# PREGNANCY OUTCOME IN WOMEN EXPOSED TO AGRICULTURE-ORGANOPHOSPHORUS PESTICIDES

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**Abstract**

**Background:** Organophosphorus (OP) pesticides are widely used all over the world and locally. Its toxic effects are reported. However, the effects on the pregnant women and their neonates is not fully addressed.

**Aim of the work:** The detection of the potential effects of OP agricultural exposure on pregnancy outcome.

**Methods:** The study included 100 pregnant women, living at rural areas of Damietta and the Great Cairo Governorates. The study was performed between January 2020 and January 2023. Each woman was clinical evaluated by history taking and physical examination. Factors related to the work included OP exposure and use of safety measures. The pregnancy confirmed by ultrasound at 6-8 weeks of gestation. Any malformation was recognized. Ultrasound was repeated at 12-13 and 19-21 weeks for follow up. Blood samples were drawn at 19-21 weeks of gestation to measure pseudo-choline esterase enzyme activity, then women were categorized into those with normal or reduced values of AChE. Women followed up to the delivery and the detection of major malformation was the primary outcome, while the secondary outcome includes minor malformations, miscarriages, premature births, birth weight, gestational age at delivery, and presence of fetal distress or other neonatal complications.

**Results:** The reduction of activity was reported for 60 women, and it was significantly associated with increased previous abortions (20.0% vs 5.0%) and congenital malformations (15.0% vs 2.5%). The gestational age at delivery, and birth weight, were significantly reduced in women with lower AChE. The neonatal respiratory distress was significantly increased in patients with reduced than normal AChE (26.7% vs 10.0%). The AChE values were significantly and proportionately correlated with gestational age, birth weight and Apgar scores at the first and fifth minutes.

**Conclusion:** OP exposure exerts a potential developmental health hazards on pregnancy outcome, such as reduction of the gestational age, birth weight and increased congenital malformation due to OP exposure.

**Keywords:** Pesticides; Congenital Malformations; Miscarriage; Birth weight; Agriculture; Pregnancy Outcome

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## Introduction

In many developing countries, the pesticides use has progressively increased over the years. Organophosphorus (OP) was widely used for public good for a long time. However, these pesticides are associated with variable adverse effects on every aspect of the human health **(1).** OP compounds are used for pest control in different formulations (e.g., powders, sprays, shampoos and even systemic insecticides). In addition, they are frequently used as household, garden and farm pesticides. Examples of OP compounds include Chlorpyrifos, parathion, diazinon and malathion. OP compounds are highly toxic to all animals, including pets, livestock and humans. However, some compounds are far more toxic than others **(2).**

All OP pesticides are fat soluble. Thus, they are easily absorbed through the skin and transported throughout the whole body. These chemicals exert their insecticide and toxic effects by the inhibition of the acetylcholinesterase (AChE) enzyme, which normally degrades acetylcholine in nerve synapses. This results in a buildup of acetylcholine (Ach) and overstimulation of its receptors. The effect of frequent and multiple exposures is additive **(3).**

Pesticides exposure can occur via many exposure pathways, including household use of pesticides products, dietary exposure to pesticides residues, and exposure to agricultural drift. Pregnant women are at increased risk of exposure with widespread use of the pesticide. Pesticides had been detected in amniotic fluid, the umbilical cord blood and infant urine, indicating fetal exposure **(4-6).**

Previous literature detected an increased risk of major fetal malformations and a trend towards adverse pregnancy outcome, self-reported by agricultural women exposed to pesticides. However, the majority of these studies are retrospective in nature **(7,8).**

## Aim of the work

The current work aiming to detect the potential impact of agricultural worker's exposure to OP pesticides, mainly its association with pregnancy outcome.

## Patients and methods

### Patients:

The present study included 100 pregnant women, living at rural areas of Damietta Governorate and the Great Cairo. They were selected from Al-Azhar University Hospitals (Damietta and Cairo). The study was performed between January 2020 and January 2023.

The inclusion criteria were pregnant women age at 18-35 years to avoid the effect of advanced maternal age. Women were excluded if their exposure was before pregnancy and for a short period, women exposed to substances other than OP, women with chronic medical disease, multiple pregnancy, and those who refused to participate in the study.

For each woman, the assessment included full history taking, including patient demographics and obstetric history, defining the method of OP exposure, the use of safety measure, complete clinical evaluation at the first antenatal visit with complete review of all body systems. The ultrasound examination was performed at 6-8 weeks of gestation to confirm pregnancy and detect any congenital malformations early in pregnancy. Then, the ultrasound was repeated at 12-13 weeks, and 19-21 weeks for follow up. Any medical or obstetric complication during pregnancy was confirmed and documented. Blood samples were drawn at the third visit (at 19-21 weeks of gestation), to measure pseudo-choline esterase enzyme activity, as the highest concentration of AChE were found at approximately 20-22 weeks of gestation. The analysis of AChE was completed after the method described by **Wilson et al. (9).** According to results of AChE, women were categorized into two groups, those with normal activity and those with reduced activity. Both were compared for studied variables.

