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Heavy metal contamination of prenatal vitamins

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ABSTRACT

Prenatal vitamins are often consumed daily during gestation and postnatally for up to 18–24 months with the belief that supplementation achieves better outcomes. Detrimental effects of gestational exposure to adverse chemical agents are gathering increasing attention. This study was designed to assess toxic element contamination in prenatal supplements.

Twenty-six commonly used prenatal vitamin brands including one prescription brand were collected from Canadian health-food outlets and pharmacies, and tested for toxic element contamination. Results were compared to established endpoints.

All samples contained Lead with average amounts being (0.535 µgm), 20/51 samples exceeded established standards for lead toxicity (0.50 µgm/day), with one sample yielding 4. µgm/day. Three samples registered inorganic arsenic levels above acceptable limits. Cadmium levels did not exceed current standards. Toxic elements such as Aluminum, Nickel, Titanium and Thallium were detected in all samples.

Cumulative intake of prenatal supplement over many months may constitute a significant source of toxic element exposure to the mother and offspring. With several samples exceeding known standards for gestational toxic element exposure, guidelines for routine monitoring and reporting are required. In keeping with recommendations from the International Federation of Obstetrics and Gynecology, industry regulation would be welcomed to protect expectant mothers and their vulnerable offspring.

1. Introduction and background

The gestational period on the continuum of human life is a phase of particular vulnerability to toxic exposures, including adverse chemical agents [1]. With the high toxicant-to-mass ratio of the fetus at a critical time of growth and development, adverse exposure during pregnancy presents a particular risk. Unfolding evidence in the medical literature confirms that toxicant exposures to reproductive-aged women and consequently to their developing progeny by vertical transmission are responsible for myriad developmental and long-term health problems [1–6].

Along with the recognition of potential fetal origins of chronic pediatric and adult disease [1–6], a constellation of three primary factors has contributed to the escalating concern regarding vertical transmission of toxic agents:

i) Epidemiological studies by major groups such as the Centers for Disease Control confirm that toxic chemical agents are now polluting the bodies to some degree of most men, women, children and newborns in North America [7,8];
ii) Recent research suggests that because of an immature detoxification capability, developing children in-utero may accrue and thus experience higher levels of toxicant exposure than their mothers [9].
iii) Most health professionals providing specialized maternity care do not explore myriad sources of gestational contamination as they lack training in environmental and toxicological determinants of fetal compromise [10].

Alongside concern about gestational exposures, there is increasing attention to natural health product (NHP) contamination, including toxicity within prenatal supplements [11]. It has become routine for most women in the developed world to consume a prenatal vitamin supplement to secure gestational nutrient sufficiency and to maximize pediatric health outcomes. Yet, it is known that a number of toxic metals and metalloids such as lead, cadmium, arsenic and mercury, sometimes found in NHPs, may result in adverse outcomes in pregnancy and the offspring [12–14].

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Recognizing the widespread threat and impact of toxic chemical exposures from myriad sources during pregnancy and lactation, the International Federation of Obstetrics and Gynecology (FIGO), an organization overseeing maternity health care throughout much of the world, has endeavored to focus concern to the issue of vertical transmission of toxic agents [15] and recommended that training on toxicants and environmental health become a fundamental part of health care education to diminish sources of adverse fetal exposure. This study was designed to research the possibility of toxic element contamination in a variety of commonly consumed prenatal supplements – a product ingested by most women in the developed world during gestation and lactation.

2. Methods

2.1. Collection of prenatal vitamins

Prenatal vitamins were collected from assorted retail outlets including several health food stores, pharmacies, as well as food retailers within a large metropolitan city – Edmonton, Alberta, Canada. All available prenatal brands found were acquired and included – no brands were excluded. Altogether, 26 varieties of prenatal vitamins were collected, with 16 samples having more than one lot number to determine intra-product variances. 51 samples in total were sent for analysis to ALS Scandinavia labs. Some products only had one lot number in multiple locations throughout the metropolitan area, and thus we were only able to test one batch of these particular brands.

