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Adverse Effect of Diclofenac Exposure during Pregnancy on Mother and Fetus; A Systematic Review

Tilahun Beyene Handiso[1], Bahailu Balcha Bachore[2], Shemsu Nuriye Hagisso[2], Markos Selamu Jifar[1]

1 Wachemo University
2 Wolaita Sodo University

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Abstract

Introduction

Since 1974, diclofenac has been used to treat the pain and swelling associated with rheumatic illnesses as a non-steroid anti-inflammatory medication (NSAID). It is one among the world's most extensively used non-steroidal anti-inflammatory medications (NSAIDs). Non-steroidal anti-inflammatory medicines have been shown to cause embryotoxicity and teratogenicity in experimental animals in a few studies, however there is no strong evidence of this impact in people.

The aim of this study was to conduct a systematic assessment of the effects of diclofenac exposure on the mother and fetus during pregnancy.

Methods

This study included all experimental, quasi-experimental, and observational research that were published in the English language and published up to the date of the review. PROSPERO (The International Prospective Register of Systematic Reviews) ID=CRD42019135608 was used to register the protocol. This study employed a three-step search technique. PubMed, Medline, SCOPUS, Web of Science, Embase, cinihal, Google, several university repositories, and Google scholar were among the databases searched. The titles and abstracts were then examined by two independent reviewers to see if they met the review's inclusion criteria. At the study level, two independent reviewers critically assessed eligible studies. The review's methodological quality was assessed at the result level using standardized critical assessment instruments from the Joanna Briggs Institute (JBI) for observational studies. Specific details about the demographics, study procedures, interventions, and outcomes of significance to the review purpose are included in the data retrieved from the studies. Due to the conclusion and type of the data, statistical pooling was not viable. As a result, the results were presented in a narrative format.

Results

A total of 1,490,679 participants were found in three relevant papers (two cohorts and nested case-control studies). Diclofenac exposure during pregnancy raises the chance of low birth weight in the fetus, as well as the risk of

spontaneous abortion and vaginal bleeding in the mother.

Conclusions

Diclofenac exposure during pregnancy has negative consequences on the fetus and the mother. As a result, taking Diclofenac during pregnancy may have negative consequences for both the mother and the fetus, and more primary Randomized Control Trials (RCTs) are needed.

Tilahun Beyene Handiso[1*], **Bahailu Balcha Bachore**[2], **Shemsu Nuriye Hagisso**[2], **Markos Selamu Jifar**[1]

[1] *Wachemo University, College of Medicine and Health Science, School of Public health, Hossana, Ethiopia*

[2] *Wolaita Sodo University, College of Medical and Health Science, School of Public Health, Wolaita Sodo, Ethiopia*

[*]**Corresponding Author:** Tilahun Beyene Handiso

Email Address: tilahunbeyene44@gmail.com

Phone: +251916356889

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Introduction

Since 1974, Diclofenac has been used to treat pain and inflammation associated with osteoporosis. It is based on benzene acetic acid non-steroidal anti-inflammatory medication (NSAID). It is used to treat rheumatic and non-rheumatic pain, fever, and inflammation.. It is found in stomach acids (25 and 50 mg), rapid cracking of the mouth (25 and 50 mg), oral solution powder (50 mg), slow and controlled excretion forms (75, 100, or 150 mg), candles (50 and 100 mg), and injectable forms (50 and 75 mg)[1][2][3][4].

Rheumatic disease in pregnancy may need therapy in order to maintain the mother's health and, as a result, support the health of the fetus. However, there is a dearth of understanding concerning the use of anti-inflammatory pharmaceuticals such as Diclofenac during pregnancy, making it difficult to provide these medications to patients. On the usage of Diclofenac during pregnancy, there is limited and conflicting information. Maternal exposure of Diclofenac during the first trimester of pregnancy indicates rapid accumulation of the drug in the fetus from the adverse effect of embryos shown in animals[5][6].

