ABSTRACT: A recent paper by Changalvala et al. reported finding significantly higher levels of serum fluoride (p<0.05) in 150 pregnant women, at 20 or more weeks of gestation, in Karnataka, India, with the complex multisystem disease of pre-eclampsia, than in a control group of 150 pregnant women without pre-eclampsia (1.8±0.66 and 0.18±0.31 mg/L, respectively). Whether the association between a raised serum fluoride and pre-eclampsia might be one of causation rather than association, has been discussed with respect to two of the nine Bradford Hill criteria for establishing a causal relationship, coherence and plausibility, and it was considered plausible that fluoride might be able to affect the development of the disease. Although a review by Rana et al. did not list lead as a risk factor for pre-eclampsia, this has been established in other studies and controlling for blood lead levels would be appropriate in future studies of the relationship between fluoride and pre-eclampsia.

Keywords: Coherence; Pathophysiology; Plausibility; Pre-eclampsia, Serum fluoride, Blood lead.

A recent paper by Changalvala et al. reported finding significantly higher levels of serum fluoride (p<0.05) in 150 pregnant women, at 20 or more weeks of gestation, in Karnataka, India, with the complex multisystem disease of pre-eclampsia, than in a control group of 150 pregnant women without pre-eclampsia (1.8±0.66 and 0.18±0.31 mg/L, respectively). Whether or not the association between a raised serum fluoride and pre-eclampsia might be one of causation rather than association, has been discussed with respect to two of the nine Bradford Hill criteria for establishing a causal relationship, coherence and plausibility, and it was considered plausible that fluoride might be able to affect the development of the disease. Although a review by Rana et al. did not list lead as a risk factor for pre-eclampsia, this has been established in other studies and is relevant for research on the relationship between fluoride and pre-eclampsia.

Poropat et al. performed a systematic review and meta-analysis of 11 studies to examine the association between pre-eclampsia and lead poisoning. They found that blood lead concentrations were significantly and substantially associated with pre-eclampsia (k = 12; N = 6069; Cohen’s d = 1.26; odds ratio = 9.81; odds ratio LCL = 8.01; odds ratio UCL = 12.02; p = 0.005). Eliminating one study produced a homogeneous meta-analysis and stronger estimates, despite the remaining studies coming from eight separate countries and having countervailing risks of bias. They concluded that blood lead concentrations in pregnant women are a major risk factor for pre-eclampsia, with an increase of 1 µg/dL being associated with a 1.6% increase in the likelihood of pre-eclampsia, which appears to be the strongest risk factor for pre-eclampsia yet reported. They recommended that pregnant women with historical lead exposure should routinely have blood lead concentrations tested, especially after mid-term, and that women with concentrations higher than 5 µg/dL should be actively monitored for pre-eclampsia and be advised to take prophylactic calcium supplementation. They also advised that all pregnant women should be actively avoid lead exposure.

In his 2006 book *The great lead water pipe disaster*, Troesken noted that although the causes of eclampsia are probably manifold, undue lead exposure appears to be a contributing factor in at least some cases today. He observed that recent research suggests that eclampsia is related to the level of various metals in the mother’s system and that too much or too little of any of these metals might induce eclampsia, or its less severe antecedent pre-eclampsia. He wrote that
during the later stages of pregnancy, metals are mobilized from the mother’s skeleton and enter her bloodstream and soft tissues. These include copper, zinc, sodium, potassium, calcium, and magnesium, which at appropriate levels, are necessary and desirable for foetal development. However, toxic metals such as lead and cadmium are also mobilized as 90% of all the lead in the human system is stored in the bone.

