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Review

Heavy metals in miscarriages and stillbirths in developing nations

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ABSTRACT

Objectives: Cases of miscarriage and stillbirths due to heavy metal poisoning continue to be on the rise in developing nations. In these countries like Nigeria, the menace of miscarriage is not readily linked to heavy metal exposure. This could be as a result of insufficient scientific data available due to poor documentation and inadequate public health education on the consequences of these heavy metals on maternal health. The heavy metals mercury, lead and cadmium are toxicants which have been shown to cross the placental barrier to accumulate in fetal tissues. *Methods:* For this review, relevant databases were searched for original scientific reports and a total of 100 articles were retained for analysis. Required data was extracted from these studies and their methodology assessed. *Results:* Miscarriages and stillbirths were observed from exposure to five heavy metals namely; mercury, arsenic, lead, chromium and cadmium. These heavy metals were associated with increased incidence of miscarriages in developing nations. In Nigeria, women with history of miscarriage had blood lead levels >25 μg/dL during pregnancy with approximately 41.61% increase in miscarriage incidence. Cadmium blood level was found to be 85.96 ± 1.09 μg/dl with a 9.50% increase in miscarriage incidence in women exposed to mercury in comparison to the unexposed group. For chromium, a 1.60% increase in the incidence of miscarriage in women exposed to chromium was reported. For cadmium and arsenic, 83.93% and 5.88% increase in incidence were reported respectively. Similar data were obtained for Jamaica (mercury = 7.29 ± 9.10 μg/l), Egypt (Cadmium = 1.17%; Lead = 32.33%). *Conclusion:* Medical practitioners and Toxicologists involved in women health in sub-Sahara Africa SSA should consider if these heavy metals can become additional biomarkers in the diagnosis of miscarriages and stillbirths.

Contents

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1. Introduction

It is the hope of every couple to be able to have children, but evidence are abound which suggest that environmental toxicants reduce couples' ability to conceive and not all pregnancies result in a live birth. In fact both paternal and maternal exposures to environmental toxicants may be associated with fetal death. Occupational exposure is often cited as a risk factor for female fertility, as well as for early pregnancy loss and pre-term delivery. Miscarriage an abrupt end of a pregnancy at a stage where the embryo or fetus is not capable of surviving independently [1], is the most common adverse pregnancy outcome with aggravating emotional consequences for affected individuals and families. Miscarriage is a critical indicator of embryotoxicity. It is an important outcome for the study of embryotoxic effects of chemicals including environmental contaminants and drugs [2–4] and a vital end point to track the progress of reproductive health programmes and their impact on maternal health.

Often times miscarriages are not accounted for and ignored. Maternal and women reproductive health related indicators therefore miss a significant number of unreported pregnancies that are often not seen by health professionals. This significant reproductive health outcome has added a challenge on the paucity of data on miscarriage rates in sub-Sahara Africa. Whereas studies from developed countries report rates of miscarriage in clinically recognised pregnancies [5–8], studies of miscarriage in low-income and middle-income countries face additional challenges as most miscarriages occur without any contact with the formal healthcare system and are not registered.

In Kenya, reviews using regional estimates project the risk of miscarriages and stillbirths in 2007 to be 12.2% and 3.3% per pregnancy, respectively [9–11]. In a comparison of women with induced abortion, spontaneous abortion and ectopic pregnancy in Ghana, Schwandt and co workers recorded 75% spontaneous abortion. Incidences of miscarriage in women continues to be on the rise across the globe and this is attributable to factors which could be genetic, biological (e.g. bacteria and viruses), social (e.g. stress), lifestyle (e.g. tobacco smoking and alcohol consumption), environmental (e.g. exposure to certain chemicals/dangerous gases/heavy metals) etc [4,12,13].

Heavy metals are environmental pollutants with deleterious effects on for wildlife and humans [14–16]. Heavy metals found in the environment are released from a wide variety of sources and humans are exposed to these metals, through occupational, accidental and sundry exposures. Recent studies indicate that elevated blood levels of heavy metals e.g. lead persist in many low and middle-income developing countries around the world at much higher level than in the more developed countries [17,18].

Abnormal incidences of pregnancies e.g. miscarriages, menstruation or sperm properties may each serve as an indicator of reproductive toxicity in humans [19]. Miscarriage also known as 'Spontaneous abortion' is of public health importance in developing nations [20]. It can be defined as a pregnancy that typically terminates naturally (not induced) during the first 7–28 weeks of gestation [19]. Women are generally exposed to heavy metals presence in the environment everyday often without knowing [21]. Long exposure to some of the persistent chemicals/metals has been documented to cause disruption in the fetal developmental process and pregnancy outcome [4]. Studies have shown that heavy metals like lead (Pb), cadmium (Cd), and mercury (Hg) have toxic effects on reproductive outcome and are also associated with miscarriages [21]. Skeletal lead can be mobilized from bone during pregnancy and passed on from mother to the fetus [22]. Studies in animal models and accidental poisoning in humans revealed that lead, cadmium and mercury resulted in miscarriages stillbirth and even fetal malformation [21].

