Original Article

Effect of Bisphenol A Level in Follicular Fluid on ICSI OutCome

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Abstract

Background: Infertility is the disability of a couple to obtain pregnancy after one year of sexual intercourse that is unprotected and regular. Bisphenol A (BPA) is an industrial chemical, that is produced in huge quantities worldwide. It is utilized as a raw material in multiple industries, and assorted as one of the endocrine-disrupting chemicals, as it can interfere with hormone activity. Bisphenol A may have a role in the reproduction process and may impact oocyte's maturity, meiotic division of germ cells, or fertilization rate. This study aimed to assess the impact of Bisphenol A level in follicular fluid on ICSI outcome.

Methodology: The study was conducted at the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies / Al Nahrain University, Baghdad /Iraq, at the interval extending from October 2021 to April 2022. Sixty infertile women enrolled in this study. BPA levels in follicular fluid were evaluated through an enzyme-linked immunosorbent assay (ELISA) technique.

Results: Of 60 patients enrolled in this study, 22 patients (36.3%) became pregnant. Bisphenol A was detected in follicular fluids (FF) of all patients. The mean follicular fluid BPA level was significantly lower in pregnant women in comparison with that of non-pregnant women (45.44±1.73 ng/ml versus 68.23±6.77 ng/ml, respectively P = 0.01). A significant positive correlation was detected between BPA levels in follicular fluid and Grade 3embryos (r=0.539, p=0.021).

Conclusion: Bisphenol A can be detected in follicular fluids of all patients undergoing IVF/ICSI. Elevated BPA levels in the follicular fluid may affect IVF/ICSI outcomes (embryo quality and pregnancy rate).

Keywords: Bisphenol A (BPA), Follicular Fluid, ICSI Cycle, Infertility.

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INTRODUCTION

Infertility is a worldwide health issue, that affect approximatly 8 to 12% of the couples (Boivin, Bunting, Collins, & Nygren, 2007). It is described as the lack of ability of a couple to gain a pregnancy after12 months of sexual intercourse without contraceptive barriers (World Health Organization, 2021).

Recently, there was a quiet reduction in the fertility rate all over the world (Vasilopoulos et al., 2019) in both sexes, which may be related to the industrial revolution and growing environmental contamination (Tsatsakis et al., 2019). EDCs are exogenous chemicals that can impair hormones synthesis, metabolism, and function (Gregoraszczuk & Ptak, 2013).

Bisphenol A is an organic man-made compound and one of the most interesting environmental contaminants.
It is recognized as an endocrine-disrupting chemical (EDC) (Husain & Qayyum, 2013).

Initially, BPA was produced in 1891 by chemist Alexander P Dianin. It is widely used as raw material in several manufacturers mainly in the manufacturing of polycarbonate plastics and epoxy resins, for instance, in the internal coating of food cans and water bottles as cited by (Ohore & Zhang, 2019).

About 7.7 million metric tons of BPA had been consumed each year globally in 2015 and there was an elevation in the rate of consumption at about 4.8% from 2016 to 2022 (Gao et al., 2021). With time and due to recurrent exposure to heat the products containing BPA can leach it into food and liquids (Brede, Fjeldal, Skjevrak, & Herikstad, 2003). Food ingestion is the main source of human exposure to BPA (Chen, Shen, & Chen, 2016). The pathways via which BPA exerts its effects on reproduction are not accurately understood BPA can cumulate in reproductive organs and behave as an endocrine disrupting chemical as biphenol A structure is similar to the estrogen structure (reviewed in (Vandenberg, Hauser, Marcus, Olea, & Welshons, 2007). 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., 2011).

Additionally, BPA can also bind to other reproductive hormone receptors (androgen and progesterone receptors), which play cardinal roles in the female genital tract development and pregnancy maintenance (Asencio-Hernández, Kieffer, & Delsuc, 2016).

BPA can interfere with the steroidogenesis process by reduction of StAR (Steroid Acute Regulatory Protein), which regulates the initial step of adrenal steroidogenesis and P450 aromatase, by which the synthesis of Estradiol (E2) is interrupted and follicular atresia is increased. These changes were observed in human disorders that are associated with infertility, polycystic ovary syndrome, and endometriosis (Santangeli et al., 2017). Furthermore, BPA has multiple impacts on the ovary. For example, the relationship between exposure to Bisphenol A and low antral follicle counts (Souter et al., 2013).

