Drinking water disinfection by-products exposure and health effects on pregnancy outcomes. A systematic review

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Abstract

Background: Epidemiological studies have found that maternal exposure to disinfection by-products (DBPs) may lead to adverse pregnancy outcomes although the findings tend to be inconsistent. The objective of this study was to systematically review the evidence in association to drinking water disinfection by-products exposure in relation to adverse pregnancy outcomes.

Methodology: Peer-reviewed articles were identified using electronic databases searched for studies published in English language. Studies selected for review were evaluated for exposure assessment, confounders, and analyses risks of bias in the selection, outcomes assessment and attrition.

Results: A comprehensive search and screening has yielded a total of 32 studies, of which 12 (38%) reported a statistical association between maternal exposure to disinfection by-products and adverse pregnancy outcomes. A maternal exposure to trihalomethanes (THMs) shows an increased risk of small for gestational age (SGA) and slightly increased risk of pregnancy loss. Risks of bias were low-moderate among the studies included in the review.

Conclusions and recommendations: Evidence on association relating to adverse pregnancy outcomes to disinfection by-products exposure is still less significant. There is a need for future robust research on this field, with the use of urinary TCAA biomarkers as a direct exposure assessment method for this field.

Key words: adverse pregnancy outcomes, disinfection by-products exposure, drinking water

1. Introduction

The use of disinfectants as a drinking water treatment step in developing countries has led to an effective decrease of waterborne diseases (World Health Organization (WHO). 2011). Since then, chlorine and other related compounds are being used globally because of successes and milestones in public health protection. It has been known for more than 20 years that chlorination of surface water produces chloroform and other toxic compounds that are health risks (Rook 1974). Identified disinfection by-products up to date are more than 700 (Nieuwenhuijsen *et al*. 2009a; Richardson *et al*. 2007). The most commonly studied DBPs are trihalomethanes (THMs) and haloacetic acids (HAAs) as they occur in higher concentrations in tap water compared to others.

The health effects of drinking water disinfection by-products on adverse pregnancy outcomes has been previously reviewed; however, the conclusions of these reviews varied broadly, from indicating association to suggesting no association of disinfection by-products on pregnancy outcomes (Bove *et al*. 2002; Hwang and Jaakkola 2003; Grellier *et al*. 2010; Nieuwenhuijsen *et al*. 2009b, 2010). Additionally, previous reviews that have been publishing on this subject did not assess the risk of bias among included articles studied.

The objective of this chapter was to systematically review the evidence on the risks of spontaneous abortion (miscarriage), preterm or premature birth (PTB), low birth weight (LBW) and small for gestational age (SGA) associated with exposure to different drinking water disinfection by-products.

2. Methodology

The current study followed Preferred Reporting Items for Systematic reviews and Metal-Analyses (PRISMA) guidelines and guidance of observational studies in epidemiology criteria (Moher *et al.* 2009) (**Form 1**). The study received ethical approval from the Faculty of Health Sciences, University of Pretoria (reference no. 115/2016).

2.1. Study question

The pertinent question to this study was: evaluating the evidence/literature on risk of spontaneous abortion (miscarriage), preterm or premature birth (PTB), low birth weight (LBW) and small for gestational age (SGA) among women exposed to different drinking water disinfection by-products during pregnancy.

2.2. Inclusion and exclusion criteria for this review

Observational studies that measure the association of drinking water disinfection by-products maternal exposure and adverse pregnancy outcomes were included in this review. Published studies in peer reviewed journals from 1986 to 2016 formed part of the investigation. We limited ourselves to articles published in English with females as participants and articles conducted in communities or populations. Studies with information on 1) trihalomethanes (THMs) 2) haloacetic acids (HAAs) 3) haloacetonitriles (HAs) 4) haloketones (HANs) 5) bromate and 6) chlorate as selected drinking water disinfection by-products were included: The studies which provide rational information on the method of measuring of the maternal exposure to disinfection by-products and their effects on selected adverse pregnancy outcomes were considered for inclusion in the review. Studies with less than 30 participants, and summarised publications and studies using chlorination and monochloramination in other matrices or contexts other than drinking water disinfection were excluded from this review.

2.3. Types of studies

Peer-reviewed observational studies, retrospective or prospective cohort studies, case-control studies, and cross-sectional studies were included in the review.

2.4. Type of participants

In this review, we included studies identifying the pregnant women exposed to various drinking water disinfection by-products during time of pregnancy (at any time of gestation).

2.5. Exposure assessment

Data regarding maternal exposure to drinking water disinfection by-products obtained via three sources were eligible for inclusion; (1) measurement of participants' urine TCAA levels as a biomarker; (2) measuring of disinfection by-products from drinking water source (i.e. residential tap water); (3) linking data obtained from municipal or national monitoring database on water quality measurements, follow-on estimated value for women's exposure during time of pregnancy.

2.6. Outcomes assessment

We included studies that reported data on either four of the following outcomes: (1) pregnancy loss or spontaneous abortion (miscarriage); (2) Premature/preterm birth or premature delivery (PTB or PTD), defined as gestational age of less than 37 weeks; (3) Low birth weight (LBW), defined as birth weight of less than 2.5 kg; and (4) Small of gestational age (SGA), defined as birth weight below the 10^{th} percentile for gestational age.

2.7. Search strategy

Searches were performed using PubMed, Medline and Google scholar electronic database using the terms and key words and a combination of the key words. Additional data were extracted from grey literature which include but is not limited to World Health Organisation, ProQuest dissertations as well as Theses database and conference proceedings. Water industry such as the South African Water Research Commission (WRC) were also used to search for data. The phrases and keys used were based on the terminology commonly used

in this subject which include: “drinking water disinfection by-products”, “chlorination of water”, “monochloramination of water”, “chlorination disinfection by-products”, “chloramination disinfection by-products”, “exposure to disinfection by-products”, “disinfection by-products health effects”, “haloacetonitriles”, “haloketones”,“trihalomethanes”, “haloacetic acids”, “bromate”, “chlorate”, chlorination disinfection by-products”, “chloramination disinfection by-products”, “birth outcomes”, “adverse pregnancy outcomes”, “gestational age”, “premature birth or preterm birth”, “birth weight” (**Appendix A**). The searched articles were screened from their titles and abstracts to select the eligible studies.

2.8. Methods of review

2.8.1. Data extraction

Two reviewers independently evaluated each of the full texts of eligible studies and any disagreement was resolved via discussion, with the help of a third reviewer. Data extracted from each were piloted on to data collection form without modifying its origin. Lists of confounders were also collected before being adjusted for in the analysis in the studies. The included articles were then assessed for quality (**Table 2**).

2.8.2. Risk assessment of bias among included studies

The tool to assess the quality was adopted from Shah and Zao (2009) (**Appendix B**) with the scale from none to high bias. The table includes the following characteristics: selection, exposure assessment, outcome assessment, confounding factor, analytical and attrition bias.

2.8.3. Data synthesis

A systematically review of these was made rather than to perform meta-analyses, as heterogeneities were recognized in previous reviews. We did not assess statistical heterogeneity and publication bias, as the meta-analyses were not performed. However, studies were assessed for methodological differences and data were reported.

3. Results

3.1. Description of studies

Search results and the number of studies are summarized in **Figure 1** with the reasons for exclusion of the studies from this review. Detailed characteristics of all included studies are reported in **Table 1**.