Recurrent miscarriages more often engender physical and psychological harms to the patients with attendant socio-economic problems. Hence, researches on the prevention and treatment of recurrent miscarriage are of significantly clinical and social importance. In sub Saharan Africa where clinical practice is evenly routine and medical education hinged on old medical curriculum which has not considered the exposure science and environmental toxicants in medicine with most physicians rarely thinking outside the box [23,24], the place of heavy metals in women health and pregnancy outcome is seriously advocated. Little is understood about the pathways to induced abortion in sub-Saharan Africa. To our knowledge, no systematic review and/or meta-analysis has reported on the effect of heavy metals in miscarriages and stillbirths in developing nations. Given the widespread heavy metal exposure in developing nations, an understanding of the impact of these toxic metals on maternal and fetal health is relevant for public health policy.

To fill this gap, this review evaluates the current state of knowledge about the link between heavy metals and miscarriages in women from developing nations, considering possible implications on maternal health. For the purpose of this review five heavy metals implicated in spontaneous abortion/miscarriage will be probed and these include mercury, lead, cadmium, arsenic and chromium. This is aimed at quantifying the extent of the problem posed by these heavy metal exposure in miscarriages in developing countries.

2. Methodology

2.1. Search methods and selection criteria

To identify papers focusing on heavy metals and miscarriages, we reviewed PubMed, Medline and Google scholar databases for studies by using the following key words: heavy metals, environment, miscarriages, spontaneous abortions, stillbirths, pollution in developing nations, cadmium, lead, mercury, fetal and maternal health, birth outcomes, and fetal neurotoxicity. The search was conducted separately and the literature pooled together afterwards. Hand searching was adopted to find relevant literature that was not obtained using the regular search criteria. The search was conducted in each database separately and then combined to pool together all the literature. The pooled search database was examined and the duplicates were removed and appropriate limits were applied, and the database was saved for data extraction.

The inclusion and exclusion criteria were applied when reviewing the title and abstract of each journal article. Results were included if they reported an association between exposure to the defined heavy metals and miscarriages/birth outcomes. In addition, details on environmental exposures that occurred during pregnancy or prior to that were also included. Studies that reported metals as having nutritional value or if were not associated with pregnancy were excluded. Articles were also excluded if they were not written in English. From the literature search, it was observed that exposure to trace metals like manganese was linked in some cases to miscarriage incidence. Therefore, literature on exposure to manganese during pregnancy was also searched and included in this review. If more than one report was published from the same study, the most recent study or the study using the best assessment of heavy metal and/or outcome was included. Most relevant characteristics of eligible studies including study design, study size, location and country of study, method of heavy metal assessment, exposure marker for heavy metal exposure contrast, exposure dose, type of adverse pregnancy/infant mortality and their definitions, year of publication, year of data collection, adjustment for adequate confounders, and study results (i.e., measures of association) were recorded in a standard data extraction

form. The information collected from all these articles is reported in this review.

Initially, a total of 100 articles were retained for this review. After pooling the searches and removing the duplicates a total of 85 studies were retained for data extraction. In the course of data extraction process a total of 32 articles were excluded as they were not relevant to the focus of this review; thus a total of 53 articles were included in this review. These articles probed the link between maternal exposure to heavy metals and miscarriages in developing nations. The retained articles investigated the exposure to lead, arsenic, cadmium, chromium and mercury before and during pregnancy in relation to their impact on maternal and infant wellbeing.

3. Results

3.1. Important heavy metals involved in miscarriages and stillbirths

Heavy metals are generally referred to as chemical elements with a specific gravity that is at least five times the specific gravity of water [14]. In minute quantities, some heavy metals are important nutrient components for a healthy life, and these group of metals are known as the "essential elements" (e.g. iron, copper, cobalt and zinc) and present in everyday foods like vegetables, fruits, [15,25]. However, with rapid industrialization and urbanization, environmental pollution with these heavy metals have become a major public health concern especially in developing nations. Some of these heavy metals persist in nature and can be a cause of damage to human health and subsequently, death [26].

Some key heavy metals like arsenic (As), cadmium (Cd), lead (Pb) and mercury (Hg) have been shown to exhibit endocrine disrupting properties and are termed Endocrine disrupting compounds 'EDCs' [27]. The exposure to these heavy metals during pregnancy are believed to have adverse effects on the mother and the fetus [28]. EDCs interact with the endocrine or hormonal system producing adverse birth outcomes, it is therefore pertinent to further investigate the relationship between exposure to toxic heavy metals and the possible endocrine disrupting effects that may be incurred during pregnancy [28].

The placenta an organ formed by the fusion of maternally and embryonically derived tissue inside the uterus is commonly regarded as a major selective barrier preventing the transfer of harmful substances while allowing the passage of nutrients and oxygen from mother to fetus and hence protects embryo and fetus from harmful exposures [29,30]. Potential toxic metals tend to hamper placental function at many levels, e.g. signaling, production and release of hormones and enzymes, transport of nutrients and waste products, implantation, cellular growth and maturation, and finally, at the terminal phase of placental life, i.e. delivery [31]. However studies have shown that the placenta cannot prevent the passage of toxins like thalidomide or mercury which subsequently accumulate in fetal tissues [32]. Heavy metals have been indicated to cause deleterious effects on placental functions some of which are well-known to cross the placenta and accumulate in fetal tissues [33].