Generally, BPA has been revealed in different tissues, including adult sera, breast milk, urine (Vandenberg et al., 2007), follicular fluid, and amniotic fluid (Ikezuki, Tsutsumi, Takai, Kamei, & Taketani, 2002).

Follicular fluid (FF) is a complex biological fluid that is secreted inside growing antral follicles and encloses the developing oocyte. It contains different types of molecules, such as proteins, steroid hormones, polysaccharides, metabolites, reactive oxygen species (ROS), and antioxidants. The primary function of these molecules is to harmonize oocyte and follicular maturation and protect follicular cells from physical or oxidative damage (Mariani & Bellver, 2018).

MATERIAL AND METHODS

Sixty infertile women enrolled in this cross-sectional study. The study was conducted at the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies / Al Nahrain University, Baghdad /Iraq, at the interval extending from October 2021 to April 2022. The participants were selected according to certain criteria.

The age of participants was from 20 to 42 years, with a 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 a primary or secondary type of infertility, and with normal ovarian reserve (depending on FSH, AFC, and AMH) were contributed to the study. Whereas, Patients who had uterine abnormality (congenital and acquired), whose partner had severe male factors, or whose partner had testicular biopsy were excluded. Also, the study excluded women who had frozen embryo transfere. All participants received written informed consent after an explanation of the study procedure.

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

A flexible GnRH antagonist protocol for controlled ovarian hyper stimulation (COH) was applied for all participants, in which recombinant FSH (Gonal F, 75IU) was initiated on the day2 of the cycle. When the largest follicle attained a diameter of 12- 14 mm GnRH antagonist (Cetrotide) was administered at a dose of 0.25 mg daily until three or more follicles gained 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.

Measurement of Bisphenol A in follicular fluid

On the day of oocyte retrieval, the follicular fluid samples among the several mature follicles containing oocytes were recovered for each patient during the oocyte retrieval procedure by means of a transvaginal follicular aspiration. The follicular fluid (FF) samples were centrifuged immediately at 3000 rpm for 10 minutes to remove cell debris and granulosa cells from the samples. The prepared follicular fluid was stored immediately at -20℃ until the time of the assay to prevent any sample alteration. Bisphenol A levels were evaluated through an enzyme-linked immunosorbent assay (ELISA) technique. The kit was purchased from My Bio Source® and labeled as a human Bisphenol A ELISA kit.

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. To detect the cutoff value that predicts a positive finding, receiver operator characteristic (ROC) curve analysis was utilized with its corresponding area under the curve (AUC), accuracy level, sensitivity, specificity, and level of significance (P).

RESULTS

Classification of the Study Group

Sixty infertile women involved in this study were categorized, depending on the results of the pregnancy test (P.T) which was achieved at 14 days after embryo transfer, into two groups, figure (1):

1. Pregnant group, consisting of; twenty two women (36.7%).
2. Non-pregnant group, consisting of; thirty eight women (63.3%).

The comparison between these two groups of infertile females using demographic features, Bisphenol A concentrations in the follicular fluid of the retrieved follicles, oocytes and embryos morphology.

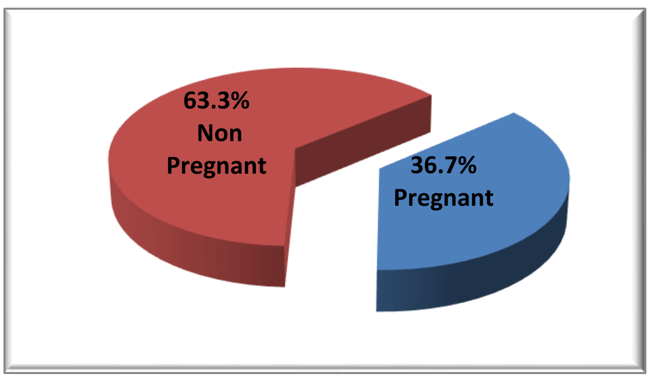

Figure 1. The result of ICSI pregnant and non-pregnant.

