BJMS
Borneo Journal of Medical Sciences

REVIEW ARTICLE

Lithium as Neglected Drinking Water Parameter and Effect on Foetal Growth: A Review

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Received: 12 January 2025

Accepted: 24 June 2025

Published: 05 January 2026

DOI: https://doi.org/10.51200/bjms.v20i1.5997

Keywords: *Environment, Infant, Newborn, Metals, Health*

ABSTRACT

Lithium (Li) is a metal that is currently very important due to its use in several industrial activities. Recently, Li has been recognised as an emerging environmental pollutant, attracting numerous researchers globally due to its high environmental concentration, particularly in surface water. Several neonatal health impacts due to Li exposure from drinking water were extensively studied and reviewed previously, such as prematurity, miscarriages, and hypothyroidism. This review aims to assess the impact of Li exposure through drinking water on foetal growth parameters, specifically examining the relationship between maternal Li concentrations and foetal measurements. We searched articles published between January 1, 1990, and September 10, 2024, using five electronic databases. A total of 36 articles were eliminated during the screening process. Ultimately, just one article (n = 1) was approved in this review. In the particular study, they found a negative correlation between maternal blood Li levels (median 25; range 1.9–145 µg/L) and urine Li levels (median 1645; range 105–4600 µg/L) and all foetal measurements (body, head, and femur) during the second trimester, as well as birth length. A rise of 100 µg/L in blood Li was generally linked to a 2 cm reduction in birth length and foetal growth. Existing evidence indicates a negative association between Li exposure from drinking water and foetal development. Additionally, the long-term health implications for offspring exposed to Li in utero, primarily

through contaminated drinking water, are under-researched, underscoring the need for more comprehensive studies that examine both immediate and chronic health outcomes.

INTRODUCTION

Lithium (Li) is a metal that is currently very important due to its use in several industrial activities such as lithium-ion battery production, ceramic, glass, and grease production. (Kavanagh et al., 2018). Recently, Li has been regarded as an emerging environmental pollutant and has attracted many researchers globally due to its high environmental concentration, especially in surface water (Bolan et al., 2021; M. R. Rafi'i et al., 2024; Robinson et al., 2018). Furthermore, it was found in several studies that several non-mining countries for Li around the world (Italy, Hungary, Korea, Austria) also surprisingly found a significant Li concentration in their water bodies, which were between 60.8µg/L and 689.4µg/L (Choi et al., 2019; Dobosy et al., 2023; Giotakos et al., 2013; Pompili et al., 2015).

Although Li is a natural component of soil, rock, and groundwater, human activities have increased its concentrations much higher in watersheds. Furthermore, anthropogenic activities have also deposited Li chemically dissolved in rivers and physically transported Li into the ocean and river bed sediments (Bolan et al., 2021; M. R. Rafi'i et al., 2024). Additionally, it is essential that Li also tends to accumulate in aquatic systems due to its high mobility and solubility. In addition, urban runoff can also spread this Li material contamination to the heads of other surrounding drain systems and main water bodies (Mrozik et al., 2021). However, Li continues to be a largely overlooked criterion in drinking water quality assessment and control in most countries, despite the availability of more evidence on its potential impact on human health through surface water sources (Liew et al., 2023; M. R. Rafi'i et al., 2024; Mahmudiono et al., 2023).
Besides that, Li has had a very long history with therapeutic benefits for psychiatry in general, and most of all for mood disorders. Management or control of the manic phase of bipolar disorder is assisted by its property of acting as a manic depression mood stabiliser. (Rybakowski, 2020). Several studies have shown that when Li is used therapeutically to treat depression, it can affect foetal development. In addition to that, it is a cause for great concern since it shows that mild exposure to Li during pregnancy can interfere with essential development processes, which can create adverse effects, including low birth weight with associated neurological impairments.(Diav-Citrin et al., 2014; Jacobson et al., 1992).

In addition, with the shift in global focus on the health of mothers and children to protect vulnerable groups (pregnant women and their developing foetuses), it is now time again to reassess the recently discovered impurities in potable water, such as Li, and their health impacts on them. Several neonatal health outcomes of Li exposure via potable water were debated and examined in great detail previously, such as prematurity, spontaneous abortions, and hypothyroidism (Fornaro et al., 2020; Poels et al., 2018). However, there are few studies on Li exposure from drinking water consumption and its impact on foetal development. Furthermore, the relative importance of Li exposure from prescribed medicines versus consumption of drinking water is never debated, and we now have very few review articles of the evidence in print. Therefore, this review aims to assess the impact of Li exposure through drinking water on foetal growth parameters, specifically examining the relationship between maternal Li concentrations and foetal measurements such as body size, head circumference, and femur length, as well as birth outcomes like birth length by synthesising the published research on Li exposure through drinking water and its possible implications for foetal growth.