Evidence in animals' shows that exposure to Diclofenac during pregnancy had significant changes in histopathology of the vital organs, bile ducts, sinusoidal diameter, and testicular tissue have been observed[7].

Another study in experimental animals showed that oral administration of Diclofenac to pregnant mice during the premenstrual stage and the period of organogenesis resulted in significant effects on function, mortality, fetal reconstruction, and weight loss and length. Abnormal visceral and skeletal abnormalities in the fetus were observed in a

similar investigation[8].

There is no conclusive evidence that NSAIDs are safe in people[9]. A few reports have shown that non-steroidal anti-inflammatory drugs use cause fetal toxicity and teratogenicity among experimental animals but are unknown to humans[10]. Diclofenac can be taken during the first and second trimesters but not during the third trimester, according to some user manuals, while others advise against taking it at all during pregnancy. There are contradicting recommendations this is due to lack of available evidence. This demonstrates that there is evidence as well as a knowledge gap.

As a result, the purpose of this review was to conduct a systematic review of the effects of Diclofenac exposure during maternal and uterine pregnancy.

Review question

What are the effects of Diclofenac on the fetus and mother during pregnancy?

Methods

Types of studies and Inclusion criteria

Studies conducted on pregnant women with Diclofenac exposure and its effect on pregnancy. All experimental studies, quasi-experimental and observation, a complete free text available, published to date for review were considered for inclusion in this review.

This review considered experimental studies, cohort studies, case-control studies for inclusion. This review also included an explanatory case structure that included a series of cases, individual case reports, and integrated case studies. This review takes into account studies that have been published in English so far. This systematic review was carried out using JBI's systematic review of performance evidence method and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2009 guideline. (Additional file). This review was registered in PROSPERO (The International Prospective Register of Systematic Reviews) (https://www.crd.york.ac.uk/prospero/displayrecord.php) ID=CRD42019135608)

Search strategy

The search strategy was aimed to in both published and unpublished studies.The three-step search strategy was used. A preliminary limited search of Pubmed, Medline, SCOPUS, Embase, Clinical, **Web of Science, Google, Google scholar,** followed by an analysis of the text content contained in the title and abstract, in addition to the index ways of describing the article When performed on all included databases, the second step search identified keywords and index terms. When implemented on all considered databases, text words are comprised in the pertinent headings and

summarizing, in addition to the index words used to describe the article; the second step search recognized keywords and index terms. The first keywords and phrases used for searching were **“**Diclofenac “ OR “Voltaren” OR “Diclofenac Sodium]” AND “Pregnant women” OR Pregnant mothers” OR “Pregnant” AND “Effect” OR “Outcome” OR “Consequence ” OR “Result” OR “Abortion” OR “Toratogenic ” OR” Congenital malformation ”. MeSH terms (Medical Subject Headings) and Boolean operators were used to search PubMed were (((((("Effect"[Text Word] OR "Outcome"[Text Word]) OR "Consequence"[Text Word]) OR "Result"[Text Word]) OR ((((((((((((("abort"[All Fields] OR "aborted"[All Fields]) OR "aborter"[All Fields]) OR "aborters"[All Fields]) OR "aborting"[All Fields]) OR "abortion s"[All Fields]) OR "abortion, induced"[MeSH Terms]) OR ("abortion"[All Fields] AND "induced"[All Fields])) OR "induced abortion"[All Fields]) OR "abortion"[All Fields]) OR "abortions"[All Fields]) OR "abortive"[All Fields]) OR "abortively"[All Fields]) OR "abortives"[All Fields]) OR "aborts"[All Fields])) OR "Toratogenic"[Text Word]) OR "congenital malformation"[Text Word]

Third, a reference list for all reports and articles submitted for search, as well as additional references to enhance comprehensive search.English-language studies, humanities, clinical trials, comparatively published research studies to date, and full-text findings were used to filter the study findings for further evaluation. Gray text searches, including Google, various university repositories, and a Google expert have been used. (Table 1 in below appendix part)

Study selection

All related documents were gathered after a search, and duplicates were eliminated. The articles and summaries were then evaluated against the review's inclusion criteria by two reviewers. Differences of opinion within evaluators were handled with the help of a third reviewer at each stage of the study selection process.

