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The association between exposure to multiple environmental chemicals and recurrent pregnancy loss

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Abstract

Recurrent pregnancy loss (RPL) is one of the most frustrating problems in reproductive medicine because the etiology is often unknown.

The current study was conducted to investigate the possible associations of polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs) and organophosphates(OPs), and unexplained RPL.

This cross-sectional study included 52 cases with definite diagnosis RPL and 49 pregnant controls with normal obstetric history .Plasma levels of PCBs, OCPs and OPs were looked for using (GC/MS) technique.

Plasma levels of PCB28, PCB52, PCB118 and PCB180, p, p'- DDE, dieldrin and ethion were significantly higher in women presented with unexplained RPL in comparison to their levels in the control group ($P < 0.05$). Moreover, the plasma levels of PCB52, PCB180, dieldrin, alachlor, heptachlor epoxide and diazinon were significantly higher ($p < 0.05$) in those who were exposed to environmental chemicals than those who did not report such event.. Those who reported exposure to PCB 28, PCB 52, PCB 180 and ethion were 1.2, 2.2, 3.2, 5.2 times, respectively more likely to have RPL respectively, and this was statistically significant (OR = 1.16, 2.20, 3.16, 5.22; 95% CI= 1.1-3.8, 1.3-4.6, 1.9- 5.2, 2.6- 7.4 respectively).In conclusion: This study suggests that high plasma levels of PCBs ,OCPs and OPs are associated with increased risk of RPL

Keywords:*Environmental chemicals, PCBs.Pesticides. Gas Chromatography/Mass Spectrometry (GC/MS). Recurrent pregnancy loss (RPL).*

Abbreviations: PCBs, polychlorinated biphenyls; OCPs, organochlorine pesticides; OPPs ,organophosphorus pesticides; CI, confidence interval; OR, odds ratio; SD, standard deviation.

1. Introduction

Recurrent pregnancy loss (RPL) , defined as the loss of three or more consecutive pregnancies,affects1% of couples trying to conceive. (1).

Risk factors for RPL include epidemiological factors, antiphospholipid syndrome, genetic factors, anatomical anomalies, endocrine disorders, immune factors, infective agents and Inherited thrombophilic defects. However, In about half of the cases no definite cause could be detected.(2)

Previous studies showed an association between exposure to environmental chemicals as pesticides and poor reproductive outcome, including spontaneous abortion. They possibly act as endocrine disruptors (3).
Endocrine disrupting chemicals are of particular interest as potential contributory agents in the development of recurrent pregnancy loss because they alter steroid synthesis or action , lead to immune impairments(4), and can interrupt elements of reproductive function via epigenetic modification(5).
Polychlorinated biphenyls (PCBs) are persistent in the environment and in food chains because of their high resistance to abiotic and biotic degradation(6). Maternal exposure to PCBs may affect pregnancy outcomes (7). Dietary PCB exposure increases the rate of spontaneous abortion and stillbirth in animals(8), (9). Only a few epidemiologic studies have examined the association between maternal exposure to PCBs and pregnancy outcomes in humans. However, recent cohort studies failed to support an association between maternal serum levels of chemicals and adverse pregnancy outcomes in women exposed to PCBs (10),(11),(12).Thus, it is controversial whether maternal exposure to PCBs is associated with adverse pregnancy outcomes in humans (13)
OCPs can induce endocrine dysfunctions, immunological changes, oxidative stress and DNA damage (14), (15),(16). Previous studies have reported high levels of DDT isomers and its metabolites in women with spontaneous abortion(17),(18), (19). However, studies regarding role of other OCPs in RPL are scarce (20).
Multiple chemical exposures are of increasing concern. Assessment of exposure to multiple chemicals has been identified as an important research area (21),(22) .
The aim of the current study is to evaluate the possible association between exposure to some environmental toxins and unexplained RPL.