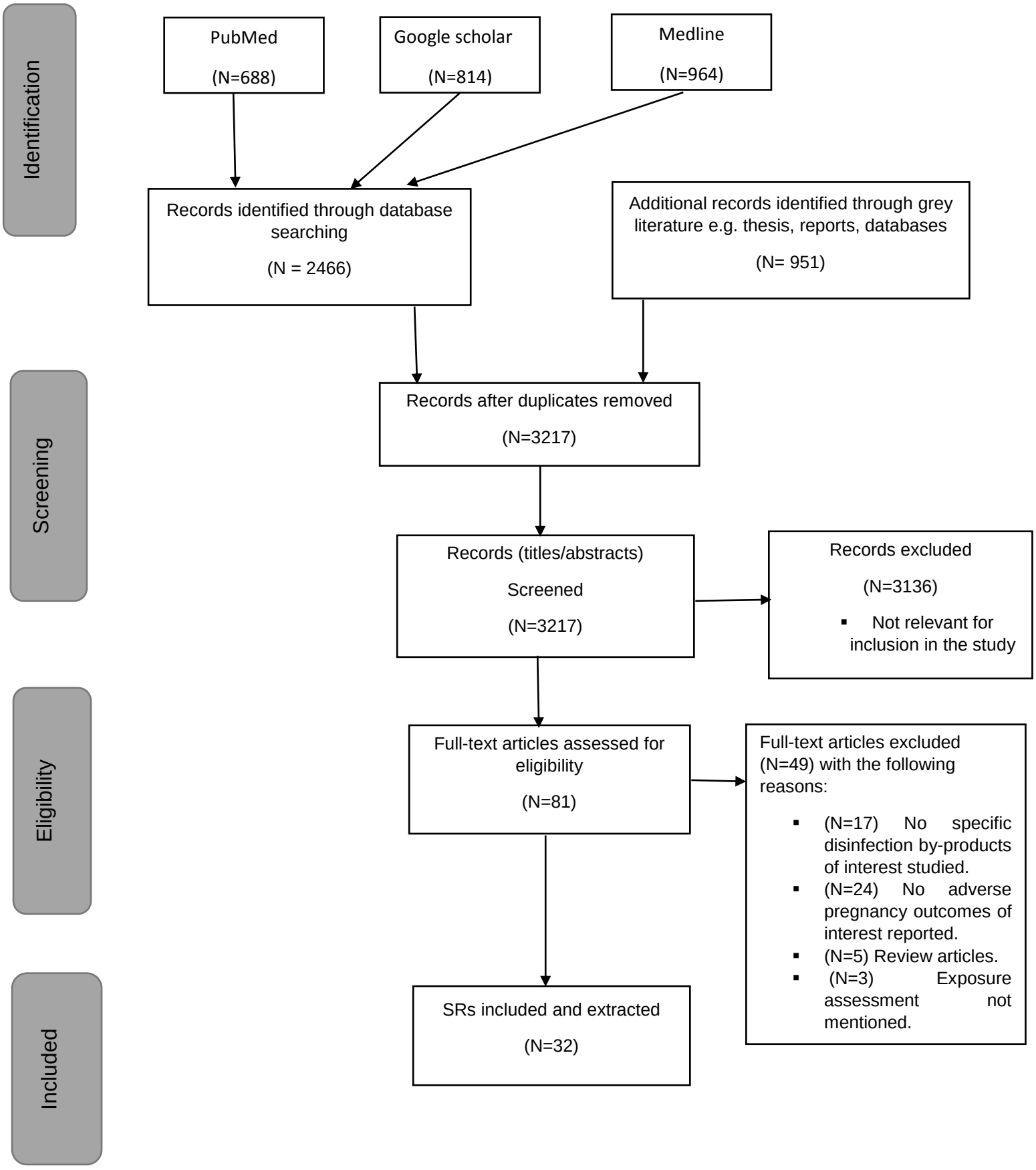

Figure 1 Flow diagram of search, screening and study selection

Table 1: Characteristics of included studies

Author (year)	Study details	Exposure measurement details	DBPs studied	Outcome studied	Outcome assessment details
Aggazzotti *et al*. (2004)	1999-2000; case-control study in Italy; n= 1194.	Collection of water and Questionnaire on mother's personal habits.	THM, chlorite and chlorate	Preterm birth (PTB) and small for gestational age (SGA).	Interviews and Medical records
Botton *et al*. (2015)	2003-2008; prospective cohort study in Gipuzkoa, Sabedell, Valencia, Spain and and 2007-2008; cohort study in Crete (Greece RHEA study); n=2216.	Interviews at recruitment. Collection of water sample in the tap covering the study areas and data abstracted from monitoring program.	THM	Birth weight (BW).	Medical records and log books.
Bove *et al*. (1995)	1985-1988; Cross-sectional study; n=80 938 live births and n= 598 fetal deaths.	Water quality data obtained from monitoring program run by companies.	THM	SGA, Low Birth Weight (LBW), PTB, BW	Birth databases and medical records.
Ca *et al*. (2016)	2011-2013; prospective Cohort in Wuhan and Xiagan, Hubei, China; n=1184	Questionnaires used.	TTMs	BW, Birth length (BL) and SGA.	Clinical birth records.
Costet *et al.* (2011)	2002-2006; PELAGIE cohort in France; n= 3,421	National database was used to estimate individual exposure to THMs together with the measuring the maternal urinary TCAA exposure.	THMs and HAAs	Fetal growth restrictions (FGR), PTB	Midwives, paediatricians and medical records.
Danileviciute *et al*. (2012)	2007-2009; Nested–control study part of Kaunas (Lithuania) cohort in European. n=682	Water-use questionnaire and residential exposure index were used. Blood samples were also used to measure the internal dose of individual exposure.	THMs, HAAs, HANs, HAs, chloropicrin and choral hydrate	LBW, SGA.	Medical records.
Doods *et al*. (1999)	1988-1995; retrospective cohorts study in Canada; n= 93 295.	Water quality data obtained from monitoring program.	TTHM	LBW, SGA.	Medical records and database.
Gallagher *et al.* (1998)	1990-1993; retrospective cohorts study in Colorado, USA; n=1893	Data obtained from monitoring program	TTHM	LBW, SGA and preterm delivery (PTD).	Medical records and database
Grazuleviciene *et al*. (2011)	2007-2009; prospective cohort study in Kaunas (Lithuania); n=4161	Questionnaire was used to interview the participants on water use activities.	THMs	LBW, SGA and BW.	Medical records.
Hinckley *et al*. (2005)	1998-2003; retrospective cohorts study in Arizona, USA; n=48119.	Water quality data obtained from monitoring program.	THMs and HAAs	LBW, PTB.	Vital records and birth records.
Hoffman *et al.* (2008)a	2000-2004; prospective cohorts study in US; n= 2039.	Water samples collected in each site. Interviews conducted from the participants.	TTHM and HAAs	PTB	Medical records, vital records and self-reports.

