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In utero exposure to arsenic in tap water and congenital anomalies: A French semi-ecological study

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ABSTRACT

Introduction: Congenital anomalies (CA) are responsible for high rates of mortality and long-term disabilities. Research on their risk factors including environmental factors is needed. Studies on exposure to arsenic (As) in tap water and the risk of CA have not provided conclusive evidence, particularly when levels of exposure were low (from 10 to 50 µg As/L). The main objective of this study was to assess the association between exposure to As in tap water and the risk of any major CA. The secondary objectives were to assess this association for the most common types of congenital anomalies (in the heart, musculoskeletal, urinary and nervous systems).

Methods: A semi-ecological study was conducted from births recorded at the University Hospital of Clermont-Ferrand, France, in 2003, 2006 and 2010. The medico-obstetric data were available at individual level. Children with congenital anomalies were identified from the database of the regional registry of congenital anomalies: the Centre d'Etudes des Malformations Congénitales Auvergne (CEMC-Auvergne). As exposure was estimated from the concentrations of As measured during sanitary control of tap water supplied in the mothers' commune of residence (aggregate data). French guidelines for As in tap water were used to identify the two groups: "≥ 10 µg As/L group" and "[0–10) µg As/L group". Multivariable logistic regression models were fit.

Results: 5263 children (5.1% with a CA) were included. In stratified analysis by gender of the child, positive associations between As exposure exceeding 10 µg/L and risk of any major CA (adjusted OR = 2.41; 95%CI: 1.36–4.14) and of congenital heart anomalies (adjusted OR = 3.66; 95%CI: 1.62–7.64) were only shown for girls. No association was found for boys.

Conclusion: This French semi-ecological study provides additional arguments for the association between exposure to As exceeding 10 µg/L in tap water and the risk of CA especially in a context of low exposure. Further studies are needed to better understand the interaction between arsenic exposure and child gender.

1. Introduction

According to WHO estimates, congenital anomalies (CA) are responsible for 10% of neonatal deaths worldwide (WHO, 2016). In children with CAs who survive, malformations such as congenital heart defects, neural tube defects and cleft palates, largely contribute to long-term disability and functional, psychological and/or aesthetic impairment (Amedro et al., 2015; Mahboubi et al., 2015; Schneuer et al.,

Abbreviations: aOR, adjusted odds ratio; As, arsenic; Audipog, Association des utilisateurs de dossiers informatisés en pédiatrie obstétrique et gynécologie; BMI, body mass index; CEMC-Auvergne, Centre d'Etude des Malformations Congénitales Auvergne; CPDP, multidisciplinary prenatal diagnostic centre; EUROCAT, European Registration of Congenital Anomalies and Twins; iAs, inorganic arsenic; NICU, neonatal intensive care unit; SISE-Eaux, Système d'Information en Santé-Environnement sur les Eaux; WHO, World Health Organization

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In Europe, the prevalence of CAs was estimated at 2.0% among live births and 2.5% among total births in 2013–2015, and is increasing over time (EUROCAT, 2017). In France, the total prevalence of CA increased from 1.9% in 1982–1984 to 3.1% in 2012–2015 (EUROCAT, 2017). Certain risk factors for CAs, like alcohol use, folic acid deficiency and medications, are modifiable while others, such as family history and maternal age, are not. Many CAs are still of unknown origin (Harris et al., 2017; Simeone et al., 2016). Certain authors have pointed to the role of environmental contaminants in the development of CAs (Brender et al., 2006; Brender and Weyer, 2016). Exposure to certain metals and metalloids, including arsenic (As), has been posited as one of those factors (Brender et al., 2006; Kwok et al., 2006; Mazumdar et al., 2015; Rudnai et al., 2014; Sanders et al., 2014; Zierler et al., 1988).

As, which is naturally present in the earth's crust, is a water contaminant in numerous countries including Bangladesh, Taiwan, Chile, Argentina, United States, Croatia and France. More than 100 million individuals worldwide are chronically exposed to As in drinking water at concentrations above the WHO guideline of 10 µg/L (Shankar et al., 2014; WHO, 2011). Chronic exposure to As in water has been identified as a risk factor for cutaneous, cardiovascular and endocrine disorders and for certain cancers (Marie et al., 2018; Shankar et al., 2014; WHO, 2001).