Gulson et al. studied the extent of lead mobilization from the maternal skeleton during pregnancy and lactation in a longitudinal cohort study in an urban environment of European female immigrants of child-bearing age (18 to 35 years) to Australia whose skeletal lead isotopic composition had been determined to be different from that in their current environment. They used two groups of women as control subjects: (i) a matched immigrant nonpregnant group and (ii) a second-generation Australian pregnant group. High-precision lead isotopic compositions and lead concentrations were measured in the maternal blood and urine prenatally, monthly during gestation, and postnatally for 6 months, and also in the infant blood and urine for 6 months. Environmental measures were sampled quarterly for a 6-day duplicate diet, house dust and water, and urban air and gasoline. The interim findings were that the maternal blood lead levels were generally low, with a geometric mean of 3.0 µg/dL, and ranged from 1.9 to 20 µg/dL. Increases in blood lead of approximately 20% during pregnancy were detectable, even in subjects with low blood lead levels. The skeletal contribution to the blood lead level, based on isotopic measurements, exhibited a mean increase (and standard deviation) of 31±19% with a range from 9% to 65%. Earlier studies that used lead concentrations only have suggested that blood lead levels increased only during the second half of pregnancy. This increase in blood lead levels has also been observed in the present study. However, in two subjects the increases in total blood lead were also detected in the first 2 months of pregnancy. The changes in the isotopic composition and blood lead during gestation for the Australian pregnant controls were negligible. The ratio of cord/maternal blood lead levels varied from 0.54 to 1.05, and the ratio for the isotopic composition was 0.993 to 1.002. The results confirmed that lead is mobilized from skeletal stores at an accelerated rate during pregnancy and is transferred to the fetus. These results also showed that mobilization from the long-term stores (i.e., bone) contributes significantly to the blood lead levels during pregnancy. The exposure of the fetus to lead during pregnancy has implications for interpretations of neurobehavioral disorders attributed to only postnatal exposure. Even after 800 days of residence in Australia, the contribution of European skeletal lead to blood lead in nonpregnant subjects could be on the order of 50%, and the current maternal blood lead level may give no indication of the former high skeletal lead burden.

Multani noted in 2010 that 33% of over 370 samples of water from the top 26 cities of India tested positive for a harmful content of lead. Out of these, 31% of the samples failed to adhere to the World Health Organization standard of a lead content of less than 10 ppb, while 2% of the samples failed to meet even the lenient Indian norm of 50 ppb. A high content of lead was found in ground water (bore well / well water) with up to 41% of the samples being unfit for drinking. Over 15% of the municipal water samples had a high content of lead. The three cities reported on from Karnataka, the state in which 95% of the subjects studied by Changalvala et al. lived, were all in the (i) low risk category (Bangalore, Mangalore, and Mysore). Other low risk cities were Ahmedabad, Hyderabad, Indore, Bhopal, Chandigarh, and
Lucknow. The classifications of the other cities were: (ii) medium risk: Chennai, Ludhiana, Surat, Ghaziabad, Jamshedpur; (iii) high risk: Delhi, Coimbatore, Madurai, and Bhubaneshwar; and (iv) alarming: Kolkata, Kochi, Mumbai, Pune, Nasagpur, Nashik, and Guwahati. The cities with high municipal water lead levels were: Kochi (100%), Ludhiana (60%), Bhubaneshwar (50%), Maduri (20%), Chennai (20%), and Guwahati (20%).

Lead contamination due to the use of low quality PVC pipes, which leach lead because of their content of lead-based stabilizers or plasticizers, in sanitation, plumbing, and agriculture is one of the major contributing factors to groundwater lead pollution in India.\(^9\) A typical low quality PVC pipe contains less PVC resin (55%) and more calcium carbonate (30%) together with more than 15% of a lead-based stabiliser. PVC resin costs 4× more than calcium carbonate. In contrast, a high quality PVC pipe might contain more PVC resin (85%) and less calcium carbonate (15%) together with a stabilizer not containing lead or cadmium (<5%). PVC plumbing pipes have a very long life of up to 75 years, are cheap compared to galvanised iron pipes, are more durable, have a longer life, and have zero corrosion. Therefore, these pipes are preferred by the consumer. However, if the lead in poor quality pipes continues to leach for long periods, this may affect a residential population for two to three generations.

Fluoride and lead share in common some mechanisms for producing toxicity such as affecting enzymes and causing oxidative stress which are relevant to the aetiology of pre-eclampsia.\(^4,10\) Lead interferes with Ca\(^{2+}\) dependent enzymes, like nitric oxide synthase, and the vascular endothelium, with impairment of nitric oxide signalling, is now regarded as the main target organ for the toxic effect of lead.\(^10\) In clarifying the nature of the relationship between fluoride and pre-eclampsia in future studies, controlling for blood lead would be appropriate, keeping in mind, as noted by Gulson et al.\(^8\) that the blood lead levels in pregnancy may reflect past as well as current lead exposure.

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