TTHMs= total trihalomethanes; THM= trihalomethanes; HAA= haloacetic acids; TCCA= trichloroacetoc acid; TOX=total organic halide; PTB= Preterm birth; SGA= small for gestational age, BW= birth weight; LBW= low birth weight, BL= birth length; FGR= fetal growth restrictions

Table 1. (Continue)

Author (year)	Study characteristics	Exposure assessment details	DBPs studied	Outcome	Outcome assessment details
Hoffman *et al*. (2008)b	2000-2004; US communities Cohort study; n=2766	Water samples were collected at a respective location in the distribution system. Self-reporting information on water-use was also collected.	TTHMs, HAAs and TOX)	SGA.	Medical records.
Horton *et al*. (2011)	2000-2004; US Community cohort study consist of two sites: Chlorinated DBP site (n=27 062 birth); Brominated DBP site(n=3946)	Weekly collections of water samples from representative location sites (i.e. Chlorinated-Brominated containing DBP) were used.	TTHMs, HAAs and (TOX)	SGA, PTB.	Birth records.
Ileka-Priouzeau *et al*. (2015)	2006-2008; Quebec, Canada case-control study; cases (n=330); controls (n=1100)	Water Samples were measured for HANs and HAs combined with the previous data on THMs and HAAs.	HANs, HAs, THMs and HAAs	SGA.	Birth certificates and medical records.
Iszatt *et al.* (2014)	2000-2005 and 2005-2007; Case -control study in UK;n= 472,526 live births and n=2631 stillbirths	National water quality data base was used to assign the individual exposure.	THMs	LBW.	Birth records.
Kogevinas *et al*. (2016)	2002-2010; prospective cohorts study in France Greece, Lithuania, Spain and UK; n=14 0005.	Water samples collected and additional data from regulatory monitoring program. Questionnaire administered to the participants.	THM	SGA, LBW, PTB.	Birth records.
Kumar *et al*. (2014)	1998-2003; Cross-sectional study in New York state; n=1,528,681 singleton live births.	Exposure data obtained from public water system were maternal residence at the time of child birth.	TTHMs	LBW, SGA, PTB.	Birth certificate records.
Levallois *et al*. (2012)	2006-2008; Quebec, Canada case-control study; cases (n= 571); controls (n= 1925)	Chlorination by-products concentration were measured in the tap water at the participant's residence.	THMs and HAAs	SGA.	Birth certificates and medical records.
Lewis *et al*. (2006)	1999–2001; retrospective cohort study in Massachusetts; n= 40,514 records of singletons birth.	Water sampling for total trihalomethanes were used to estimate the exposure on maternal residence at birth and gestational age.	THMs	LBW	Registry of vital records
Lewis *et al*. (2007)	1999–2001; retrospective cohort study in Massachusetts; n=39,593 records of singletons birth.	Water sampling for total trihalomethanes were used to estimate the exposure on maternal residence at birth and gestational age.	TTHMs	PTB.	Birth certificates
Maclehose *et al*. (2008)	2000-2004; prospective cohorts study in US; n=2506.	Sampling of water at respective points. Questionnaires were administered to the participants.	THMs, HAAs, TOX	Pregnancy loss	Medical records.

TTHMs= total trihalomethanes; THM= trihalomethanes; HAA= haloacetic acids; TCCA= trichloroacetoc acid; TOX=total organic halide; PTB= Preterm birth; SGA= small for gestational age, BW= birth weight; LBW= low birth weight, BL= birth length; FGR= fetal growth restrictions

Table 1. (Continue)

Author (year)	Study characteristics	Exposure assessment details	DBPs studied	Outcome	Outcome assessment details
Patelarou *et al*. (2011)	2007-2008; prospective cohort study in Crete ('Rhea' study), Greece. n=1359.	Questionnaires administered. Tap water samples were also collected in representative mother homes for DBPs analysis.	THMs	SGA, LBW, PTB.	Interview after birth.
Rivera-N´u˜nez and Wright (2013)	1996-2004; retrospective cohort study in Massachusetts; n=12,394 live infants.	Public water systems have been used and participants have been assigned the exposure together with collection of water samples in area.	THMs and HAAs	BW, SGA, PTD.	Birth certificates
Savitz *et al.* (1995)	1988-1991; case-control study in Central North Carolina. Miscarriage; case 418 and controls 341; Low birth weight 464; Preterm delivery 586; controls 782	Water quality data obtained from regulatory monitoring program. Telephone interviews and person to person questionnaire were conducted to the participants.	THM	Miscarriage, PTD, LBW	Medical records.
Savitz *et al*. (2006)	2000–2004; prospective cohort study in three US; n=2,409 women.	Water samples were analysed from three US locations, one referred to chlorinated DBP site, one referred to brominated DBP site and low DBP site.	THM, HAA and TOX	Spontaneous abortion.	Medical records.
Summerhayes *et al*. (2012)	1998 -2004; retrospective cohort study in New South Wales, Australia; n=314,982 births.	THM data were obtained from the water supply database were participants residing.	THM	SGA.	Midwives data collection records.
Toledono *et al*. (2004)	1992-1998; retrospective cohorts study in UK; n=1 million	Collection of water samples for quality.	TTHM	LBW	National birth registers and health statistics at UK
Villanueva *et al*. (2011)	2000-2008; prospective cohort in Spain; n= 2074	Interviews were conducted from the participants. THMs were ascertained based on sampling campaigns program and additional water quality data were obtained from local authorities and water companies.	THM	SGA, LBW, PTD	Birth outcomes recorded by trained midwives at delivery.
Waller *et al.* (1998)	1989-1991; prospective cohorts study (Pregnancy Outcome Study) in California; n=5144	Water quality data was obtained from water utilities. Questionnaires were conducted from the participants.	THM	Spontaneous abortion	Hospital discharge, medical records, birth registry and follow-up interviews
Wright *et al.* (2004)	1995-1998; retrospective cohorts study in Massachusetts, Boston, USA; n=282 645	Water quality data were abstracted from department of environmental protection records. Water samples were also collected for analysis.	TTHM and HAAs	SGA, BW, PTD	Birth certificates.

TTHMs= total trihalomethanes; THM= trihalomethanes; HAA= haloacetic acids; TCCA= trichloroacetoc acid; TOX=total organic halide; PTB= Preterm birth; SGA= small for gestational age, BW= birth weight; LBW= low birth weight, BL= birth length; FGR= fetal growth restrictions

Table 1. (Continue)

Author (year)	Study characteristics	Exposure assessment details	DBPs studied	Outcome	Outcome assessment details
Yang *et al.* (2004)	1994-1996; retrospective cohort study in Taiwan; n= 182, 796; 128 municipalities	Water quality data obtained from authorities (TWSC).	THMs	LBW, PTD.	Registration of births and vital records.
Yang *et al*. (2007)	200-2002; cross-sectional study in Taiwan; n=90,848 women residing in the 65 municipalities	Maternal exposure was assigned with the previous data of TTHMs concentration for the municipality of residence at birth.	THM	LBW, SGA, PTD.	Birth registry.
Zhou *et al*. (2012)	2008-2009; cross-sectional study in Wuhan, China; n=398	Face-to-Face interviews were conducted. Collection of urine samples were also collected from the participants.	HAA (TCAA)	BW	Birth records.

TTHMs= total trihalomethanes; THM= trihalomethanes; HAA= haloacetic acids; TCCA= trichloroacetoc acid; TOX=total organic halide; PTB= Preterm birth; SGA= small for gestational age, BW= birth weight; LBW= low birth weight, BL= birth length; FGR= fetal growth restrictions

3.2. Quality assessment of included studies

Risks of bias assessment of the included studies were studied. Of 32 studies included, 26 (81%) had an overall low risk of bias, whereas 6 (19%) had an overall moderate risk of bias. In exposure assessment, moderate risks of bias were assigned to the studies due to indirect use of exposure methods employed. Most studies had no risk of bias for outcome assessment, confounder adjustments and participants' selection (see **Appendix C**. for details).

