

Supplementary material.

Drinking water arsenic and adverse reproductive outcomes in men and women: A systematic PRISMA review.

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Introduction

This supplementary material includes search strategy, specifics of data extraction, elaboration of selection process and specifics on quality assessment of included literature in the systematic PRISMA review.

Text S1: Search strategy (PubMed/Medline)

(arsenic[MeSH] OR arsenic OR arsenic poisoning[MeSH] OR arsenic poisoning) AND (drinking water[MeSH] OR drinking water OR potable water OR ground water[MeSH] OR ground water OR water pollution[MeSH] OR water pollution OR tap water) NOT (rats OR rat OR mice OR mouse OR animals OR animal) AND (pregnancy[Title/Abstract] OR Reproduction[MeSH] OR reproduction OR fertility[MeSH] OR fertility OR fecundity OR infertility[MeSH] OR infertility OR subfertility OR menstruation disturbances[MeSH] OR menstruation disturbances OR adverse reproductive outcomes OR reproductive techniques, assisted[MeSH] OR assisted reproductive technology OR ART treatment[Title/Abstract] OR fertility treatment OR reproductive techniques[MeSH] OR reproductive techniques OR time-to-pregnancy[MeSH] OR time to pregnancy OR pregnancy Rate[MeSH] OR pregnancy rate OR pregnancy outcome OR abortion, spontaneous[MeSH] OR abortion OR miscarriage OR fetal loss OR fetal death OR fetal mortality[MeSH] OR fetal mortality OR pregnancy loss OR pregnancy complications[MeSH] OR pregnancy complications OR semen analysis[MeSH] OR semen analysis OR sperm quality OR semen quality OR sperm count OR sperm motility OR spermatogenesis[MeSH] OR spermatogenesis)

Search conducted on 24.5.19. Repeated on 13.11.19.

Text S2: Data extraction form

The following information was extracted from all included studies:

- Author
- Study title
- Country of origin
- Year of publication and journal
- Study design
- Study population /size and selection
- Exposure
- Outcome
- Confounding control
- Results
- Data for quality scoring using the Newcastle-Ottawa Scale.

Text S3: Elaborated reasons for exclusion

PubMed/Medline, Embase and Scopus database searches:

- The computerised literature search resulted in n=786 citations (PubMed/Medline: n=160; Embase: n=335; Scopus: n=291)
- Duplicates in the three databases: n=355
- From PubMed, Embase and Scopus searches in total included: n=431

Reference list search:

- Potential unique citations: n=2
- Duplicates (i.e. included in the search from PubMed, Embase and Scopus: n=0)

Total number of unique records identified: n=433

Records excluded based on title and abstract: n=399

Full-text articles assessed for eligibility: n=34

Full text articles excluded due to the following reasons: n=26

- Wrong outcome, instead reporting: n=6
 - o Preterm delivery, size at birth [1]
 - o Stillbirth, infant mortality [2]
 - o Stillbirth, birth defects, birthweight [3]
 - o Preterm birth, size at birth [4]
 - o Arsenic levels in drinking water [5]
 - o Neoplasms, endocrine, nutritional and metabolic diseases, blood diseases, nervous system diseases circulatory system diseases, ischemic heart disease, cerebrovascular disease, heart failure, respiratory system diseases, digestive system diseases, urinary system diseases, skin and subcutaneous tissue diseases, musculoskeletal and connective tissue system diseases [6]
- Wrong study design, instead the following designs: n=13
 - o Commentary [7, 8]
 - o Cross-sectional [9-14]
 - o Summary [15, 16]
 - o Book chapter [17, 18]
 - o Conference abstract [19]
- Wrong exposure assessment, instead reporting: n=4
 - o Blood samples [20]
 - o Urinary samples [21-23]
- Doublet: n=1
 - o [5]
- Language restriction: n=2
 - o [24, 25]

Text S4: Newcastle-Ottawa scale (NOS)

Characteristics and risk of bias table for publications on arsenic exposure from drinking water and spontaneous abortion.

Table S4: Newcastle-Ottawa scale scores

Author, year, country	Study design	Risk of bias			
		Selection	Comparability	Exposure/ outcome	Total NOS-score
Women					
Ahmed et. al, 2019, Bangladesh [26]	Prospective cohort study	****	**	**	8
Aschengrau et. al, 1989, US [27]	Case-control study	****	**	**	9
Banu et. al, 2013, Bangladesh [28]	Prospective cohort study	***	-	*	4
Bloom et. al, 2014, Romania [29]	Case-control study	***	**	***	8
Mukherjee et. al, 2005, India [30]	Retrospective cohort study	*	-	*	2
Rahman et. al, 2007, Bangladesh [31]	Prospective cohort study	***	**	*	6
Susko et. al, 2017, Romania [32]	Retrospective cohort study	**	**	**	6
Men					
Sengupta et. al, 2013, India [33]	Case-control study	**	**	**	6

In each category (i.e. selection, comparability and exposure/outcome), a range of zero to four * could be awarded. The maximum total NOS-score is 9. Studies with a total NOS-score ≥ 7 are considered high quality studies.

Text S4.1: Explanatory forms – Newcastle-Ottawa Scale.

To ensure standardised scoring, this explanatory form has been made. Only those items from the NOS that needed a stricter definition are mentioned below. To access the full NOS see [34]

Text S4.1.1: Cohort studies

Selection

- 1) Representativeness of the exposed cohort: The average *woman of fertile age* OR *man of fertile age* in the community.
- 3) Ascertainment of exposure: A * is awarded if a drinking water sample was taken from a supply that could be linked to the exposed/unexposed person's home address or was designated primary source of drinking water.

Comparability

- 1) Comparability of cohorts based on the design or analysis: *Maternal age* is chosen as the most important control factor for women and *smoking* is chosen as the most important control factor for men. Other factors for women include: Parity, previous abortions, educational level, smoking during pregnancy. Other factors for men include: BMI, age.

Outcome

- 1) Assessment of outcome: In cases where information on outcome is based on self-report, no * is awarded – even if the information is obtained by a healthcare worker.
- 2) Was follow-up long enough for outcomes to occur: Adequate follow up period is set at *12 months* after enrolment (it will thus leave a sufficient margin for all outcomes of relevance to occur).
- 3) Adequacy of follow up of cohorts: A small number lost is defined as <20%. It must, however, be stated that differences between groups should be considered, and a large difference should lead to a downgrading and thus no * should be awarded.

Text S4.1.2: Case-control studies

Selection

- 3) Selection of Controls: *Community controls* will be defined as an uncomplicated pregnancy. Even though most pregnant women will have contact with medical facilities during their pregnancies, it will not categorise them as *hospital controls* as routine check-ups and labor are not of a pathologic nature.
- 4) Definition of Controls: A * will be awarded if it is described that the controls are women with uncomplicated pregnancies and normal deliveries (no preterm delivery, stillbirth, malformed children), as these outcomes might have a shared pathogenesis with spontaneous abortion.

Comparability

- 1) Comparability of cases and controls based on the design or analysis: *Maternal age* is chosen as the most important control factor for women and *smoking* is chosen as the most important control factor for men. Other factors for women include: Parity, previous abortions, educational level, smoking during pregnancy. Other factors for men include: BMI, age.

Exposure

- 3) Ascertainment of exposure: A * is awarded if a drinking water sample was taken from a supply that could be linked to the case/control's home address or was designated primary source of drinking water.

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