

ACUTE POISONING DURING PREGNANCY POSES A PARTICULAR CHALLENGE TO HEALTH CARE PROVIDERS

BY

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ABSTRACT

Background: Acute Poisoning is the third leading cause of injury-related hospitalization during pregnancy after traffic accidents and falls. Managing a pregnant patient involves managing two patients at once, the mother and the fetus. **The aim of this review** is to highlight the challenge facing health care providers during management of poisoned pregnant since this dual management paradigm is often seen as a complex balancing act, benefits to the mother against risks to the fetus and vice versa. Added to this the relative lack of literature to support or refuse any given treatment recommendation. The higher acuity of the critically ill patient brings this situation to its sharpest point as the death of mother, fetus, or both becomes an ever more likely possibility. This review discusses the mode of exposure and how it affects the outcome of poisoning during pregnancy, the physiological changes during pregnancy that alter the toxins response and effects, the general management measures, decontamination, antidotal therapy and specific considerations and recommendations in cases of most common intentional or unintentional toxic exposure during pregnancy. **Conclusion:** poisoning in pregnancy can occur in several ways, including suicide attempt, and accidental exposures and the best approach to all poisoned pregnant patients is to treat the mother in the same way as if she were not pregnant. Improved maternal survival will typically lead to improved fetal survival

Key words: *Poisoning, pregnancy, challenges, management paradigm*

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INTRODUCTION AND EPIDEMIOLOGY

Acute Poisoning is the third leading cause of injury-related hospitalization during pregnancy after traffic accidents and falls (Weiss, 1999). According to the American Association of Poison Control Centers' (AAPCC) National Poison Data System (NPDS), approximately 7500–8000 poisoning cases in pregnancy are phoned-in to poison control centers in the USA each year (Bronstein et al., 2011, Bronstein et al., 2012 and Mowry et al., 2013). In a study of non-natural (homicide, suicide, accident, undetermined) deaths associated with pregnancy over a 6 year period, 52.5% had a positive toxicology report postmortem, with drug toxicity as the cause of death in 13.2% (Hardt et al., 2013). A study through the Toxicology Investigators Consortium attempted to quantify the patterns of pregnant patients who are evaluated at the bedside by a toxicologist (Mowry et al., 2013). Of the 17,529 medical toxicology consultations recorded during the study period, 103 (0.6%) involved pregnant women. Of these, 88.7%

involved pharmaceutical overdoses, 51.5% of which were intentional exposures. A total of 25.2% of these cases involved acetaminophen, followed by sedatives/hypnotics (18.4%) and opioids (16.5%) (Zelner et al., 2015). Czeizel and coworkers reported that 61% of suicide attempts during pregnancy occurred before completion of the first trimester either unwanted pregnancies and related tension or crisis. In Egypt, there is limited data describing poisoning exposures in pregnant women. However, A study done by Poison Control Center, Ain Shams University Hospitals, Egypt during 2019 including Cairo, Kaliobeya, Giza, Upper Egypt, Other delta and Suez canal governorates demonstrated that incidence of toxic exposure was more common among females compared to males (54.8% versus 45.2%) and in the age of child bearing period (15-25 and 25-40). Drug poisoning represented about 59.5% while non-drug poisoning was 40.5%. (Abdelhamid, 2021).

1-Challenges facing health care providers in cases of acute poisoning during pregnancy:

1.1. Dual management paradigm:

Managing a pregnant patient involves managing two patients at once, the mother and the fetus. This is often seen as a complex balancing act, benefits to the mother against risks to the fetus and vice versa (*Kevin et al., 2017*). The potential for an immediate life threat or possible life-long implications for both the mother and fetus, including teratogenicity of the poison or its antidote give the situation greater complexity in addition to that data on exposure patterns and management of confirmed, consequential poisonings in pregnant women are limited (*Zelner et. al., 2015*).

As a general rule, if the mother is optimally treated, the fetus will be treated as well. Conversely if treatment delayed or withheld over concern of inducing fetal harm and the mother's care is compromised, both maternal and fetal outcome will be jeopardized. The well-being of mother should be the foremost of concern in treatment of toxic pregnant woman with close monitoring. The best approach to all poisoned pregnant patients is to treat the mother in the same way as if she were not pregnant. Improved maternal survival will typically lead to improved fetal survival (*Zipursky et al., 2020*).

Possible pregnancy outcome complications after an accident of acute poisoning:

- Miscarriage:

Flint and colleagues observed the results of pregnancy in 61 women who overdosed during pregnancy (*Flint et al., 2002*). In this group, there was double the rate of miscarriages but no increased risk in congenital abnormalities or premature deliveries.

- Teratogenicity:

The fear of teratogenicity related to an acute drug overdose seems to be unwarranted in most cases according to two studies by Czeizel and colleagues (*Czeizel et al., 1984 and Czeizel et al., 1997*). The first study evaluated 1399 cases over a 30-year period and found no increase in congenital abnormalities in women with a "semilethal" overdose, defined as patients who ingested an

overdose amount sufficient to cause unconsciousness for 1 day (*Czeizel et al., 1984*). A later study found no difference in teratogenicity in infants exposed to a drug overdose by the mother at 3–8 weeks of gestation (*Czeizel et al., 1997*). Although the data are limited, it seems that the fetus in the "vulnerable phase" of 18–60 days of gestation either dies from the poisoning or survives without an increased risk for congenital abnormalities. These studies are based on a limited number of exposures; the potential for teratogenicity still must be considered for specific substances. This concern is further borne out by a later study by Petik and colleagues which showed an increased rate of mental retardation in children born after a maternal overdose on a combination insomnia treatment (amobarbital, glutethimide, and promethazine) but not with any of those drugs in isolation (*Czeizel et al., 1997*).

