Impact of prenatal triclosan exposure on gestational age and anthropometric measures at birth: A systematic review and meta-analysis

Mehri Khoshhali¹, Mohammad Mehdi Amin^{2,3}, Ali Fatehizadeh^{2,3}, Afshin Ebrahimi^{2,3}, Ensiyeh Taheri^{2,3}, Roya Kelishadi¹ ¹Department of Pediatrics, Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran, ²Environment Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran, ³Department of Environmental Health Engineering, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran

Background: Exposure to endocrine disrupting chemicals such as triclosan (TCS) leads to disrupting the endocrine system and consequently effect on the birth outcomes. The findings of studies in this field are controversial. **Materials and Methods:** This systematic review and meta analysis was conducted based on the identified published papers in Scopus, Web of Science, and PubMed up to November 2019. All steps, including searching, screening, data extracting, and quality assessment, were done by two independent researchers. **Results:** Finally 15 published papers selected. The number of participants in whom the association of TCS exposure was assessed with birth weight, birth length, birth head circumference, and gestational age were 9112, 4311, 2854, and 3181 mother infant pairs, respectively. The pooled analysis showed that TCS exposure during pregnancy leads to increasing the birth weight for boys with β = 3.97 and 95% confidence interval (CI) (-3.98, 11.92), and girls with β = 5.37, 95% CI (-6.00, 16.75), but the association was not statistically significant. In addition, according to fixed effects models, the TCS exposure was not significantly associated with birth length (-0.008, 95% CI [-0.049, 0.034]), birth head circumference (-0.01, 95% CI [-0.08, 0.06]), and gestational age (-0.005, 95% CI [-0.017, 0.006]). Likewise, analysis for data segregated by gender of infants revealed similar results. **Conclusion:** The obtained results depicted that the TCS exposure with variation of birth length, head circumference, and gestational age duration. In fact, the results showed the evidence of null associations between maternal TCS exposure and birth outcomes.

Key words: Birth length, birth weight, gestational age, head circumstance, triclosan

How to cite this article: Khoshhali M, Amin MM, Fatehizadeh A, Ebrahimi A, Taheri E, Kelishadi R. Impact of prenatal triclosan exposure on gestational age and anthropometric measures at birth: A systematic review and meta-analysis. J Res Med Sci 2020;25:61.

INTRODUCTION

Birth outcomes, such as birth weight, birth length, birth head circumference, abdominal circumference, and gestational age, have been associated with an increase in newborn's morbidity and mortality and the risk of disability, cerebral palsy, visual problems, learning disabilities, and respiratory problems.^[1-3]

Access	this article online
Quick Response Code:	Website: www.jmsjournal.net
	DOI: 10.4103/jrms.JRMS_918_19

The causes of adverse birth outcomes such as low birth weight and small for gestational age are multifactorial and are not clear yet. Exposures to chemicals with estrogenic and/or antiandrogenic effects can disrupt the endocrine system functions, i.e., endocrine-disrupting chemicals (EDCs) such as phenolic compounds might affect birth outcomes through different hormone-related mechanisms.^[4,5]

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

Address for correspondence: Dr. Ensiyeh Taheri, Department of Environmental Health Engineering, School of Health, Isfahan University of Medical Sciences, Hezar Jarib Ave, Azadi Squre, Isfahan 73461-81746, Iran. E-mail: e_taheri_83@yahoo.com

Prof. Roya Kelishadi, Pediatrics Department, Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Hezar Jarib Ave, Azadi Squre, Isfahan 73461-81746, Iran. E-mail: roya.kelishadi@gmail.com

Submitted: 11-Dec-2019; Revised: 27-Jan-2020; Accepted: 19-Feb-2020; Published: 30-Jun-2020

Phenolic compounds include various classes of chemicals including parabens, triclosan (TCS), and bisphenols. They are the common components used in consumer products that have tendency to cause hormonal disturbances during *in utero* and *ex utero* development.^[4,6] Exposure to these compounds usually occurs using personal care products in adults. The presence of these compounds in blood, milk, and amniotic fluid can be the exposure route for embryo and infants.^[6,7]

In several consumer products including toothpaste, mouthwash, disinfectants, and soaps, the TCS is used as a bactericide and fungicide agent. Due to the widespread usage of consumer products, the people are broadly exposed to TCS through both ingestion and dermal route. Conducted studies on the US and China national population reported that in 74% and 98.2% of urine samples, TCS was detected.^[8,9] In addition, TCS was detected in other biological fluids such blood and breast milk. The endocrine-disrupting properties of TCS include the influence of the antiandrogenic activity and thyroid hormone function.^[4,7]

From 2008 up to now, numerous studies have been conducted to investigate the likelihood relationship of prenatal TCS exposure and birth outcomes. Different results were reported for the associations of TCS concentrations with birth outcomes such as birth weight and length, as well as gestational age.^[10-12]

Taken together, exposure to TCS during intrauterine life may influence fetal growth and consequently birth outcomes; however, controversial findings led to uncertainty in this regard.