MATERIALS AND METHODS

Article search strategy and databases

We searched articles published between January 1, 1990, and September 10, 2024, using five electronic databases (PubMed, Scopus, Web of Science, Cochrane Library and Ovid). The search terms included: (lithium) AND (water OR surface water OR drinking water OR river OR lake OR pond OR wetland OR lagoon) AND (foetal growth OR foetal advancement OR foetal development OR foetal gain) as in Table 1. Only original research and observational human studies were accepted as the basis for article inclusion.

Table 1: Search Strategy

Database	Search String
Scopus	TITLE-ABS-KEY (("lithium") AND ("water" OR "surface water" OR "drinking water" OR "river" OR "lake" OR "pond" OR "wetland" OR "lagoon") AND ("fetal growth" OR "fetal advancement" OR "fetal development" OR "fetal gain"))
Web Of Science	ALL= (("lithium") AND ("water" OR "surface water" OR "drinking water" OR "river" OR "lake" OR "pond" OR "wetland" OR "lagoon") AND ("fetal "))
PubMed	((("fetal"[MeSH Terms])) AND (("growth and development"[All Fields] OR "growth"[All Fields] OR "growth"[MeSH Terms] OR "advance"[All Fields] OR "advancement"[All Fields])) AND (("surface"[All Fields] OR "surfaces"[All Fields] OR "water"[All Fields] OR "drinking water"[MeSH Terms] OR "drinking water"[All Fields] OR "rivers"[All Fields] OR "rivers"[MeSH Terms] OR "lakes"[MeSH Terms] OR "lakes"[All Fields] OR "lake"[All Fields] OR "ponds"[MeSH Terms] OR "ponds"[All Fields] OR "pond"[All Fields] OR "wetlands"[MeSH Terms] OR "wetlands"[All Fields] OR "lagoon"[All Fields] OR "lagoons"[All Fields] OR "lagoons"[All Fields] OR "water"[MeSH Terms] OR "water"[All Fields] OR "waters"[All Fields])) AND (("lithium"[MeSH Terms])))
Cochrane Library	((lithium) AND (fetal growth OR fetal development OR fetal size OR birth length OR anthropometry OR birth weight OR head circumference OR femur length))
Ovid	((lithium) AND (drinking water OR surface water OR water supply OR groundwater OR "tap water") AND (fetal growth OR fetal development OR birth weight OR birth length OR anthropometry OR head circumference OR femur length))

Reviews of a narrative, scope, or systematic nature were not accepted and were excluded from this review. Editorial papers, conference proceedings, and conference papers are intended not to be included in the article exclusion criteria, since it is likely that they will contain duplicate data from the primary research published paper. Articles that are not in English are also intended to be excluded. However, during the article searches by the three databases, no articles fulfilled the exclusion criteria. Finally, the articles that satisfied the requirements were imported into the EndNote reference manager.

M.R. or S.A. assessed the titles and abstracts of the identified articles for possibly relevant studies, and the full text was retrieved for those that passed this screening stage. We also looked for other research in the references of relevant review papers and full-text articles.

Data extraction and analysis

EndNote Reference Manager software (Clarivate, London, UK) was used to compile the articles. The selection procedure that resulted in the final number of articles included in this review is described in full in Figure 1 (PRISMA diagram) for the identification, screening, and exclusion process. After our initial search yielded 46 results, duplicate articles (n = 9) were removed by reference managers or manual search techniques during the automatic article identification phase. Ultimately, the EndNote software filtered 37 publications based on their titles and abstracts. A total of 36 articles were eliminated during the screening process for the following reasons: 1) irrelevant title (n = 22); 2) heavy metals other than Li (n = 2); 3) different context—not discussing foetal growth (n = 10); and 4) review (n = 2). After that, full text for (n=1) articles was collected. Ultimately, just one article (n = 1) was approved and featured in this review.

