DIMETHOATE SELFPOISONING IN A 35-36 WEEK OF PREGNANCY: A CASE REPORT AND LITERATURE REVIEW

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INTRODUCTION
Organophosphates (OPs) compounds are a diverse group of chemicals used widely in both domestic and agricultural settings. While the benefits have been considerable, pesticides are responsible for 1 million serious accidents and 3 million suicidal poisonings worldwide each year leading to 250-350,000 deaths as a result, 2/3 of which are related to OPs poisonings [Eddleston M et al., 2007].

The exposure can be accidental or suicidal, occupational, bystander exposure, or exposure of the general public who consume food items containing pesticide residues [Weissmann-Brenner A, David A, Vidan A and Hourvitz A, 2002]. They have many toxicological effects on the body, mediating through inhibition of a array of essential enzymes having serine as a conserved active site, including Acetylcholinesterase (AChE) and Butyryl cholinesterase (BuChE), by undergoing nucleophilic attack to produce a serine-phospho ester adduct [Dhotre S N, Katkam R V, Joshi NG, Deshpande K H, 2014].

The publications present are limited from the national database on the use of pesticides for suicide in Europe. However the subjective estimation for the proportion and annual number of pesticide suicides in Europe is 3.7% [Gunnell D, Eddleston M, Phillip M R and Konradsen F, 2007]. Despite of the fact that surveillance systems and statistics are scarce. Pesticide poisoning, the cases of deaths have been gradually become a major public health problem for Albanian public during the two last decades [Sula Z et al, 2015]. Studies on acute OPs pesticide poisonings during pregnancy are rare, all over the world. The published data present in detail approximately 30 pregnancies in which accidental or deliberate exposure to OPs occurred, based mostly on case reports [Christof Schaefer, Paul W.J. Peters, Richard K Miller, 2014]. Maternal toxicity is present, and when exposure occurs in later pregnancy, there may be a risk of associated neonatal toxicity [Solomon G.M, and Moodley J, 2007]. However, poisonings with these compounds, at any stage of pregnancy would not usually be regarded as medical grounds for termination of pregnancy or any additional fetal monitoring [UKTIS, 2002]. Individual cases may result in serious adverse events for both the mother and the fetus or neonates [Solomon G.M, and Moodley J, 2007, UKTIS, 2002].

In this case report we will present an acute self poisoning with dimethoate in a 25-year-old pregnant woman in the end term pregnancy. Dimethoate is moderately toxic (World Health Organization class II, 2004) by ingestion, inhalation and dermal absorption. The product creates a metabolite called dimethoxone that plays a dominant role in the toxicity of dimethoate for insects and mammals, which is about 10 times more toxic and it is more of a potential inhibitor to cholinesterase activity than dimethoate. Though there are major differences concerning the toxicity, the OPs and carbamates (CRB) poisoning is a life-threatening event that requires prompt resuscitation and usage of antidotes as the basis of current therapy [Leibson T and Lifshitz M, 2008].

CASE REPORT
A 25 year-old-pregnant woman, 35-36 weeks of pregnancy ingested about 50 ml of a dimethoate, OP compound. The episode happen home sited in one region of Albania about 13°30' on 28.11.2014 where the patients has been arrived 14°30' with intoxications sign vomiting, myotic pupils and difficulty in breath. While the health status of the patient deteriorated, the relatives confirmed that the woman has received pesticide which was in its original container labelled “dimethoate”. The patient herself confirmed that she had used only that product. The staff of regional hospital has decided to transfer at Intensive Care Unit of Tirana University Clinic (ICU) due to the complicated situation when the risk for woman and the foetus was very high. She was confused with a Glasgow Coma Scale of 13/14 (E4 M5 V4), slightly cyanotic with visible sweating and continuous nausea and dry heaves. The blood pressure (BP) was 94/48 mmHg, pulse rate was 98 beats/minutes, respiratory rate was 26 breaths / minute, SpO2 94 % and temperature was 35.9°C. She had reduced urine output and reduced skin turgor. The patient had a typical odor of the pesticide. There were no localized neurological signs,
and pupils were pinpoint not reacting to light, the reflexes were brisk and there was fine muscular fasciculation visible on eyelids and tongue. Chest auscultation revealed bilateral Ronchi localized mainly in lung’s bases. There were no abnormal rumors on heart auscultation while the rhythm seemed normal. Peripheral vessels were normal and without peripheral edemas. The abdomen was palpable without hepatosplenomegaly. The 35-36 week of pregnancy was confirmed clinically and by ultrasound examinations where the fetus was live and the intoxications of the fetus exists due to the placenta barrier

Though the elapsed time from exposure to hospital arrival was about 4 hours, the staff based on typical aroma of pesticide, instituted gastric lavage with a large quantity of warm water.