In brief, the associations between maternal TCS exposure and newborn's birth size remain unclear. The previous studies demonstrated the positive or negative direction of association and sex-specific differences which have been not well proved. Therefore, in this study, we systematically reviewed the current literatures and conducted a meta-analysis to find the association between maternal TCS exposure and birth weight, birth length, birth head circumference, and gestational age.

METHODS

This review was done based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews.^[13]

Eligibility criteria

Study requirements

Studies with a cohort and cross-sectional design were included. No restrictions on publication date and language were applied in the search date until November 2019.

Participants, exposure, and outcome measures

To evaluate the association between TCS exposure of pregnant women and birth outcomes, the mother–infant pairs were considered. The pregnant women participating in studies were healthy women in each stage of pregnancy, without any history of specific illnesses or long-term use of medications. The maternal urinary TCS during pregnancy as a TCS exposure biomarker and also the infant characteristics including birth weight, birth length, birth head circumstance, and gestational age were targeted birth outcomes. Studies with a cohort and cross-sectional design were included only if they met the inclusion criteria and studies with any intervention were excluded. The presented data in full text of selected manuscripts and their appendices were used for meta-analysis.

Information sources and search strategy

The comprehensive search in electronic bibliographic databases including Scopus, Web of Science, and PubMed was carried out. The following terms using Medical Subject Headings (MeSH) comprise "birth outcome" OR "fetal growth" OR "birth weight" OR "birth size" OR "Fetal Macrosomia" OR "gestational age" OR "preterm birth" AND "Triclosan" and their relating terms and various words encompassing them were used as keywords for searching in database. For achieving a thorough list of all researches covering these combinations of keywords, truncations such as AND and OR were used based on Boolean logic.^[14] More details on search strategy are presented in Supplementary Table 1.

Data management, screening process, data extraction, and quality assessment

For data management, the EndNote software X8 (Thomson Scientific, USA) was used. After duplicates removal from EndNote library, the screening was done as follows:

- Titles and abstracts checking: Two independent researchers screened the studies based on their title and abstract. The irrelevant studies were removed, and when there is a doubt about an article, researchers decided after discussing, otherwise it was postponed to the next stage.
- Full-text checking: The full-text articles identified in the previous stage were checked based on inclusion criteria, and the data collection form was completed for each paper in this stage and contains first author's last name, year of publication, study location, sample size, and outcomes. To find additional related studies, the reference lists of included papers were checked.

The published checklist by the National Heart, Lung and Blood Institute for Quality Assessment of Observational Cohort and Cross-sectional Studies was used by two reviewers to assess the risk of bias of the included papers based on the scoring system.^[15] The checklist contains 14 questions about research question or objectives, population specification and definition, participation rate, recruitment and uniformity, sample size, priority of exposure and outcome, timeframe, exposure categorizing, independent variables, definition and assessment, outcome measures and blinding, attrition bias, and control of confounding. The studies were rated as either good, fair, or poor based on the mentioned criteria.^[16]

Statistical analysis

The regression (β) coefficient values of selected studies were applied for pooled analysis. The potential heterogeneity across studies was evaluated using the Cochran's *Q*-test and expressed using the *I*² index. The pooled results were calculated by the fixed-effects model (for *I*² < 50%) or the random-effects model (for *I*² > 50%). Publication bias was evaluated by the Egger's and Begg's tests.^[17] All statistical analyses were conducted using software Stata 12.0 (StataCorp, College Station, Texas, USA).

RESULTS

From 149 identified studies, 15 studies were included in the meta-analysis after title, abstract, and full-text checking [Figure 1]. All these studies had evaluated the effect of prenatal TCS exposure on at least one of the birth outcomes including birth weight, birth length, birth head circumference, and gestational age and were conducted in

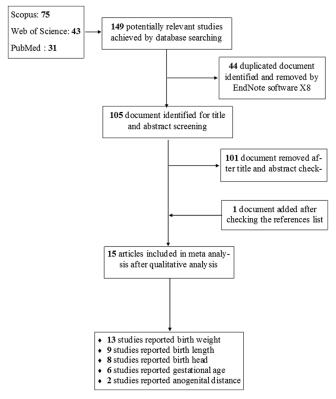


Figure 1: The study selection process in brief

different countries without any geographical restriction. From 15 selected studies, 12 studies were cohort and 3 studies were cross-sectional studies. The number of studies that reported the association of TCS exposure with birth weight, birth length, birth head, and gestational age was 13,^[4,7,10-12,18-25] 9,^[4,6,7,11,12,18,22,23,26] 8,^[4,6,7,12,18,19,22,26] and 6,^[4,6,11,12,22,25] respectively. All studies had evaluated the prenatal exposure to TCS and growth in both male and female neonates, except 2 studies that investigated it in male infants.^[18,21]

More details related to the included studies are available in Table 1. The results (after the agreement between both independent researchers) of the quality assessment for included studies are summarized in Table 2 and showed that all included studies had good quality and low risk of bias.