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).

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/m2)		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 ofinfertility (Mean±SEM)Yr		6.6 ± 0.76	8.1± 0.85	0.25

Significant (p≤0.05), NS : No-significant.

Comparison between pregnant and non-pregnant in means of BPA levels in follicular fluid

Table (2) shows a Comparison between pregnant and non-pregnant in means of BPA levels in follicular fluid, The BPA levels are expressed as (ng/ml).In the pregnant group, the BPA level (Mean ± SEM) in follicular fluid was (45.44±1.73), while in the non-pregnant group the BPA levels(Mean ± SEM) were highly significant (68.23±6.77, p=0.01).

Table 2. Comparison between pregnant and non-pregnant in BPA level in follicular fluid

The group	Mean ± SEM of BPA in follicular fluid (ng/ml)
Pregnant	45.44±1.73
Non-pregnant	68.23±6.77
P-value	0.01*

Significant* (p≤0.05)

Predictive role of follicular fluid Bisphenol A (BPA); pregnancy outcome following assisted reproduction

To obtain a cutoff value for the level of follicular fluid 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 for the follicular fluid bisphenol A was ≤52.83ng/ml with sensitivity and specificity levels of 95.45% and 39.47%, respectively; the cutoff values had a significant level (P=0.034).

Table 3. Characteristics of ROC curves

Characteristics	Follicular Fluid Bisphenol A (ng/ml)
Cut off value	≤52.83
AUC (95 % CI)	0.650(0.516 - 0.769)
Sensitivity	95.45
Specificity	39.47
P-value	0.034*

Significant*(p<0.05)

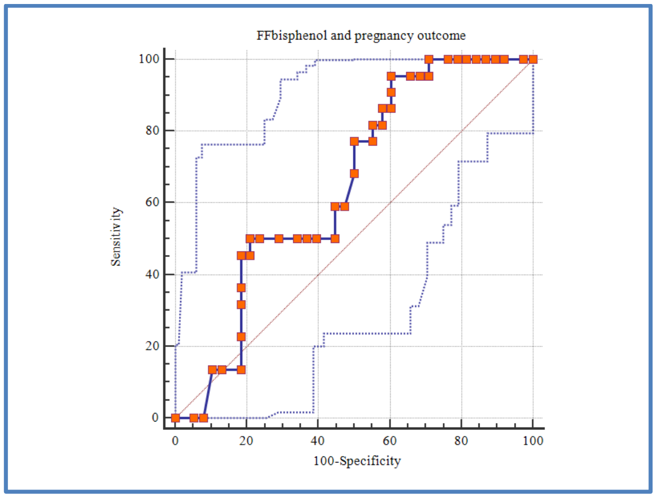

Figure 2. ROC curve of follicular fluid BPA as a predictor of pregnancy

Correlations between follicular fluid BPA with patient's ICSI parameters

Despite the absence of a significant correlation between follicular fluid Bisphenol A and most ICSI parameters,BPA level in follicular fluid demonstrated a significant positive correlation with grade 3 embryos (r=0.539 & p=0.021).

Table 3. Correlations between follicular fluid BPA with patient's ICSI parameters

Variable		Follicular BPA
Total Oocytes	r	0.210
	p	0.107
Metaphase I	r	0.155
	p	0.346
Metaphase II	r	0.190
	p	0.145
Germinal vesicles (GV)	r	-0.065
	p	0.727
Abnormal	r	-0.069
	p	0.711
Maturity index	r	-0.049
	p	0.710
Fertilization rate	r	-0.220
	p	0.090
Grade 1 embryo	r	-0.034
	p	0.817
Grade 2 embryo	r	-0.058
	p	0.733
Grade 3 embryo	r	0.539*
	p	0.021
Embryo transfer	r	-0.129
	p	0.325

Significant*(p<0.05)

Discussion

In the current study the pregnancy rate was (36.7%), which is lower than that in Europe, where the mean pregnancy rate per embryo transfer was (40.2%) after ICSI ((ESHRE), 2022).