Assessment of methodological quality

At the study level, appropriate studies were critically assessed by two reviewers. The evaluation took place at the level of quality results of the review methods using critical measurement tools based on the Joanna Briggs Institute for observation studies[11]. This decision was made in accordance with the review list's rules. From less than 50% is considered exclusion.

Data extraction

Data extracted from the study included specific information about people, study methods, interventions, and key outcomes in the purpose of the review highlighting specific details. The authors of the paper tried contacting, the studies included in this review to request missing or additional information, but there was insufficient and inaccurate data to combine estimates; only text data was extracted.

Statistical analyses

Statistical **pooling was not carried out; this was because**data extracted from each study **on** the fetal and maternal outcome was broader in scope as a result, the findings presented narratively**. To facilitate the conclusion, data synthesis of findings from included studies was performed.**

Results

The database search found 35 records from published searches as well as clinical trial records. After the duplicates were removed, a total of 18 records were evaluated based on their titles and abstracts. As a specific report on Diclofenac exposure during human pregnancy, 15 of the 18 full-text articles tested for eligibility were excluded. Thus, three relevant articles were identified with a total of 1,490,679 participants[12][13][14]. (Figure 1)

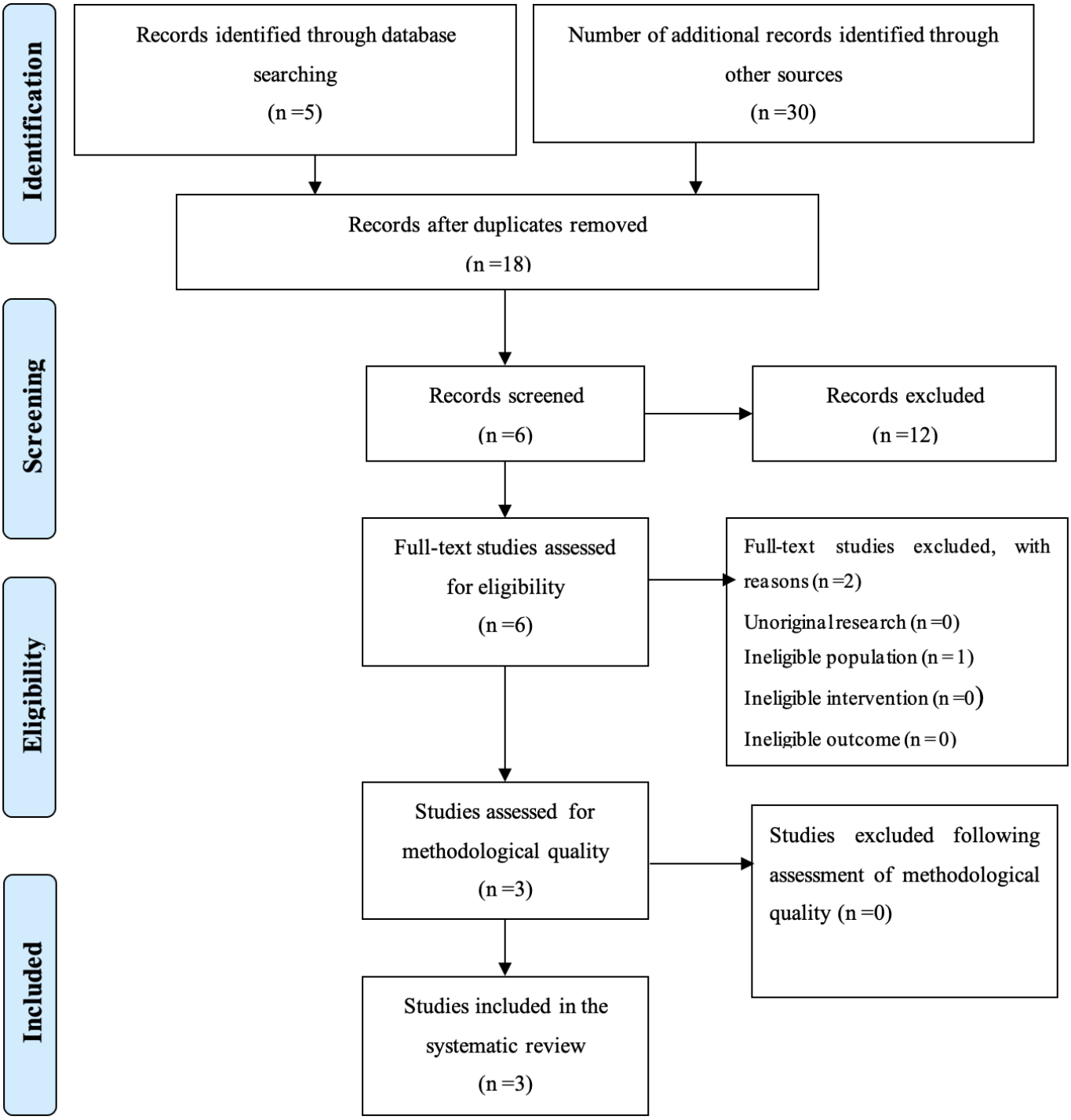

Figure 1. *Flow diagram depicting the number of records retrieved, screened, and included in the process.*

The effect of Diclofenac exposure during pregnancy

From the reviewed studies, evidence has shown that Diclofenac exposure during late pregnancy increases the risk of low birth weight in the fetus; however, no evidence of congenital malformations has been observed[12].

Another study found that taking Diclofenac during pregnancy was strongly linked to an increased risk of spontaneous abortion. Other studies have found that women exposed to Diclofenac/misoprostol have an increased risk of miscarriage[13]. Of the three studies included, two studies (66.7%) showed exposure to Diclofenac during pregnancy

increased the risk of spontaneous abortion [13][14].