The heavy metals mercury, lead and cadmium are key toxicants that are well-documented to cross the placenta and to accumulate in fetal tissues with subsequent deleterious effects [30]. This particular group of heavy metals have been shown to alter the delicate maternal-fetal balance, hence causing long-term damage to the newborns [30,33].

3.2. Lead

In the early part of the 20th century, there were reports of pregnant women occupationally exposed to high levels of lead in England and Hungary [22]. This exposure however was associated with frequent spontaneous abortions, stillbirths, premature births, and neonatal deaths, compared with mothers in occupations unexposed to lead poisoning [22]. The WHO documents that about 120 million people have lead levels above 10 μg/dL across the globe with approximately 40% of the children having blood lead levels above 5 μg/dL [14]. Out of this population 97% of the affected children reside in developing nations [14]. Lead has been shown to be present in contaminated drinking water, lead based paints, leaded gas, news print and coloured ads, hair dyes, pesticides, pencils, fertilizers, tobacco smoke, cosmetics and ceramics [14,21,34].

Lead is a known neurotoxin and it is highly poisonous to the fetus with negative impact on fetal growing and brain development [35]. Lead interferes with synaptic transmissions as well as cellular adhesion molecules leading to blockade of cell migration during in the nervous system development [36]. Over 90% of the lead body burden is localized in the bone with an average half-life of about 10 years [37]. Research has shown that during pregnancy and lactation in humans, lead is released from the maternal skeleton and transferred to the fetus/infant via the placenta and breast milk respectively which then subsequently affect the developmental process of the central nervous system in the new born [24,38,39].

A recent study in Nigeria investigating the prenatal burden of exposure to lead at delivery indicated that the maternal mean blood lead value was significantly higher than the lead value of the cord, with a 100% prevalence of blood lead level (BLL) above maximum permissible level 10 μg/dl in both the maternal and cord BLLs [24]. This result is consistent with the results obtained from a Saudi Arabian hospital on 1578 women where lead was found in all cord and maternal blood and in 96% of placental tissues [40]. However, the cord blood lead levels (BLLs) found in other developing countries such as, Mexico, India, Pakistan, and Tanzania were in general lower than the levels obtained from a study carried out in Nigeria, indicating a higher level of lead exposure [24,41–43]. Prenatal lead exposure in Mumbai, India, though low (5.1 μg/dl), was shown to be about 2–3 times higher than that observed in more developed countries like Canada or Italy [42].

Research has documented that in expecting mothers both exogenous and endogenous exposure to lead represents a significant source of lead exposure during pregnancy [28,44]. Lead is stored in the human body over a long term and probable changes in metabolism during the storage could provide insight on specific periods in which lead exposure was highest [28]. Over 90% of lead accumulated in the human body in childhood years is stored in the skeleton [45]. Lead has been shown to be mobilized from the skeleton during pregnancy because high level of calcium requirements. Calcium is supplied by the bones via mobilization if this requirement is unmet to make up for the deficiency and hence promoting a co-mobilization with stored lead which is transmitted to the fetus from the placenta during a period of crucial central nervous system development [22,45].

Blood lead levels have been categorised into four classes and these include; normal (<4 μg/dl), mild (5–9 μg/dL), moderate (10–14 μg/dL) high (15–20 μg/dL). Blood concentrations higher than these levels is termed 'severe' [46,47]. Research has established that females who suffered from lead intoxication during their pre-adult days have a significantly high incidences of spontaneous abortion [48]. However, studies carried out in some countries regarding mild to moderate lead intoxication have not supported this claim with no significant positive correlation [45,48].

Work carried out by Faikoglu and coworkers in Istanbul, Turkey, to ascertain if there is any relationship between early pregnancy loss and maternal plasma lead levels revealed no significant correlation between the pregnant woman who were exposed to lead

intoxication and those who spontaneously aborted [45]. In this study, the concentration of lead in the plasma was probed in 20 women with a history of spontaneous abortion before the 20th gestational week, and the results were compared with 20 control patients with viable intrauterine pregnancy. Data obtained showed a mean lead level of 18.8 μg/dL in the cases of pregnancy loss and 22.1 μg/dL in the control patients, indicative of no significant relation between early pregnancy loss and maternal plasma lead levels. However, further investigation showed that the subjects studied had no lead deposits in their skeleton to be mobilized because of the pregnancy [45]. There is evidence that the history of spontaneous abortion is related to the plasma/blood Pb ratio, which could be due to a greater availability of placental barrier-crossing Pb for a given blood Pb concentration in some women [49]. Exposure to lead has been associated with spontaneous abortion, stillbirth and high rates of infant mortality [50,51]. Lead abortion pills with 32 μg lead each (256 μg Pb per day for the recommended dose of 8 pills) were used in the early 1900s, and use of new lead pipe in potable water systems for cities without corrosion control led to an exponential increase in miscarriages and stillbirth [50,51].