Effect of prenatal triclosan exposure on birth weight

Of the 13 studies that have reported the relationship of TCS exposure and birth outcomes,^[4,7,10-12,18-25] two studies have included only male infants^[18,21] and the remaining studies have investigated both male and female infants. Moreover, 4 studies reported the birth weight Z-score.^[22-25] The total population from 13 included studies was 9112 mother-infant pairs. The pooled analysis of TCS exposure was associated with the increased birth weight for boys and girls, 3.97, 95% confidence interval (CI) (-3.98, 11.92), and 5.37, 95% CI (-6.00, 16.75), respectively, and decreased birth weight for both - 0.032, 95% CI (-11.59, 11.53), using the random-effects models. However, none of these effects were significant. A significant heterogeneity was detected for the meta-analysis of effect TCS exposure on birth weight for total ($I^2 = 54.0\%$, P = 0.043) [Figure 2]. In addition, the pooled effect of TCS exposure on birth weight Z-score was not also significant for girls, boys,

Study ID	ES (95% Cl)	% Weigh
Boys		
Philippat C (2016)	4.60 (-49.05, 58.25)	0.99
Lassen TH (2016)	-5.20 (-18.55, 8.15)	8.33
Huo W (2018)	1.54 (-16.23, 19.31)	6.05
Lester F; Naïve (2018)	18.67 (1.45, 35.89)	6.28
Lester F; BLUP (2018)	19.11 (-5.19, 43.41)	3.91
Ouyang F (2018)	0.03 (-26.02, 26.08)	3.51
Philippat C (2019)	-1.98 (-18.03, 14.07)	6.84
Ding G (2017)	• 89.72 (-59.43, 238.87)	0.14
Subtotal (I-squared = 13.0%, p = 0.329)	3.97 (-3.98, 11.92)	36.04
Girls		
Lassen TH (2016)	4.70 (-7.45, 16.85)	9.09
Huo W (2018)	-10.99 (-28.18, 6.20)	6.30
Lester F; Naïve (2018)	5.82 (-11.98, 23.62)	6.03
Lester F; BLUP (2018)	6.97 (-13.99, 27.93)	4.85
Ouyang F (2018)	37.20 (6.90, 67.50)	2.75
Subtotal (I-squared = 47.8%, p = 0.105)	5.37 (-6.00, 16.75)	29.02
Total		
Huo W (2018) 🔶	-4.71 (-17.11, 7.69)	8.93
Lester F; Naïve (2018)	11.85 (-0.47, 24.17)	8.98
Lester F; BLUP (2018)	13.28 (-2.86, 29.42)	6.79
Messerlian C (2018)	-38.00 (-76.00, -0.00)	1.86
Philippat C (2012)	-6.00 (-31.00, 19.00)	3.74
Wolff MS (2008)	-11.00 (-33.50, 11.50)	4.38
Ding G (2017)	* 72.79 (-35.38, 180.96)	
Subtotal (I-squared = 54.0%, p = 0.043)	-0.03 (-11.59, 11.53)	34.94
Overall (I-squared = 34.2%, p = 0.068)	3.38 (-2.13, 8.88)	100.00
NOTE: Weights are from random effects analysis		
-	200	
-239 0	239	

Figure 2: Forest plot of beta-coefficients for the effect of triclosan exposure on birth weight by gender

Khoshhali, et al.: Prenatal triclosan exposure and birth outcomes

Table 1: Characteri	stics of t	the studies in			
Author, year	Country	Participants	Maternal urine sampling time	Outcomes	Study type
Wolff et al., 2008 ^[12]	USA	Mothers and infants	Third trimester	Birth weight - birth length - head circumference - gestational age	Cohort study
Philippat <i>et al.</i> , 2014 ^[18]	France	Mother-son	Second or third trimester	Birth weight - birth length - head circumference	Cohort study
Lassen <i>et al</i> ., 2016 ^[7]	Denmark	Mothers and infants	Third trimester	Birth weight - birth length - head circumference - abdominal circumference - anogenital distance	Cohort study
Ding <i>et al.</i> , 2017 ^[4]	China	Mothers and infants	Delivery time	Birth weight - birth length - head circumference - gestational age - ponderal index	Cross-sectional study
Etzel <i>et al.</i> , 2017 ^[22]	USA	Mothers and infants	Second and third trimesters	Birth weight - birth length - head circumference - gestational age	Cohort study
Geer <i>et al.</i> , 2017 ^[6]	USA	Mothers and infants	third trimester	Birth weight - birth length - head circumference - gestational age	Cohort study
Ferguson <i>et al.</i> , 2018 ^[23]	USA	Mothers and infants	Second and/or third trimester	Birth weight - birth length	Cohort study
Huo <i>et al.</i> , 2018 ^[11]	China	Mothers and infants	Delivery time	Birth weight - birth length - gestational age	Cross-sectional study
Lester <i>et al.</i> , 2018 ^[10]	Canada	Mothers and infants	First or second trimester	Birth weight - low birth weight - small for gestational age - large for gestational age	Cohort study
Messerlian <i>et al.</i> , 2018 ^[19]	USA	Mothers and infants	Cannot determine	Birth weight - head circumference	Cohort study
Ouyang <i>et al.</i> , 2018 ^[20]	China	Mothers and infants	Delivery time	Birth weight - gestational diabetes mellitus	Cross-sectional study
Wu <i>et al.</i> , 2018 ^[24]	China	Mothers and infants	First, second, and third trimesters	Birth weight - birth length	Cohort study
Aker <i>et al.</i> , 2019 ^[25]	USA	Mothers and infants	Second and third trimesters	Birth weight - gestational age	Cohort study
Philippat et al., 2019 ^[21]	France	Mother-son	Second or third trimester	Placental weight - birth weight - placental-to-birth weight ratio	Cohort study
Philippat <i>et al.</i> , 2012 ^[26]		Mother-son	First or second or third trimester	Birth weight - birth length - head circumference	Cohort study