2.2. Sample preparation for element analysis

For liquid products, samples were diluted 10-fold with 1.4 M HNO3 (SP grade). For solid products, approximately 0.25 g of sample were subjected to closed-vessel MW-assisted digestion (MARS-5 oven, 600W 1 h holding time) using 5 ml concentrated HNO3 (SP grade), 0.5 ml H2O2 (PA grade) and 0.02 ml HF (SP grade). After digestion, solutions were diluted with 1.4 M HNO3 (SP grade) providing a final dilution factor of approximately 500. A set of digestion blanks and matrix-matched CRM were prepared together with each digestion batch. All solutions were spiked with In (internal standard, at 2 µg/l) and analyzed by Inductively Coupled Plasma mass spectrometry using the state of the art Sector-Field High Resolution Mass Spectrometry ICP-SFMS (ELEMENT2, ThermoScientific) using combination of internal standardization and external calibration.

2.3. Sub–speciation for arsenic

0.7–1 g of a subsample was weighed into a 50 ml PE centrifuge tube and 10 ml of 0.1 M phosphoric acid in 50% methanol solution was added. The mixture was shaken overnight (> 16 h) on a mechanical shaking machine. The sample was then centrifuged at 3500 rpm for 5 min. The supernatant was filtered through with membrane (0.45 um pore size) into 12 ml polypropylene tubes. Aliquot of the extracts were then diluted 10 fold with MQ-water. Procedural blanks of 0.1 M phosphoric acid was also treated in the same way as samples. The final diluted solutions were transferred into HPLC vials.

Fresh mixed calibration standards of As(III) (arsenite), As(V) (arsenate), DMA (dimethylarsinate), and MMA (monomethylarsonate) at two concentration levels (at 5 and 10 ug/l) were prepared by serial dilutions from their respective individual 1000 mg/l stock solutions. To serve as a quality control, a mixed standard with concentration of 1 µg/l of each Quality Control Samples (QCS) and spiked samples were also prepared. MQ-water was used as calibration blank. The final calibration solutions QCS and spiked samples were transferred into High Performance Liquid Chromatography (HPLC) vials. For the HPLC separation of As species, a Hamilton PRP-X100 anion-exchange with gradient elution of 60 mM potassium phosphate was employed. Following the separation, post column eluent was mixed with stream of 1ug/l antimony (internal standard) in 10% nitric acid. The mixed solution then merges with a stream of 1% sodium borohydride in 0.2% sodium hydroxide solution to form volatile hydride. The gaseous hydride was purged by auxiliary argon to feed into the ICP-MS (Element 2 ICPMS system) for detection.

Integration of chromatographic peaks, construction of external calibration curve (linear regression) was carried out using the Xcalibur™ Software (Thermo Scientific).

3. Results

3.1. Minerals found in prenatal vitamins

Prenatal vitamins are generally a mixture of vitamins and minerals. Our analysis showed consistent findings of the listed minerals as outlined on the product label, although the amounts listed and the actual amounts in many samples varied considerably. This finding has previously been discussed with other research reported in the literature [16]. Further discussion on the minerals found in our prenatal samples tested and discussion of them in relation to the protection against assimilation of toxic minerals [17] will be reserved for subsequent publications.

3.2. Toxic elements found in prenatal vitamins

There are established upper limits of ingestion on a daily basis of toxic elements from various organizations. However, few organizations have set limits for reproductive toxicity in relation to gestational and/or lactational exposure. The most stringent are from Proposition 65 in California and the US Pharmacopeia as listed in Table 1.

This discussion will be limited to the more common toxic metals and metalloids including mercury (Hg), lead (Pb), arsenic (As), cadmium (Cd), and aluminum (Al), as well as some emerging toxic elements such as Nickel (Ni), Titanium (Ti) and Thallium (Tl) as outlined in Table 2.

3.2.1. Mercury

Mercury was detected in 14/50 samples but levels were well within acceptable standards (< 0.3 µgm/day) with the highest level of exposure at 0.095 µgm/day. Levels below 0.3 µgm/day are considered to be within acceptable limits.

3.2.2. Lead

All 51 samples provided more than 0.1 µgm/day of Pb exposure. The overall average amount was 0.535 µgm/day, above the Proposition 65 limit (P65L) of 0.5 µgm/day for prenatal vitamins. Of the 26 products analyzed, 14 (more than half of the samples tested) had higher levels, with one product providing 4.0 µgm/day. Cumulative exposure per pregnancy (including 90 days preconception and 270 lactational days) was about 341 µgm on average, and 2.56 mg for the brand with the highest amount of Pb.