1.2. Mode of exposure:

The intentional exposure increases the risk of exposure to multiple drugs with different drug class and in large doses since the patient intend self / fetus harm (*Zelner et. al., 2015*). Although the majority of all poisoning exposures in pregnancy is un-intentional (*Gummin et al., 2017*), yet the intentional exposure as suicidal attempts or gesture have been reported (*Czeizel et al., 1999, Flint et al., 2002 and Zelner et. al., 2015*). It even exceeded the percentage of unintentional exposure, where 51.5 % involved intentional exposures, most commonly to pharmaceutical agents, followed by unintentional pharmaceutical exposures (10 %) and withdrawal syndromes (9 %). Non-opioid analgesics were the most common class of agents encountered (31 %), followed by sedative-hypnotics/ muscle relaxants (18 %), opioids (17 %), and anti-depressants (10 %) (*Zelner et. al., 2015*). Currently, in addition to over-the-counter medicines such as acetaminophen, aspirin, and iron with perceived abortifacient effects, herbal preparations are being used (*Kevin et al., 2017*). In a prospective observational study of 43 women who ingested known or perceived abortifacients, ingestions were most common in the first trimester (79 %). Acetaminophen was the most common drug ingested

(30.2%), and polysubstance were common (35%) (*Kevin et al., 2017*).

1.3. Physiologic changes of pregnancy:

Pregnancy represents a special population due its physiologic changes affecting drug and toxin absorption, distribution, metabolism, excretion, and trans-placental passage resulting in alteration in toxin response and potential fetal effects (*Timothy et al., 2007*).

1.3.a. Overall Physiological Changes: in pregnancy there is increase in body mass, water, fat and temperature

1.3.b. Pharmacokinetic Changes (*Timothy et al., 2007 and Kevin et al., 2017*):

- **Absorption:** increased drug absorption by all routes since
Gastrointestinal (GI) absorption is altered secondary to delayed gastric emptying, decreased GI motility, prolonged transit time through the GI tract. During pregnancy, there is delayed but more complete GI absorption of drugs.
Pulmonary changes including increased minute ventilation and tidal volume while residual capacity decreases may increase respiratory absorption of inhaled toxin such as carbon monoxide (CO) which may be more serious in pregnant women because they also have less respiratory reserve to compensate for any respiratory insult.
The potential for dermal exposure and absorption is enhanced by increased surface area of skin and increased blood flow to skin. However, there is lack of relevant clinical data
- **Distribution:** Increased drug distribution due to increased plasma volume and extracellular fluid volume and fat stores with decreased albumin level. Free drug concentration in pregnancy is increased and available to move freely to tissues and target organs including the placenta. However, these free drugs accounts for increased clearance rate.
- **Metabolism:** In pregnancy hepatic elimination pattern is inconsistent and unpredictable as enzyme induction can be variable together with no clinically significant changes in hepatic blood flow or bile excretion
- **Renal excretion:** Increased drug excretion due to increased renal blood flow, glomerular

filtration rates with increased urine output this may be reflected on increased clearance rate of drugs.

Fetal blood pH changes during gestation:

Changes in serum pH at different times during pregnancy cause the ionization of some drugs, leading to changes in tissue penetration and elimination. Early in pregnancy, the fetal pH is elevated compared with the maternal pH. Weak acids, such as salicylates, phenobarbital, valproic acid (VPA), trimethadione, phenytoin, thalidomide, warfarin, and isotretinoin, pass through the placenta in an electrically neutral state, but in the relatively alkaline fetal fluids, they may become ion trapped. This explains how xenobiotics accumulate in an embryo (*Fine, 2015*). Late in gestation, the fetus's blood becomes 0.10–0.15 pH units more acidic than the mother's blood (*Omo-Aghoja, 2014*), and weak bases likewise diffuse into and become trapped within the fetus

Placental Barrier Effect: maternal fetal unit is complex in the term of drug deposition and pharmacokinetics. Toxins with Low molecular weight, High lipid solubility, low ionization and reduced protein binding can cross placenta by passive diffusion (e.g. lead, cobalt, selenium, digitalis, b blockers, and salicylates....etc (*Rudge et al., 2009*). A common exception to this rule is iron, which enters the placenta by receptor-mediated endocytosis (*Curry et al., 1990*). On the other hand placenta can act as barrier for some toxins or antidotes that are highly ionized and tend to be more protein bound

Fetal Factors: The fetus has physiologic characteristics that can protect it from or make it more susceptible to the toxic effects of maternal poisoning. The fetal oxygen-hemoglobin dissociation curve lies to the left of the mother's. This position allows the fetal hemoglobin to bind oxygen at a lower PO₂. However, the hyperbolic shape of the fetal oxyhemoglobin curve also can be a disadvantage because fetal tissues are less able to extract oxygen from the hemoglobin. Also, because the curve is steep, a shift to the right because of acidemia results in decreased binding of fetal hemoglobin to oxygen at lower PO₂.

The fetus also has a physiologic reflex response to hypoxia. This response consists of apnea, bradycardia, systolic hypertension, peripheral vasoconstriction, and lactate production. The vagally mediated response to hypoxia causes a direct negative inotropic response, which can be reversed with atropine. The peripheral vasoconstriction allows shunting of the blood to critical organs, such as the heart, brain, adrenals, and placenta. While beneficial for oxygenation, in a poisoned patient this reflex theoretically increases toxin delivery to vital tissues (*Selden and Burke, 1988*).

Near-term maternal and fetal changes (*Fine, 2015*): Late in gestation, maternal free fatty acids increase, displacing protein-bound drugs, such as diazepam and VPA, from serum proteins. This displacement results in potentially greater toxicity by reducing the natural “chelator” effect of these proteins. In contrast, the hyperdynamic state of the pregnant patient causes glomerular filtration rate increases, and more renally cleared substances potentially can be excreted in the urine

1.4. Misdiagnosis of pregnancy:

A female may undergo unintentional drug overdose without knowing that she is pregnant especially in the early pregnancy. All poisoned females in the child bearing period should undergo pregnancy test (grade III according to Grading System for Levels of Evidence Supporting Recommendations in Critical Care Toxicology) (*James et al., 2022*).

