

# 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.

Thank you for the opportunity to review this paper. This systemic review has good intentions but needs additional edits before publication. The heavy focus on animal data is misleading. Given that we have human data available, this should be the main concentration of the paper and the animal data should be consolidated into a sentence or two with a clear explanation as to why we cannot routinely rely on these types of experiments. The authors should focus on making sure their thoughts are clear. Many sentences are worded confusingly, and were difficult to follow. Additionally, outcomes should be discussed chronologically (e.g. pool all miscarriage info, then birth defects, then pregnancy complications). There is no mention of premature closure of the ductus arteriosus which is an important consideration for use of this class of medications in the third trimester of pregnancy. The lack of data on dose and duration of use should be addressed thoroughly, as this is important. Someone taking one pill of Diclofenac at 20 weeks is much different than someone who is a daily user. Lastly, I'd suggest focusing your review on the effects on the fetus (not the mother as well). Please see additional comments below on word choice, grammar, typos, understanding of the content, etc.

## **Introduction:**

"It is ~~one~~ among the world's most extensively used non-steroidal anti-inflammatory medications (NSAIDs)"

Change "of this impact in people" to "of these outcomes in human pregnancy."

Results: "(two cohorts and nested case-control studies)" – How many case control studies? 1 to add up to 3?

Introduction: Remove extra period after "inflammation"

This sentence is confusing: "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)." Are you referring to the types of products Diclofenac is found in, or the form (oral, injectable, etc.)? Could be written much more clear.

"Maternal exposure of Diclofenac" should read "Maternal exposure TO Diclofenac"

“Diclofenac can be taken during the first and second trimesters but not during the third trimester” You should expand on who says this and why third trimester use is discouraged.

This phrase: “maternal and uterine pregnancy” reads strange to me.

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### **Methods:**

“Inclusion” in header does not need to be capitalized

Consider replacing term “pregnant women” with “person who is pregnant” or “pregnant person” per new inclusive guidelines.

Under search strategy, the term ““Toratogenic” is misspelled twice.

Add space: “comprehensive search.English-language”

Under Data Extraction: “The authors of the paper tried contacting, the studies included” there is no need for a comma here.

Under Statistical Analysis: This sentence **“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”** **Should be separated into two thoughts/sentences.**

### **Results:**

This thought needs to be clarified: “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.” The first sentence should state that the available data does not find a risk for birth defects. Then you can go on to say that with exposure later in pregnancy, a risk for low birth weight has been observed. As is, it reads that there is no risk for birth defects with exposure in the third trimester – which doesn’t make sense, timing wise.

Spontaneous abortion data should be mentioned first in this section. It feels out of order as it.

66.7% comment is not necessary as it’s such a small sample size (just 3 studies)

“Studies have shown that expectant mothers exposed to Diclofenac had an increased risk of miscarriage” is repetitive. You have just reviewed the spontaneous abortion data and this statement is likely not necessary.

Premature closure of the ductus arteriosus needs to be commented on.

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#### 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” is poorly worded. Consider something like: “There is limited data on the use of Diclofenac in pregnancy with just three studies out of Norway, Quebec, and Denmark available.”

“Diclofenac exposure during late pregnancy is toxic to both the mother and the fetus.” This thought needs to be defined. Toxic, how?

This sentence is poorly worded: “This study did not use time and dosage of Diclofenac used due to data during treatment (Diclofenac taken) was incomplete” and should be rephrased, as this is an important point you need to make. Perhaps: “Because there was missing/incomplete information from the studies available, we could not evaluate effects of dose or duration of use.”

“fetal birth defects” should just be birth defects or congenital anomalies to be consistent with previous word choice.

“In a study from Quebec and Denmark” should read “In studies from....”

Under evidence from experimental animals thought you say “teratogenicity, birth defects” which are the same.

Conclusion should be more clearly stated (more specific than just “negative effects”)

“Primary” does not need to be capitalized.

You mention “vaginal bleeding in the mother” in the abstract but do not go into detail in the discussion section. A reference and more thorough discussion is needed if you are going to conclude that “Diclofenac exposure during pregnancy has negative consequences on the fetus **and the mother.**” I would prefer focusing on just the fetus for this review.