M.R. compiles pertinent data from chosen studies using standard tables, such as the researcher's name, the year the study was published, the study's design, the article's title, the location, and other significant discoveries. All authors scrutinised the research findings from the publication to gather scientific proof of Li's impact on human foetal growth, which was showcased in the results section.

initiative began in October 2012. The study was observational and prospective. In this study, a mother-child cohort was established to evaluate the potential health effects of early exposure to Li and other water pollutants. All pregnant women with an expected delivery date between October 2012 and December 2013 were invited to participate. The research also examined the concentrations of Li in drinking water, urine, and blood to evaluate exposure. Because arsenic, boron, and caesium are also prevalent in the drinking water at the research location, the study assessed these elements in the same medium to account for any potential confounding factors. The study used inductively coupled plasma mass spectrometry (ICP-MS, Agilent 7700× ORS ICP-MS, Agilent Technologies, Tokyo, Japan) for all elements, with the collision/reaction cell set to either helium mode (arsenic) or no gas mode (Li, boron, and caesium).

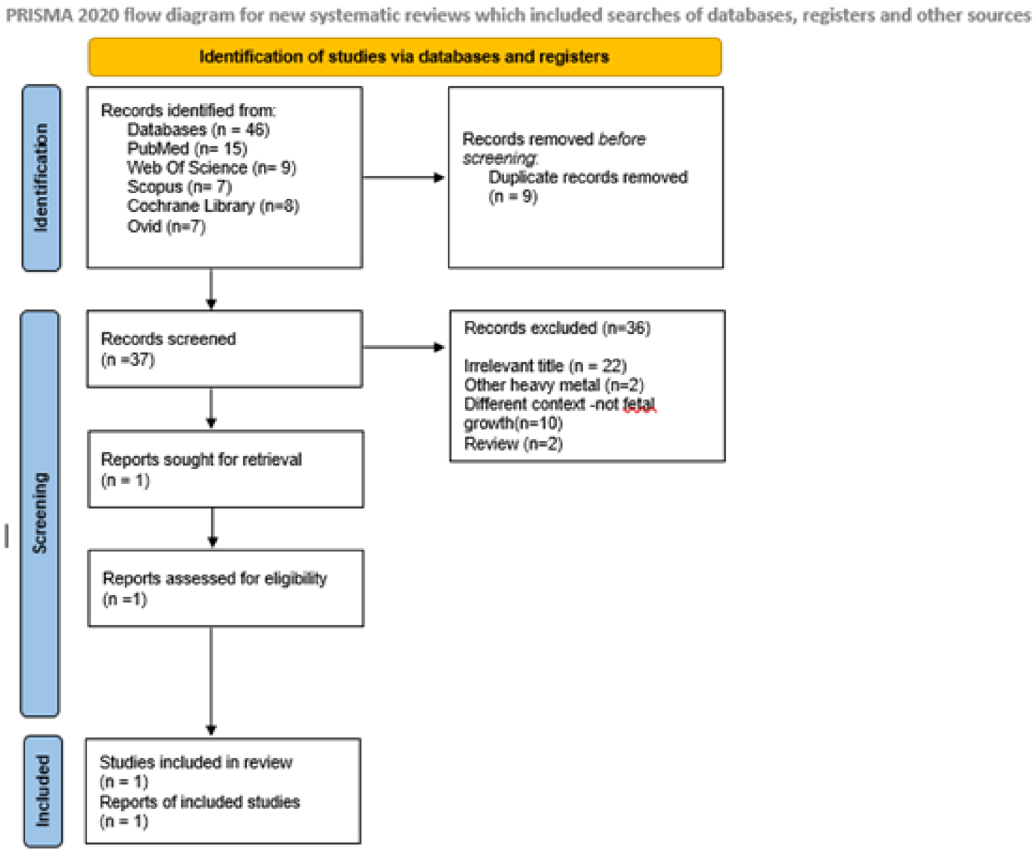

Figure 1: PRISMA Flow Diagram for Study Selection

RESULTS

This review focuses on Li's research on water pollution and its impact on prenatal development. Only one article in this study examined the effect of high Li concentration in drinking water on foetal growth and was chosen based on the screening criteria. This is probably because this review is highly focused and deals with a niche area.

