Supplementary Material

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Full search strategy PubMed/Medline

A searched was conducted May 2nd in PubMed/Medline with Medical Subject Heading (MeSH) terms combined as below:

((((("Nitrates"[Mesh]) OR "Nitrites"[Mesh])) AND ((((("Drinking Water"[Mesh]) OR "Water Supply"[Mesh]) OR "Groundwater"[Mesh]) OR "Water Pollution"[Mesh])) AND (((((((("Infertility"[Mesh]) OR "Menstruation Disturbances"[Mesh]) "Time-to-Pregnancy"[Mesh]) OR "Pregnancy Rate"[Mesh]) OR "Reproductive Techniques, Assisted"[Mesh]) "Semen Analysis"[Mesh]) OR "Spermatogenesis"[Mesh]) OR "Pregnancy Complications"[Mesh]) OR "Fetal Mortality"[Mesh])

Additionally, the following search using free text terms was conducted to include new non-indexed literature:

((((((("Nitrates"[Mesh]) OR Nitrate) OR "Nitrites"[Mesh]) OR Nitrite)) AND (((((((("Drinking Water"[Mesh]) OR Drinking Water) OR Potable Water) OR Tap Water) OR "Water Supply"[Mesh]) OR Water Supply) OR "Groundwater"[Mesh]) OR Ground Water) OR "Water Pollution"[Mesh])) AND ((((((((((((((((((((("Infertility"[Mesh]) OR Infertility) OR "Menstruation Disturbances"[Mesh]) OR Menstruation Disturbances) OR "Time-to-Pregnancy"[Mesh]) OR Time-to-Pregnancy) OR "Pregnancy Rate"[Mesh]) OR Pregnancy Rate) OR "Reproductive Techniques, Assisted"[Mesh]) OR Assisted Reproductive Technology) OR "ART Treatment") OR Fertility Treatment) OR "Semen Analysis"[Mesh]) OR Semen Quality) OR Sperm Quality) OR "Spermatogenesis"[Mesh]) OR Spermatogenesis) OR "Pregnancy Complications"[Mesh]) OR Abortion) OR Miscarriage) OR "Fetal Mortality"[Mesh]) OR Fetal Mortality) OR Reproductive Outcomes) OR Adverse Reproductive Outcomes)

The search was made with English language restriction and included only published literature. There was no restriction according to publication period. Both human and animal studies were included.

Data extraction form

Data according to the following items were 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 assessment using the Newcastle-Ottawa Scale (NOS) and SYRCLE's risk of bias tool

In animal studies, data according to the following items were also extracted:

- Duration of study
- Baseline characteristics
    - Animal source
    - Age at beginning of study
    - Animal species

Elaborated reasons for exclusion

PubMed/Medline + Embase + Cochrane search:

- The computerized literature search resulted in n=139 citations (PubMed: n=69; Embase: n=68; Cochrane: n=2)
- Duplicates in the three databases: n=43
- From PubMed, Embase and Cochrane searches in total included: **n=96**

Literature from other sources (including reference list search):

- Potential unique citations: n=5
- Duplicates (i.e. included in the search from PubMed, Embase and Cochrane: n=0)
- From search in reference lists in total included: n=5

Scopus search: 0

Total number of unique records identified: n=101

Records excluded based on title and abstract: n=79

Full-text articles assessed for eligibility: n=22

Full text articles excluded due to the following reasons: n= 10;

- Reporting the wrong outcome, instead reporting:
    - Body weight, hematological parameters etc. [1]
    - Congenital malformations [2]

    n=2

- Reporting the wrong exposure, instead reporting:
    - Samarium nitrate [3]

- Nitrate with ethyl urea [4]
- Poisoning, subcutaneous injection [5]
- Mixture assimilating groundwater contamination [6]

n=4

- Insufficient data reporting
  - Oruc 2009 [7]

  n=1

- Wrong study design, NOT case-control study, cohort study or randomized control trial (RCT), instead:
  - Case-report [8]
  - Cross-sectional [9]
  - Ecological study [10]

  n=3

Studies included in the review: n=12 (human n=1; animals n=11)

Quality assessment

Newcastle Ottawa Scale (study on human outcomes)

Explanatory form, case-control studies

This explanatory form was made to ensure standardized scoring. Not all items from the Newcastle-Ottawa Scale (NOS) are mentioned below, as no explanation on the scoring was thought necessary. For the full NOS see Wells et al..