2. Patients and methods

This is a cross sectional study. It was carried out on 101 women recruited from the outpatient clinic of the Women Health Hospital, Assiut University, Egypt. Women were enrolled into the study between January 2010 and January 2011. They were classified into 2 groups: 52 cases with definite diagnosis of missed abortion and history of three or more events of RPL and 49 controls with normal first trimester pregnancy and normal obstetric history. Women with hormonal disorders (uncontrolled diabetes ,uncontrolled thyroid dysfunction), uterine abnormalities (Subseptate uterus , uterus fibroids, adhesions), anti-phospholipid syndrome, immunological causes of miscarriages, hypertension, bacterial vaginosis, TORCH infections, tuberculosis, carriers of chromosomal translocation, active smokers were excluded from both the groups. The spouses of these women were also with normal karyotype, normal sperm count and normal sperm morphology. The women we included in this study were of relatively homogenous group and they were similar in terms of demographical characteristics such as age, weight, BMI, food habits, drinking water supply, living style and socioeconomic status. Cases with RPL meeting these exclusion criteria are termed unexplained RPL.A questionnaire survey of the women was used to collect general demographic information. Cases were classified into exposed to pesticides (no. 10) and non exposed (no. 42) women with unexplained RPL. Informed consent was obtained from each participant woman. The study was approved by the Ethics Committee of Faculty of Medicine, Assiut University.

Venous blood samples (10 ml) were collected aseptically from all subjects via vein puncture in a sterile collecting tube containing k3 EDT as an anticoagulant, then centrifuged at 4000 rpm for 10 minutes. The separated plasma was collected and stored at -20°C for further analysis.

Exposure data and biological sample collection

Eligible women who agreed to participate in the study answered a structured questionnaire that gathered retrospective information related to each one of their pregnancies, specifically about the mother's social-demographic characteristics, exposure to chemicals at home and at work, characteristics of their floricultural work, reproductive history (number of pregnancies, their result and char-acteristics of the newborn), folic acid supplementation before or dur-ing pregnancy, clinical history (diabetes mellitus, high blood pressure, hyper or hypothyroidism), and tobacco and alcohol consumption. Those pregnancies that ended before 20 weeks of gestation were classified as abortions. The assessment of exposure to floricultural work (a proxy of pesticide exposure) was based on information from the questionnaire, which included specific data about the mother's work activity during each of the pregnancies that took place within the last 10 years. Exposure to floricultural work for each of these was classified as:
1. Exposed: pregnancy in which the mother worked as afloriculturist
during the period between 3 months before the beginning of the pregnancy and the first five months

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of pregnancy, which we will call the Acute Risk Period (ARP).
2. Not exposed: A pregnancy in which the mother did not work as a floriculturist during the ARP.

Instrumentation

The samples were assayed at the Analytical chemistry unit, ACAL, University of Assiut with an A state-of-the-art Gas Chromatograph, analytical system equipped with temperature programming capability, splitless injector, capillary column, and Mass Quadrupole Spectrometry detector (GC/MS) (7890A/5975B). A computer data system is MSD ChemStation E.0201.1177 used for measuring peak areas and heights from Agilent Technologies.
Mann-Whitney-U-test was used. Multivariate logistic regression models were used for statical analysis .A significant p value was considered when it is < 0.05.
Samples are analyzed using these conditions; their data are collected in Fig. 1 and 2 shows the GC/MS as examples of the patient and control samples applying the foregoing experimental conditions.

Results

The unexplained RPL group and the control groups were matched and there were no statistically significant differences between them as regard to maternal age and residence (Table 1).

Table 1 Socio-demographic difference between the two groups (cases vs. controls)

	Case (No=52)	Control (No=49)	P-value
Mean Age ± SD	28.4 ± 6.8	26.1 ± 5.7	> 0.05*
Residence			
• Rural	36 (69.2%)	33 (67.3%)	> 0.05**
• Urban	16 (30.8%)	16 (32.7%)	

*T-test analysis was used to compare the mean difference between the two groups
**Chi-square analysis was used to compare the difference in proportions
--Significance level is considered when p < 0.05

Maternity characteristics of RPL cases

The number of living children and abortion were 2.0±1.8 and 3.6±2.6 in the control and study groups respectively (Mean±SD).