3.2.3. Cadmium

All of the 51 samples had some level of Cd. The average in all products was 0.37 µgm/day. Eight of the 26 products resulted in exposure levels greater than 0.5 µgm/day; these levels, however, were all below the P65 and USP accepted levels.

3.2.4. Arsenic

All 51 samples had some level of total As with an average exposure of 0.42 µgm/day. Four samples had more than 1.0 µgm/day exposure. On As speciation sub-analysis of these four samples, however, most of this arsenic was organic (considered much less toxic) rather than the highly toxic inorganic form. When considering the inorganic As species, of the 4 samples tested, nonetheless, 3/4 samples had > 0.1 µgm/day–above the acceptable (P65L) limit, with one having 0.4 µgm/day of

Table 1
Established Toxicant Limits in Supplements (μgm/day) or water* (μgm/l) adapted and expanded from [28] with USP standard included.

Toxic Element	U.S. California Proposition 65 (P65) and Environmental Protection Agency	European Union	Australia	World Health Organization85	US Pharmacopeia (purity limits for pharmaceuticals)	Gestational Limits1
Mercury (Hg)	0.3	4.2	2.4 Inorganic Hg 0.96 Methyl Hg	1.37 (Methyl Hg in children)	1.5 per oral daily dose	O.6 for Methyl Hg
Lead	0.5	21	NE	21	0.5 per oral daily dose	Concern at low levels. 0.5 established for reproductive toxicity (P65)
Cadmium	4.1	6	15	6	0.5 per oral daily dose	NE
Arsenic	0.1 (inorganic)	13.0	NE	12.85	2.5 per oral daily dose	NE
Aluminum	7000	4286	12,000	NE	NE	NE
Nickel	100* (EPA)	168	NE	350	60	NE
Titanium	NE	NE	NE	NE	NE	NE
Thallium	2*(EPA)	NE	NE	NE	NE	NE

NE – Not established.
European/WHO/Australian levels were established by convention as representing 10% of the daily total toxicant intake after conversion of values expressed in mg/kg/week for an average adult weight of 60 kg.

toxic trivalent or pentavalent As.

3.2.5. Aluminum

All 51 samples contained Al – this element is often used as a filling agent and has no known biological function. The average amount of aluminum in the prenatal vitamins was 157 μgm/day, with a maximum of 835 μgm/day – well within acceptable limits. 3 samples had levels above 420 μgm of daily Al exposure. (This level would be more than 10% of the daily maximum allowed from all sources according to daily exposure limits set by the European Union.)

3.2.6. Nickel

All 51 samples contained Ni. The upper limit of exposure for Ni according to the USP guidelines is 60 μgm/day and the maximum found in any sample was 34 μgm/day. The average was about 5 μgm/day.

3.2.7. Thallium

All 51 samples contained Tl. The range of Tl present in the prenatal vitamins was from 0.001 μgm/day to 0.186 μgm/day with an average exposure of 0.04 μgm/day. Three of the samples had levels above 0.1 μgm/day, –considered significant because of the toxicity of this element.

3.2.8. Titanium

All 51 samples contained Ti. Titanium levels ranged from less than 0.1 μgm/day to 0.4 mg/day. Ti is likely used as a filling agent or colorant in some prenatal vitamins.

3.3. Consistency between supplement batches

Sixteen of the 26 supplement brands had testing performed on 2 or more different lot numbers. All lots tested had a remarkable level of contaminant consistency with less than 20% variation in concentration of Pb, Hg, Cd, and Al between different batches of the same brand, which may indicate that the sourcing of the ingredients that make up the product, or the manufacturing process was the same.

4. Discussion

Contamination of NHPs is a concerning problem being discussed at length in the medical literature [11,18–20]. With particular vulnerability of the developing fetus, attention to NHPs consumed in pregnancy is imperative. In this study, we endeavored to determine if products routinely ingested during gestation and lactation were a cause for concern.

It is encouraging that few samples in our study had any detectable

Table 2
Toxic Elements: Minimum, Maximum, Average and Standard Deviation in μgm daily exposure including number above known upper limits.