Development in recent times have promoted measures leading to minimised lead exposure to humans, nevertheless exposure to this heavy metal continues to be a major public health concern in developing nations. Studies have revealed that while blood lead levels (BLLs) in many developed countries have declined continuously over the years, in Nigeria however; high BLL continue to be on the increase [23]. In Nigeria, many sources of environmental lead exposure exist. A major source is leaded gasoline. With intense public health campaign, a plan was put in place to reduce the lead composition of Nigerian gasoline from 0.74 g/L to 0.15 g/L as at 2002 but this remained an illusion till date [23]. Due to the long biological half-life of lead, the environment being a major source of exposure, still contains significant levels of the compound [52]. Lead accumulation and persistence in the soil can occur in industrialized areas where lead is used as a raw material and this poses an important heath hard to living near such areas [53].

Herbal remedies have also been shown to be another important source of lead exposure. A recent report has highlighted metal contamination in the form of arsenic cadmium, lead and mercury in traditional Chinese remedies [54,55]. In 2004, it was reported that 13 out of 70 herbal remedies from south Asia sold in Boston contained high levels of lead [56]. Another study by Orisakwe and co-workers in southern Nigeria revealed that a high percentage of food crops and fruits violated the permissible limits of lead and cadmium as set by WHO, EU and EPA respectively and this poses a major public health concern [17]. Understandably the most serious source of lead exposure today is lead contaminated dust and soil. Leaded gasoline, point sources such as manufacturing plants, artisanal mining, smelting, and deteriorating exterior lead paint all can contaminate the soil. Soils in close proximity to roads and residential homes painted with lead paints have lead levels, respectively, 30–2000 ppm and 10,000 ppm higher than permissible stipulated by Environmental Protection Agency standards for residential soil (400 ppm in play areas and 1200 ppm in other areas of the yard (CDC 1991, USEPA 2001). Household dust lead levels can be exaggerated by Lead-laced soil from roadways of high traffic and deteriorating interior lead-based paints which may pose held risk for both pregnant women and the fetus. Pregnant women who engage in pica behavior are at particular danger of lead exposure [57].

Maternal Blood lead levels increase in pregnancy, rising overall by 20–30% [39,48,58]. Blood lead levels follow a U-shaped pattern—increasing slightly in early pregnancy, falling mid-pregnancy, and rising dramatically in the third trimester. Increasing blood lead levels could be a result of increased maternal absorption in pregnancy or mobilization of lead out of maternal bone. Several studies suggest that at least some of this increase is a result of maternal bone demineralization during pregnancy. It has been shown that serum calcium levels declined during pregnancy as lead concentrations increased, suggesting that lead leached out of maternal bone as calcium was mobilized to meet fetal demands [58]. Furthermore another report by Markowitz confirmed that the fetus can act as a lead sink, siphoning off lead from maternal stores, improving maternal lead levels at its own expense [59,60]. Lead is freely transported across the placenta since maternal and cord blood lead levels are similar [54]. Blood lead levels >25 μg/dL during pregnancy have long been recognized to increase the risk of abortion and stillbirths [53,59,60]. In fact relatively low-exposure levels have also been found to increase the risk of spontaneous miscarriage [48]. Women with increasing blood lead levels had higher incidences of miscarriages. This hypothesis is consistent with data obtained from two studies carried out in Nigeria. From these studies, women with history of miscarriage had blood lead levels >25 μg/dL during pregnancy. However, data obtained by Ajayi et al. revealed a 41.61% increase in miscarriage incidence while work by Otebhi and Osadolor an increase by 8.9% [13,85]. In Egypt, studies by Ahmed et al., 2007 revealed a 32.33% increase in miscarriage incidence in women exposed to lead [118]. In another study blood levels of 5–9 μg/dL were associated with an odds ratio for miscarriages of 2.3. At blood levels of 10–14 μg/dL, the odds ratio increased to 5.4 and at blood levels of 15 μg/dL, the odds ratio increased to 12.2 [61].

Lead is not associated with any known important physiological role in the body, however its toxicity stems from its ability to mimic other biologically important metals, most notably calcium, iron, and zinc which function as cofactors in many enzymatic processes. Lead binds to and interact similar enzymes as these metals but, due to its distinct chemistry, it functions as a false cofactor, hence interfering with the ability of the enzyme to catalyze its normal physiological reactions. A major mechanism by which these heavy metals act is by the generation of free radicals i.e. reactive oxygen species (ROS) and reactive nitrogen species(RNS) that may result in oxidative stress which has been reported to influence the female reproductive system adversely [62,63]. Reactive oxygen species affect multiple physiological processes from oocyte maturation to fertilization, embryo development and pregnancy.

Furthermore, lead is now known to induce production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and hence this heavy metal is able to generate oxidative stress in the body of humans occupationally exposed to lead and experimental animal models treated with varying lead concentrations [64,65].

3.3. Cadmium

Cadmium is a non-essential heavy metal and similar to arsenic, it is commonly found underground within rocks, sediments, soils and dust [66]. However, It can then be absorbed by plants/crops from the soil [15,66]. Cadmium can be found in sources like cigarette smoke, contaminated drinking water, paints, welding and from shellfish [34]. In addition, cadmium is used in many industrial processes and is associated with products like batteries, plastics, alloys, and fertilizers [66].