Patients were followed till the delivery, and the primary outcome is the detection of major congenital malformations. Major malformation was defined as any anomaly that has an adverse effect on either the function or the social acceptability of the newborn. The secondary outcome of interest was the rate of minor malformation, miscarriages, premature births, birth weight, gestational age at delivery, and presence of fetal distress or other neonatal complications.

### Statistical analysis of data:

Data were transferred to a personal computer, classified, and analyzed with SPSS (version 16) (SPSS Inc. Chicago, USA) for windows and for all the analysis a p value<0.05 was considered statistically significant. Data was shown as mean, standard deviation. Chi square test was done for qualitative variable analysis. Student ttest is a test of significance used for comparison between two groups having quantitative variables. Analysis of covariance (ANCOVA) was done to adjust the

effect of other confounders of pregnancy outcome as age in years and education level.

**Results**

In the current work, 40 women had normal AChE activity. But the reduction of activity was reported for 60 women. The reduction of AChE was significantly associated with increased previous abortions (20.0% vs 5.0%) and congenital malformations (15.0% vs 2.5%). In addition, the gestational age at delivery, and birth weight, were significantly reduced in women with reduced AChE than those with normal values. Furthermore, the neonatal respiratory distress was significantly increased in patients with reduced than normal AChE (26.7% vs 10.0% respectively). The neonatal Apgar score was also significantly reduced in the groups of reduced than Normal AChE. However, no significant difference was reported for women' age, parity, diseases associated with pregnancy, and congenital major malformations (Table 1).

In the current work, the acetyl choline esterase values were significantly and proportionately correlated with each of gestational age, birth weight and Apgar scores at the first and fifth minutes (Table 2). This confirms the association between pesticides toxicity and unfavorable outcome.

**Table (1):** Choline esterase activity and women characteristics in the study groups

| | | Normal (n=40) | Reduced (n=60) | Test | P value |
|---|---|---|---|---|---|
| AchE activity (mean±SD) | | 7749.00±1413.76 | 3062.86±453.86 | 23.90 | <0.001* |
| Age (years) (mean±SD) | | 25.37±2.20 | 25.98±2.84 | 1.14 | 0.26 |
| Parity (mean±SD) | | 2.42±0.78 | 2.33±0.91 | 0.52 | 0.60 |
| Previous abortion (n,%) | | 2 (5.0%) | 12 (20.0%) | ***4.48*** | ***0.034**** |
| Disease associated with pregnancy | Gestational diabetes | 2 (5.0%) | 9 (15.0%) | 2.45 | 0.11 |
| | Preeclampsia | 2 (5.0%) | 8 (13.3%) | 1.85 | 0.17 |
| Congenital major malformation | | 0 (0.0%) | 2 (3.3%) | 1.36 | 0.24 |
| Congenital minor malformation | | 1 (2.5%) | 9 (15.0%) | ***4.17*** | ***0.041**** |
| Gestational age at delivery | | 38.15±1.05 | 35.47±2.78 | ***5.82*** | ***<0.001**** |
| Birth weight (g) mean±SD | | 3299.00±122.26 | 2789.08±334.54 | ***9.22*** | ***<0.001**** |
| Neonatal respiratory distress | | 4 (10.0%) | 16 (26.7%) | ***4.16*** | ***0.041**** |
| Apgar score | First minute | 7.52±0.93 | 5.58±0.89 | ***10.49*** | ***<0.001**** |
| | Fifth minute | 8.70±0.46 | 7.65±0.82 | ***7.34*** | ***<0.001**** |

**Table (2):** Correlation between AchE and other variables

| | AChE | |
|---|---|---|
| | r | p |
| Age | -0.141 | 0.162 |
| Parity | 0.031 | 0.756 |
| GA | 0.501** | <0.001* |
| Birth weight | 0.666** | <0.001* |
| Apgar 1 | 0.695** | <0.001* |
| Apgar 5 | 0.583** | <0.001* |

**Discussion**

The current work aimed to investigate the potential impact of agricultural OP pesticides exposure on the pregnancy outcome. The significant reduction of Acetylcholine esterase (indicating organophosphorus toxicity) was reported in 60% of all exposed females. Women with reduction of AchE was significantly associated with higher rates of previous abortion, congenital malformations, preterm delivery and reduced birth weight. Neonatal respiratory diseases were significantly increased in women with reduced AChE. This was confirmed by significant and proportionately correlation between AchE levels and each of gestational age, birth weight and Apgar scores at the first and fifth minutes. Women with normal levels of AchE irrespective of their exposure could be explained by different duration of exposures, different doses of different OP substances. In addition, it may reflect the response of individuals to OP exposure and whether it is the first time of exposure or it is a re-exposure **(10).**