2- General rules in treatment of poisoning in pregnancy:

Stabilization of the patient: The same aggressive supportive care that is provided to a non-pregnant poisoned patient should be administered to a pregnant patient (Grade III) (*Zipursky et al., 2020*). In general, if a toxin is causing seizures or hemodynamic instability in the mother, it also is having negative effects on the fetus. The optimal approach is to treat the mother; this is especially true in the critically poisoned patient. Aggressive supportive care involves attention to airway, breathing, circulation, and neurologic disability. Maintenance of a patent airway, 100 % oxygen administration, and if

the patient is third trimester and is hypotensive, left lateral decubitus positioning along with two large-bore intravenous lines and aggressive fluid management are critical. Moving the patient to the left lateral decubitus position prevents the enlarged uterine fundus from compressing the inferior vena cava, which can decrease the central venous pressure 30–70 %. If this position is not feasible, such as during chest compressions, manual leftward uterine displacement away from the inferior vena cava is also effective (Figure 1) (*Merchant et al., 2022*). Cardiac drugs and unsynchronized cardioversion up to 300 J have not been found to be harmful to the fetus. The 2020 advanced cardiovascular life support (ACLS) guidelines include an algorithm for pregnant cardiac arrest patients and specifically recommend using typical ACLS drugs and doses. Open-chest cardiac massage has been suggested to reduce the required dose of epinephrine, which can cause vasoconstriction of the utero-placental arteries. In contrast to most other instances of open-chest cardiac resuscitation, however, it is crucial not to cross-clamp the aorta because doing so would interrupt immediately utero-placental blood flow (*Vanden Hoek et al., 2010 and Merchant et al., 2022*).

If there is a change in mental status, dextrose, naloxone, and thiamine may diagnose and treat the related causes of central nervous system depression. The benefit of reversing a mother’s respiratory depression and hypoxia from an opiate overdose far outweighs the risk of opiate withdrawal in the fetus. Fetal heart monitoring is an important factor if the fetus is of a gestational age at which it is potentially viable (*Gimovsky et al., 1995*). Emergent cesarean section may be necessary if there is fetal distress in the later stages of pregnancy. This therapy provides theoretical benefits to the mother by reducing circulatory load and to the fetus by removing it from a hypoxic/acidotic environment. A number of case reports have also described dramatic return of spontaneous circulation, after cardiac arrest in general, and recovery after peri-mortem cesarean section (*Merchant et al., 2022*).



Figure (1): Manual leftward uterine displacement away from the inferior vena cava

Decontamination: There is no approach to GI decontamination that could be applied empirically to all patients including pregnant women who overdose. Each patient must be assessed individually to choose the appropriate method with some additional considerations to pregnant females.

Syrup of ipecac: is contraindicated in pregnant patients because of increased abdominal and thoracic pressure with repeated emesis and may be teratogenic (*Evan, 2017*). Currently, syrup of ipecac should not be used in any poisoned patient (Grade III)

Gastric lavage: There are reports of gastric lavage in the pregnant patient. The indications and contraindications are the same as those for non-pregnant patients. Because GI motility is slowed during pregnancy, delayed gastric lavage is theoretically attractive in the potentially life-threatening ingestion. However, the latest review of the literature related to non-pregnant patients, re-enforced the principle that gastric lavage should not be routinely used in oral overdose, if at all (*Benson et al., 2013 and Evan, 2017*) (Grade II-2-3). Gastric lavage is not a current, practical method of gastric decontamination and does not have a routine role in gastrointestinal decontamination of the pregnant patient, except in rare circumstances (such as if patients presented very early (less than an hour after their ingestion) or for those patients who took a very large or dangerous overdose, where an antidote does not exist (e.g., verapamil) (grade III) or if the patient has bezoars (*Tenenbein, 2013*).

Activated charcoal (*Kevin et al., 2017*): can be an effective decontamination procedure, as

it is in non-pregnant patients (Grade II-2-3). AC itself is not absorbed and in theory should pose no direct harm to the fetus – in fact there have been no reports of fetal toxicity from AC. Similar to gastric lavage in pregnant patients, slowed gut motility may allow AC to be effective even if given more than 1–2 h after ingestion, in an awake, cooperative patient following a potentially lethal ingestion with no other effective antidote available. The activated charcoal dose for adolescents and older is 25–100 g. Aspiration and bowel obstruction are the primary risks to the mother (Grade III). Although activated charcoal may decrease drug absorption if administered shortly after ingestion, there are no studies showing that its use alters the outcome of poisoned patients.

Cathartics (*Kevin et al., 2017*): such as magnesium citrate and sorbitol, have no role in GI decontamination and should not be administered due to the potential for electrolyte abnormalities and possibly induce premature labor. Moreover, Cathartics do not add to the efficacy of AC.

Whole-bowel irrigation (WBI) (*Thanacoody et al., 2015*): has been reported in pregnant patients in many cases such as iron toxicity, sustained released drugs, lead and cocaine. The indications and contraindications for WBI are the same for pregnant and non-pregnant patients. It prevents absorption by attempting to enhance the flow of xenobiotics through the gut. In order to achieve this, a nasogastric or orogastric tube must be placed. Large amounts, approximately 1–2 l/h, of osmotically balanced polyethylene glycol solution (PEG) are administered until the

patient has at least two clear, liquid stools. WBI may be started or continued in the ICU.

Enhanced elimination: Although the supporting literature is limited, enhanced elimination with multiple-dose activated charcoal (MDAC) should be as effective and safe as single-dose AC in pregnant patients. The few indications for possible MDAC therapy are the same as those in non-pregnant patients (e.g., ingestion of a potentially highly toxic amount of theophylline, phenobarbital, carbamazepine, dapsone, or quinine). MDAC for these drugs is supported in the literature because of effective “gut dialysis” or interruption of enterohepatic circulation in non-pregnant patients (*Zelner et al., 2015*).