Studies assessing the association between exposure to As in water during pregnancy and the occurrence of CAs have yielded divergent results (Brender et al., 2006; Kwok et al., 2006; Mazumdar et al., 2015; Rudnai et al., 2014; Sanders et al., 2014; Zierler et al., 1988). In two studies performed in Bangladesh, the exposure to As in water at high levels (As levels up to several hundred µg/L) was associated with an increased frequency of all major CAs (adjusted OR = 1005; 95%CI: 1.00–1.01) (Kwok et al., 2006) and a decrease in the protective effect of folic acid on the risk of myelomeningocele (Mazumdar et al., 2015). Increased frequency of CAs was reported by two studies (in the United States and Hungary) conducted in a context of lower exposure (As in water < 20 or < 50 µg/L) but only for certain types of congenital heart defects (Rudnai et al., 2014; Zierler et al., 1988). Other studies showed no significant link between *in utero* exposure to As in water and the occurrence of congenital heart defects or other CAs such as neural tube defects, limb's malformation and oral palates (Brender et al., 2006; Sanders et al., 2014). Findings of other studies using biomarkers (concentrations of As in the placenta, hair or urine) were also divergent, showing an increased risk of congenital heart defects (Jin et al., 2016), but not of any major CA (Karakis et al., 2015) nor of neural tube defects (Brender et al., 2006; Jin et al., 2013).

The main objective of this study was to assess the association between *in utero* exposure to As in tap water and the risk of any major congenital anomaly. The secondary objectives were to assess the association between *in utero* exposure to As in tap water and the risk of the most common types of congenital anomalies (in the heart, musculoskeletal, urinary and nervous systems).

2. Material and methods

2.1. Local context

Owing to its volcanic origins the Auvergne region in France, where our study was conducted, is particularly concerned by the presence of naturally occurring inorganic As (iAs) in its subsurface. Tap water is predominantly obtained from groundwater sources that are in contact with deep geological strata. As a result, there is a natural contamination of water by iAs in Auvergne that, in the absence of extensive treatments for water purification, can lead to levels greater than those recommended by the French guidelines for As in the drinking water. Decree n°2001–1220 of 20 December 2001 lowered the recommended amount of As in drinking water in France from 50 to 10 µg/L (République Française, 2001). Since then, management measures such as more stringent of purification treatments and disuse of underground water sources highly contaminated by As have been progressively implemented in Auvergne by health authorities. As we have described elsewhere (Marie et al., 2018), the number of inhabitants supplied with water whose As concentration was higher than 10 µg/L (and more rarely than 50 µg/L) steadily decreased, from 140 000 (10.5% of the population) in 2001 to 31 000 (2.3%) in 2010 (ARS Auvergne, 2015, 2007). Hence, up to the year 2010 the Auvergne was an appropriate region in which to assess the effects of exposure to low levels of As (between 10 and 50 µg/L) on the occurrence of chronic diseases. It was decided to select the three years of 2003, 2006 and 2010 for investigation in our study because for the intermediate years, data on As levels in water may have fluctuated due to implementation of management measures.

2.2. Study design

A semi-ecological study (Künzli and Tager, 1997) was conducted in which data concerning exposure to As were aggregate (at the level of the mothers' commune), and medical, obstetrical and neonatal data including the diagnosis of CA were collected retrospectively on an individual basis after childbirth.

2.3. Subjects

The study population was made up of the children born at the Clermont-Ferrand University Hospital in Auvergne, which is the only level III hospital of the Auvergne region i.e. having maternity units with both a neonatology unit and a neonatal intensive care unit (NICU). It is one of the 10 Auvergne maternity units (1 level III, 6 level II, 3 level I), which are coordinated by a perinatal network. The only multidisciplinary prenatal diagnostic centre (CPDP) is located in the level III university hospital centre and works with both the perinatal network and the Centre d'Etudes des Malformations Congénitales en Auvergne (CEMC-Auvergne). The purpose of the CPDP is to promote access to all types of prenatal diagnosis, serve as a clinical and laboratory reference centre for patients and physicians, and provide opinions and advice concerning diagnosis, treatment and prognosis to the physicians and clinical pathologists who contact them when they suspect an anomaly in an embryo or foetus. All fetal ultrasound anomalies identified throughout the region are presented to the CPDP for assessment at a weekly staff meeting, with remote participation and teleradiology, in accordance with national guidelines.

Up to 2009, there were two maternity departments in the teaching hospital, the Polyclinique and the Maternité Hôtel-Dieu. In 2010, the two were merged. Inclusion criteria for our sample were children born at the Hotel-Dieu of Clermont-Ferrand between 1 January and 31 December 2003 and 2006, and children born at the Clermont-Ferrand University Hospital between 1 January and 31 December 2010. Stillbirths and intrauterine deaths, defined as births occurring ≥22 weeks gestational age or with a birthweight ≥500 g, and medical terminations of pregnancy for fetal malformation at any gestational age were also included. Exclusion criteria were: children born at the Polyclinique (because this maternity department did not supply data to the national Association of Users of Computer Records in Paediatrics, Obstetrics and Gynaecology [Audipog] in the years selected for study in this survey); children whose mothers were not resident in Auvergne at the time of birth and those whose commune of residence at the time of birth was unknown; children with chromosomal abnormalities, genetic syndrome, sequences (i.e., pattern of multiple anomalies derived from a single known or presumed prior anomaly or mechanical factor) or associations (i.e., unrelated anomalies from more than one system with no unifying diagnosis and recognized associations that are not regarded as a syndrome) (http://www.eurocat-network.eu/). During the three years under study, there were 6597 births in the maternity departments