Cadmium concentration in the human body has been shown to increase with age and accumulates in kidney cortex with a long biological half-life of 17–30 years [67,68]. In addition, women have demonstrated higher concentrations of cadmium in blood, urine, and kidneys than in men [37,69,70]. A probable explanation for the elevated cadmium levels in women could be that the absorption of cadmium increases significantly at low iron levels,

suggestive of a rather compensatory mechanism of uptake for iron and cadmium [37]. It is documented that the duodenal metal transporter (DMT1) responsible for the mobilization of iron into the mucosa cell is up-regulated by iron deficiency. This transporter however, has affinity for cadmium [71] which explains the elevated of cadmium observed at decreasing iron stores observed in different groups of pregnant and non-pregnant in recent studies women and in children [37,72]. In other words, iron deficiency during pregnancy results in elevated cadmium absorption and subsequent high body burden [73]. Research has documented that a high incidence of miscarriage in women is associated with a high cadmium level in the body [21]. Furthermore, studies involving animal models examined the effects of cadmium exposure and data generated from these studies confirm the endocrine disrupting property of cadmium [28]. Vaiserman and coworkers demonstrated that cadmium mimicked estrogen effects resulting in the proliferation of both uterine and mammary tissues [73]. Cadmium can mimic the effect of the endogenous oestrogen receptor agonist, oestradiol, which leads to oestrogen receptor activation. While the effects of cadmium on the endocrine system are no longer in doubt, the exact mode of action is still being studied. At the molecular level there appears to be a 'cross-talk' between the oestrogen receptors and growth factor receptor. This 'cross-talk' appears necessary for estrogen signalling in mammary cells to divide or differentiate. These events are critical for explaining several risk factors including pregnancy related challenges. Data from experimental animals suggest that cadmium mimics estrogenic effects and this leads to the proliferation of both uterine and mammary tissues [73]. Results from in vitro studies have also indicated that cadmium may directly affect hormone-production in steroid hormone- producing ovarian cells [28].

Animal studies have revealed an important vulnerability to cadmium toxicity in late pregnancy, this is coupled with increased cadmium absorption [30]. Cadmium influences placental transport of calcium and zinc, induces early decidualization of endometrial stroma cells, inhibits trophoblast cell migration by influencing actin cytoskeletal organization, reduces the synthesis of leptin, promotes corticosterone concentrations and interrupts placental progesterone production [30,74,75].

It has been reported that regular consumption of fish and meat also lead to higher levels of cadmium in human hair, 14.05 ± 71.54 mg/g and 14.72 ± 64.11 mg/g respectively compared with those consuming it less frequently 1.93 ± 10.29 mg/g and 0.93 ± 5.78 mg/g respectively among residents of the Canary Archipelago [76]. The association between cadmium and miscarriage was investigated in some developing nations such as Nigeria, Sudan and Egypt. Results obtained highlighted that while an increase in miscarriage incidence was observed in Nigeria (83.93%) and Egypt (1.17%), a decrease in miscarriage incidence was observed for the population studied in Sudan (27.32%) [13,85,119].

Cadmium can also inhibit the transcription of LDL-receptor mRNA, which leads to a decrease in supply of cholesterol substrate needed for placental progesterone production [77,78]. In addition, higher concentrations of cadmium in the body have been indicated to alter the secretory patterns of a number of reproductive hormones, including luteinizing hormone (LH) and follicle- stimulating hormone (FSH) [77].

3.4. Mercury

High levels of mercury exposure could be through petroleum products, fungicides, cosmetics, hair dyes, thermometers, vaccination, silver dental fillings and consumption of salt water fish [34]. Mercury on its own, does not affect intrauterine growth [79,80], however, an increased risk for miscarriage has been documented [81].

Mercury exists in the environment in two forms: organic (methyl mercury) and inorganic mercury. Organic mercury is more prevalent in aquatic ecosystem and exposure is via consumption of seafood while inorganic mercury is airborne where exposure occurs via occupational activities [28,82,83]. Organic mercury is a major public health concern because it has posed to be a more frequent source of mercury poisoning to both humans and animals [28]. Methylmercury (MeHg), is a well-known neuro-toxicant and human exposure occurs more frequently via consumption of seafood especially the carnivorous fish and marine mammals which have been shown to contain mercury in the milligram per kilogram range [28,68]. Since the half-life of MeHg in maternal blood is about 2 months, this indicates that MeHg exposure before the development of pregnancy will lead to fetal exposure over a reasonable part of early fetal life [37].

Some studies have examined the association of paternal exposure to mercury and an increased risk for spontaneous miscarriage [84]. Women occupationally exposed to elemental mercury vapour had more spontaneous abortions than non-exposed women as shown in another study. In Nigeria, there was a significant increase ($\rho < 0.001$) in the mean blood mercury level of pregnant women with history of pregnancy complications compared with the pregnant and non-pregnant women that are without history of pregnancy complications [85]. The association between mercury exposure and miscarriages was investigated in developing countries such as Nigeria and Jamaica, results revealed mercury blood concentration of 85.96 ± 1.09 μg/dl and 7.29 ± 9.10. μg/l respectively [13,120]. Another study by Otebhi and Osadolor revealed a 9.5% increase in miscarriage incidence in women exposed to mercury in comparison to the unexposed group [85].