Selection

3) "Community controls" equals uncomplicated pregnancies (e.g. no spontaneous abortion). Most women are involved with hospital facilities at some point during pregnancy, but this does not label them "hospital controls".

4) A * will be awarded if it is described that the controls are women with uncomplicated pregnancies, meaning NO preterm delivery, stillbirth, malformed children, as these outcomes might have a shared pathogenesis with spontaneous abortion.

Comparability

1a) The most important confounding factor was chosen to be "maternal age", controlling for this is awarded a *

1b) Either adjusting or stratification is considered adequate for awarding a *

Exposure

1) Is rewarded a * if a nitrate drinking water sample was taken from a supply that could be linked to the case/control home address and time between sample and pregnancy outcome is stated.

Scores

Table S1. Characteristics and details on quality assessment of studies on human outcomes according to Newcastle Ottawa Scale.

First Author, Year, Country	**Study Design**	**Risk of bias**			
		Selection	**Comparability**	**Exposure/ outcome**	**Total NOS-score**
Aschengrau, 1989, US [11]	Case-control	****	**	***	9

In each category the minimum of * awarded is zero, the maximum depending on the category, being as follows: selection: four *; comparability: two *; exposure: three *. The maximum total NOS-score is 9, high-quality scores are > 7.

SYRCLE's Risk of Bias tool (studies om animal outcomes)

Table S2. Results for quality assessment of animal studies using SYRCLE's Risk of Bias tool [12].

		1: Random allocation sequence	2: Similar animals	3: Allocation (algorithm) concealment	4: Random housing	5: Blinding of investigators and/or caretakers	6: Random animal selection for outcome assessment	7: Blinding of outcome assessor	8: Incomplete data addressed	9: Free of selective reporting	10: Free of other bias	Total scores for each study		
												High	Low	Unclear
Aly 2010 [13]		Unclear	Low	Unclear	Low	Unclear	Low	Unclear	Low	Unclear	Unclear	0	4	6
Amini 2016 [14]		Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	Unclear	Unclear	0	2	8
Amini 2017 [15]		Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	Unclear	Unclear	0	2	8
Amini 2018 [16]		Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Unclear	0	1	9
Anderson 1978 [17]		Unclear	Low	Unclear	Low	Unclear	Low	Unclear	Low	Unclear	Unclear	0	6	4
Anderson 1985 [18]		Unclear	Low	Unclear	Low	Unclear	Low	Unclear	Low	Unclear	Unclear	0	4	6
Attia 2013 [19]		Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear	High	Unclear	Unclear	1	2	7
Greenlee 2004 [20]		Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear	High	Unclear	Unclear	1	2	7
National Toxicology Program 2001 [21]		Unclear	Low	Unclear	Low	Unclear	Low	Unclear	Low	Unclear	Low	0	5	5
Pant 2002 [22]		Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	0	2	8
Sleight 1968 [23]		Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	Unclear	Unclear	0	2	8
Total scores for each of the ten items	High	0	0	0	0	0	0	0	2	0	0			
	Low	0	7	0	6	0	8	0	8	0	1			
	Unclear	11	4	11	5	11	3	11	1	11	10			

Scores: High/low/unclear risk of bias. Explanation:

- 'Yes' to signaling question = low risk of bias
- 'No' to signaling question = high risk of bias
- Subject of signaling question not addressed in article = unclear risk of bias

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