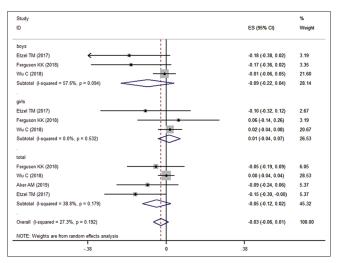


Figure 3: Forest plot of beta-coefficients for the effect of triclosan exposure on birth weight Z-score by gender

and total. The heterogeneity was not significant for them (P > 0.05) [Figure 3]. The P values for Begg's test and Egger's test for birth weight were 0.538 and 0.419, respectively, that revealed no obvious publication bias among these studies. However, Begg's test and Egger's test for birth weight Z-score suggested publication bias, P < 0.001, respectively. Trim-and-fill analysis was conducted, but no study was filled. This showed that the publication bias had a nonsignificant effect on the results.

Effect of prenatal triclosan exposure on birth length

Birth length association with prenatal TCS exposure was investigated in 9 studies.^[4,6,7,11,12,18,22,23,26] Except Philippat *et al.*'s study,^[18] all other studies survived both genders of infants and contain 4311 mother–infant pairs.

The pooled analysis of TCS exposure was not significantly associated with the birth length for boys (0.016, 95% CI [-0.029, 0.062]), girls (-0.02, 95% CI [-0.062, 0.022]), and total (-0.008, 95% CI [-0.049, 0.034]) based on fixed-effects models. Furthermore, there was no significant heterogeneity for them [Figure 4]. Begg's test and Egger's test revealed no obvious publication bias among these studies; the *P* values for these tests were >0.05 (*P* = 0.558 and 0.124, respectively).

Effect of prenatal triclosan exposure on birth head circumference

The extracted data from 8 studies^[4,6,7,12,18,19,22,26] related to effect TCS exposure on birth head and covering 2854

Table 2: Quality assessment of included studies							
Criteria	Wolff 200	Wolff <i>et al.</i> , Philippat 2008 ^[12] <i>et al.</i> , 2014 ^[18]	t Lassen ^[18] <i>et al.</i> , 2016 ^[7]	Ding <i>et al.</i> , 7 2017 ^[4]	, Etzel <i>et al</i> ., 2017 ^[22]	Geer <i>et al.</i> , 2017 ^[6]	Ferguson <i>et al.</i> , 2018 ^[23]
1. Was the research question or objective in this paper clearly stated?	Xe	Yes Yes		Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Xe	Yes Yes	Yes	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	Xe	Yes Yes	Yes	Yes	Yes	Yes	Yes
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion being in the study prespecified and applied uniformly to all participants?	imilar exclusion criteria for pants?	Yes Yes	Yes	Yes	Yes	Yes	Yes
5. Was a sample size justification, power description, or variance and effect provided?	and effect estimates Ye	Yes Yes	Yes	Yes	Yes	Yes	Yes
6. For the analyses in this paper, were the exposure (s) of interest measured prior to the outcome (s) being measured?		Yes Yes	Yes	Yes	Yes	Yes	Yes
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?		CD CD	CD	CD	CD	CD	CD
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure or exposure measured as continuous variable)?		Yes Yes	Yes	Yes	Yes	Yes	Yes
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?		Yes Yes	Yes	Yes	Yes	Yes	Yes
10. Was the exposure (s) assessed more than once over time?	Z	No No	No	No	yes	No	No
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?		Yes Yes	Yes	Yes	Yes	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?		Yes Yes	Yes	Yes	Yes	Yes	Yes
13. Was loss to follow-up after baseline 20% or less?	Xe	Yes Yes	Yes	Yes	Yes	Yes	Yes
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure (s) and outcome (s)?		Yes No	Yes	Yes	Yes	Yes	Yes
Criteria Huc 20	Huo et al., Lester et al., 2018 ^[11] 2018 ^[10]	al., Messerlian et al., 2018 ^[19]	Ouyang <i>et al</i> ., 2018 ^[20]	Wu <i>et al.</i> , 2018 ^[24]	Aker <i>et al.</i> , 2019 ^[25]	Philippat <i>et al.</i> , 2019 ^[21]	Philippat et al., 2012 ^[26]
1. Was the research question or objective in this paper clearly stated?	Yes Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	Yes Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes Yes	Yes	Yes	Yes	Yes	Yes	Yes
 Was a sample size justification, power description, or variance and effect estimates provided? 	Yes Yes	Yes	Yes	Yes	Yes	Yes	Yes
 For the analyses in this paper, were the exposure (s) of interest measured prior to the outcome (s) being measured? 	Yes Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	CD	CD	CD	CD	CD	CD	CD

5

Contd...