3.3. Outcomes

Adverse pregnancy outcomes according to various drinking water disinfection by-products were assessed. Studies included in the review reported various drinking water disinfection by-products; however, the majority of studies reported on THMs followed by HAAs or both. The results below are classified according to individual disinfection by-products. The details of level of exposure, time of exposure and birth outcomes are reported in **Tables 2-1** to **2-5.**

2.3.1. Trihalomethanes (THMs)

Twenty-nine studies reported data on adverse pregnancy outcomes following THMs exposure (**Table 2-1**). Studies reported on various levels of exposure, ranging from 0-108.8 µg/L. 16 studies were investigating the association between THMs exposure and SGA, and 13 studies reported on either PTB, PTD, LBW and pregnancy loss or both. Ten studies reported on exposure to THMs during third trimester, 13 studies during entire pregnancy, five studies reported on either both (first trimester and entire pregnancy) or (second trimester and third trimester) or only second trimester's maternal exposure. One study reported on (first, second, third trimesters and entire pregnancy) THMs exposure. Nine studies reported on evidence of association between maternal THMs exposure and adverse pregnancy outcomes (Aggazzotti *et al*. 2004; Cao *et al*. 2016; Dodds *et al*. 1999; Grazuleviciene *et al*. 2011; Iszatt *et al*. 2014; Kumar *et al*. 2014; Levallois *et al*. 2012; Maclehose *et al*. 2008; Rivera-Nu˜nez and Wright 2013). These studies were conducted in countries like US, UK, Canada, China, Italy and Europe. Twenty studies reported no association between THMs exposure and adverse pregnancy outcomes-see Table 2-1.

2.3.2. Haloacetic acids (HAAs)

The exposure to HAAs and adverse pregnancy outcomes were explored in 12 studies (**Table 2-2**). The levels of exposure to HAAs were ranging from 0.1-75.9 µg/L among studies. Five studies reported on exposure to HAAs and SGA, four studies reported on

exposure to HAAs and PTB/PTD, five studies on either LBW, BW or BWT. Two studies reported on exposure to HAAs and pregnancy loss. Hoffman *et al*. (2008b), Hinckley *et al*. (2005), Wright *et al*. (2004) and Zhou *et al*. (2012) reported exposure to HAAs during (third trimester); six studies reported on exposure during entire pregnancy (Costet *et al*. 2011; Danileviciute *et al*. 2012; Grazuleviciene *et al*. 2011; Horton *et al*. 2011; Savitz *et al*. 2006; Maclehose *et al*. 2008), Hoffman *et al*. (2008a) reported on (first trimester and entire pregnancy) and Rivera-N´u˜nez and Wright (2013) reported on (second and third trimester). Eight studies were conducted in US, two in Europe, one in China and one in France. A slightly positive association between adverse pregnancy outcomes and high level of HAAs exposure were reported among the studies- see **Table 2-2**.

2.3.3. Haloacetaldehydes (HAs)

Two studies (Danileviciute *et al*. 2012; Ileka-Priouzeau *et al*. 2015) reported on adverse pregnancy outcomes following HAs exposure (**Table 2-3**). The levels of exposure to HAs were ranging from 1.0-9.00 µg/L. Both articles studied HAs exposure and SGA or LBW or both. Studies were conducted in Europe and Canada respectively. No association between HAs exposure and SGA or LBW were reported.

2.3.4. Haloacetonitriles (HANs)

Three studies (Aggazzotti *et al*. 2004; Danileviciute *et al*. 2012; Ileka-Priouzeau *et al*. 2015) reported on pregnancy outcomes following chloropicrin and chloral hydrate exposure (**Table 2-4**). The levels of exposure were ≥ 200 µg/L for chlorate or chlorite concentrations. Two studies reported on exposure to HANs during the entire pregnancy and one during third trimester. Studies reported on (SGA and PTD), (SGA and LBW), and SGA respectively. Studies were conducted in Italy, Europe and Canada. None of the studies reported an association.

2.3.5. Total Organic Halide (TOX)

Four studies (Hoffman *et al*. 2008b; Horton *et al*. 2011; Savitz *et al*. 2006; Maclehose *et al*. 2008) reported data on TOX and pregnancy outcomes (**Table 2-5**). The levels of exposure to TOX were ranging from 18.7-186 µg/L. Three studies were conducted during entire pregnancy and one during the third trimester. The adverse pregnancy outcomes reported were either pregnancy loss, SGA or PTB. A slightly positive association between pregnancy loss with an increased TOX exposure were reported- see **Table 2-5**.

Table 2-1: Exposure to THMs and adverse pregnancy outcomes

Author (year)	Level of exposure	Time of exposure	Birth outcomes	Results (statistical)
Aggazzotti *et al.* (2004)	10µg/L to 30µg/L	Third trimester	PTD, SGA	OR=1.38; (95% Cl: 0.92-2.07) for term SGA OR= 0.84; (95% Cl: 0.59-1.19) for preterm birth
Bove *et al*. (1995)	>100ppb	First trimester Entire pregnancy	LBW, SGA, PTB	OR= 1.42; (50% Cl: 1.22-1.65) for LBW OR =1.50; (50% Cl: 1.36-1.65) for PTB. Mean decrease in BW 70.4g (50% Cl: -58.2 to -82.6)
Ca *et al*. (2016)	5.3 to 52.3 ng/L	Third trimester	BW, SGA	Mean birth weight decrease (–60.9 g; 95% CI: –116.2, –5.6) OR= 2.25; (95% CI: 1.01-5.03) for SGA
Danileviciute *et al.* (2012)	1.3 to 21.9 µg/L	Entire pregnancy	LBW, SGA	OR= 4.37; (95% CI: 1.36–14.08) for LBW OR= 5.06; (95% CI: 1.50–17.05) for SGA
Dodds *et al*. (1999)	0-49 µg/L, 50-74 µg/L,75-99 µg/L and ≥ 100 µg/L	Third trimester	LBW, SGA, PTB	RR=1.8; (95% Cl: 0.99-1.18) for SGA. RR=1.04; (95% Cl:0.92-1.18) for LBW. RR=0.97; (95% Cl: 0.87-1.09) for PTB. RR=0.89; (95% Cl: 0.64- 1.23) for VLBW.
Gallagher *et al*. (1998)	Low (0-49 ppb) and high (≥ 50 ppb)	Third trimester	LBW, PTD, term LBW	OR=1.5; (95% Cl: 0.8-3.0) for LBW. OR=2.6; (95% Cl: 1.1-6.1) for term LBW. OR=0.9; (95% Cl: 0.4-2.0) for PTD.
Grazuleviciene *et al*. (2011)	1.3 to 21.9 µg/L	Entire pregnancy	LBW, SGA	AOR= 2.17; (95% CI: 1.19-3.98) for LBW AOR=1.19; (95% CI: 0.87-1.163) for SGA
Hinckley *et al*. (2005)	≥ 53 µg/L for TTHMs	Third trimester	Term LBW	OR=1.11; (95% Cl: 0.94-1.31)
Hoffman *et al*. (2008)a	33.1-55.0, 55.1-66.3, 66.4-74.8 and 74.9-108.8 µg/L	First trimester Entire pregnancy	PTB	OR range from 0.5 to 1.25 with 95% Cl ranging from (0.3-0.8) and (0.96-1.64), respectively.
Hoffman *et al*. (2008)b	< 80 µg/L and ≥80 µg/L	Third-trimester	SGA	RR= 2.0; (95% CI: 1.1-3.6)

SGA= Small for gestational age; PTB= premature or preterm birth; PTD=premature or preterm delivery; LBW= low birth weight; BWT= mean birth weight; BW= birth weight; HR= Hazard ratio; RR= relative risk; OR= odds ratio; AOR= adjusted odds ratio; CI= confidence interval.