Hemodialysis and hemoperfusion in pregnancy is uncommon (*Nadeau-Fredette et al., 2013*). Most experience seems to be with patients with chronic renal failure or with acute renal failure from non-toxicologic causes and few case reports (*Jenq et al., 2005 and Kneser et al., 2013*). It seems reasonable to consider use of dialysis in the poisoned pregnant patient. If dialysis would be indicated in a non-pregnant patient, it is indicated in a pregnant patient as well (Grade III) (*Kevin et al., 2017*).

Antidote: There is minimal literature on the beneficial or harmful effects of antidotal therapy in pregnancy. However, there are well-documented cases of maternal and fetal mortality caused by withholding an antidote because of fear of inducing fetal teratogenicity. Using antidote to reverse the toxic manifestations in the mother increase the chance of fetal wellbeing (*Kevin et al., 2017*).

Indication for ICU admission: For any given poisoning, the indications for ICU admission do not substantially change with pregnancy and should be based on the mother’s hemodynamic parameters. Physiologic changes in pregnancy, such as tachycardia and dilutional anemia, should be accounted for when making level of care triage decisions. Prenatal care records, when available, can be helpful in establishing the patient’s baseline during this pregnancy (*Kevin et al., 2017*).

3- Special considerations in common toxins:

According to *Zelner et al., 2019; Zipursky et al., 2020; James et al., 2022* the most frequently reported toxins exposures involving pregnant patients were analgesics, sedative hypnotics, antidepressants especially selective serotonin reuptake inhibitors, opioid, alcohol, street drugs (cocaine, methamphetamine), iron, pesticides, alcohols and carbon monoxide.

3.1. Acetaminophen (*Kevin et al., 2017*): (considered “safe” in pregnancy when taken in therapeutic doses. Acetaminophen is contained in many other over-the-counter preparations). It crosses the placenta and has the potential for fetal hepatotoxicity and in acute intoxications can cause spontaneous abortion and stillbirth.

Fetal death from APAP overdose has been reported in all trimesters. Maternal NAPQI does not cross the placenta. Maternal APAP, however, does cross and has the potential to produce toxic fetal concentrations. The fetus’s ability to produce NAPQI from APAP begins as early as 14 weeks’ intrauterine life and increases until term. The fetus’s ability to detoxify APAP by conjugation with sulfate and glucuronide remains impaired until after birth, possibly shunting more APAP through cytochrome P450. In the first trimester cytochrome P-450 system is immature, which is unable to form the toxic metabolite N-acetyl-p-benzoquinoneimine. The ability of 19-week and 22-week fetal liver tissue to form oxides verifies cytochrome P-450 activity at this age of development. The third-trimester fetus, therefore, appears to be at greatest risk for direct toxicity from APAP. Nevertheless, fetal loss appears to be most common in the first trimester—not because the fetus is necessarily poisoned, but because maternal illness is more likely to lead to fetal loss at that time. Treatment of pregnant patients for acetaminophen toxicity should be the same as that for non-pregnant patients, with some differences as noted previously (Grade III) (*Timothy et al., 2007*).

Placental transfer of NAC (a class B medication) in humans has been documented with concentrations in the umbilical cord blood similar to maternal levels). Because

considerations of lack of first-pass effect through the fetal liver (compared to the maternal intake of NAC), most authorities prefer the parenteral use of the antidote during pregnancy. When NAC is given intravenously at currently used therapeutic doses, serum levels are 10 to 100 times higher.

At least one authority has recommended consideration for delivery of the mature fetus by cesarean section so that NAC therapy can be administered directly to the baby at risk (i.e., when maternal serum APAP concentrations are toxic).

Limited studies and data regarding the risk benefits comparison between giving the mother NAC or benefits of delivery followed by direct newborn NAC therapy. Given the potential for a non-reassuring fetal condition, fetal monitoring of viable pregnancies is recommended during therapy (*Timothy et al., 2007*).

3.2. Salicylates: (Present in multiple OTC preparations and available without prescription). It should be avoided in 3rd trimester because it affects neonatal coagulation and cause premature closure of ductus arteriosus. It crosses the placenta and toxicity occurs due to its metabolites (salicylic and gentisic acids) (*Timothy et al., 2007*). A greater proportion of salicylate enters the fetal brain than the maternal CNS. The fetus also has decreased capacity to buffer salicylate-induced metabolic acidosis. Lastly, metabolism and excretion of salicylate are decreased in the fetus in large doses. So although the toxic dose is 150mg/kg but given the fetus's ability to concentrate salicylate, concern arises when an acute, single maternal ingestion exceeds 75 mg/kg. Salicylate levels may not peak until 24 hours after the drug is absorbed (*Chyka et al., 2007*). Treatment of the mother should be initiated at lower serum salicylate concentrations than one would initiate for a non-pregnant patient (Grade III) (*Timothy et al., 2007*). Stabilization of patient, decontamination (AC 1 g/kg dose up to a ratio of 10 g of activated charcoal: 1 g of salicylate, is recommended (*Kevin et al., 2017*) and serial salicylates serum level. Urinary alkalization using NaHCO₃ (when serum salicylate levels increase to greater than 25 mg/dL (180 umol/L) to account for

these differences in fetal salicylate levels (Grade III). Hemodialysis may be indicated at lower serum salicylate levels (normal at 100mg/dl), since neonatal toxicity and intrauterine fetal demise have both been documented with maternal salicylate levels in the 50–60 mg/dL range (*Farid et al., 2011*). Emergent delivery is considered optimum treatment by some (*Zipursky et al., 2020*).

Opioids (*Timothy et al., 2007 and ACOG, 2012*): Some opioids, particularly codeine, have been associated with birth defects including congenital heart defects. Chronic heroin risk has been associated with a variety of poor fetal outcomes including fetal growth restriction, preterm labor, and fetal death. In the case of heroin, there is a theory that these effects are from both repeated exposure and repeated withdrawal. Heroin overdose present with triad of respiratory depression, miosis, CNS depression. While opioid withdrawal is typically not life threatening, it can precipitate preterm labor and fetal distress. The treatment of opioid withdrawal creates a concern regarding naloxone use in pregnancy. Naloxone (2mg doses) should be used only in the case of maternal overdose with hypoxia and potential airway compromise in order to save the mother's life (Grade III). The starting intramuscular dose of naloxone for a pregnant woman should be the lowest of the range, 400 µg and repeated every 4 min until the person is breathing and responsive especially in cases of long acting opioids (e.g. methadone –Sustained released opioid) as their effect last for 6-8 hrs while naloxone 30min -2 hrs. Pregnant patients who may be dependent on opioids should be observed for signs and symptoms of withdrawal and managed as needed to prevent fetal distress (Grade III).