**Reshi et al. (11)** in their review showed that, reproduction is the most sensitive process in human physiology and affected by exposure to OP pesticides. It could be associated with ovarian dysfunction and disruption of hypothalamic–pituitary–gonadal axis. **Fan s, et al. (12)** attributed ovarian dysfunction to the interference

with the epigenetic modification and disruption of the expression of clock genes. Furthermore, **Vahabi Barzi et al. (13)** explained the increased abortions, teratogenic and birth defects with OP exposure by increased apoptosis in the developed embryos. **Wang et al. (14)** studied the effects and mechanism of OP esters on the environment and humans. They reported that, these esters are associated with harmful effects on nearly each organ in the body and ascribed these effects to the oxidative stress mechanism of these substances. **Kaboli Kafshgiri et al. (15)** found different histological changes in the ovarian and uterine tissue, and increased oxidative stress levels after exposure to OP pesticides. **Patisaul et al. (16)** demonstrated that OPs can alter neurodevelopment by interfering with non-cholinergic pathways. It includes perturbation of glutamate and gamma-aminobutyric acid and disruption of the endocrine system.

Combining the results of the previous studies, it could be evident that, OP pesticides exerts its harmful effects on the pregnant women, pregnancy outcome and their neonates by different mechanisms, mainly direct on the reproductive system by alteration in hormonal levels, or direct oxidative stress process. Otherwise, indirect effects were also presented by the different effects on other systems mainly neuronal transmitters and genotoxic effects **(17-21).**

In line with the current study, it had been reported that, chronic low exposures to OP during a specific window (e.g., preconception and perinatal periods) have been reported to be associated with a range of adverse birth outcomes. For example, in experimental studies, the chronic maternal and paternal exposures to some OP pesticides during preconception and early pregnancy are associated with increased risk for a range of congenital anomalies. In addition, the clinical human studies revealed that maternal and in utero exposures to OP induced neural tube defects **(22, 23)**, anencephaly **(24, 25),** spina bifida **(23),** cleft lip with or without cleft palate **(26),** nervous system defects**,** limb reductions **(23),** cryptorchidism and hypospadia **(27),** multiple anomalies and fetal death **(28).** In addition to these organ-specific defects, **Regidor et al. (8)** has described significant increases in fetal death from congenital anomalies in regions where higher amounts of pesticides were being used. In addition, **Hanke and Jurewicz (29),** reported that there is evidence to suggest that exposure to pesticides, both occupational and environmental, may contribute to spontaneous abortion, stillbirth and female infertility. However, it is not known if OP exposure per se leads to fetal deaths.

Women with lower values of AchE had preterm birth and reduced birth weight than those with normal values. These results are in line with **Shirangi et al. (30)** who reported that, there was a 5-fold increase risk of small for gestational age (SGA) for mothers exposed to OP pesticides. They concluded that, the maternal exposure to OP pesticides is associated with impaired fetal growth. In addition, **Gan H et al. (2023)** conducted a scoping review and suggested that OP exposure during pregnancy is associated with disruption of pregnancy and neonatal health, including abnormal thyroid function and reduced birth size.

As regard major malformation, it was reported in 3.3% of women with reduced AChE; no case was reported in women with normal AchE, with significant difference between those with reduced and normal values of AChE. As regard minor malformation, it was significantly increased in women with reduced than those with normal AchE values (125.0% vs 2.5%). These results agreed with those reported by **Nurminen (32)** who reported that, human maternal exposure to pesticides used in agriculture has been associated with the induction of orofacial clefts. In addition, there is considerable evidence of a positive association between workers' pesticide exposure and birth defects **(33).** A higher risk of limb anomalies was found to be associated with maternal exposure to pesticides **(34).** Moderate increases in risk for spina bifida, hydrocephaly and limb reduction defects as well as cryptorchidism and hypospadias were reported in a study conducted among offspring of Norwegian farmers based on data recorded over 34 years **(23).**

Epidemiological studies have reported that maternal–fetal transfer of organophosphate pesticides may occur **(35),** reducing fetal growth and shortening gestation **(36).** In addition, **Perera et al. (37),** reported decreased birth weight and length in association with blood measurements of the parent compound Chlorpyrifos in pregnant women of New York City.

On the other side, **Berkowitz et al. (38),** found no adverse relationship between any measures of fetal growth or length of gestation and maternal urinary levels of OP pesticide. Finally, other investigators report little or no association between OP exposure and adverse health effects such as miscarriage, pre-term delivery, small-for-gestational-age births and sex ratios **(36,39, 40),** and congenital malformations such as nervous

system defects, cardiovascular defects, oral clefts, hypospadias or epispadias, musculoskeletal defects and non-specific anomalies. This contradiction could be attributed to the window (timing) and duration of exposure. In addition, pesticide formulations, the active ingredients, other components such as solvents, carriers and emulsifiers, may be responsible to great variability of toxic or no effects of pesticides in previous literature.

**In conclusion**, data of the present study reflect a potential developmental health hazards on pregnancy outcome, such as lower gestational age, reduced birth weight and increased congenital malformation due to OP exposure. Long-term controlled prospective studies with larger numbers of pregnant women and infants is needed to generalize the potential adverse health hazards of in utero exposure to OP on pregnancy outcome.

**Conflict of interest:**
None

**Financial Disclosure:**
None

**Data Availability:**
Data available on reasonable request

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