Table 2-1 (continue)

Author (year)	Level of exposure	Time of exposure	Birth outcomes	Results (statistical)
Horton *et al*. (2011)	60.7 to 75.9 µg/L (chlorinated site). 58.9 to 67.4 µg/L (brominated site)	Entire pregnancy	SGA, PTB	AOR=1.02; (95% CI: 0.91-1.15) for SGA and AOR=0.93; (95% CI: 0.84-1.04) for PTB in chlorinated site. AOR= 0.81; (95% CI: 0.53-1.24) for SGA and AOR= 1.16; (95% CI: 0.77-1.74) for PTB in brominated site.
Iszatt *et al*. (2014)	27.6 to 55.2 µg/L	Entire pregnancy	Still birth, LBW	Decrease in chloroform from 30 to 65 µg/l shows percentage decrease in low birth weight by -9% (-12, -5) and very low birth weight -16% (9-24, -8) rates.
Kogevinas *et al*. (2016)	≥ 10 µg/L	Entire pregnancy	SGA, LBW, PTB	OR= 10 µg/L = 1.02; (95% Cl: 0.95, 1.10) for LBW, OR = 0.99; (95% Cl: 0.94, 1.03) for SGA and OR = 0.98; (95% Cl: 0.9, 1.05) for PTB
Kumar *et al*. (2014)	0 to 40 µg/L	Entire pregnancy	LBW, SGA, PTB	OR= 1.14; (95% CI: 1.08–1.21) for LBW; OR= 1.14; (95% CI: 1.08–1.20) for PTB and OR= 1.10; (95 % CI 1.04–1.16) for SGA
Levallois *et al*. (2012)	>80 µg/L and < 80 µg/L	Third trimester	SGA	AOR= 1.5; (95% Cl: 1.1–1.9)
Lewis *et al*. (2006)	≥70 µg/L	Second trimester	LBW	OR= 1.50; (95% CI: 1.07-2.10)
Lewis *et al*. (2007)	≥60 µg/L	Third trimester	PTB	HR= 1.13; (95% CI: 0.95-1.35)
Maclehose *et al*. (2008)	3.7 to 67.3µg/L	Entire pregnancy	Pregnancy loss	AOR = 1.2; (95% CI :1.0–1.4)
Patelarou *et al.* (2011)	0.39 to 8.74 µg/L	Entire pregnancy	SGA, LBW, PTB	OR= 0.7; (95% CI 0.4 - 1.4) for LBW. OR= 1.1; (95% CI 0.6 -2.2) for SGA. OR= 0.8; (95% CI 0.5 -1.3) for PTD.
Rivera-N´u˜nez and Wright (2013)	37.5 to 38.1 µg/L	Second and third trimester	BWT, SGA, PTD	AOR=1.02; (95% CI 0.97 -1.07) for SGA. AOR= −17; (95% CI: −24 to −11) for BWT. AOR =1.02; (95% CI: 0.96 to 1.08) for PTD.

SGA= Small for gestational age; PTB= premature or preterm birth; PTD=premature or preterm delivery; LBW= low birth weight; BWT= mean birth weight; BW= birth weight; HR= Hazard ratio; RR= relative risk; OR= odds ratio; AOR= adjusted odds ratio; CI= confidence interval.

Table 2-1 (continue)

Author (year)	Level of exposure	Time of exposure	Birth outcomes	Results (statistical)
Savitz *et al*. (1995)	≥ 40.8ppb	Entire pregnancy	Miscarriage, PTD, LBW	AOR = 2.8; (95% CI: 1.1–2.7) for miscarriage. AOR= 1.2; (95% CI: 0.8-1.7) for preterm birth. AOR=1.3; (95% CI: 0.8-2.1) for LBW.
Savitz *et al*. (2006)	≥75 µg/L	Entire pregnancy	Pregnancy loss	OR= 1.1; (95% CI: 0.7-1.7)
Summerhayes *et al*. (2012)	≥0.3 µg/L	Third trimester	SGA	RR=1.04; (95% CI:1.02– 1.06)
Toledono *et al*. (2004)	(< 30 µg/L), (30–59 µg/L), (≥ 60 µg/L)	Entire pregnancy	LBW	OR = 1.09; (95% CI: 0.93-1.27) for LBW and OR = 1.05; (95% CI: 0.82–1.34) for VLBW.
Villanueva *et al.* (2011)	5.9 µg/L to 114.7 µg/L	First, second, third trimester and the Entire pregnancy	SGA, LBW, PTB	OR= 1.005; (95% CI: 0.97-1.032) for PTB. OR= 1.003; (95% CI: 0.990-1.017) for SGA. Birth weight was reduced 0.45 g; (95% CI: –1.36 to 0.45) for total residential chloroform uptake and increased 0.16 g; (95% CI: –1.38 to 1.70) for total brominated THM uptake.
Waller *et al*. (1998)	≥120 µg/L	First trimester	Spontaneous abortion	AOR=1.8; (95% CI: 1.1-3.0)
Wright *et al*. (2004)	> 40 µg/L.	Third-trimester	SGA, BW, PTD	OR = 1.25; (95% CI:1.04-1.51) for SGA and mean birth weight –27 g; (95% CI: –54 to –1).
Yang *et al*. (2004)	Not mentioned	Entire pregnancy	LBW, PTD.	AOR = 1.37; (95% CI: 1.20-1.56) for PTD and 1.05; (95% CI: 0.94–1.18) for LBW.
Yang *et al*. (2007)	0–4.93 mg/L, 4.93–13.11 mg/L, >13.11 mg/L	Entire pregnancy	SGA, LBW, PTD	AORs in medium versus low and high versus low exposure categories were 0.98; (95% CI :0.90–1.08) and 1.03; (95% CI: 0.94–1.13). respectively. for term LBW; 1.02; (95% CI: 0.93–1.13) and 1.09; (95% CI: 0.99–1.19), respectively. for PTD; they were 0.99; (95% CI: 0.94–1.05) and 0.99; (95% CI: 0.94–1.04), respectively. for SGA

SGA= Small for gestational age; PTB= premature or preterm birth; PTD=premature or preterm delivery; LBW= low birth weight; BWT= mean birth weight; BW= birth weight; HR= Hazard ratio; RR= relative risk; OR= odds ratio; AOR= adjusted odds ratio; CI= confidence interval.

Table 2-2: Exposure to HAAs and adverse pregnancy outcomes

Author (year)	Level of exposure	Time of exposure	Birth outcomes	Results (statistical)
Costet *et al*. (2011)	7.4 µg/L	Entire pregnancy	PTB	AOR= 0.8; (95% CI: 0.3-2.6)
Danileviciute *et al.* (2012)	0.1 to 0.5 µg/L	Entire pregnancy	LBW, SGA	Not mentioned
Grazuleviciene *et al*. (2011)	0.1 to 0.5 µg/L	Entire pregnancy	LBW, SGA	Not mentioned
Hoffman *et al.* (2008)b	21.2 to 5.9 µg/L	Third-trimester	SGA	RR=1.3; (95% CI: 0.7-2.4)
Horton *et al*. (2011)	58.9 to 75.9 µg/L	Entire pregnancy	SGA, PTB	Not mentioned
Rivera-N´u˜nez and Wright (2013)	20.0 to 20.1 µg/L	Second- and third-trimester	BWT, SGA, PTD	AOR=1.10; (95% CI: 0.94 -1.29)
Savitz *et al*. (2006)	45.2 to 45.9 µg/L	Entire pregnancy	Pregnancy loss	Not mentioned
Hinckley *et al.* (2005)	≥ 19 µg/L	Third trimester	Term LBW	
Hoffman *et al*. (2008)a	17.9 to 22.0, 22.1-31.5, 31.6-40.4 and 40.5 to 52.8 µg/L	First trimester Entire pregnancy	PTB	OR= 0.5 and 1.1; 95% CI: (0.3- 0.8) and (0.8-1.7), respectively.
Maclehose *et al.* (2008)	1.7 to 12.3 µg/L	Entire pregnancy	Pregnancy loss	OR= 1.2; (95% CI: 1.0–1.4)
Wright *et al.* (2004)	≤ 58 µg/L	Third trimester		OR=–0.9 days; (95% CI: –1.7 to –0.1) for SGA OR = 1.48; 95% CI, 0.84 to 2.61). for PTD
Zhou *et al*. (2012)	0.9 µg/g Cr to 123.3 µg/g Cr and 2 µg/L to 57.7 µg/L, respectively	Third-trimester	BW	AOR= 20.6g; (95% CI: −84.1, 125.3).