Table 2: Contd								
Criteria	Huo <i>et al.</i> , 2018 ^[11]	Lester <i>et al.</i> , 2018 ^[10]	Messerlian <i>et al.</i> , 2018 ^[19]	Ouyang <i>et al</i> ., 2018 ^[20]	Wu <i>et al.</i> , 2018 ^[24]	Aker <i>et al</i> ., 2019 ^[25]	Philippat et al., 2019 ^[21]	Philippat et al., 2012 ^[26]
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure or exposure measured as continuous variable)?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
 Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? 	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Was the exposure (s) assessed more than once over time?	No	No	No	No	yes	No	No	No
 Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? 	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13. Was loss to follow-up after baseline 20% or less?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure (s) and outcome (s)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CD: Cannot determine								

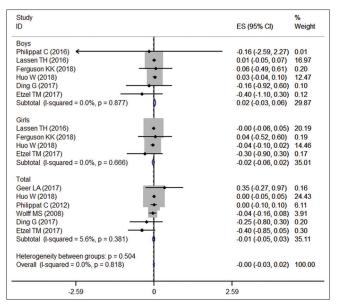


Figure 4: Forest plot of beta-coefficients for the effect of triclosan exposure on birth length by gender

mother–infant pairs were used. The pooled analysis of TCS exposure was associated with the decreased birth head for boys – 0.04, 95% CI (–0.10, 0.01); –0.02, 95% CI (–0.05, 0.01), for girls; and – 0.01, 95% CI (–0.08, 0.06), for both using the random-effects models. However, none of these effects were significant. A significant heterogeneity was detected for the meta-analysis of effect TCS exposure on birth head for total ($I^2 = 55.8\%$, P = 0.045) [Figure 5]. Begg's test and Egger's test revealed no obvious publication bias among these studies; the P values for these tests were >0.05 (P = 0.330 and 0.308, respectively).

Effect of prenatal triclosan exposure on gestational age

The pooled analysis of extracted data from 6 studies^[4,6,11,12,22,25] explained that the TCS exposure of 3181 pregnant women and gestational age of their infants showed that TCS exposure was not significantly associated with the gestational age for boys (-0.028, 95% CI [-0.068, 0.012]), girls (-0.028, 95% CI [-0.063, 0.007]), and total (-0.005, 95% CI [-0.017, 0.006]) based on fixed-effects models. Furthermore, there was no significant heterogeneity for them [Figure 6]. The *P* values for Begg's test and Egger's test were 0.436 and 0.534, respectively. Therefore, there was no publication bias among these studies (P > 0.05).

Effect of prenatal triclosan exposure on anogenital distance Anogenital distance (AGD) refers to the distance from the anus to the genitals in neonatal as a sexually dimorphic was studied in 2 included studies. The prenatal TCS exposure does not have any association with AGD in girls in both studies, but its effect on reduced AGD at 3 months of age in boys was significant (P < 0.10), as reported Lassen *et al.*^[7,27]



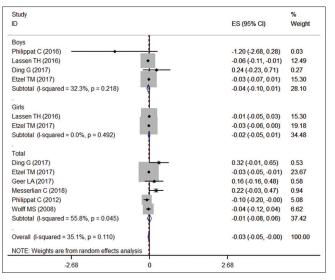


Figure 5: Forest plot of beta-coefficients for the effect of triclosan exposure on birth head by gender

DISCUSSION

The present study is focused solely on reviewing the studies that have investigated the association of prenatal exposure to TCS with birth outcomes. We performed a comprehensive search of PubMed, Web of Science, and Scopus databases using a well-defined search strategy and with no language and time restrictions applied.

After duplicates removal and studies screening, 15 remained studies were systematically reviewed to determine the association of prenatal TCS exposure with birth outcomes. In all included studies, the maternal TCS urinary concentration was considered as a biomarker of the pregnant women's exposure to TCS.

For accounting the unpublished studies, the publication bias was investigated. The Begg's and Egger's tests for birth weight, birth length, birth head circumference, and gestational age were revealed no obvious publication bias. However, the Begg's and Egger's tests for birth weight Z-score were suggested significant publication bias. In addition, trim-and-fill analysis resulted that the publication bias had no significant effect on the obtained results.

Our study revealed the association between maternal TCS exposure and increasing birth weight for boys and girls, but the association was not statistically significant. However, maternal TCS exposure does not have any significant effect on birth weight, length, head circumference, and gestational age.