3.3. Iron preparations: (it is prescribed routinely during the prenatal period; as a result, it is a concern for potential overdose in pregnancy). Iron seems to have little direct toxicity to the fetus because it does not diffuse passively across placenta but acts through a receptor-mediated endocytosis. Animal and human studies of iron toxicity showed that elevated maternal serum iron concentrations are not reciprocated in the fetal circulation (*Curry et al., 1990*). Iron does not

affect the fetus directly but does so indirectly through poisoning of the mother. The placenta provides an effective barrier to iron, leaving the fetus reliant on the well-being of the mother for its survival (*Lacoste et al., 1992*). The peak serum iron concentration occurs in the range of 2–4 h, and using the total iron-binding capacity to predict the severity of poisoning is inaccurate (*Taftachi et al., 2012*). Treatment must focus on the sum of many different data points to determine what is most appropriate. Greater than 60 mg/kg ingestion, hypotension, mental status depression, metabolic acidosis, GI bleeding, shock, and serum iron level greater than 500 µg/Dl all are signs of a severe iron poisoning and are indications for deferoxamine administration (Grade III evidence). It chelates free iron and is excreted by the kidneys. Some clinicians take a more conservative approach and treat a pregnant patient with a serum iron concentration greater than 350 µg/dL (62.5 mmol/L). The usual intravenous dose of 15 mg/kg/h with the upper limit of 6 g in 24 h is often quoted and still cited in the package insert. The reason for this limit is to avoid hypotension and acute lung injury. A firm standard for the limits of deferoxamine therapy has yet to be shown in clinical trials. Reviews of multiple case studies have shown no direct link between deferoxamine treatment in humans with iron toxicity and teratogenicity. More reassurance of the safety of deferoxamine in pregnancy is provided by the fact that deferoxamine does not cross the placenta in the ovine model (*Blanc et al., 1984; McElhatton et al., 1991; Singer and Vichinsky, 1999*).

3.4. Selective serotonin reuptake inhibitors (SSRI): (e.g. fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil) (*Alfredo and Victor, 2022*): it crosses the placenta. poisoning has no clinical significance. At very high doses, SSRIs may trigger serotonergic syndrome with or without signs of the anticholinergic syndrome. In the third trimester, intense uterine contractions and fetal heart rate anomalies have been reported with SSRI intoxication. Most fatalities have been reported with either large doses (>150 times the daily dose) or with the presence of co-ingestants such as ethanol,

benzodiazepines, or tricyclic antidepressants. It is Complicated by neonatal withdrawal syndrome (irritability, vomiting, and convulsions, etc). Treatment includes stabilization with using fluids and direct vasopressors (e.g. epinephrine) for hypotension Activated charcoal (1g/kg for decontamination). treatment of seizures by Benzodiazepines (Lorazepam 12 mg IV every 5 minutes). High potency neuroleptics (haloperidol) for agitation and Agitation associated with the anticholinergic syndrome may be best treated with physostigmine (initial dose: 0.52.0 mg slow IV over 35min).Symptomatic care include nifedipine or labetalol for severely hypertensive. Lidocaine for Ventricular tachycardia Symptomatic bradyarrhythmia (e.g. with hypotension) should be treated with atropine or temporary pacing. If patient is hyperthermic (>104°F [>40°C]) use benzodiazepines and external cooling.

3.5. Cocaine: most pregnant women who use this substance do not receive any prenatal care (*Little, 1993*). others falsely think that cocaine speeds labor. Cocaine can increase the length of labor, however, and exacerbates pain sensation (*Dombrowski et al., 1991*). Complications associated with cocaine use in pregnancy are abruptio placentae, decreased fetal growth, preterm labor, urinary congenital abnormalities, neurobehavioral abnormalities, and fetal demise (*Slutsker, 1992*). Cocaine administered to the pregnant female caused increased vascular resistance, decreased uterine flow, increased fetal heart rate and blood pressure, and lower fetal oxygen content (*Roe et al., 1990*). Progesterone may increase cocaine's cardiovascular toxicity in the pregnant patient. The fetus also has reduced levels of cholinesterase, but the placenta has sufficient activity to allow metabolism of some of the cocaine before it crosses the placenta and affects the fetus (moderate degree of protection).To decrease morbidity and mortality, BZD is the medication of choice to treat the agitated, seizing, or tachycardia despite fear of respiratory depression of fetus since the benefits outweigh the risks.phenobarbital is preferred over phenytoin owing to the latter's known teratogenic effects on the fetus.

Nitroglycerin may be used for hypertension, and rapid external cooling for hyperthermia is essential. If chest pain is present, investigation and treatment of possible myocardial ischemia are warranted (*Timothy et al., 2007*).

3.6. Methamphetamines: one of the most commonly used illicit drugs in pregnancy, yet studies on MA-exposed pregnancy outcomes have been limited because of retrospective measures of drug use, lack of control for confounding factors: other drug use, including tobacco; poverty; poor diet; and lack of prenatal care. MA use during pregnancy is associated with shorter gestational ages and lower birth weight, especially if used continuously during pregnancy. Stopping MA use at any time during pregnancy improves birth outcomes, thus resources should be directed towards providing treatment and prenatal care (*Wright et al., 2015*). Stabilization of patient and treatment of seizures by benzodiazepines and phenobarbital in cases of refractory cases. Agitation may be treated with haloperidol combined alpha and B blockers such as labetalol are used for hypertension and tachycardia. Nitrates, b-blockers, aspirin and pain killers are used for treatment of cardiac ischemia. Treatment of rhabdomyolysis by i.v fluids and NaHco₃ to avoid precipitation of myoglobin in renal tissue as it will prevent the acidic urine ph. Hemodialysis may be done in severe cases (*Karila et al., 2010; Maranella et al., 2019 and Richards et al., 2019*).