Toxic element	Mercury	Arsenic	Lead	Cadmium
# of samples with detectable levels	20/51	51/51	51/51	51/51
Average	0.012	0.421	0.535	0.373
Minimum	0	0.08	0.124	0.061
Maximum	0.099	2.208	4.002	0.975
Standard deviation	0.015	0.519	0.619	0.265
Cumulative 640 days average/maximum	N/S	269.4/1413.1	340.8/2560	238.7/624
# of Products above acceptable levels	0/26	3/26	14/26	0/26

Toxic element	Aluminum	Nickel	Titanium	Thallium
# of samples with detectable levels	51/51	51/51	51/51	51/51
Average	158.5	0.655	99.36	0.040
Minimum	2.14	0.081	0.080	0.001
Maximum	834.7	33.64	400.79	0.186
Standard deviation	182	6.1	115.2	0.051
Cumulative 640 days average/maximum	101120/534208	419.2/21529.6	63590/256505	25.6/119.04
# of Products above acceptable levels	3/26	0/26	N/E	0/26

N/S = non significant, N/E = not established.

mercury. This is in contrast to other studies on NHPs where levels in some reports have been high [11]. Elevated levels tend to be found particularly in products containing marine sourced Omega 3 DHA or EPA products that are not distilled [11]. Yet, six of the products tested in this study had DHA or EPA as part of the prenatal nutrients and none had mercury levels that exceeded acceptable levels.

4.1. Contamination of prenatal vitamins

All prenatal vitamins in this study contained some As, Pb, and Cd and the amount varied between levels considered safe to levels that far exceed guidelines. (Table 1) The finding of arsenic usually reflects organic arsenide – an agent commonly found in seafood. It is generally considered to be relatively safe because the body is able to eliminate it quickly after ingestion [19]. Inorganic As, on the other hand, is quite toxic with trivalent and pentavalent forms being especially hazardous [21]. Unfortunately, three prenatal vitamins tested in our sample had inorganic As levels that were of concern. Prenatal As exposure has recently been associated with impact on genetic homeostasis with resulting inflammation and atherosclerotic disease in adults. Levels of As in the general population have also been found to be negatively associated with fetal growth in utero [22]. Even modest exposure levels have been associated to increase risk of infections in infants along with detrimental birth outcomes including decreased birth weight, head and chest circumference [23,24].

A major concern is the amount of Pb found in these samples with average results (0.535 μgm/day) resting above Proposition 65 and USP limits. Furthermore, it is noteworthy that some products consumed daily in pregnancy had exposure levels greater than 4 μgm/day. These results are in keeping with previous results from the U. S. Food and Drug administration (USFDA) done in 2008 almost 10 years ago where average Pb levels in prenatal vitamins were 0.845 μgm/day. At that time the USFDA considered these levels safe within their provisional total tolerable intake levels of 25 μgm/day for pregnant women [25]. Prenatal vitamins are only a small portion of the total daily intake and Pb is found in food and water as well as tea [26–28]. It is known that impairments of behavior and cognitive function in children (exposed prenatally or as young children) are repeatedly linked to chronic exposure of far lower levels than considered by the UAFDA [14]. In addition to daily exposure, when one considers cumulative Pb ingestion, (as Pb tends to accrue) the bioaccumulated level of consuming daily Pb for many months is potentially problematic.

The Agency for Toxic Substances and Disease Registry states that there may be no threshold for Pb with regards to developmental impact on children. In other words there are no safe limits for Pb. Prenatal lead exposure is associated with a greater risk of premature delivery [29] and reduced postnatal growth [30]. Prenatal lead exposure affects neurodevelopment of children with lower mental development scores linked to increasing exposure [31,32]. Prenatal exposure also may contribute to schizophrenia in adulthood as well as dementia [5,33]. Some types of congenital heart disease may be related to maternal Pb exposure [34], an exposure that has also been associated with higher blood pressure and kidney effects in girls but not boys [35,36]. It is also known that calcium supplementation may decrease fetal lead exposure [37] and magnesium and zinc may protect the NMDA receptor in the brain and attenuate the detrimental effect of lead [38].