Meanwhile, the patient started to receive IV perfusions with electrolytes, bicarbonate, antacids and cortisone. She received 3 mg atropine and continued taking perfusion. Biochemical routine tests revealed WBC 12.7x10^9 mm^-3, RBC 3.7x10^12, Hb 10.4 g/dl, glucose 90 mg/dl, urea 28mg/dl, bilirubin 0.8 mg%, SGPT 321U/l. Taking into consideration the patient status, the pregnancy, available resources and the lack of experience on such cases of poisoning, the patient was transferred to the National Clinical Toxicology Service in Tirana.

She arrived to the ICU University Hospital Centre in Tirana eight hours after exposure. On arrival, she continued to be agitated and disoriented, with profuse sweating, cyanosis, dyspnoea, fasciculation, weakness and myosis. The atropine was first line treatment with a doses 8mg per hour, increased from previous which was 3 mg at the beginning. It was started superficial oxygenation, airway cleansing and it was completed with ECG registration and routine biochemical samples including Butyryl cholinesterase test. Based on the specific situation and severity of the OP's poisoning that might have required mechanical ventilation, high doses of atropine and other medications that could damage the foetus, the medical staff decided that the patient had to be transfer to the obstetrical hospital for an intervention. The obstetricians after clinical examination and ultrasound examination, adding up blood type and screen, cross match and complete blood count as well as coagulation studies, decided for an emergent caesarean delivery. As pre-medication, they added antibiotics (Vancomycin 50mg 2 times per day and Gentamycin 12mg per day ) and Ephedrine 10 mg. They applied local anaesthesia with bupivacaine with adrenaline 2.5 mg/kg and then a low segment caesarean section with foetus viva and healthy. After observation for 1.5 hours, the mother was brought back to the UHC Intensive Care Unit (ICU) under precautions of a multidisciplinary team. The results of biochemical tests taken since the first ED arrival had revealed a depression of plasma acetylcholinesterase (AChE) as it was 820 U/L (normal value 1800-6600 U/L). In addition, there was an acidosis pH 7.28 and bicarbonate 21mEq/l, K 3 mEq/l, Na 138 mEq/l, Ca 8.1mEq/l, Mg 1.3mEq/l, pCO2 48 mmHg, BUN 42 mg/dl, glucose mg/dl.

The clinical signs and symptoms were more dominated by muscle weakness, fasciculation, sweating with SpO2 92%, blood pressure 88/60 mmHg, frequency 96 minute. In such circumstances the atropline doses were increased to 2 mg per hour with continuous perfusion with electric infusion pump, diazepam 10 mg titrated to clinical status also sodium bicarbonate 8.5 mEq - 100 mL, ceftriaxone 3g IV, oxytocin 10 mg day, enoxaparin 0.4 mL per day, magnesium 25% 10 ml IV, potassium 7.5% - 80 mEq. She continued treatment for two days more at the Intensive Care Unit where the doses of atropline were adjusted according to clinical manifestations. On 02. 12. 2014 the patient was consulted again by an obstetrician who evidenced a normal post- caesarean status and recommended using oxytocin and enoxaparin doses. The BuChE level on that day was 1050U/L in CBC, WBC 10.4x10^9 mm^-3, RBC 3.4x10^12, Hb 9.4 g/dl, glucose 110 mg/dl, urea 41mg/dl, bilirubin 0.9 mg%, SGPT 44IU/l. In the same day patient was transferred to the clinical toxicology ward, where she continued to receive atropline 1 mg h, diazepam 5-10 mg, perfusions, electrolytes, antacids, oxytocin 10 mg, wound care and started to take oral feeding. On 04.12.2014 the patient showed minor nicotinic symptoms with slight muscular weakness, sweating with emotional labiality, worried for her child who was quite well at the obstetrical hospital. The level of BuChE was 1130 U/l, with RBC 3.5 10^12 mm^-3 and Hb 9.8 g/dl, the SpO2 was, 98%, pH 7.42, bicarbonate 23 mEq/l, potassium 4.2mEq/l and sodium 148 mEq/l. The lungs were clear, PA 110/70 mmHg, FR 86 minute, and pupils were not more myotic, so the atropline was reduced at 3 mg day. She was consulted by a psychiatrist and a psychologist whom had not seen any psychopathological disorder. The self-poisoning attempt was committed as a momentary emotional crisis in the interrelation context. The next day she left the hospital in order to be followed up by community health and social services.

**DISCUSSIONS**

Despite facts, in our service the poisonings treatments of acute OP are common, the actual case presented a real challenge, considering the presence of two lives, the stage of pregnancy, presumed large quantity of dimethoate ingested, its intrinsic toxicity and the clinical presentation. The practical approach of this case was based on empiric experience, and on risk assessment for both lives mother and baby, but this was mixed in terms of ambiguity and fear due to the missing guidelines.