3.7. Carbon monoxide: During a normal pregnancy, endogenous production of CO increases carboxyhemoglobin (COHb) 20–40 % above normal levels of this increase in maternal COHb, 30–40 % is from an increase in maternal erythrocyte load. The fetus contributes 15 % of the COHb increase. The instigator of this increase is progesterone, which induces the catabolism of hemoglobin by hepatic microsomal enzymes. The minute ventilation also increases during pregnancy. The baseline increased burden of CO and the increased minute ventilation make the pregnant woman more susceptible to CO poisoning (*Aubardand Magne, 2000*).

Fetal hemoglobin complicates the situation because its oxygen binding curve is already

hyperbola shaped and steep at low pressures of oxygen. Decreased ability of tissues to extract oxygen from the fetal hemoglobin and increased susceptibility to a precipitous drop in oxygen saturation result. In acute maternal CO exposure, the CO slowly crosses the placenta by passive diffusion (*Timothy et al., 2007*). In humans, the fetal COHb concentration reaches maternal levels in 14–24 h and a state of equilibrium in 36–48 h, with percent fetal COHb 15–20 % greater than the maternal percentage. In acute exposure, death by anoxia occurs well before COHb concentrations increase. The CO elimination half-life is 2 h in the mother and 7 h in the fetus. The sum of the effects from fetal hemoglobin, prolonged elimination, delayed peak in fetal COHb concentration, and elevated concentration of COHb in the fetus places the fetus at greater risk for morbidity and mortality than the mother. There are multiple case reports of the mother's exhibiting minimal to no toxicity, with simultaneous significant adverse effects or death in the fetus. Similar to the situation in non-pregnant patients, the CO level, expressed as percent COHb, does not correlate well with severity of toxicity. Fetal COHb levels are not realistically obtainable, making a history of exposure along with clinical signs and symptoms in the mother the only guide for therapy. Multiple sources point out that maternal symptoms of altered mental status, neurologic deficits, seizures, and coma are better predictors of fetal toxicity than are COHb concentrations (*Kosaki et al., 2021*).

Teratogenicity varies with the timing of the exposure. Case reports suggest the possibility that exposure in the embryonic stage leads to neurologic, skeletal, and cleft palate deformities. During the fetal phase, anoxic encephalopathy and growth restriction may result. In the third trimester, premature delivery is reported and possibly decreased immunity, right-sided cardiomegaly, and delay in myelin formation (*Kosaki et al., 2021*).

Primary treatment of CO toxicity involves removal of the mother from the source of exposure and starting therapy with 15 L of 100 % oxygen via nonrebreather mask and give it five times longer than normal adult for

possible adequate reduction of CO in fetus (*Fine, 2015*).

HBO therapy has been advocated as the treatment of choice for pregnant patients exposed to CO (*Weaver et al., 2001*). HBO therapy can reduce the elimination half-life of CO from 4 to 6 h on room air, to roughly 20 min. Normobaric oxygen and HBO therapy increases dissolved oxygen, accelerates dissociation of CO from hemoglobin, and shifts the oxygen-hemoglobin curve back to the right. Nonetheless, the efficacy of HBO therapy in preventing neuropsychiatric sequelae from CO in the pregnant patient, which is the endpoint of the major studies, is unknown. As expected, pregnant patients have been excluded from HBO research as a therapy for CO poisoning. A Cochrane Review in 2011 found conflicting evidence in existing randomized controlled trials regarding HBO therapy for CO poisoning in non-pregnant patients (*Buckley et al., 2011*). Therefore, there are no evidence-based recommendations for HBO therapy for pregnant patients poisoned from CO, only opinions (Grade III).

Suggested indications for HBO therapy in the pregnant patient are a maternal COHb level greater than 15–20%, maternal neurologic signs or symptoms, and evidence of fetal compromise (*Friedman et al., 2015*). If maternal or fetal signs of CO toxicity persist 12 h after initial HBO therapy, a repeat session has been proposed. It has been recommended that 100% oxygen continue five times longer in pregnant patients than standard treatment duration in non-pregnant patients to allow greater removal of CO from the fetal hemoglobin (Grade III). In addition, there are specific areas of concern for the fetus treated with HBO. High PO₂ is known to be teratogenic and to cause retinopathy, cardiovascular defects, and premature closure of the ductus arteriosus. An animal study showed similar adverse effects (*Silverman and Montano, 1997*).

Several human case reports and studies strongly advocate HBO therapy in pregnant patients. The safety of HBO therapy in pregnant patients was studied prospectively in 44 women, all of whom tolerated the procedure well, and no morbidity was seen in

the mother or the fetus. A prospective French series from 1983 to 2008 found no difference in early childhood development (as late as age 6 years) between those who received HBO for CO in utero and unexposed age matched controls, further emphasizing the apparent safety of HBO in pregnant patients (*Wattel et al., 2013*).

In addition to the described standard therapy of CO poisoning, fetal heart monitoring is indicated in the late second and third trimesters. Poor variability and late decelerations are indications of fetal distress. One review article cautioned that immediate delivery of the fetus before HBO therapy carries a high risk of perinatal death. The authors concluded that HBO therapy should be considered before performing an emergency cesarean section (*Aubard and Magne, 2000*). This recommendation is based solely on theoretical considerations, however, and there are no data to support this from clinical trials.

3.8. Pesticides: Organo-phosphorous poisoning during pregnancy is a life-threatening condition for the woman and fetus. Spontaneous abortion and fetal death had been reported. Atropine acts as a physiologic antidote, effectively. A few literatures on the usage of atropine during pregnancy has been reported and shown no any adverse effect on fetus (*Adhikari et al., 2011*). However, atropine can affect the fetal heart rate or inhibit fetal breathing and can cause neonatal mydriasis when used in large doses for maternal OP poisoning at term. So, the dose of atropine required to antagonize muscarinic effects in the mother also adversely affected the fetus in utero (*Sun et al., 2015*).