SGA= Small for gestational age; PTB= premature or preterm birth; PTD=premature or preterm delivery; LBW= low birth weight; BWT= mean birth weight; BW= birth weight; HR= Hazard ratio; RR= relative risk; OR= odds ratio; AOR= adjusted odds ratio; CI= confidence interval.

Table 2-3: Exposure to HAs and adverse pregnancy outcomes

Author (year)	Level of exposure	Time of exposure	Birth outcomes	Results (statistical)
Danileviciute *et al*. (2012)	1.0 µg/L	Entire pregnancy	LBW and SGA	Not mentioned
Ileka-Priouzeau *et al*. (2015)	8.78 to 9.00 µg/L	Third trimester	SGA	OR=1.4; (95% CI: 0.9 -2.1)

SGA= Small for gestational age; LBW= low birth weight; OR= odds ratio; CI= confidence interval.

Table 2-4: Exposure to HANs (chloropicrin and chloral hydrate) and adverse pregnancy outcomes

Author (year)	Level of exposure	Time of exposure	Birth outcomes	Results (statistical)
Aggazzotti *et al.* (2004)	Chlorites=216.5 µg/L; chlorates = 76.5 µg/L	Entire pregnancy	PTD, SGA	AOR: 1.38; (95% CI: 0.92–2.07)
Danileviciute *et al.* (2012)	< 1.0 µg/L	Entire pregnancy	LBW, SGA	Not mentioned
Ileka-Priouzeau *et al.* (2015)	1.80-1.86 µg/L	Third trimester	SGA	OR= 1.1; (95% CI 0.7–1.6)

SGA= Small for gestational age; LBW= low birth weight; PTD=premature or preterm delivery; OR= odds ratio; AOR= adjusted odds ratio; CI= confidence interval.

Table 2-5: Exposure to TOX and adverse pregnancy outcomes

Author (year)	Level of exposure	Time of exposure	Birth outcomes	Results (statistical)
Hoffman *et al*. (2008)b	≤ 173.8 µg/L	Third-trimester	SGA	RR= 1.3; (95% CI: 0.7–2.3)
Horton *et al*. (2011)	170.8 to 186.1 µg/L	Entire pregnancy	SGA and PTB	AOR= 1.01; (95% CI: 0.90-1.13) for SGA AOR= 0.96; (95% CI: 0.87-1.05) for PTB
Savitz *et al.* (2006)	173.7 to 182.3 µg/L	Entire pregnancy	Pregnancy loss	AOR= 1.2; (95% CI: 0.8-1.8)
Maclehose *et al*. (2008)	18.7 to 178.8 µg/L	Entire pregnancy	Pregnancy loss	AOR= 1.5; (95% CI:1.2–1.8)

SGA= Small for gestational age; PTB= premature or preterm birth; AOR= adjusted odds ratio; RR= relative risk; CI= confidence interval

3. Discussion

We used a systematic review of 32 studies to assess the associations between exposure to drinking water disinfection by-products and adverse pregnancy outcomes. We identified various disinfection by-products on adverse pregnancy outcomes of spontaneous abortion (miscarriage), preterm or premature birth (PTB), low birth weight (LBW) and small for gestational age (SGA). Various disinfection by-products include THMs, HAAs, HAs, HANs and TOX found in drinking water.

In this review, 38% of the studies included in the review reported on evidence of association between maternal exposure to drinking water disinfection by-products and adverse pregnancy outcomes. This was consistent with the findings from Grellier *et al*.'s (2010) review, were 40% of studies included were statistically associated with birth outcomes. THMs were associated with SGA and slightly with LBW or pregnancy loss. Higher concentrations of HAAs and TOX exposures were slightly associated with SGA and pregnancy loss respectively. The evidence of any association between other drinking water disinfection by-products (HAs, HANs) and adverse pregnancy outcomes is still inconclusive. The examination of drinking water disinfection by-products and adverse pregnancy outcomes or birth outcomes is still a challenge in most epidemiological studies.

Our reviewed articles demonstrated different exposure assessments methods used, of which, 31% of the studies used exposure data obtained from national or local database housed-by water utilities/industries whereas, 34% of the studies used water sampling campaigns to measure the disinfection by-products concentrations around the residential areas while 22% studies used both water sampling campaigns and national or local database from water utilities/industries to assign the exposure to the participants wherein some instance relies on questionnaire for personal habits. The indirect approach of measuring exposure assessments is still the most common applied methodology because it is less costly.

Recently, other methods of measuring exposures in epidemiological studies have been explored. For instance, the use of blood samples to measure the internal exposure was reported by Danileviciute *et al*. (2012) in this review. Blood THMs decrease within minutes to hours after exposure; however, slower partitioning out of adipose tissue and the relatively high (e.g. daily) frequency of exposure events such as showering/bathing are thought to produce steady-state blood concentrations (Savitz 2012). Costet *et al.* (2011) and Zhou *et al*. (2012) also explore the use of urine samples to measure the Trichloroacetic acid (TCAA) levels. Trichloroacetic acid is one of major haloacetic acid (HAAs) and is being used as a biomarker because it is stable, unmetabolized in urine and is not readily degraded through the collection and storage processes (Smith *et al.* 2013). The eradication half-life of TCAA is between 2-6 days which gives enough information on urinary concentration (Savitz 2012). Both studies show a positive evidence of using a biomarker for exposure assessment.

In this review, included studies were performed in well developed countries and the effects of exposure on adverse pregnancy outcomes can vary according to the country in which the study is being conducted as the regulatory standards differs. Countries like European Union, the US, the UK, Australia, China and others (e.g., Canada, Italy) have set their standards which benchmark against the WHO drinking water quality guidelines of 2011. For instance, European Communities (EC) has set the drinking water quality standard for total THMs to 100µg/l (WHO. 2011). The United States have set a regulatory standard for THMs to 80 µg/L and 60 µg/L for five haloacetic acid and 10 µg/L for bromate and 1000 µg/L for Chlorite (USEPA. 2011). Canada has set a limit of 80 µg/L level for THMs with provisional maximum acceptable concentrations (MACs) of 100 µg/L level of the THMs according to the guidelines for Canadian drinking water quality of 2003 (Rodriguez *et al*. 2004).

Previous review by Bove *et al*. (2002) found moderate association between THMs exposure and birth outcomes (SGA and spontaneous abortions). Their results correlate with the findings from the review conducted by Grellier *et al*. (2010), where SGA was associated with exposure to total trihalomethanes, of which, 9 Studies included in Grellier *et al*. (2010)

review, none found statistical significant on associations of disinfection by-products with preterm birth (Dodds *et al*. 1999; Gallagher *et al*. 1998; Hoffman *et al*. 2008a; Kramer *et al*. 1992; Lewis *et al*. 2007; Savitz *et al*.1995; Wright *et al*. 2003, 2004; Yang *et al*. 2007). Our results have both similarities and differences compared with the previous reviews. However, none of the previous reviews have used the PRISMA guidelines. In addition, impact based on individual drinking water disinfection by-products was not observed from previous reviews.