There is a obvious lack of database concerning poisoning in the women of reproductive age and specifically during pregnancy. The publications of poisoning during pregnancy are rare case studies and case series [McClure
Jacek Sein Anand et al, 2005 described three possible reasons of intoxications during pregnancy, such as: attempted suicide, accidental overdose and induction of abortion. The rate of suicidal notion in pregnancy is significantly associated with psychiatric disorder. In the observation of Toxicology Investigators Consortium (2010-2012), the exposures of pregnant women constituted 0.6% of all toxic exposures, 51.5% of which were intentional, most commonly to pharmaceutical agents. The most commonly antidotes used were N-Acetylcysteine, sodium bicarbonate, flumazenil. In this report, the self-poisoning supposed to happen in a momentary emotional crisis due to a quarrel with her husband.

Psycho-social factors which may also contribute to the increase in the rate of maternal suicide attempts during pregnancy include: young age, unplanned pregnancy, unmarried status or recent divorce, unemployment, and difficult access to safe abortion services [Irene Zelnher et al.2015]. In the report of Karadaş S et al. pregnant cases constituted 7.5% of all women admitted with acute intoxication, 77% of whom were suicidal and 23% were accidental, whereas, McClure CK et al. reported that on women of reproductive age and during pregnancy with acute poisoning; 69.6% of cases occurred after suicidal intake and 21.5% were accidental. The rates of acute poisonings were 39.2%, 31.1% and 29.7% in the first, second and third trimesters, respectively [Karadaş S, GürlerA, Aydınl 1, 2011]. Although modern analytical toxicology and the rapid accessibility of support from poison information centers enable treating physicians to address each case individually [Dieter M. and Herbert D. 2013], the highly variable natural history and difficulty in determining the dose OP compound ingested make predicting outcome for an individual person inaccurate and potentially hazardous [Eddleston M, Singh S, and BuckleyN, 2007].

In this case the diagnosis was based on the features of cholinergic crisis, the odor of OP in the gastric contents, history, and on the label of the product container brought to Emergency Department (ED) by relatives. The depressed level by about 45% of BuChE obtained after eight hours after exposure arguably confirmed the dimethoate poisoning.

Predicting severity of OP poisoning and outcome is serious issue, especially in a pregnant woman, when exposure occurs in later pregnancy, due to the risk of associated neonatal toxicity. This requires the identity of the OP and its kinetics to be taken into consideration. Both poisoning severity score (PSS) and GCS are equally important instruments in predicting mortality. If GCS is ≤ 13 at presentation patient need to be treated aggressively and monitored very closely [Davies J O, J, Eddleston M and Buckley N A, 2008]. In our case, the GCS (13/14pt), the level of BuChE (820U/l), eight hour after exposure, as well as time delay over hour since exposure to regional hospital arrival and general clinical status of patient were the argument to consider a moderate dimethoate poisoning. Muley A et al 2014. reported that acetyl cholinesterase <1000, SpO₂ < 85% at room air, GCS ≤ 12 and time elapsed after exposure before treatment ≥ 2 hours, are the initial parameters which have a significant association with morbidity and can be used to develop a severity scoring system in acute OP poisoning case. BuChE activity on admission can provide useful information but it must be interpreted critically with definite knowledge of the ingested OP, whereas OP concentration on admission may be potentially useful, particularly for dimethoate poisoned patients [Davies J, Roberts D, Eyer P, NICK Buckley N, and Eddleston M, 2008]. In our case however, it was impossible to measure the level of blood AChE and dimethoate in serum due to technical reasons. The identification of specific OPs compound is important for the treatment, because the AChE is not reactivated by oximes in all OPs compounds, as in case of S-alkyl OPs poisoned patients, moreover it does not correspond with clinical severity.[Eddleston M et al, 2009]

Dimethoate is moderately toxic OPs [World Health Organization, 2004], however, it is not solely responsible for the toxicity, instead, co-formulates are an important element of OP toxicity, though both cause fall in systemic vascular resistance, cyclohexanone mechanism of its effect in dimethoate is unclear [Eddleston M et al, 2012]. The typical clinical presentation of severe dimethoate poisoning is quite distinct from that of other OP pesticides: many patients present with hypotension that progresses to shock and death within 12–48 h post-ingestion with a case fatality in excess of 80% [Davies J, Roberts D, Eyer P, Buckley N, and Eddleston M, 2008]. A part from conventional therapy advanced measures like fresh frozen plasma and hemoperfusion can be considered in earlier stages when patient is hemodynamically stable [Gupta S, Shukla D. A, 2014]. The path physiology of this syndrome is not clear. The involvement of cardiovascular system was present, in this patient but, the clinical scenario was dominated by cholinergic crisis with its central and peripheral signs of acetylcholine overstimulation.