Exposure to Cd prenatally may result in a reduced head circumference at birth and may have a detrimental effect on growth for the first 3 years [39]. Low-level prenatal exposure to Cd has been associated with adverse effects on neurodevelopment mostly in decline in the social domain of development [40]. The level of Cd exposure, mainly as a result of smoking during pregnancy, has been associated with a worsening of children's cognitive functioning in preschool (with a 2–3 point lower IQ), but there was some protective effect from selenium and iodine [41]. Maternal Cd exposure may also result in preterm low birth weight with a greater effect on girls than boys [42]. Atopic dermatitis has also associated with prenatal exposure to Cd [43].

Although Al exposure prenatally in humans has not been extensively studied, the literature does support reducing exposure postnatally. Intravenous feeding solutions with substantial aluminum have an effect on the subsequent neurologic development in preterm infants [44]. Studies done in pregnant rats exposed to aluminum had significant changes in tissue distribution of essential minerals with significant higher copper levels in the brain and significantly increased Ca, Cu, Mg, Mn, and Zn in kidneys [45].

Although Ni is considered a relatively inert element there is evidence it may increase iron absorption at least in rats [46]. The upper tolerable limit of Ni according to the USP standard is 60 μgm/day. The highest level in our prenatal vitamins was 34 μgm/day. Prenatal exposure in rats has been shown to cause facial, skeletal and eye malformations [47,48]. Excess Ni has been associated with some sensitivity such as contact dermatitis and a diet high in Ni may easily exceed the amount known to cause dermatitis flares [49].

Thallium exposure in the prenatal period has been linked to low birth weight [50]. Prenatal Tl exposure in a rat study demonstrated adverse impact on the developing autonomic nervous system [51].

It is unknown how much of the titanium in prenatal vitamins is submicron or nanosized. Most coatings on tablets that use Ti for whitening are of larger size and not of concern; nanoparticle Ti as used in food, cosmetics, paper and paints, however, is potentially problematic [52]. Submicron particles of 70–35 nm size have been shown to cause pregnancy complications in mice [53]. Thus, if some of Ti is submicron, there is potential concern. Although studies in humans are not available, several adverse effects of titanium on rats have been described, such as an increase in the prefrontal cortex of dopamine [54], depressive behaviors [55], and gene expression related to central nervous system development and function [56].

4.2. Other safety measures

It is possible to reduce absorption of toxic elements when essential minerals are in abundance [17]. Vitamin D will enhance the absorption of essential minerals such as Mg and Ca, as well as absorption of toxic elements, when essential minerals are in short supply [17]. Likewise, adequate essential minerals will protect the body from absorbing toxic elements which are listed in descending order of importance in this protection: Se > Ca > Mg > Fe > Zn > Cu. All prenatal vitamins had some Ca, Mg, Fe, Zn, Cu, K, Na, and manganese. However some had negligible amounts. Four of the vitamins tested did not include Se, which is the most protective. Discussion of these important nutrients will take place in a forth-coming article.

4.3. Cost correlation

The cost range of the samples was quite substantial with the lowest cost tablet at $0.03/day to a high of $2.06/day. A cost/benefit analysis on these vitamins revealed no correlation between product cost and the level of contamination. Interestingly, however, the most expensive sample provided the highest levels of toxicants. Being labeled as non-GMO, organic or pesticide-free did not correlate with the level of toxic element contamination. The reality that some lower cost products are able to achieve less contamination suggests that safer products with less accrued toxic elements are possible to achieve.

4.4. Sourcing of contamination

NHPs including prenatal vitamins represent the end result of many stages of development, all of which involve possible routes for toxic element contamination. Raw materials that make up the supplement may be sourced from various countries, including nations with less stringent controls over water, air and soil pollution [57,58] as well as agricultural practices. Plant products may absorb toxic compounds

from soil, water and air that have been contaminated with toxic elements (some of the prenatal vitamins are derived from plant extracts). Marine products are often polluted as a result of considerable contamination of bodies of water from an array of sources.

Another possible route for toxicant contamination is transport. Open-bed trucks, for example, may facilitate transfer of exhaust (commonly containing cadmium) into components of the supplement. Raw materials may be processed in undesirable factory conditions allowing contamination. Some products may be diluted with contaminated products or fillers when sold by weight. Intentional additives to supplements may be introduced for perceived therapeutic value, and may also be subject to contamination depending on their sourcing. In review, there are myriad potential sources of toxic element contamination.