Studies have shown that expectant mothers exposed to Diclofenac had an increased risk of miscarriage[12].

Methodological quality

JBI's standardized assessment tools and case-control studies were used to evaluate the quality of the study. (Tables 3 and 4 in below appendix part)

Therefore, the quality of the included study methods is all evidence of low quality, depending on the results of critical assessment. Therefore, recommendations are submitted accordingly.

Characteristics of included studies

Three human studies are included: one from Denmark, one from Norway, and one from Quebec. All of these studies were observational studies. The Danish study included all pregnancies registered for 14 years from 1997 to 2011 with a study population (n = 1,348,507). The Norwegian study was a Norwegian student with a Norwegian child nationwide who would cohort for seven years from 1999 to 2006 and who participated in a comprehensive study of (n = 90,417). The Quebec study was the Nested case-control Study Pregnancy Registry for 51,755 women. (Table 2 in below appendix part)

Discussion

There are few reports available on the effects of exposure to Diclofenac during pregnancy, these three studies involving individuals are Norway, Quebec, and Denmark studies.

Diclofenac exposure during late pregnancy is toxic to both the mother and the fetus. The risks include a higher risk of miscarriage and a lower birth weight.This study did not use time and dosage of Diclofenac used due to data during treatment (Diclofenac taken) was incomplete. This may affect the quality of evidence[12]. The same research showed no evidence of fetal birth defects[12]. These findings do not agree with studies from experimental animals confirming significant changes in embryonic morphological, organ, histopathologic, and cytological[5][6][7][8][15][16]. Though this study is done on mammals, difference could be physiology difference between human and rat but alarming for further evaluation of evidence.

In a study from Quebec and Denmark, exposure to Diclofenac during pregnancy increases the risk of spontaneous abortion[13][14]. However, the combined use of Diclofenac/misoprostol was studied in Denmark. Misoprostol is abortogenic medication used for unintended pregnancies.This increased risk of spontaneous abortion may be due to confounding effect of the misoprostol is highly suspected.