Exposure to OP in pregnancy poses problems for both mother and fetus in terms of toxicity [Solomon G.M, and Moodley J, 2007] and the lack of evidence based studies and rarity of published literature make the clinical management based solely on specific situations and resources in disposition, and there has no definite strategy focused on maintaining pregnancy.

In this case arguments over which was based the emergent delivering through cesarean section in 35-36 week of pregnancy gestation were based on empirical experience on acute OP in pregnancy and clinical judgments, but we couldn’t say that it was the necessary
intervention. The newborn baby did not show any OP or atropine toxicity. However, considering that mother and baby fortunately had not any negative consequence, in a certain sense justified the adopted approach. Sun L. et al. 2015 presented two cases of pregnant women acutely poisoned by OP, where one fetus died of spontaneous abortion and the other one died of non-coordinated uterine action. The two women had no significant complications during postpartum period. Sebe A et al., 2005 reported a case of OP's chlorpyrifos poisoning of pregnant women causing fetal death. While, Solomon GM et al. 2007, reported that though maternal organophosphate poisoning may result in serious adverse effect for the fetus or neonate, the infant did not demonstrate any signs of OP poisoning. In the report of Kamha A et al. 2005, the diagnosis was confirmed by plasma BuChE which was found to be 161U/L, while the patient fully recovered and deliver a healthy baby 12 weeks later without signs or symptoms of OP poisoning. The major differential diagnosis is carbamate poisoning, which is clinically indistinguishable, however organophosphate poisoning may mimic acute overdoses with other anti cholinesterase’s complications in pregnancy, such as eclampsia and seizures, metabolic derangements and other medical problems [Solomon G.M, and Moodley J. 2007].

Maternal toxicity is likely to be a major determinant of risk to the fetus. [UKTIS]. In the study of Adhikari K et al. 2011, the mortality was 9.52% and spontaneous abortion was 4.3%. All patients received atropine injection until atropinisation.

In this case, although atropine started after 4 hours of exposure full atropinisation was reached after delivery, because of the fear of its effect over the fetus, concretely after 12 hours of OP exposure. After atropinisation the doses of atropine 2 mg h, was given through programmable syringe pump. While oximes lacked in our country market, diazepam was administered to a dose of 5-10 mg day. Symptomatic drugs, such as electrolytes, and resuscitation liquids, bicarbonate and antibiotics prophylaxis in addition to postpartum medical care were used accordingly. The ventilator support, except superficial oxygen, was not necessary, and post caesarian section period was quite normal. The atropine dose was gradually weaned where its toxicity was strictly monitored in about five days. Though the level of BuChE continue to restitute gradually, it did not followed the clinical status of patient which was improved in almost five days. Decision to use pralidoxime is based on the limited literature available on its use in pregnancy [Kamha A A, Al Omary I Y.M, Zalabany H. A, Hanssens Y and Adheir F S, 2005]. Atropine rapidly crosses the placenta, and firm recommendations for atropinisation are lacking [Eddleston M, Buckley NA, Checketts H, Senarathna L, Mohamed F, Sheriff MH, 2004]. The treatment during pregnancy should be the same as for the non-pregnant patient and the maternal toxicity following OP exposure is likely to be a major determinant of risk to the fetus [UKTIS]. Common clinical practice for atropine, is to administer sufficient doses to keep the heart rate greater than 80 beats per minute, systolic blood pressure above 80 mmHg, and the lungs clear [Eddleston M, Singh S, and Buckley N, 2007].

CONCLUSION
The intoxication treatment was based on the empiric experience for the handling pregnant poisoned patients, in circumstance where resources and infrastructure for diagnosis and treatment for acute poisoning are limited. While evidence about treatment in pregnancy are lacking, approach to treatment will depend on the type of OP dose and its intrinsic toxicity, the gestation period, presence of maternal toxicity and time interval between poisoning and maternal treatment. Clinicians should be aware of the unique circumstances, maternal and fetal risks, and management principles of the acutely poisoned pregnant woman.

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Abbreviations
Ops - Organophosphates
AChE – Acetylcholinesterase
BuChE - Butyrylcholinesterase
CRB - carbamates
Intensive Care Unit - ICU
BP - Blood Pressure
SpO2 - Peripheral capillary oxygen saturation,
WBC – White Blood Cell
RBC – Red Blood Cell
Hb – Hemoglobin
SGPT – Serum Glutamic-pyruvic transaminase
PSS – Poisoning severity score

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