Study Characteristic

The study in this review was conducted by (Harari, Langeén, et al., 2015) In Argentina, the

A total of 180 women were successfully enrolled in the study, with the majority (68%) being over 30 years of age. Besides that, about 19% of women in the study were either overweight (BMI 25.0 to 30.0) or obese (BMI>30.0). The maximum mean concentration of urinary Li(mean=2516µg/L (1078-4598)) can be observed in women with the highest mean Li concentration in blood (mean=47(31.3-145µg/L)). The maximum mean concentration of water Li can also be observed (mean= 750µg/L (6.5-958)) in women with the highest mean Li concentration in blood (mean=47(31.3-145µg/L)). Blood and urine Li had a Spearman's correlation coefficient of 0.84 (p<0.001), water and blood Li of r=0.40 (p<0.001), and water and urine Li of r=0.44 (p<0.001). While urine Li increased steadily throughout gestation, blood Li increased during pregnancy, especially in the last trimester.

Relationship of Drinking Water Li Exposure and Foetal Growth

In this particular study, they found a negative correlation between maternal blood Li levels (median 25; range 1.9–145 µg/L) and urine (1645; range 105–4600 µg/L) and all foetal measurements (body, head, and femur) during the second trimester, as well as birth length (β −0.53 cm per 25 µg/L increase in blood Li, (95%CI −1.0; −0.052). A rise of 100 µg/L in blood was generally linked to a 2 cm (about one standard deviation) reduction in birth length and foetal growth.

DISCUSSION

A study in this review suggests that pregnant women who are exposed to high levels of Li in drinking water may have unfavourable effects on the development of their unborn child. Li levels in the blood and urine consistently showed inverse relationships with all foetal dimensions (head, femur, and abdomen) during the second trimester, suggesting that Li has an impact early in pregnancy. This study's findings are consistent with previous studies that observed this particular impact (Diav-Citrin et al., 2014; Källén & Tandberg, 1983; Wittström et al., 2024). Furthermore, higher levels of Li may cause suppression in foetal growth on prolonged exposure to Li medications. Although both studies relate the Li exposure to medication usage by pregnant women rather than from drinking water exposure, the similar mechanism of its toxicity on the foetus suggests that all these studies are comparable (Mohamed et al., 2023; Schrijver et al., 2024).

Surprisingly, two animal studies found different results in their offspring's weight after their paternal mice were exposed to two doses of Li during pregnancy via drinking water (Messiha, 1993; Mroczka et al., 1983). A population of mice from the initial experiment receiving a higher Li concentration had no variation in their offspring's weight. In contrast, a control experiment involving a population of mice receiving a reduced Li concentration showed a corresponding reduction in the weight of their offspring. In addition, a recent animal study also suggested that a combination of Li in the form of Lithium chloride (LiCl) with dexamethasone can also promote growth failure due to glucocorticoids. In other words, it was found in their experimental study that LiCl can stop glucocorticoids from causing rat metatarsal growth failure in vitro (Soucek et al., 2024). Therefore, this inconclusive finding requires further animal studies to understand the effect of Li on the offspring's weight.

Moreover, there are several mechanisms responsible for Li's effect on foetal development. It was found that Li's interference with the Wnt/β-catenin pathway is at the core of its effects on foetal development. This pathway regulates key processes of cell proliferation, differentiation, and apoptosis during embryogenesis.(Kurgan et al., 2019; Nery et al., 2014). Additionally, Li may also inhibit the activity of glycogen synthase kinase-3β (GSK-3β), thereby leading to dysregulation of the Wnt signalling pathway. Therefore, improper signalling via the pathway can result in characteristic atypical cellular responses at critical points of foetal organ development, and the resultant disruption can manifest clinically in terms of structural defects or defective tissue and organ development. (Jope, 2003; Zhu et al., 2014).

Besides that, endocrine disruption is another pathway through which Li can affect foetal growth. Li may also alter thyroid hormone levels by interfering with iodine uptake and the synthesis of thyroid hormones (Ahmed et al., 2021). Since thyroid hormones are crucial for neurodevelopment and skeletal growth in the foetal period, their dysregulation can also lead to developmental delays and low birth weight (Czarnywojtek et al., 2020). Moreover, maternal hypothyroidism or subclinical thyroid dysfunction that occurs during pregnancy due to Li induction may also further exacerbate these risks (Harari, Bottai, et al., 2015).