Evidence from experimental animal studies suggests that there is evidence of prolonged time during pregnancy[7], teratogenicity[5][6][16], birth defects, as well as morphological changes in the nerves and skeleton[17], as well as histopathological changes in the liver, kidneys, and testicles[7]. Evidence has shown that a teratogenic effect on an animal's fetus can be teratogenic in humans[16]. As a result, the hypothesis that Diclofenac is teratogenic in humans emerges from this analysis. The limitations of this review are the effect of Diclofenac on mother and child is a broad

concept in the sense as a result we fail to focus on the specific outcome; as a result, pooling the estimate is incredibly hard. Therefore, narrative result may not show strong evidence. Although attempts were made to specify and compile the estimate, relevant data were not reported in the included studies. These reviews include studies that gather data on Diclofenac exposure but there is no evidence that the mother is taking the drug or not and there is no information on the concurrent use of other drugs that may confound the effect. Evidence is supported by animal studies due to the paucity of data on human subjects. The effects on animals may not reflect the effect of Diclofenac in human subjects.

Conclusions

Although there are limited numbers of primary studies on the area, which enable us to produce sufficient evidence, available studies in humans and animals have suggested that exposure to Diclofenac during pregnancy has a negative effect on fetuses and mothers. Taking Diclofenac while pregnant has risk for both the mother and the fetus. Availability of inadequate data suggests that Primary studies on the area needed to be conducted.
Research needed focusing on specific effects of Diclofenac is needed to pool the estimates of Primary studies. The studies had been conducted on the topic are observational studies, so controlled trials should be conducted.

List of Abbreviations

NSAIDs- non-steroid anti-inflammatory drugs

PROSPERO- The International Prospective Register of Systematic Reviews

PRISMA- Preferred Reporting Items for Systematic Review and Meta-Analysis

JBI-Joanna Briggs Institute

RCTs-Randomized Control Trials

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Conflicts of interest

All authors declare that no conflict of interest.

Authors' contributions

The International Committee of Medical Journal Editors authorship criteria were met by all authors.

TBH- conception, design, search, analysis, report writing, administration, manuscript writing(PI)

BBB- analysis, manuscript writing

SNH- analysis, manuscript writing

MSJ- analysis, manuscript writing

Appendix

Table 1. Search strategy

S no	Query	Results
#1	Pregnant women [tw] OR Pregnant mothers [tw] OR Pregnant [tw]	182,230
#2	Diclofenac [tw] OR Voltaren [tw] OR Diclofenac Sodium [tw]	13,098
#3	Effect [tw] OR Outcome [tw] OR Consequence [tw] OR Result [tw] OR Abortion [TW] OR Toratogenic [tw] OR Congenital malformation [tw]	5,860,334
#1 AND #2 AND #3	(((((("Effect"[Text Word] OR "Outcome"[Text Word]) OR "Consequence"[Text Word]) OR "Result"[Text Word]) OR ((((((((((((("abort"[All Fields] OR "aborted"[All Fields]) OR "aborter"[All Fields]) OR "aborters"[All Fields]) OR "aborting"[All Fields]) OR "abortion s"[All Fields]) OR "abortion, induced"[MeSH Terms]) OR ("abortion"[All Fields] AND "induced"[All Fields])) OR "induced abortion"[All Fields]) OR "abortion"[All Fields]) OR "abortions"[All Fields]) OR "abortive"[All Fields]) OR "abortively"[All Fields]) OR "abortives"[All Fields]) OR "aborts"[All Fields])) OR "Toratogenic"[Text Word]) OR "congenital malformation"[Text Word] Limit to English language	41
	(((((("Effect"[Text Word] OR "Outcome"[Text Word]) OR "Consequence"[Text Word]) OR "Result"[Text Word]) OR ((((((((((((("abort"[All Fields] OR "aborted"[All Fields]) OR "aborter"[All Fields]) OR "aborters"[All Fields]) OR "aborting"[All Fields]) OR "abortion s"[All Fields]) OR "abortion, induced"[MeSH Terms]) OR ("abortion"[All Fields] AND "induced"[All Fields])) OR "induced abortion"[All Fields]) OR "abortion"[All Fields]) OR "abortions"[All Fields]) OR "abortive"[All Fields]) OR "abortively"[All Fields]) OR "abortives"[All Fields]) OR "aborts"[All Fields])) OR "Toratogenic"[Text Word]) OR "congenital malformation"[Text Word] Limit to Free full text	9
	(((((("Effect"[Text Word] OR "Outcome"[Text Word]) OR "Consequence"[Text Word]) OR "Result"[Text Word]) OR ((((((((((((("abort"[All Fields] OR "aborted"[All Fields]) OR "aborter"[All Fields]) OR "aborters"[All Fields]) OR "aborting"[All Fields]) OR "abortion s"[All Fields]) OR "abortion, induced"[MeSH Terms]) OR ("abortion"[All Fields] AND "induced"[All Fields])) OR "induced abortion"[All Fields]) OR "abortion"[All Fields]) OR "abortions"[All Fields]) OR "abortive"[All Fields]) OR "abortively"[All Fields]) OR "abortives"[All Fields]) OR "aborts"[All Fields])) OR "Toratogenic"[Text Word]) OR "congenital malformation"[Text Word] Limit to Human population	5
Total Pubmed database search		5