Frequency of environmental chemicals detection among patients with RPL vs. controls

PCBs were detected more frequently in cases presenting with RPL than in the control group. Also ,organochlorines (DDE, Dieldrin) and Organophphates (Ethion) were detected more frequently in cases presenting with RPL than in the control group. However, each of the following compounds was detected in one case only: Alachlor,

Table2 : Frequency of environmental chemicals detection among patients with RPL vs. controls

Variable	Case (No=52)	Control (No=49)	P-value*
Polychlorinated biphenyls (PCBs)			
• PCB28	39 (75%)	7 (14.3%)	< **0.001**
• PCB52	44 (84.6%)	35 (71.4%)	> 0.05
• PCB118	47 (90.4%)	11 (22.4%)	< **0.001**
• PCB180	41 (78.8%)	15 (30.6%)	< **0.001**
Organochlorine			
• DDE	22 (42.3%)	5 (10.2%)	< **0.001**
• Dieldrin	17 (32.7%)	7 (14.3%)	< **0.05**
Organophosphate			
• Ethion	33 (63.5%)	9 (18.4%)	< **0.001**

Table 3 Frequency of environmental chemicals detection among the studied patient

	n = 52	n	%
Polychlorinated biphenyls (PCBs)			
• PCB28		39	75%
• PCB52		44	84.6%
• PCB118		47	90.4%
• PCB180		41	78.8%

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Organochlorine		
• DDE	22	42.3%
• Dieldrin	17	32.7%
• Alachlor	1	1.9%
• Aldrin	7	13.5%
• Epoxide	1	1.9%
Organofluorine		
• Trifluralin	1	1.9%
Organophosphate		
• Chlorpyrifos	1	1.9%
• Ethion	33	63.5%
• Diazinon	4	7.7%

Epoxide, Trifluralin, Chlorpyrifos, Disulfoton, Lindane .Aldrin, Diazinone, Parathyone were detected in only few cases.(Tables 2&3). The following compounds were detected in RPL cases and were not detected in the control group :Organochlorine(Aldrin,epoxide) and Organophosphate(Diazinon)

Logestic regression model for exposure to environmental chemicals among the cases with RPL

The final logistic model for number of abortion among the studied patients was deduced as those who reported exposure to PCB 28, PCB 52, PCB 180 and ethion were 1.2, 2.2, 3.2, 5.2 times respectively more likely to have RPL respectively and this was statistically significantly (OR = 1.16, 2.20, 3.16, 5.22; 95% CI= 1.1-3.8, 1.3- 4.6, 1.9- 5.2, 2.6- 7.4 respectively.

Table 4:. Logestic regression model for exposure to environmental chemicals among the cases with RPL

	AOR**	95% CI**	P-value
• **PCB28**	1.16	1.1-3.8	< **0.001**
• **PCB52**	2.20	1.3-4.6	< **0.01**
• **PCB180**	3.16	1.9-5.2	< **0.01**
• **Ethion**	5.22	2.6-7.4	< **0.001**

*Final model included PCB28, PCB52, PCB180 and Ethion
**Adjusted Odds Ratio, CI= Confidence Interval

Concentration of environmental chemicals levels in plasma

Concentration of environmental chemicals levels in plasma among the two groups (unexplained RPL and controls)

Four PCBs (PCB 28, PCB52, PCB118 and PCB180) and four pesticides; two organochlorines (DDE and dieldrin) and two organophosphorous (chlorpyrifos and ethion) were investigated. There were significant higher plasma levels of PCB 28, 52, 118 and 180, p, p'- DDE, dieldrin and ethion in the unexplained RPL women than their levels in the control group ($P < 0.05$). (Table 5)