TCS is a phenol derivative that, unlike other phenolic compounds, is identified as a safe and tolerable compound with low acute toxicity. The main mechanism suggested for

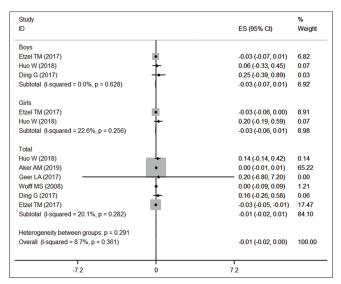


Figure 6: Forest plot of beta-coefficients for the effect of triclosan exposure on gestational age by gender

describing how TCS can affect the fetal growth is as follows: disrupting the levels of thyroid hormones through increasing their hepatic metabolism.^[4,22] The mentioned mechanism is the suggested mechanism based on animal studies.^[28,29] The effect of TCS on thyroid hormones is inconsistent, and reported associations in human studies included the positive, negative, or nonexistent association.^[8,30-32]

Thyroxin availability is an effective factor on the fetus growth and development, and the fetus is dependent on maternal thyroxin during the first trimester and the function of the fetal thyroid starts after the 12nd week of gestation. However, the fetus gain the most weight during the third trimester of pregnancy. The urine samples collected around the 28th week of pregnancy may be better for the assessment of fetal growth effects. The half-life of TCS is <24 h, and as a short-lived compound, its concentration varies during and across days. This fluctuation is higher in spot urine samples than in long-term samples.^[7,22,33] At all included studies in the current review, the spot urine samples that were derived dominantly in the second and third trimesters and rarely in the first trimester were used for exposure assessment. It seems that a single spot urine sample cannot clearly reflect the average of exposure to the TCS during the entire pregnancy. It can be the possible reason for controversial results reported for the association of prenatal exposure to TCS with birth outcomes.

The limitation related to current review are including: the urine sampling in different pregnancy stages in various study and once sampling in most of studies.

CONCLUSION

The present systematic review showed no significant association between maternal exposure to TCS and birth

outcomes. According to obtained results, we recommend the conduction of more studies on TCS detection in diverse biological matrixes (blood, cord blood, urine, and placenta) and in diverse pregnancy stages to evaluate the effect of TCS exposure during pregnancy on birth outcomes. Due to the limitation of these studies, it is wise to limit TCS exposure in pregnancy, especially in the maternal period.

Acknowledgments

The authors would like to thank the Isfahan University of Medical Sciences of Iran (Project No. 298243 and Ethics code: IR.MUI.RESEARCH.REC.1398. 674) for the financial support of this work.

Financial support and sponsorship

This study was financially supported by the Isfahan University of Medical Sciences.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- 1. Kinney MV, Lawn JE, Howson CP, Belizan J. 15 million preterm births annually: What has changed this year? Reprod Health 2012;9:28.
- Setiawan C. Background Paper 6.23 Neonatal Conditions. Priority Medicines for Europe and the World a Public Health Approach to Innovation; 2013. p. 1-50.
- Tough SC, Schopflocher D, Svenson L. Maternal Risk Factors in Relationship to Birth Outcome: Report: Health Surveillance. Canada: Alberta Health and Wellness; 1999.
- 4. Ding G, Wang C, Vinturache A, Zhao S, Pan R, Han W, *et al.* Prenatal low-level phenol exposures and birth outcomes in China. Sci Total Environ 2017;607-608:1400-7.
- Weng YH, Yang CY, Chiu YW. Risk assessment of adverse birth outcomes in relation to maternal age. PLoS One 2014;9:e114843.
- Geer LA, Pycke BFG, Waxenbaum J, Sherer DM, Abulafia O, Halden RU. Association of birth outcomes with fetal exposure to parabens, triclosan and triclocarban in an immigrant population in Brooklyn, New York. J Hazard Mater 2017;323:177-83.
- Lassen TH, Frederiksen H, Kyhl HB, Swan SH, Main KM, Andersson AM, *et al.* Prenatal triclosan exposure and anthropometric measures including anogenital distance in danish infants. Environ Health Perspect 2016;124:1261-8.
- Ley C, Pischel L, Parsonnet J. Triclosan and triclocarban exposure and thyroid function during pregnancy-A randomized intervention. Reprod Toxicol 2017;74:143-9.
- 9. Wang X, Ouyang F, Feng L, Wang X, Liu Z, Zhang J. Maternal urinary triclosan concentration in relation to maternal and neonatal thyroid hormone levels: A prospective study. Environ Health Perspect 2017;125:067017.
- 10. Lester F, Arbuckle TE, Peng Y, McIsaac MA. Impact of exposure to phenols during early pregnancy on birth weight in two Canadian cohort studies subject to measurement errors. Environ Int 2018;120:231-7.
- 11. Huo W, Xia W, Wu C, Zhu Y, Zhang B, Wan Y, *et al*. Urinary level of triclosan in a population of Chinese pregnant women and its

association with birth outcomes. Environ Pollut 2018;233:872-9.