Table 2. *Characteristics of included studies*

Study	Study design	Participants	Intervention	Comparator	Length of follow-up	Outcomes
K Nezvalová-Henriksen, et al. (2013)[12]	Cohort	Pregnant women (90,417)	Diclofenac	Usual care	1999 - 2006	Effect on fetus
Jon T. Andersen, et al. (2015)[13]	Cohort	Pregnant women (1,348,507)	Diclofenac	Usual care	1997 - 2011	Effect on fetus
Hamid R. et al. (2011)[14]	Case control	Pregnant women (51, 755)	Diclofenac	Usual care	-	Effect on fetus
Total		1,490,679				

Table 3. *Critical appraisal results of eligible studies (for cohort studies)*

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
K Nezvalová-Henriksen, et al. (2013)[12]	Y	Y	Y	Y	Y	Y	U	U	NO	Y	Y
Jon T. Andersen, et al. (2015)[13]	U	Y	U	Y	Y	Y	Y	U	NO	NO	Y
Total %	50%	100%	50%	100%	100%	100%	50%	0	0%	50%	100%

Y = Yes, N = No, U = Unclear; JBI critical appraisal checklist for cohort studies:Q1 = Were the two groups similar and recruited from the same population?;Q2 = Were the exposures measured similarly to assign people to both exposed and unexposed groups?; Q3 = Was the exposure measured in a valid and reliable way?;Q4 = Were confounding factors identified?; Q5 = Were strategies to deal with confounding factors stated?;Q6 = Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?; Q7 = Were the outcomes measured in a valid and reliable way?;Q8 = Was the follow up time reported and sufficient to be long enough for outcomes to occur?; Q9 = Was follow up complete, and if not, were the reasons to loss to follow up described and explored?; Q10 = Were strategies to address incomplete follow up utilized?;Q11 = Was appropriate statistical analysis used?

Table 4. *Critical appraisal results of eligible studies (for case control studies)*

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Hamid R. et al.(2011)[14]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Total %	100%	100%	100%	100%	100%	0%	100%	100%	100%	100%

Y = Yes, N = No, U = Unclear; JBI critical appraisal checklist for cohort studies:Q1 = Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?;Q2 Were cases and controls matched appropriately?; Q3 = Were the same criteria used for identification of cases and controls?;Q4 = Was exposure measured in a standard, valid and reliable way? ; Q5 = Was exposure measured in the same way for cases and controls?;Q6 = Were confounding factors identified?; Q7 = Were strategies to deal with confounding factors stated?;Q8 = Were outcomes assessed in a standard, valid and reliable way for cases and controls?; Q9 = Was the exposure period of interest long enough to be meaningful?; Q10 = Was appropriate statistical analysis used?

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