonello et al. 2020 [20])**. Yenigül et al. (2021) suggested that a negative association between embryo quality with serum BPA levels(Yenigül

Through assessment of the embryological stage of IVF/ICSI programs, there was no significant effect of the serum bisphenol A on oocyte count, number of mature

oocytes, number of GV, maturity index, and fertilization rate. A previous study **(Poormoosavi et al. 2019 [22])** reported the same result that the levels of BPA in serum did not affect mature oocytes (MII) .

Lee et al. (2018) **(Lee YM et al.,2018 [23])** have noticed an adverse role of BPA on the quality of gametes and embryos; anywise, the mechanism of this effect is not understood yet. It was supposed that BPA is associated with meiotic arrest, changes in the structure of the meiotic spindle, impairment of chromosomal alignment, and a high incidence of aneuploidy **(Hunt & Hassold, 2008 [24]; Machtinger et al. 2013 [25])**. BPA exposure induces Reactive oxygen species (ROS), which may induce cell apoptosis and senescence **(Wang et al. 2016 [26])** and increase the number of degenerated oocytes **(Machtinger et al. 2013 [25])**. These speculated mechanisms may explain the statistically significant positive relation of immature oocytes (MI) and abnormal oocytes with serum BPA levels demonstrated in the present study. These results go with **(Lenie et al. 2008 [27]; Fujimoto et al. 2011 [28]).**

Also, there was a negative correlation between BAP level in serum and the number of grade 1 embryos, and there was a positive correlation with grade 3 embryos. These results in consistent with Syrkasheva et al. (2021) **(Syrkasheva A and Yenigül et al., 2021[29])** Who concluded that the increased level of bisphenol A in the blood or serum may be correlated with a decrease in the quality of oocytes and embryos in ART. Conversely, Kim et al. (2021) **(Kim MJ et al. 2021 [30])** noted that there is no significant relation between serum bisphenol A levels and outcomes of IVF, such as normally fertilized oocytes, good embryo quality, and pregnancy rate.

Contrary to **(Syrkasheva et al. 2021 [29])** and **(Kim et al. 2021 [30]; Alzaidi, Z. et al.,2021[31])** who observed that the pregnancy rate is not affected by the level of BPA in blood,

the present study shows that the higher pregnancy rate was in the patient's group of lower serum BPA levels. However, the difference was statistically nonsignificant. The small sample size and cross-sectional design are the limitations of this study.

6- Conclusion

In conclusion, Bisphenol A can be detected in sera of all infertile females undergoing IVF/ICSI. Significant associations between BPA in relation to reproductive outcomes among women attending a fertility center were noticed. High serum BPA level adversely affects oocytes and embryos quality. It is associated with increased numbers of immature oocytes (MI), abnormal oocytes, and Grade III embryos. Whereas high serum BPA levels are associated with decrease numbers of Grade I embryo

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Author Contribution

Sarah Hamza performed the study, and Muayad Abbood Essra M. Al-Esawee supervised the work .

Conflict of Interest

The authors declare no conflict of interest .

Ethical Clearance

The study was approved by the Ethical Approval Committee.

Financial Disclosure

There is no financial disclosure.

Ethical Clearance

The study was approved by the Ethical Approval Committee

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