This review has demonstrated several strengths. To our knowledge this marks the first review to assess associations of adverse pregnancy outcomes using PRISMA guidelines. The method of reviewing also assesses the maternal exposure to individual drinking water disinfection by-products. Risk assessment of biases in the included studies and analyses of exposure-outcome measurement also gives strength to this review. However, the review has limitations also. We did not retrieve the raw data for studies included in the review. We also limit our searches strategies to English language publications only. The scope was that they may be low possibility of different results in non-English language articles.

Health determinants factors that contribute to adverse pregnancy outcomes should be considered when interpreting the results. Therefore, our data in most studies included in the review were extracted after adjusting the confounders. Another limitation, like other reviews, is that the adverse pregnancy outcomes definitions are not the same across the studies. These limitations are important to consider when considering the conclusions of this review. The purpose for this article was to assess on associations or risks, not to disprove or prove causality.

5. Conclusion

Mothers' exposures to common (THMs, HAAs) drinking water disinfection by-products have association with adverse pregnancy outcomes. In addition, the concentration levels of DBPs studied varied between studies. Most studies are being conducted in developed countries were the set standards are well established and regulated. Evidence of any association between other drinking water disinfection by-products (HAs, HANs) and adverse pregnancy outcomes is still inconclusive. However, the absence of association results does not demonstrate the absence of health effects on pregnancy outcomes. Likewise, a statistical significance does not always suggest clinical importance. Difficulty in measuring exposure, inappropriate time of measurement and interaction between drinking water disinfection by-products may have resulted in absence of association in most studies. The use of urinary TCCA biomarkers as a direct exposure assessment method is deemed to be the future on this field.

5.1. Implications for practice

Health impacts associated with disinfection by-products is a global issue in public health perspectives. The findings of this review underline the need of action to be taken in reduction of exposure to disinfection by-products, especially during pregnancy. The association of THMs and pregnancy outcomes indicates that exposure to high THMs concentration during pregnancy is harmful to the foetus. The association of other health determinants factors and birth outcomes are important as indicated in other studies. National, regional and local water industries efforts are needed to reduce the production of disinfection by-products in drinking water. Even though common disinfection by-products are regulated internationally, exposure to disinfection by-products can vary according to individual actions such as water activities habit especially during pregnancy as many tend to consume more water than normal.

5.2. Implications for research

Future studies need to focus on underlying the biological mechanisms to understand the impact of individual contaminants as well as the interactions between them. Previous studies have underlined the key areas where research is needed to improve the understanding of the association between disinfection by-products in drinking water and adverse pregnancy outcomes (Villaneuva *et al*. 2015) include biological mechanism of action is necessary and use of cohort studies with the use of biomarkers. Studies with large sample size are needed to have sufficient statistical power (Villaneuva *et al*. 2014) and a better understanding of pathways by which disinfection by-products or contaminants cause birth outcomes (Ferguson *et al*. 2013). Developing countries must also form part of this assessment in this field in order to add to the exiting knowledge.

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Appendix A. Search results for Medline

Set#	Searched for	Databases	Results
S1	pub((drinking water disinfection by-products) OR (chlorination OR monochloramination of water) OR (exposure to disinfection by-products OR disinfection by-products health effects) OR (trihalomethanes OR haloacetic acids) OR (haloacetonitriles OR haloketones) OR (bromate OR chlorate) AND (adverse pregnancy outcomes OR birth outcomes) OR (birth defects OR gestational age) OR (premature birth OR preterm bith) OR (birth weight)) AND **female**(yes) AND **peer**(yes) AND **human**(yes) AND rtype.**exact**("Journal Article" OR "Observational Study") AND la.exact("**English**") AND pd(1986-2016)	MEDLINE®	964°

°Number of Duplicates removed from our search and from our result count

Appendix B. Tool used for assessment of quality of included studies

Bias	None	Low	Moderate	High
Selection	• Consecutive unselected population • Sample selected from general population rather than a select group • Rationale for case and control selection explained • Follow up or assessment time explained	• Sample selected from large population but selection criteria not defined • A select group of population (based on race, ethnicity, residence etc.) studied	• Sample selection ambiguous but sample may be representative • Eligibility criteria not explained • Rationale for case and controls not explained • Follow up or assessment time not explained	• Sample selection ambiguous and sample likely not representative • A very select population studied making it difficult to generalize findings
Exposure assessment	• Direct questioning (interview) or completion of survey by women at the time of exposure or close to the time of exposure • Direct measurement of exposure (laboratory)	• Assessment of exposure from global dataset • Indirect assessment (postal survey, mailed questionnaire) • Recall of exposure <1 year of birth	• Recall 1-5 years after birth • Extrapolating data from population exposure sample (with some assumptions) and not direct assessment at any time	• Recall >5 years after birth • Indirect method of assessment (obtaining data from others and not from mother or father)
Outcome assessment	• Assessment from hospital record, birth certificate or from direct question to women regarding birth weight	• Assessment from administrative database • Direct question to women regarding gestational age	• Assessment from "open-ended' questions (was your baby early? or premature? or small? or before due date)	• Assessment from non-validated sources or generic estimate from overall population
Confounding factor	• Controlled for common confounders	• Only certain confounders adjusted	• Not controlled for confounders	
Analytical	• Analyses appropriate for the type of sample • Analytical method accounted for sampling strategy in cross-sectional study • Sample size calculation performed and adequate sample studied	• Analyses not accounting for common statistical adjustment (e.g. multiple analyses) when appropriate • Sample size calculation not performed, but all available eligible patients studied • Sample size calculated and reasons for not meeting sample size given	• Sample size estimation unclear or only sub-sample of eligible patients studied	• Analyses inappropriate for the type of sample/study
Attrition	• 0-10% attrition and reasons for loss of follow up explained • All subjects from initiation of study to the final outcome assessment were accounted for	• 0-10% attrition and reasons for loss of follow up not explained • 11-20% attrition, reasons for loss of follow up explained	• 11-20% attrition but reasons for loss of follow up not explained • >20% attrition but reasons for loss of follow up explained • All subjects from initiation of study to final outcome assessment not accounted	• >20% attrition, reasons for loss of follow up not explained

Adopted from (Shah PS and Zao J. 2009).