Penhyclidine hydrochloride (PHC) is a new, domestically developed anticholinergic drug that focuses on M₁, M₃, and M₄ receptors and shows little inhibition for cardiac M₂ receptors. Because of higher specificity of PHC for M₃ receptors compared with M₂ receptors, PHC has few effects on HR and myocardium oxygen consumption. Early studies showed that PHC had better curative effects on AOPP than atropine (*Luo et al., 2010*). The antagonizing effect of PHC on isolated rat uterus contraction induced by

acetylcholine is stronger than that of atropine denoting that PHC is potential candidate drug for uterus contraction induced by OP compounds and may be used to treat OP during pregnancy (*Xiao et al., 2009*).

Administration of magnesium sulfate to animals poisoned with OP pesticides has been shown to improve outcome and at the same time it can effectively decrease the intensity of the contractions in women for hypertonic uterine contractions (*Sun et al., 2015*). There are no epidemiologic studies evaluating the risks of oximes in pregnancy, but these antidotes should be used when there is a clear maternal risk of morbidity or mortality associated with poisoning (*Bailey, 2003*).

3.9. Envenomations (*Brown et al., 2013*):

Clinically significant envenomation in pregnancy is reported for snakes, spiders, scorpions, jellyfish, and hymenoptera (bees, wasps, hornets, and ants). Adverse obstetric outcomes including miscarriage, preterm birth, placental abruption, and stillbirth are associated with envenomation in pregnancy. The limited available literature suggests that adverse outcomes are primarily related to venom effects on the mother. Optimization of maternal health such as management of anaphylaxis and antivenom administration is likely the best approach to improve fetal outcomes despite potential risks to the fetus of medication administration during pregnancy. Obstetric evaluation and fetal monitoring are imperative in cases of severe envenomation.

The medical literature regarding envenomation in pregnancy includes primarily retrospective reviews and case series. The limited available evidence suggests that optimal management includes a venom-specific approach, including supportive care, antivenom administration in appropriate cases, treatment of anaphylaxis if present, and fetal assessment. The current available evidence suggests that antivenom use is safe in pregnancy and that what is good for the mother is good for the fetus. Further research is needed to clarify the optimal management schema for envenomation in pregnancy.

3.10. Food poisoning (*Tam et al., 2013*):

Hormonal changes that occur during pregnancy decrease cell-mediated immune function, thus increasing the susceptibility of pregnant women to certain types of infections. Food-borne pathogens of special concern for pregnant women include *Listeria monocytogenes* and *Salmonella enterica*, as maternal infection might increase the risk of adverse pregnancy outcomes.

Maternal infection might be asymptomatic or it might present with mild flu like symptoms, including fever, muscle aches, and gastrointestinal symptoms, such as nausea or diarrhea. In contrast to maternal illness, fetal or neonatal infection is often severe and potentially fatal. Sequelae of intrauterine infection include spontaneous abortion, stillbirth, preterm labor, and early-onset neonatal sepsis.

Salmonella infection (for which pregnant women are not at increased risk) typically presents with fever and gastrointestinal symptoms, such as nausea, vomiting, stomach cramps, and diarrhea; however, bacteremia, which is estimated to occur in approximately 4% of cases, might lead to intrauterine sepsis.

Infection by seafood-related pathogens has not been well studied in pregnancy, and for the most part infection is limited to the gastrointestinal tract and is usually self-limiting.

The molecular weight of the botulinum toxin is approximately 150 kDa; therefore, it is unlikely to cross the placenta via passive diffusion. A case report in which a woman acquired botulism during pregnancy suggested that there is no increased risk to the fetus.

Appropriate management of maternal listeriosis with a broad-spectrum antibiotic (e.g. ampicillin or penicillin) can reduce the risk of adverse fetal outcomes. Like other food-borne illnesses, treatment of sea food poisoning is aimed at maintaining adequate fluid and electrolyte balance, with severe or invasive bacterial infection requiring treatment with antibiotics. Penicillins, cephalosporins, and fluoroquinolones are commonly used and are not associated with an increased risk of birth defects or any other adverse pregnancy outcomes.

3.11. Lead toxicity: Exposure to high concentrations of lead during pregnancy may result in adverse outcomes including spontaneous abortion, impaired intrauterine growth, premature rupture of the membranes and/or preterm labour, reduced infant head circumference, and impaired neurodevelopment in the child. However, these risks have not been clearly quantified. The decision to provide chelation therapy can be approached in two ways: to save the mother or to reduce fetal BLLs. To save the mother's life, 70 mcg/dL is the level at which an expert would chelate regardless of trimester. After organogenesis is mostly complete, chelation therapy for women with BLLs of 45 mcg/dL or higher should be considered (*Brown, 2013*). There are reports of teratogenic effects in animals during the first trimester with chelation therapy. The decision to treat, however, should not be limited to this blood level. It should be based on the patient's history, whether the source is known, and if that source can be removed. DMSA is the treatment of choice

3.12. Toxicity of Pregnancy-Related Medications: Magnesium Sulfate toxicity affects the mother and the fetus. For the mother, this toxicity typically occurs by an error in the rate of administration. The patient may have flushing, headaches, blurred vision, nausea, nystagmus, lethargy, hypothermia, urinary retention, loss of the patellar reflex, or ileus. Respiratory muscle paralysis and cardiac conduction disturbance up to arrest. The effect of magnesium on the fetus is variable. The classic result in the neonate is hypotonicity, which may affect diaphragmatic function and increases the rate of perinatal mortality, even when there is little effect on the mother (*Herschel and Mittendorf, 2001*). The treatment of magnesium toxicity involves attention to airway, breathing, and cardiovascular status. Intubation and vasopressors with aggressive supportive care are the mainstays of treatment. Intravenous calcium may serve as an antidote to the effects of magnesium toxicity. Maintaining a urine output of at least 100 mL/4 h also can ensure elimination of the magnesium (Grade III evidence). Maternal hemodialysis may be

indicated in cases of severe hypermagnesemia (*Lu and Nightingale, 2000*).