- Wolff MS, Engel SM, Berkowitz GS, Ye X, Silva MJ, Zhu C, *et al.* Prenatal phenol and phthalate exposures and birth outcomes. Environ Health Perspect 2008;116:1092-7.
- Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Ann Intern Med 2009;151:264-9.
- 14. Basu A. How to Conduct Meta-Analysis: A Basic Tutorial; 2017.
- National Heart Lung and Blood Institute. Quality Assessment tool for Observational Cohort and Cross-Sectional Studies. National Heart Lung and Blood Institute; 2019.
- Diez-Fernández A, Álvarez-Bueno C, Martínez-Vizcaíno V, Sotos-Prieto M, Recio-Rodríguez JI, Cavero-Redondo I. Total dairy, cheese and milk intake and arterial stiffness: A systematic review and meta-analysis of cross-sectional studies. Nutrients 2019;11:1-4.
- Borenstein M, Hedges L, Higgins J Rothstein HR. Introduction to Meta-analysis. Chichester, UK: John Wiley and Sons; 2009. p. 9
- Philippat C, Botton J, Calafat AM, Ye X, Charles MA, Slama R, *et al.* Prenatal exposure to phenols and growth in boys. Epidemiology 2014;25:625-35.
- 19. Messerlian C, Mustieles V, Minguez-Alarcon L, Ford JB, Calafat AM, Souter I, *et al.* Preconception and prenatal urinary concentrations of phenols and birth size of singleton infants born to mothers and fathers from the Environment and Reproductive Health (EARTH) study. Environ Int 2018;114:60-8.
- 20. Ouyang F, Tang N, Zhang HJ, Wang X, Zhao S, Wang W, *et al.* Maternal urinary triclosan level, gestational diabetes mellitus and birth weight in Chinese women. Sci Total Environ 2018;626:451-7.
- 21. Philippat C, Heude B, Botton J, Alfaidy N, Calafat AM, Slama R, *et al.* Prenatal exposure to select phthalates and phenols and associations with fetal and placental weight among male births in the EDEN cohort (France). Environ Health Perspect 2019;127:17002.
- 22. Etzel TM, Calafat AM, Ye X, Chen A, Lanphear BP, Savitz DA, *et al*. Urinary triclosan concentrations during pregnancy and birth outcomes. Environ Res 2017;156:505-11.
- Ferguson KK, Meeker JD, Cantonwine DE, Mukherjee B, Pace GG, Weller D, et al. Environmental phenol associations with ultrasound and delivery measures of fetal growth. Environ Int 2018;112:243-50.
- 24. Wu C, Li J, Xia W, Li Y, Zhang B, Zhou A, *et al*. The association of repeated measurements of prenatal exposure to triclosan with fetal and early-childhood growth. Environ Int 2018;120:54-62.
- 25. Aker AM, Ferguson KK, Rosario ZY, Mukherjee B, Alshawabkeh AN, Cordero JF, *et al.* The associations between prenatal exposure to triclocarban, phenols and parabens with gestational age and birth weight in northern Puerto Rico. Environ Res 2019;169:41-51.
- 26. Philippat C, Mortamais M, Chevrier C, Petit C, Calafat AM, Ye X, *et al*. Exposure to phthalates and phenols during pregnancy and offspring size at birth. Environ Health Perspect 2012;120:464-70.
- 27. Arbuckle TE, Agarwal A, MacPherson SH, Fraser WD, Sathyanarayana S, Ramsay T, *et al*. Prenatal exposure to phthalates and phenols and infant endocrine-sensitive outcomes: The MIREC study. Environ Int 2018;120:572-83.
- 28. Paul KB, Hedge JM, Devito MJ, Crofton KM. Developmental triclosan exposure decreases maternal and neonatal thyroxine in rats. Environ Toxicol Chem 2010;29:2840-4.
- 29. Paul KB, Hedge JM, Bansal R, Zoeller RT, Peter R, DeVito MJ, *et al.* Developmental triclosan exposure decreases maternal, fetal, and early neonatal thyroxine: A dynamic and kinetic evaluation of a putative mode-of-action. Toxicology 2012;300:31-45.
- 30. Skarha J, Mínguez-Alarcón L, Williams PL, Korevaar TIM, de Poortere RA, Broeren MAC, *et al.* Cross-sectional associations between urinary triclosan and serum thyroid function biomarker

concentrations in women. Environ Int 2019;122:256-62.

- 31. Berger K, Gunier RB, Chevrier J, Calafat AM, Ye X, Eskenazi B, *et al.* Associations of maternal exposure to triclosan, parabens, and other phenols with prenatal maternal and neonatal thyroid hormone levels. Environ Res 2018;165:379-86.
- 32. Derakhshan A, Shu H, Peeters RP, Kortenkamp A, Lindh CH, Demeneix B, *et al*. Association of urinary bisphenols and triclosan

with thyroid function during early pregnancy. Environ Int 2019;133:105123.

33. Aylward LL, Hays SM, Zidek A. Variation in urinary spot sample, 24 h samples, and longer-term average urinary concentrations of short-lived environmental chemicals: Implications for exposure assessment and reverse dosimetry. J Expo Sci Environ Epidemiol 2017;27:582-90.

