

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

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**Potential competing interests:** The author(s) declared that no potential competing interests exist.

Handiso TB et al, 2022 Adverse Effect of Diclofenac Exposure during Pregnancy on Mother and Fetus; A Systematic Review pre-print v1 in Qeios. July 1, 2022.

Review completed on July 12, 2022 by Lorraine Posobiec MS, Cell and Developmental Biology

**There are three major concerns and several minor revisions that are recommended.**

- 1. Animal Data** - There are several instances of using in vitro studies or in vivo animal studies with low amounts of animals per group with no indication of maternal toxicity that are used to justify that this drug is teratogenic in animals. However, the US FDA prescribing information shows that when Diclofenac is given at relevant doses with evidence of maternal toxicity to pregnant animals, no teratogenicity is observed. This is not reconciled or even mentioned in the paper. The US FDA does warn against using Diclofenac after 30 weeks gestation due to premature closure of the ductus arteriosus in the offspring, which is also not mentioned in the paper. Recommend removing the animal studies and using only the US FDA animal data. Recommend deleting sentences in discussion starting with 'Evidence from experimental studies...', 'Evidence has shown that...' and 'As a result the hypothesis...' as the data do not support these statements. Recommend deleting last two sentences of discussion – 'Evidence is supported by animal studies...' and 'The effect on animals...'
- 2. Use of combination study** - One of the three studies used in this review was a combination drug with Diclofenac given in combination with another drug, misoprostol, an abortogenic drug. Therefore, it is impossible to distinguish which agent to attribute the increased spontaneous abortion effect to. At least from the abstract, it does not appear that Diclofenac is given alone. Recommend either only using Diclofenac data alone, if there is any, from this paper, or excluding it from this review. Including this study, even with this sentence currently in the discussion – 'This increased risk of spontaneous abortion may be due to confounding effect of the misoprostol is highly suspected.' does not go far enough in my opinion to discharge this obvious confounder and recommend not including this study in this review paper.
- 3. Risk in Pregnancy** - In Results, the effect of Diclofenac exposure during pregnancy – change 'late' pregnancy to '2<sup>d</sup> trimester', as the results of this paper showed that 2<sup>nd</sup> trimester use was associated with low birth weight. Also, add that maternal bleeding occurred in the 3<sup>rd</sup> trimester and that there was no evidence of a reduction in infant survival rate.

## **Minor typos/word change suggestions:**

Pg 1- abstract intro – remove 'one' from second sentence.

Pg 2 – intro – suggest 'considered a' rather than 'based on'.

Pg 2 – Intro - double period in second sentence.

Pg 2 – suggest only having formulations in this sentence (exclude stomach acids, rapid cracking of the mouth and candles?).

Pg 2- last sentence in 2<sup>nd</sup> paragraph – consider deleting ‘from the adverse effect of embryos shown in animals’.

Pg 2 – suggest removing last 2 paragraphs detailing animal studies as suggested above in major comments. If keeping in, change ‘mice’ to ‘rats’ and change ‘premenstrual’ to ‘prematuring’.

Pg 3 – 2<sup>nd</sup> sentence- remove ‘A few’ and add ‘such as isopropylantipyrene’ as this sentence is not about Diclofenac.

Pg 3 – Add references for sentence starting ‘Diclofenac can be taken...’. Change ‘user manuals’ to ‘prescribing information’. Next sentence, delete ‘this is’. Remove last sentence in paragraph starting ‘this demonstrates...’ as it is redundant.

Pg 3 – Types of Studies and Inclusion Criteria – It is not clear what the inclusion criteria are. Please expand.

Pg 3 – Search strategy – 1<sup>st</sup> sentence - change ‘to in’ to ‘at’. Third sentence – add ‘the first step was...’, remove bolding, change ‘When’ to ‘was performed’ and end sentence after databases. Start next sentence with ‘The second step and delete ‘search’.

Pg 4 – first sentence – change ‘summarizing’ to ‘summaries’ and delete end of sentence (the second step search recognized keywords and index terms) as it is redundant.

Pg 4 – Search term misspelled – should be Teratogenic, not Toratogenic in two places. If this is the actual term that was used in the search, then the search should be repeated with the correct spelling.

Pg 4 – 2<sup>nd</sup> paragraph – add ‘was made’ between list and for.

Pg 4 – last sentence of Assessment of methodological quality – change ‘is’ to ‘was’.

Pg 4 – Data extraction – remove comma after contracting, consider changing ‘but there was’ to ‘when there was’

Pg 4- statistical analyses – remove bolding

Pg 6 – Results - Suggest adding reference (12, 13, 14?) and also location (Norway, Denmark, Quebec) for selected studies that were reviewed as later they are discussed by location – also add location to Table 2.

Pg 6 – Results – 1<sup>st</sup> sentence – instead of ‘evidence’, change to ‘one of the reviewed studies from Norway...’

Pg 6 - Results – The effect of Diclofenac exposure during pregnancy – 2<sup>nd</sup> sentence – change ‘another study’ to ‘a second study from Quebec with a limited number of pregnant women taking Diclofenac and add reference (14?) as data comes from only 31 women taking Diclofenac vs 82 control women. This looks like 27%, but and incidence rate of 15-20% spontaneous abortion is within background.

Pg 6 – Recommend removing study from Denmark as it is not a Diclofenac-alone study. This makes only 1/2 (50%) having an increase in spontaneous abortion, and the one study with it was a low number of pregnant women. Recommend deleting last sentence ‘Studies have shown that expectant mothers exposed ...’ as the data does not support this statement.

Pg 7 – Characteristics of included studies – suggest adding references to reviewed studies.

Pg 7 – Discussion – 2<sup>nd</sup> sentence – recommend changing to ‘Limited evidence presented here suggest that Diclofenac exposure may be toxic to the mother and fetus (again avoid ‘late’ pregnancy).

Pg 7 – 3<sup>rd</sup> sentence – include ‘maternal bleeding’.

Pg 7 – Change ‘this study’ to ‘the Norwegian study’

Pg 7 – recommend deleting two sentences starting with ‘these findings do not agree...’ and ‘though this study is done...’  
as robust in vivo data do not support this statement