4- Neonatal management: In cases of acetaminophen toxicity, studies recommended consideration for delivery of the mature fetus by cesarean section so that NAC therapy can be administered directly to the baby at risk (i.e., when maternal serum APAP concentrations are toxic or mother have DIC). In cases of salicylate toxicity, studies reported that fetal monitoring may be needed to determine the need for emergent delivery in a fetus of potentially viable gestational age which is considered optimal treatment and the neonatologist should be alerted about the increased risk of platelet dysfunction (petechiae, purpura, cephalohematoma, GI bleeding, and intracranial bleeding). In cases of CO poisoning, a study stated that immediate delivery of the fetus before HBO therapy carries a high risk of perinatal death. So, HBO therapy should be considered before performing an emergency cesarean section. However, a case report of a 41-year-old 38 weeks pregnant woman with CO poisoning (COHb<10%) underwent caesarian section and she and the infant were treated with hyperbaric oxygen therapy consisting of 100% oxygen at 2.4 atmosphere absolutes (ATA) for 90 minutes at 2.5 hours after delivery. Hyperbaric oxygen treatment was well tolerated in this neonate and was discharged 3 days later in good condition (*Kreshak et al., 2022*).

In cases of acute opioid overdose, Neonates of this mother should be treated in ICU and evaluated for withdrawal manifestations. The risk of withdrawal is variable and is related to the type of opioid, dose and timing of exposure. Infants exposed to shorter half-life drugs and who manifest no signs of withdrawal could be safely discharged after 3 days of observation whereas monitor infants exposed to drugs with a longer half-life, such as methadone, for a longer period of time (4 to 7 days). Pharmacological treatment may include phenobarbital, morphine, methadone, buprenorphine and clonidine (*Wiles et al., 2014 ; Wachman and Werler, 2019*).

CONCLUSION

The literature on poisonings in pregnancy is sparse at best, typically based on case reports, however, as with other patients, poisoning in pregnancy can occur in several ways, including suicide attempt, and accidental exposures. Pregnancy adds additional concerns for poisonings more directly related to the fetus, namely exposure to abortifacients whether intentional by the mother or malicious by another person. When treating pregnant patients, both mother and fetus must be considered. In general, the best treatment for the mother will also be the best treatment for the fetus. The risk of teratogenicity from any acute overdose or antidotal therapy is likely very low

RECOMMENDATION

- The wellbeing of mother should be the foremost of concern in treatment of toxic pregnant woman with close monitoring of the fetus.
- After acetaminophen overdose the fetal liver may not produce significant quantities of NAPQI due to immature hepatic enzymes. However, to prevent maternal toxicity oral or IV NAC should be started, ideally within 8 h of ingestion.
- The fetus is more vulnerable and unable to eliminate salicylates as well as the mother so aggressive enhancement of elimination is warranted at potentially lower maternal serum salicylate concentrations.
- Do not hesitate to administer deferoxamine because of fears of teratogenicity in the pregnant patient. The benefits of maternal survival outweigh the risks of fetal injury.
- Treat the pregnant patient with CO poisoning longer with normobaric oxygen than would be indicated for a nonpregnant patient. The role of hyperbaric oxygen therapy is inconclusive. Consultation with a medical toxicologist or, if one is not available, with a poison control center is warranted.
- The benefit of treating seizures from cocaine toxicity with benzodiazepines outweighs the risk of teratogenicity.
- Use the lowest effective dose of naloxone, and titrate as needed, to reverse respiratory depression and hypoxia and avoid withdrawal symptoms.

Appendix:

Grading System for Levels of Evidence Supporting Recommendations in *Critical Care Toxicology, 2nd Edition (Bronstein et al., 2012)*

- I- Evidence obtained from at least one properly randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
- III- Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

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التسمم الحاد أثناء الحمل يشكل تحديًا خاصًا لمقدمي الرعاية الصحية

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المقدمة: التسمم الحاد هو السبب الرئيسي الثالث لدخول المستشفى المرتبط بالإصابة أثناء الحمل بعد حوادث المرور والسقوط. تتضمن علاج المريضة الحامل علاج مريضين في وقت واحد، الأم والجنين. **الهدف من هذه المراجعة** هو تسليط الضوء على التحدي الذي يواجه مقدمي الرعاية الصحية أثناء علاج الحوامل المصابة بالتسمم، حيث يُنظر إلى نموذج العلاج المزدوج هذا غالبًا على أنه عمل موازنة معقد، وفوائد للأم ضد المخاطر التي يتعرض لها الجنين والعكس صحيح. يضاف إلى ذلك النقص النسبي في الأدبيات لدعم أو رفض أي توصية علاجية معينة. ويعتبر وضع المريضة الحامل في حالات التسمم من أقصى درجات الحالات الحرجة حيث يصبح احتمال وفاة الأم أو الجنين أو كليهما أمرًا محتملاً أكثر من أي وقت مضى. كما تناقش هذه المراجعة طريقة التعرض المتعمد أو غير المتعمد للسموم للمواد السامة وكيف تؤثر على نتيجة التسمم أثناء الحمل، والتغيرات الفسيولوجية أثناء الحمل التي تغير من استجابة السموم وأثارها، والطرق العامة لانقاذ المريضة، والعلاج بمضادات المواد السامة، واعتبارات خاصة وتوصيات في الحالات الأكثر شيوعًا.

الخلاصة: يمكن أن يحدث التسمم أثناء الحمل بعدة طرق، بما في ذلك محاولة الانتحار، والتعرض العرضي، وأفضل نهج لجميع المرضى الحوامل المصابات بالتسمم هو علاج الأم بنفس الطريقة كما لو كانت غير حامل. سيؤدي تحسين بقاء الأمهات عادةً إلى تحسين بقاء الجنين.