Supplementary Table 1: Search strategy in different database Search strategy Database Number of documents PubMed 31 delivery"[Title/Abstract]) OR "preterm birth*"[Title/Abstract]) OR "preterm birth" MeSH Terms]) OR "preterm delivery" [Title/Abstract]) OR "gestation* age" [Title/Abstract]) OR "gestation* time"[Title/Abstract]) OR "gestation* length"[Title/Abstract]) OR "gestation* duration"[Title/Abstract]) OR "birth weight"[Title/Abstract]) OR "birth weight"[MeSH Terms]) OR "birthweight"[Title/Abstract]) OR "neonatal weight"[Title/Abstract]) OR "neonate weight"[Title/Abstract]) OR "newborn weight"[Title/Abstract]) OR "weight at birth"[Title/Abstract]) OR "Fetal Macrosomia"[Title/Abstract]) OR "Fetal Macrosomia"[MeSH Terms]) OR "macrosomi*"[Title/Abstract]) OR "newborn overweight"[Title/Abstract]) OR "neonatal overweight"[Title/Abstract]) OR "growth restriction"[Title/Abstract]) OR "growth retardation"[Title/Abstract]) OR "intrauterine growth"[Title/Abstract]) OR "Fetal Growth Retardation"[Title/Abstract]) OR "Fetal Growth Retardation"[MeSH Terms]) OR "fetal growth"[Title/Abstract]) OR "birth size*"[Title/Abstract]) OR "birth outcome*"[Title/Abstract]) OR "obstetric* outcome*"[Title/Abstract]) OR "pregnancy outcome*"[Title/ Abstract]) OR "pregnancy outcome" [MeSH Terms]) OR "anogenital distance" [Title/Abstract]) OR "anogenital index"[Title/Abstract]) OR "anal genital distance"[Title/Abstract]) OR "anal genital distance"[Title/Abstract]) Web of (TOPIC:("premature delivery") OR TOPIC:("preterm birth*") OR TOPIC:("preterm delivery") OR 43 TOPIC: ("gestation* age") OR TOPIC: ("gestation* time") OR TOPIC: ("gestation* length") OR Science TOPIC:("gestation* duration") OR TOPIC:("birth weight") OR TOPIC:("pregnancy outcome*") OR TOPIC:("anogenital index") OR TOPIC: ("anal genital distance") OR TOPIC:("newborn weight") OR TOPIC:("anogenital distance") OR TOPIC:("Fetal Macrosomia ") OR TOPIC:("macrosomi*") OR TOPIC: ("newborn overweight") OR TOPIC: ("neonatal overweight") OR TOPIC: ("growth restriction") OR TOPIC: ("growth retardation") OR TOPIC: ("intrauterine growth") OR TOPIC: ("Fetal Growth Retardation ") OR TOPIC: ("fetal growth") OR TOPIC: ("birth size*") ORTOPIC: ("birth outcome*") OR TOPIC:("obstetric* outcome*") OR TITLE:("premature delivery") OR TITLE:("preterm birth*") OR TITLE:("preterm delivery") OR TITLE:("gestation* age") OR TITLE:("gestation* time") OR TITLE:("gestation* length") OR TITLE: ("gestation* duration") OR TITLE: ("birth weight") OR ITLE: ("pregnancy outcome*") OR TITLE: ("anogenital index") OR TITLE: ("anal genital distance") OR TITLE: ("newborn weight") OR TITLE:("anogenital distance") OR TITLE:("Fetal Macrosomia ") OR TITLE:("macrosomi*") OR TITLE: ("newborn overweight") OR TITLE: ("neonatal overweight") OR TITLE: ("growth restriction") OR TITLE: ("growth retardation") OR TITLE: ("intrauterine growth") OR TITLE: ("Fetal Growth Retardation ") OR TITLE: ("fetal growth") OR TITLE: ("birth size*") ORTITLE: ("birth outcome*") OR TITLE:("obstetric* outcome*")) AND (TOPIC: ("triclosan") OR TITLE: ("triclosan")) ((TITLE-ABS-KEY ("premature delivery") OR TITLE-ABS-KEY ("preterm birth*") OR Scopus 75 TITLE-ABS-KEY ("preterm delivery") OR TITLE-ABS-KEY ("gestation* age") OR TITLE-ABS-KEY ("gestation* time") OR TITLE-ABS-KEY ("gestation* length") OR TITLE-ABS-KEY ("gestation* duration") OR TITLE-ABS-KEY ("birth weight") OR TITLE-ABS-KEY ("birthweight") OR TITLE-ABS-KEY ("neonatal weight") OR TITLE-ABS-KEY ("neonate weight") OR TITLE-ABS-KEY ("newborn weight") OR TITLE-ABS-KEY ("weight at birth") OR TITLE-ABS-KEY ("Fetal Macrosomia") OR TITLE-ABS-KEY ("macrosomi*") OR TITLE-ABS-KEY ("newborn overweight") OR TITLE-ABS-KEY ("neonatal overweight") OR TITLE-ABS-KEY ("growth restriction") OR TITLE-ABS-KEY ("growth retardation") OR TITLE-ABS-KEY ("intrauterine growth") OR TITLE-ABS-KEY ("Fetal Growth Retardation") OR TITLE-ABS-KEY ("fetal growth") OR TITLE-ABS-KEY ("birth size*") OR TITLE-ABS-KEY ("birth outcome*") OR TITLE-ABS-KEY ("obstetric* outcome*") OR TITLE-ABS-KEY ("pregnancy outcome*") OR TITLE-ABS-KEY ("anogenital distance") OR TITLE-ABS-KEY ("anogenital index") OR TITLE-ABS-KEY ("anal genital distance") OR TITLE-ABS-KEY ("anal genital distance"))) AND (TITLE-ABS-KEY ("triclosan")