The present study displayed the absence of a significant difference in mean age between pregnant and non-pregnant women, which agreed with the result of (Zhang, Bu, Su, &

Zhu, 2018) who noted a reasonable low outcome in women aged 35-37 years during the first three ovarian stimulation cycles. In opposite other studies concluded that the female age is the fundamental predictor of pregnancy after assisted reproduction technique and there is a negative relation between increasing female age and the success rate of ICSI (Al-Obaidi, Mahdi, & Alwasiti, 2018; Fahad, Al-Murshedi, & Al-Khafaji, 2015). Also, the comparison between the Pregnant and Non-Pregnant women, showed that there were no significant differences in other demographic characteristics, namely body mass index (BMI), residency, educational level, occupation, lifestyle habits, type, and duration of infertility, and history of previous IVF treatment.

Data on the measurement of BPA in human follicular fluid are scarce and contradictory. The current study noticed that BPA was detected in all follicular fluid samples, which proves the theory of its ability to pass through the blood–tissue barriers, which is agreed with (Du et al., 2016). The same result was obtained by (M. J. Kim & Park, 2019) who concluded that BPA was detected in most follicular fluid samples of patients in ART programs, but its level was not correlated with the quality of oocytes/embryos, on the contrary, in (Krotz, Carson, Tomey, & Buster, 2012). BPA was not detected in follicular fluid.

The overall differences among studies could be justified by both methodological issues (BPA measurement techniques, ELISA, HPLC system, and other detection methods) and by the sample size enrolled in these studies. As well as the varying capacity of BPA metabolism between individuals

and among ethnic groups (enzymes polymorphisms). However, together with different exposure levels resulting from different geographical areas, a variable clearance rate could explain the different concentrations of BPA in body fluids (Anastasiya Syrkasheva et al., 2021a).

Female fertility is highly affected by BPA via different pathways. Recently, much evidence observed the possible adverse effects of BPA on IVF outcomes (Machtinger & Orvieto, 2014). Through assessment of the embryological stage of IVF/ICSI programs, there was a positive relationship between follicular fluid BPA levels with Grade III embryos. A similar result was observed in (A. Syrkasheva et al., 2021b). As well, (Yenigül et al., 2021) and (Lee et al., 2018) suggested that a negative association was found between follicular fluid BPA levels and embryo quality, however, the mechanisms of this effect are not well understood. This result disagreed with (H.-K. Kim et al., 2021) who concluded that the BPA levels in body fluids (serum and FF) are not associated with outcomes of IVF such as pregnancy, good quality embryo, and normally fertilized oocytes.

The correlation of BPA levels in follicular fluid with the count of oocytes retrieved, mature oocytes (MII), immature oocytes (MI and GV), and abnormal oocytes were not concluded in this study. Although the previous study (Poormoosavi, Behmanesh, Janati, & Najafzadehvarzi, 2019) reported the same results, that the levels of BPA in FF had no effect on mature oocytes (MII), it was concluded that BPA levels in FF adversely affect oocyte count and the incidence of morphological oocyte abnormalities.

The absence of relation between BPA and the number of oocytes retrieved was also stated by (Bloom et al., 2011) and (Bin, Ning, & Yu-ping, 2016; H.-K. Kim et al., 2021) in accordance with the current study.

This result could be explained by that the occurrence of endocrine disrupting substances inside the follicle could disrupt the composition of the follicular fluid (Hallberg et al., 2021), which in turn strongly affects oocyte quality, developmental competence, and the quality of the subsequent embryo (Buyuk et al., 2017; Hallberg et al., 2021). The small sample size and cross-sectional design are the limitations of this study. In addition, the impacts of other environmental contaminants can not be excluded and they may affect the results of this study.

Conclusion

From the present study, it is concluded that Bisphenol A can be detected in follicular fluids 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 follicular fluid BPA levels may negatively impact the pregnancy rate. There was a highly significant relationship between the follicular fluid level of BPA with pregnancy, and there was a significant positive relation between Grade 3 embryos and a higher level of follicular fluid BPA levels.

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Author Contribution

Herez SH, performed the study, examined and reviewed results, and manuscript writing with the help and supervision of Abbod MS, and Jawad MA.

Conflict of Interest

The authors declare no conflict of interest.

Ethical Clearance

The study was approved by the Ethical Approval Committee.

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