According to a study involving women living along the Beni River, Bolivia Brazil, have associated exposure to methylmercury and spontaneous abortion [86]. Findings from this study indicated that women who had losses of pregnancy had high methylmercury levels [28,86]. Studies have indicated that mercury possesses endocrine disrupting characteristics in that mercury may modulate the physiological levels of reproductive hormones [28]. Furthermore, it has been documented that exposure to mercury can induce female reproductive hormones like estrone and estradiol [77].

The umbilical cord blood is known to possess higher mercury levels compared to maternal blood. Furthermore, it is documented that cord blood concentrations of mercury are almost twice those in the maternal blood [30]. This could be further explained by the higher hematocrit, haemoglobin, and plasma albumin levels in fetal blood as compared to maternal blood (which enhances mercury binding in fetal blood cells), but could be more likely to be caused by active mercury transport to the fetus [30,87]. The toxicity profile of mercury in placenta includes abnormal amino acid transfer, placental oxygen consumption, enzyme activity, hormonal secretion, and membrane fluidity [30].

3.5. Chromium

Chrome is classified a heavy metal element with common forms of chemical valence of Cr (III) and Cr (VI). However, Cr (III) is an essential trace element for humans and plays a major important role in the regulation of glucose [88,89]. Cr (VI) possesses strong oxidation properties with its toxicity 100 times greater than that of Cr (III) [89,90]. Cr (VI) has the potential to enter cells easily via the nonspecific anion channel of the cytomembrane [90]. Redox reactions in cells then generates a wide array of reactive oxygen species (ROS), resulting to oxidative stress with the formation of Cr-DNA adducts and DNA–protein or DNA-Cr-DNA crosslinks. Consequently, activation of DNA- dependent protein kinases (DNA-PK)

and the P53 gene induces subsequent cell death or apoptosis [91,92].

Occupational chromium poisoning (OCP) is of public health concern. Chromium poisoning could lead to an increased risk of abortion or threatening miscarriage in female workers. In China, 18 epidemiological surveys studying occupational chromium poisoning from 1983 to 2010 with analysis of incidence of abortion associated with occupational Cr (VI), recorded an increased risk of spontaneous abortion or threatened abortion in female workers, compared to the control of non-occupational chromium exposure [90,93]. "For female workers with occupational chromium exposure, the incidence rate of spontaneous abortion or threatened abortion increased by 5.58% or 6.00%, respectively. So the risk of spontaneous abortion or threatened abortion increased by 2.31 or 20.47 times, respectively, compared to unexposed controls" [91]. A recent study carried out in Nigeria revealed that the incidence of miscarriage or spontaneous abortion increase by 1.60% in women exposed to chromium [13].

Chromium is commonly used in its hexavalent form [(chromate, Cr (VI)] in making stainless steel, leather tanning, pigment production, electroplating and in other applications. This hexavalent form exists widely in the environment and can be refined through the process of industrial melting [91].

3.6. Arsenic

Accumulations of arsenic is within bedrock, sediments and soil serves as underground reservoirs from which arsenic dissolve into aquifers; making groundwater a major source of arsenic exposure [69]. Air accruing from industrial emissions or coal-burning is another important source of arsenic poisoning [69]. Furthermore, arsenic-based herbicides and pesticides used in agriculture also serve as reservoir for arsenic as it is subsequently incorporated into the food supply chain [94,95]. Irrigation practices using arsenic-contaminated water may lead to bio-accumulation of arsenic and can subsequently place the consumer at risk when used in the growing of food crops [95].

Arsenic is considered to be highly toxic [96]. Drinking water contaminated with arsenic represents a major public health problem in south Asia, however a large population of people in the United States, Europe, and China are also exposed to arsenic levels above 10 μg/L [95]. Documentations by Aylward and coworkers report higher levels of arsenic concentration (95 μg/L) in the urine of a population of people in some regions of Bangladesh endemic with arsenic compared with the data (8.15 μg/L) obtained from a population the United States [97].

The association between arsenic exposure through drinking water and spontaneous abortion, stillbirth, and neonatal death in Bangladesh was studied by Milton and coworkers [98]. Data obtained revealed that individuals exposed to arsenic concentrations higher than 50 μg/L via drinking water had a higher risk of spontaneous abortion, stillbirth and neonatal death than subjects exposed to arsenic concentration <50 μg/L [28]. Further studies also have probed the link between arsenic exposure and abnormal obstetric effects, including spontaneous abortion, stillbirths, neonatal death, pregnancy hypertension, and gestational diabetes. Though the majority of studies were conducted in populations of some developing countries like West Bengal, India and Bangladesh, data from other populations were also studied. Research by Ahmad and coworkers concentrated on two separate populations in Bangladesh [99]. Adverse effects in population with elevated arsenic exposures (mean arsenic levels 240 μg/L) were compared with population consuming safe drinking water (arsenic levels <0.05 ppm total arsenic). Eighty percent of tube wells in the exposed village had drinking water arsenic concentrations >50 μg/L. Data obtained revealed a statistically significant ($z = 3.2$ and $p = 0.02$) greater proportion of pregnancies ended as normal live births 89.1% and 95.5% of the exposed and non-exposed populations respectively. In addition, significantly higher ($p < 0.05$) rates of spontaneous abortion (68.8), stillbirths (53.1), and preterm births (68.8) per 1000 births were obtained in the exposed population compared. Data obtained in Nigeria by Otebhi and Osadolor highlighted a 5.88% increase in the incidence of miscarriages in women exposed to arsenic compared to the unexposed group [85].