Table 5 Comparison between environmental chemicals levels (µg/L) in plasma among cases vs. controls

	Case (No=52)	Control (No=49)	P-value*
	Mean± SD		
Polychlorinated biphenyls (PCBs)			
• PCB28	23.32 ± 45.4	0.76 ± 1.9	< 0.001
• PCB52	82.95 ± 71.3	1.95 ± 3.5	< 0.001
• PCB118	50.21 ± 42.7	0.65 ± 1.6	< 0.001
• PCB180	73.9 ± 61.9	1.38 ± 1.3	< 0.001
Organochlorine			
• p,p'DDE	2.96 ± 1.7	0.03 ± 0.07	< 0.001
• Dieldrin	24.13 ± 22.7	0.61 ± 0.5	< 0.05
Organophosphate			
• Chlorpyrifos	4.23 ± 3.5	0.02 ± 0.01	> 0.05
• Ethion	20.44 ± 19.7	0.18 ± 0.1	< 0.001

*Mann-Whitney non-parametric test was used to compare the mean difference between the two groups --Significance level is considered when $p < 0.05$

Concentration of endocrine disruptor levels in plasma among Exposed and Non – exposed cases with unexplained RPL

The levels of endocrine disruptor in plasma samples were described in Table 6. We studied four PCBs; PCB 28, PCB52, PCB118 and PCB180 and nine pesticides; fiver organochlorine: p,p DDE, dieldrin, alachlor, aldrin and heptachlor epoxide; one organofluorine; trifluralin and three organophosphorus: chlorpyrifos, ethion and diazinon. The plasma levels of PCB52, PCB180, dieldrin, alachlor, heptachlor epoxide, trifluralin, and diazinon were significantly higher ($p < 0.05$) in exposed than non exposed.

Table 6 Comparison between environmental chemicals levels (µg/L) in plasma among exposed vs. non-exposed patients with RPL

	Exposed group (n=10)	**Nonexposed group (n=42)**	**P-value***
	Mean± SE		
Polychlorinated biphenyls (PCBs)			
• **PCB28**	26.32 ± 7.6	10.11 ± 6.3	> 0.05
• **PCB52**	98.75 ± 41.1	16.59 ± 10.9	< **0.05**
• **PCB118**	59.60 ± 38.2	10.76 ± 5.6	> 0.05
• **PCB180**	88.87 ± 44.7	11.01 ± 9.3	< **0.05**
Organochlorine			
• **DDE**	3.18 ± 1.3	2.05 ± 1.4	> 0.05

• **Dieldrin**	29.78 ± 10.6	0.39 ± 0.3	< **0.05**
• **Aldrin**	0.76 ± 0.4	2.83 ± 2.02	< **0.05**
• **Epoxide**	15.90 ± 5.8	0.00 ± 0.0	< **0.05**
Organofluorine			
• **Trifluralin**	1.00 ± 0.7	0.00 ± 0.0	< **0.05**
Organophosphate			
• **Chlorpyrifos**	5.24 ± 3.5	0.00 ± 0.0	> 0.05
• **Ethion**	24.42 ± 17.1	3.72 ± 2.1	> 0.05
• **Diazinon**	36.89 ± 32.5	0.00 ± 0.0	< **0.05**

*Mann-Whitney non-parametric test was used to compare the mean difference
between the two groups
--Significance level is considered when $p < 0.05$

4. Discussion

Recurrent pregnancy loss (RPL) is a condition defined as three or more consecutive abortions. Miscarriage further specifies that the abortions should occur in the first trimester(23). Currently, 70% of cases of recurrent pregnancy loss (RPL) remain unexplained. It affects 1% of couples trying to conceive .

The role of the environment toxins remains in unexplained RPL is poorly understood.