4.5. Limitations of the study

The products chosen represent a sample of convenience using products readily available in pharmacies, supermarkets and health food stores in Canada in one metropolitan area. The particular method of analysis used here would not allow for fluoride or chloride analysis. Organic labeling was not in the scope of this analysis and, as mentioned, testing for pesticides, herbicides or other organic contaminants was not performed.

Another limitation is that these vitamins were not tested against each other in regards to disintegration and dissolution standards as recommended by the USP [16]. Future studies should incorporate this aspect as well.

4.6. Recommendations

There has been increasing discussion of late as to whether a multivitamin and mineral supplement is really necessary in pregnancy for women who have a healthy diet. Regardless of specific views on this issue, maternity health practitioners recommending prenatal supplements should be aware of safety prior to making recommendations. Recognizing the widespread contamination of commonly consumed prenatal supplements, it is important to avoid recommendations that might be harmful to the mother and her developing child. As a result of the findings in this study, we have some recommendation:

- All batches of prenatal vitamins should be tested for toxic elements.
- Guidelines for maximum acceptable levels incorporating the cumulative exposure of toxic agents should be established. As standards change and become lower, such as the case for Pb, these may need to reviewed accordingly.
- All prenatal vitamins should contain sufficient essential minerals and vitamin D to potentially reduce the amount of toxic elements absorbed [17].
- Many women are already taking prenatal vitamin supplementation prior to ever seeing their health provider. Accordingly, the objective of securing avoidance of chemical toxicants appears to be best met through preconception care [1].
- To ensure the manufacture and delivery of safe and reliable prenatal supplements, all natural health products should be regulated. We recommend the implementation of stringent self-regulatory process for safety and purity by industry, with government oversight and accountability. A detailed explanation for this can be found in a previous paper on this issue [11].

Although the number of prescription prenatal supplements was limited, there was no correlation between requiring a medical prescription and level of contamination with toxic elements. These findings do not ensure that such supplements are not contaminated with other adverse chemical toxicants – as testing for the wide range of other potential toxicants was not performed as part of this study. It is absolutely possible that some supplements with low levels of toxic element contamination may have high levels of contamination with various organic toxicants such as certain pesticides, solvents, perfluorinated compounds, or other adverse agents. Similarly, it is possible that exposure to multiple toxic elements even at doses at or below regulatory limits may result in increased risks or yet unidentified hazards, that may need to be addressed in the future as information becomes available [59,60]. Hormesis, a poorly understood concept at this time, may result in a non-linear response to the level of toxic exposure [61].

5. Conclusion

Over the last four decades, there has been a dramatic increase in the prevalence of pediatric chronic disease [62]. There is considerable literature suggesting that prenatal and lactational exposure to chemical toxicants, including toxic elements, may be a significant determinant in childhood illness, including autism and cancer [6,63,64]. As highlighted by FIGO in their special release about prenatal exposures, the need for maternal health providers to be aware of, and educate patients about toxic exposure avoidance in pregnancy is unprecedented [1,15].

Prenatal vitamin supplementation during gestation and lactation is used by most women in the western world as a means to maximize the health of their progeny. The prospect of contamination gestational products being consumed by most women is sobering indeed. This study found that several prenatal supplements are contaminated with toxic elements to levels that exceed accepted standards. The cumulative total exposure to the fetus with daily maternal ingestion of such adverse agents is concerning. This finding behooves regulators to consider how to address this concern in order to preserve pediatric health and public safety. As governments are often ill equipped to assess for safety and regulate all products, as evidenced by the colossal annual morbidity and mortality associated with pharmaceutical agents [65], we recommend that the NHP industry be required to actively establish vigorous regulation to self-monitor health products at all stages, but particularly during gestational and lactational states in order to prevent teratogenic impact.

Author contributions

Conceived and designed the experiments: GS and SG
Performed the experiments: GS IR.
Analyzed the data: GS. SG
Contributed reagents/materials/analysis tools: GS SG AS.
Wrote the paper: GS SG IR.

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