Arsenic has been shown to possess endocrine disrupting capability and this is further supported by data from chicken embryos which revealed that non-cytotoxic doses of NaAsO2 resulted in the suppression of transcription of the 17β-estradiol-inducible vitellogenin II gene [28].

Arsenic exists in three oxidation states: trivalent arsenite (As (III)), pentavalent arsenate (As (V)), and elemental form. Trivalent arsenite is ten times more toxic than pentavalent arsenate while elemental arsenic is non- toxic [67]. Arsenic on the other hand also occurs in three chemical forms: organic, inorganic, and arsine gas, with inorganic arsenic and arsine gas showing high toxicity while organic arsenic shows mild toxicity [67]. Human exposure to arsenic primarily occurs by ingestion, nevertheless inhalation and skin absorption are possible. Studies have revealed that about 80–90% of a single dose of arsenite As (III) or arsenate As (V) can be absorbed from the gastrointestinal (GI) tract of humans and experimental animals [67].

Hopenhayn-Rich and group reported high perinatal and neonatal mortality in the mining area of northern Chile in association with arsenic-contaminated water [100]. In Bangladesh, Ahmad and coworkers reported a significant increase in spontaneous abortions, stillbirths, and preterm births [99].

3.7. Male mediated miscarriage

Male-mediated spontaneous abortion remain unreported in man hitherto [101,102], nonetheless some facts have emerged to suggest that the welding of stainless steel may be a relevant paternal exposure. Stainless steel fumes (not mild steel), contain hexavalent chromium [103–105], inhalation of which trigger pulmonary absorption of hexavalent chromium [104–107] with autopsy findings of former chromate exposed workers confirming high concentrations of hexavalent chromium in several examined organs [108,109]. Hexavalent chromium administration in male rodent also impairs the viability of embryos fathered by that male [110–113]. Increased risk of self-reported spontaneous abortion was previously found in spouses of stainless-steel welders, compared with spouses of non-welders [odds ratio (OR) 2.0, 95% confidence interval (95% CI) 1.1–3.51 [114], but no excess risk was found in the same cohort in analyses based on abortions treated in a hospital [115], a finding which may be explained by high risk being restricted to early (preclinical) abortions. According to Hjollund et al., 2000, there is an increased risk of early spontaneous abortion for women whose partners are engaged in stainless-steel welding during the cycle in which the woman conceived [115].

4. Miscarriages where heavy metals have been implicated in sub-Sahara Africa

Minimal data exists regarding the implications of heavy metals in spontaneous abortion and stillbirths in sub-Sahara Africa. However, recent work by Ajayi and coworkers involving 69 pregnant women (with gestational age of 0–20 weeks) aged 21–41 years yielded interesting results. From this population, thirty-five (cases) and thirty-four (controls) had previous and no history of recurrent spontaneous abortion respectively [13]. Blood samples were obtained to determine the presence of progesterone, zinc, copper,

Table 1
Blood heavy metals levels and miscarriages in developing nations.

	No miscarriage	Miscarriage	Country	Ref.
Manganese (μg/dl)	70.35 ± 1.92	85.37 ± 15.68	Nigeria	[13]
Chromium (μg/dl)	44.45 ± 1.16	45.16 ± 1.26	Nigeria	[13]
Lead (μg/dl)	60.70 ± 1.40	85.96 ± 1.09	Nigeria	[13]
	23.70 ± 0.09	25.81 ± 0.06	Nigeria	[85]
	7.98 ± 3.00	10.56 ± 1.32	Egypt	[118]
	12.33 ± 5.86	5.86 ± 1.27	Sudan	[119]
Cadmium (μg/dl)	2.49 ± 0.09	4.58 ± 0.77	Nigeria	[13]
	2.74 ± 0.25	3.20 ± 0.65	Egypt	[118]
(μg/l)	0.83 ± 0.00	0.89 ± 0.01	Nigeria	[85]
	2.05 ± 0.81	1.49 ± 0.65	Sudan	[119]
Mercury (μg/dl)		85.96 ± 1.09	Nigeria	[13]
(μg/l)	0.21 ± 0.00	0.23 ± 0.00	Nigeria	[85]
		7.29 ± 9.10	Jamaica	[120]
Arsenic (μg/l)	0.17 ± 0.00	0.18 ± 0.00	Nigeria	[85]

selenium, iron, magnesium, manganese, chromium, lead, cadmium, and vitamin E. Data obtained from this study indicated high level of serum heavy metals (cadmium, chromium and lead) and reduction of essential micronutrients (zinc, copper and vitamin E) could contribute to recurrent spontaneous abortion (Table 1) [13]. Poor nutritional intake in developing countries like Nigeria could also play a role in the aetiology of spontaneous recurrent abortion. In Nigeria, for example, many people live below the one dollar a day mark. This puts pregnant women in a difficult situation where healthy diets needed to sustain mother and fetus becomes inaccessible [13].