Evidence of adverse reproductive outcomes among population exposed to environmental contaminants together with detection of environmental contaminant residues in serum and ovarian follicular fluid of the exposed population, led to the hypothesis that chemical contaminants may be contributing to adverse reproductive outcomes. Epidemiological and experimental data indicate that the in utero exposure to environmental chemicals and prescribed drugs during pregnancy can mediate early embryonic losses, spontaneous abortion, fetal growth retardation, fetal malformations and low birth weight(24, 25). Pregnancy involves a delicate balance of hormonal and immunological functions, which may be affected by environmental substances. Many toxic substances that are persistent in the environment and accumulate in the fatty tissues may disrupt this equilibrium(26) .

These chemicals are resistant to degeneration, and, due to their lipophilic nature, they bioaccumulate and biomagnify at higher levels in our food chain. Thus, in human populations, ingestion of contaminated food is the primary source of pesticide exposure. These chemicals accumulates within the human body, especially in areas of fat storage, it has an estimated have half- life in humans of 11.5 years. Preconception and prenatal exposure to environmental chemicals are of particular importance because they may have a profound and lasting impact on health across the life course. These chemicals disrupt endocrine function and contribute to alterations in growth and development(27) .These compounds are commonly termed “endocrine disrupting compounds” (EDCS) or “endocrine disruptors” due to their ability to act as either hormone agonists or antagonists or the ability to disrupt hormone synthesis, storage or metabolism .The susceptibility of target tissues is related to the stage of development, cumulative exposure dose and the immune status of the individual (28).

In a trial to investigate the association between RPL and the level of some environmental chemicals ,namely PCBs(28,52,118,180), Organochlorine pesticides (DDE,Dieldrin ,Alachlor,Aldrin,Epoxide) ,organophspate pesticides (chlorpyrifos ,ethion,diazinon), our comparative cross sectional study was conducted.

The study included 52 cases of unexplained RPL and 49 normal pregnant women as control. The results of the present study showed that there was a significant high levels of PCBs (|PCB 28, 52, 118 and 180) and organochlorines(p, p'- DDE, dieldrin)and organophosphorus compounds(ethion) in the unexplained RPL women than their levels in the control group. Making connections between the exposure and risk assessment is a difficult but important venture (29) (30) .Risk assessments typically examine the effects of high doses of administered chemicals to determine the lowest observed adverse effect levels (LOAELs) and no observed adverse effect levels (NOAELs); reference doses, which are assumed safe for human exposure, are then calculated from these doses using a number of safety factors. Thus, human exposures to thousands of environmental chemicals fall in the range of non negligible doses that are thought to be safe from a risk assessment perspective. Yet the ever-increasing data from human biomonitoring and epidemiological studies suggests otherwise: Low internal doses of endocrine disruptors found in typical human populations have been linked to obesity (31), infertility (32) , neuro behavioral disorders (33),and immune dysfunction (34)among others. For several decades, environmental health scientists have been dedicated to addressing the “low-dose hypothesis,” which postulates that low doses of chemicals can have effects that would not necessarily be predicted from their effects at high doses. Our data was in agreement with other studies who reported a positive, monotonic, exposure-response association between preconception serum total DDT and the risk of subsequent early pregnancy losses(35) . However other studies did not report such association.

In the current study, the plasma levels of PCB52, PCB180, dieldrin, alachlor, heptachlor epoxide ,

trifluralin and diazinon were significantly higher ($p < 0.05$) in women who reported exposure to pesticides than non exposed women. This association was fond in a study of the reproductive outcome of women exposed to PCB in Yusho women (13). However , Other investigators did not find an association between RPL and PCBs(36) .

5. Conclusion

Our data showed that pregnant subjects from Assiut Governorate who exposed to PCBs and pesticides are more vulnerable to have RPL. These endocrine disruptors may affect the gametes or the endometrium. Further studies especially on IVF cycles may add more insight on the cause of early RPL.

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