Oxidative stress is also a significant factor playing a role in Li-induced disturbance of foetal development, whereby studies found that Li exposure can induce the generation of reactive oxygen species (ROS) and suppress the function of antioxidant enzymes, leading to damage to the developing foetus.(Allagui et al., 2009). Besides that, this oxidative stress may also compromise DNA integrity, disrupt normal cellular function, and interfere with angiogenesis(formation of new blood vessels necessary for placental function). Subsequently, poor placental function conditions can directly affect nutrient and oxygen delivery to the foetus as well as impair the foetus's growth (Liu et al., 2018).

Another explanation for this Li effect on foetal growth is through epigenetic modifications whereby Li exposure can alter DNA methylation and histone modification patterns, and finally influence gene expression in developing cells (Lee et al., 2015; Marie-Claire et al., 2021). Such epigenetic changes can also have lasting effects on the foetus, which can predispose it to developmental disorders, metabolic impairments, and growth defects. Moreover, both pharmacological and potable preparations of Li may also pass readily through the placenta and affect the thyroid, parathyroid, and cortisol hormonal systems, which are very important for foetal development(Broberg et al., 2011; Forhead & Fowden, 2014; Grandjean & Aubry, 2009; Harari et al., 2012; Newport et al., 2005). Furthermore, additional possible pathways of Li toxicity include those via vitamin D deficiency(Rosenblatt et al., 1989). One of the more recent animal studies (rats) also found that Li had effects on the developing brain and foetal development because a significant amount of Li becomes concentrated in the offspring's brain tissue. As a result, Li distribution in the developing brain is a valuable resource for investigating potential negative effects on brain development in offspring of Li drug-treated mothers(Chiou et al., 2021).

The implication of Li on foetal growth may also become a concern because of long-term impacts such as reduced mental capacity, low birth weight in the next generation, insulin resistance, and stunting in the early stages of life (Bennett et al., 2002; Broekman et al., 2009; Dewey & Begum, 2011; Grantham-McGregor et al., 2007; Kormos et al., 2014). A recent study also found that foetal growth may impact cardiac development, resulting in compensatory hypertrophy or persistent deficit in cardiomyocyte number (Masoumy et al., 2018). Foetal growth failure will also produce one of the most predominant harmful prenatal anomalies of man. It causes a significant number of premature deliveries and significantly increases the risks of perinatal death, neurological impairments, and chronic illness in adulthood. (Colella et al., 2018). Therefore, with the increasing risk of Li concentration in potable water due to pollution, the current foetal growth failure is a new, emerging, significant public health problem that warrants addressing and demands further studies on preventive measures to combat the threat.

The contrasting findings between studies of Li exposure through medication and drinking water underscore the complexity of its effects on foetal development. For example, while therapeutic Li doses are associated with enhanced foetal growth in some cases, environmental exposure through drinking water also appears to have adverse effects. These differences may stem from varying Li concentrations, duration of exposure, and confounding factors such as co-occurring pollutants. Additionally, mechanistic pathways, including endocrine disruption and oxidative stress, may also offer plausible explanations for these outcomes. Therefore, addressing these discrepancies requires multidisciplinary collaboration between environmental scientists, toxicologists, and public health researchers.

Limitation

It is essential to recognise that this analysis has several limitations, even though it thoroughly evaluates the possible effects of Li in drinking water on foetal growth. Firstly, only one study satisfies the review's criteria, necessitating additional studies for a more comprehensive comparison. The study in this review also needs to be interpreted cautiously because it is free of biases and confounding variables that can affect foetal development, which are not considered in this study. These variables include additional toxins in drinking water, genetic predispositions, and maternal mental health considerations. Moreover, the limited number of long-term human studies that examine the long-term effects of foetal Li exposure on neurodevelopment limits the capacity to forecast wider public health ramifications.

CONCLUSION

This review highlights the growing concern surrounding Li exposure through drinking water and its potential impact on foetal development. Existing evidence indicates a negative association between Li exposure from drinking water and foetal growth. These conflicting results from recent human and animal studies further emphasise the complexity of Li's effects on foetal development, with some studies related to Li medication exposure even reporting increased foetal growth associated with Li exposure. Additionally, the long-term health implications for offspring exposed to Li in utero, primarily through contaminated drinking water, are under-researched, underscoring the need for more comprehensive studies that examine both immediate and chronic health outcomes.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

ACKNOWLEDGEMENT

We want to thank the National University of Malaysia (UKM) for its support in the process of completing this review. s.

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