Appendix C. Results for risk of bias assessment of included studies

Author (year)	Confounder adjusted	Risk of biases						
		Selection	Exposure assessment	Outcome assessment	Confounder adjustment	Analytical	Attrition	Overall
Aggazzotti *et al*. (2004)	Maternal educational background, smoking habits, water intake, sex of the child, home cooking, tobacco exposure.	None	low	None	Low	low	low	low
Botton *et al.* (2015)	Parity, maternal smoking, maternal education, maternal weight, maternal age.	Low	none	None	low	low	low	low
Bove *et al*. (1995)	Maternal educational background, maternal race, maternal age, prenatal care, sex of the child.	Low	low	None	low	low	low	low
Ca *et al*. (2016)	Gestational age, prenatal body mass index (BMI), weight gain during pregnancy, sex of the child, Maternal educational background, household income.	Low	None	None	Low	Low	Low	Low
Costet *et al*. (2011)	Maternal age, maternal educational background, Employment status, gestational age, marital status, hypertension before or during pregnancy, and smoking and drinking habits, parity, pregnancy BMI and diabetes before or during pregnancy.	None	None	None	None	Low	Low	Low
Danileviciute *et al*. (2012)	Gestational age, marital status, maternal educational background, maternal smoking habits, paternal smoking habits, alcohol consumption, BMI, blood pressure, ethnic group, pregnancy history, sex of the child, parity, marital status, and birth year.	None	None	None	None	low	Low	Low
Doods *et al.* (1999)	Maternal age, parity, maternal smoking habits, prenatal care, neighbourhood family income, sex of the child, pre-pregnancy weight, predelivery weight.	Low	Low	None	Low	low	low	low
Gallagher *et al*. (1998)	Maternal smoking, parity, maternal age, maternal education, marital status, employment during pregnancy and prenatal care.	Low	Low	None	Low	low	low	Low

Appendix C. (continue)

Author (year)	Confounder adjusted	Risk of biases						
		Selection	Exposure assessment	Outcome assessment	Confounder adjustment	Analytical	Attrition	Overall
Grazuleviciene *et al*. (2011)	Family status, maternal educational background, smoking habits, alcohol consumption, BMI, blood pressure, ethnic group, previous preterm, sex of the child, birth year.	None	Low	None	Low	Low	Low	Low
Hinckley *et al*. (2005)	Maternal age, race, ethnicity, maternal educational background, parity, smoking habits, prenatal care.	None	Low	None	Low	low	low	Low
Hoffman *et al.* (2008)a	Maternal age, maternal race/ethinicity, maternal educational level, annual household income, employed during pregnancy, marital status, pre-pregnancy BMI, daily caffeine intake, parity.	Low	Low	None	None	None	Low	Low
Hoffman *et al*. (2008)b	Maternal age, maternal race/ethinicity, educational level, annual household income, employed during pregnancy, marital status, pre-pregnancy BMI, daily caffeine intake, parity	None	None	None	None	None	Low	Low
Horton et al. (2011)	Maternal age, maternal race race/ethinicity, marital status, maternal educational level, smoking habits, alcohol consumption, parity.	Low	None	None	Low	Low	Low	Low
Ilieka-Priouzeau *et al*. (2015)	Pre-pregnancy BMI, preeclampsia during pregnancy, gestational diabetes, uterine bleeding at the beginning of the pregnancy, parity, mother's height, age, and maternal educational level, marital status, maternal alcohol consumption during pregnancy, prematurity.	None	none	None	None	Low	Low	Low
Iszatt *et al*. (2014)	Sex of the child, parity, maternal age.	Low	Low	Low	Low	Low	Low	Moderate
Kogevinas *et al*. (2016)	Study center/area, infant sex, gestational age linear and quadratic term, mother's ethnicity and parity. Maternal age, maternal height, maternal pre-pregnancy weight, maternal education and maternal smoking during pregnancy.	None	None	None	None	None	Low	Low
Kumar *et al*. (2014)	Maternal age, maternal race/ethnicity, maternal educational level, employment status, smoking habits, prenatal care utilization, sex of the child.	Low	Low	None	Low	None	Low	Moderate

Appendix C. (continue)

Author (year)	Confounder adjusted	Risk of biases						
		Selection	**Exposure assessment**	**Outcome assessment**	**Confounder adjustment**	**Analytical**	**Attrition**	**Overall**
Levallois *et al*. (2012)	Maternal age, maternal race/ethnicity, maternal educational level, annual household income, employment status, marital status, pre-pregnancy BMI, parity, history of chronic disease, medical problem during pregnancy, maternal smoking habits during pregnancy, coffee and alcohol consumption, risky occupational exposure.	None	Low	None	None	none	none	Low
Lewis *et al*. (2006)	Sex of the child, marital status, prenatal care, maternal age, maternal race/ethnicity, maternal educational level, pregnancy history on adverse birth outcomes, maternal smoking habits during pregnancy, conception season, birth season, average per capita income, maternal chronic diseases.	None	None	None	None	None	Low	Low
Lewis *et al*. (2007)	Sex of the child, marital status, prenatal care, maternal age, maternal race/ethnicity, maternal educational level, pregnancy history on adverse birth outcomes, maternal smoking habits during pregnancy, conception season, birth season, average per capita income, maternal chronic diseases.	none	None	None	None	None	Low	Low
Maclehose *et al*. (2008)	Maternal age, maternal race/ethnicity, maternal educational level, marital status, Income, smoking habits, BMI, vitamin use.	None	None	None	Low	low	low	moderate
Patelarou *et al.* (2011)	Maternal age, maternal educational level, smoking habits during pregnancy, marital status, maternal race/ethnicity, parity, sex of the child.	None	None	None	Low	None	Low	Low

Appendix C. (continue)

Author (year)	Confounder adjusted	Risk of biases						
		Selection	**Exposure assessment**	**Outcome assessment**	**Confounder adjustment**	**Analytical**	**Attrition**	**Overall**
Rivera-N´u˜nez and Wright (2013)	Maternal age, maternal race/ethnicity, maternal educational level, smoking habits, parity, income, marital status, maternal chronic diseases, previous adverse pregnancy outcomes, weight gain during pregnancy, prenatal care.	None	None	None	None	none	Low	low
Savitz *et al.* (1995)	Maternal age, maternal race/ethnicity, maternal educational level, marital status, income, smoking habits, alcohol and caffeine consumption, BMI, age at menarche, employment status, diabetes, vitamin use.	None	None	None	none	low	low	Low
Savitz *et al*. (2006)	Maternal age, maternal race/ethnicity, maternal educational level, marital status, income, smoking habits, alcohol and caffeine consumption, BMI, age at menarche, employment status, diabetes, vitamin use, induced abortion history.	None	None	None	None	None	Low	Low
Summerhayes *et al*. (2012)	Sex of the child, child birth year, season of birth, age of pregnancy at first antenatal care visit, maternal smoking habits, maternal age, maternal country of birth, previous pregnancy history, maternal chronic diseases, socioeconomic status (SES).	None	Moderate	Low	None	None	Low	moderate
Toledono *et al*. (2004)	Sex and maternal age.	None	moderate	Low	Moderate	low	low	Moderate
Villanueva *et al*. (2011)	Maternal age, maternal height, pre-pregnancy weight, maternal educational level, marital status, parity, and maternal country of origin and paternal weight, smoking habits, gestational age.	None	None	None	Low	low	low	Low

Appendix C. (continue)

Author (year)	Confounder adjusted	Risk of biases						
		Selection	**Exposure assessment**	**Outcome assessment**	**Confounder adjustment**	**Analytical**	**Attrition**	**Overall**
Waller *et al*. (1998)	Gestational age, maternal age, smoking habits, history of pregnancy loss, maternal race/ethnicity and employment during pregnancy.	None	None	None	low	low	low	low
Wright *et al*. (2004)	Maternal chronic diseases, marital status, previous adverse pregnancy outcomes, maternal educational level, parity, prenatal care, and smoking habits, gestational age, maternal age, maternal race/ethnicity, Sex of the child, Median household, weight gain during pregnancy.	None	None	None	none	none	low	Low
Yang *et al.* (2004)	Maternal age, marital status, maternal educational level, sex of the child.	None	Moderate	Low	low	low	low	Moderate
Yang *et al.* (2007)	Maternal age, marital status, maternal educational level, sex of the child	None	Moderate	Low	Low	None	low	Moderate
Zhou *et al.* (2012)	Sex of the child, gestational age, maternal age, maternal educational level, parity, maternal disease factor presents, BMI, monthly family income, maternal smoking status, and passive smoking during pregnancy, alcohol consumption during pregnancy.	None	none	None	none	none	low	Low