While documentation of cases of heavy metal exposure remains a problem in Nigeria, recent studies by Orisakwe et al., 2012 have highlighted an abnormally elevated concentrations of lead, cadmium and nickel in some selected Nigerian fruits and vegetables [17]. Results from this work highlighted an emergency situation suggesting that from staple foods alone, the body burden of lead in an average Nigerian exceeds that of values obtained in Europe and America then it should be worthy of note that a cumulative amount from other sources could even be higher [17]. Similarly, data obtained from the analysis of heavy metal content of some herbal remedies sold in Nigeria by Amadi et al., 2012 is also indicative of elevated concentrations of mercury, antimony and tin in the products [54].

Otebhi and Osadolor, 2016 observed a significant increase ($\rho < 0.001$) in the blood toxic metals (lead, mercury, cadmium and arsenic) levels in pregnant women with history of pregnancy complications compared with women who are also pregnant but without any history of pregnancy complications [85]. Otebhi and Osadolor, 2016 findings were in agreement with other studies [116,117] including Ibadan Nigeria, where similar increases were observed to be associated with spontaneous abortion [13]. Elevated serum heavy metals (cadmium and lead) may contribute to recurrent spontaneous abortion.

It is thought that in normal pregnancy there is an oxido-reductive balance between activity of pro-oxidative factors, like free radicals, and competence of antioxidative systems, in which Se, Zn, Mn and Cu are present and which are ingredients of enzymes in the first line of defense taking part in expelling free radicals. The enzymatic antioxidants namely super-oxide dismutase, catalase, glutathione peroxidase and glutathione reductase and non-enzymatic antioxidants are influenced by dietary intake (vitamin C, vitamin E, Se, Zn, Mn, Cu, taurine, hypotaurine, glutathione, b-carotene and carotene) [121]. Increase of constitutional oxidative stress markers tend to trigger advanced and irreversible state of abortion which does not appear in mild pregnancy disorders. The exaggerated oxidative stress impact adversely on female reproduction and the pathophysiology of miscarriage [122–124]. Potential toxic metals like lead, cadmium, chromium, mercury, arsenic act by the generation of free radicals – reactive oxygen species (ROS) and reactive nitrogen species (RNS), that may precipitate oxidative stress which has been reported to influence the female reproductive system adversely [63]. There are two plausible theories about the possible pathways of the mechanism of lead induced miscarriages in pregnant women [125]. Firstly, lead can induce excessive production of Reactive Oxygen Species (ROS) which disrupt collagen being a primary target for ROS causing the membrane to lose its elasticity and eventual premature rupture of membrane with its associated risks. With regard to balance in reproductive hormones, lead disrupts the balance in reproductive hormones which is a sacrosanct for the normal progress during the course of pregnancy. Estrogen and progesterone secretion can be affected by lead via increase in luteinizing hormone and follicle stimulating hormone [126]. Exposure to metallo-hormones is ubiquitous since these chemicals are commonly used in trade and commerce and in household products. Their inherent characteristics cause these metallo-hormones to act as ligands and bind to respective hormone receptors which bind to response elements in the target genes to produce undesired downstream effects by regulating gene expression [27,127]. In man hormones play a key role in regulating cellular activities and gene functions especially the downstream manifestations as estrogenic, anti-estrogenic, androgenic and anti-androgenic effects. These alter the function and expression of important genes [73]. Interference in the hormonal activity of natural hormones by metallo-hormones could manifest into adverse reproductive and developmental effects [27]. Furthermore, Lamadrid-figueroa et al., 2007 cautioned that assessing the influence of genetic polymorphisms of lead binding proteins on the probability of suffering from miscarriage or other reproductive outcomes will be very important to identify groups particularly susceptible to the effects of lead exposure during pregnancy [49]. Perhaps the major limitation of this paper is the small number of analysed studies arising from under-reporting and poor recording keeping.

5. Conclusion

Given the ubiquity of heavy metals in sub-Sahara Africa and the masked diagnosis of miscarriages in Africa as recently reported in Sudan (24% of known causes and 76% of unknown causes) [128] and whereas majority of clinicians dealing with pregnant women with miscarriages are unlikely to suspect heavy metal toxicity in the etiology due to a general lack of knowledge regarding this

subject in the medical community. Furthermore since unique biochemical, genetic, and nutritional factors confer different susceptibilities to the effects of toxic heavy metals; thus, cases of miscarriages should be handled on an individual basis. In most part of the world other than sub-Sahara Africa the number of practitioners trained in "functional" or "orthomolecular" medicine is increasing and these practitioners are very familiar with the diagnosis and treatment of problems associated with heavy metal toxicity [129].

6. Recommendation

The continued negligence and/or ignorance of potential toxic metals in the etiogenesis of miscarriages, still birth has huge socioeconomic burdens in the developing nations especially Sub Saharan Africa SSA where the prevalence rates are feared to be higher than previously thought. It may be worthwhile for toxicologists and scientists in SSA to investigate if these heavy metals can become additional biomarkers in the diagnosis of miscarriages and stillbirths.

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