REPRODUCTIVE TOXICITY OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

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ABSTRACT

Reproductive Toxicity of Non-Steroidal Anti-Inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are the one of a drug-class that is generally consumed by most of pregnant women in the world for many different indications during their pregnancy. It is important for doctor who prescribes to know well the safety of these drugs, since these drugs are also given for indications (of illnesses) that also could give detrimental effects in pregnancy, as viral infections. Here in this article, the effects of NSAIDs drugs, especially diclofenac is assessed. This review is based on journals in studies that had been conducted to know the reproductive toxicity of NSAIDs. It is known now that NSAIDs in preconception time could affect women's fertility and in first trimester possibly could increase the risk of spontaneous abortion. In the second trimester they are associated with kidney disorder of the offspring and in the last trimester they cause premature closure of ductus arteriosus and leading to pulmonary hypertension in the newborn infants. So it is advised that the use of these drugs for pregnant women should be given only for certain indications when there are no other option for a saver drug.

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INTRODUCTION

It is important to determine the safety of NSAIDs use in pregnancy, since these drugs are the most common drugs used during pregnancy[1-4] and can be easily obtained as over-the-counter drugs. NSAIDs are indicated for analgesic, antipyretic, rheumatoid disorders, and some other indications.[5] NSAIDs act through inhibition of cyclooxygenase enzymes that is substantial for prostaglandin synthesis (Figure 1). There are 2 known cyclooxygenase (COX) enzymes: COX-1 and COX-2. COX-1 has "house keeping" function, which maintains the normal function of many organs (gastrointestinal track, kidney, nervous system, vascular and endothelial) and COX-2 is associated with inflam-

mation. Both of these COXs are important for implantation and angiogenesis in establishing early placental structures.[6] These functions explain why NSAIDs increased the risk of miscarriage when these drugs are consumed during the early pregnancy. COX-2 also stimulates angiogenesis that is important during organogenesis, which could be the mechanism of their teratogenicity. The mechanisms of angiogenesis stimulation by COX-2 are by promoting vascular endothelial growth factor through increasing mRNA transcription, directly stimulating endothelial cell by production of thromboxane A2, Prostaglandin E2 and prostacycline, upregulation of matrix metalloproteinase, and interleukin-12 production inhibition (a potent anti-angiogenic cytokine).[44]

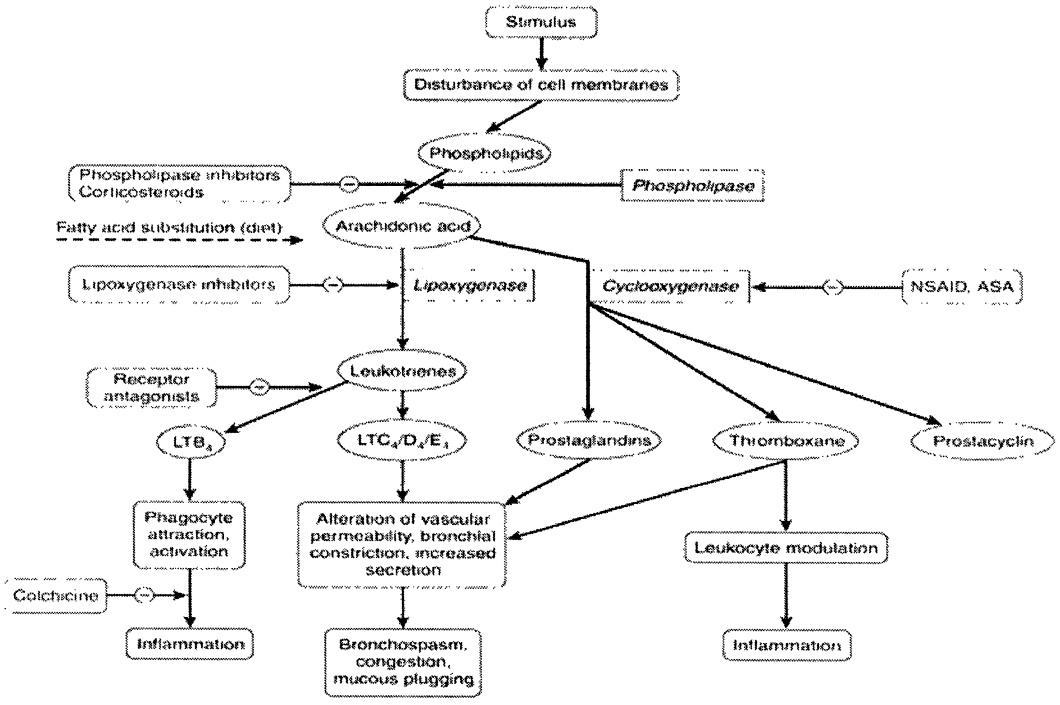

Figure :1. Prostanoid mediators derived from arachidonic acid and sites of drug action. ASA, acetylsalicylic acid (aspirin); LT, leukotriene; NSAID, nonsteroidal anti-inflammatory drug.

It had been proven that NSAIDs are transferred through placenta to the embryo/foetus since first trimester[7-9] and all NSAIDs are excreted in the breast milk with different concentrations.[3] This facts explain the subsequent detrimental effects on the embryo/foetus during the embryogenesis/organogenesis and development period caused by NSAIDs.

ANIMAL STUDIES

Animal studies to investigate NSAIDs effects in pregnancy had been widely studied, using rodents and non-rodents. NSAIDs administration in mice and rats before pregnancy also has effect in fertility and successful pregnancy, since COX-1 and COX-2 has role in ovulation, fertilization and implantation.[10-12] Studies in rodents and non-rodents in mice, rats, rabbits, monkeys and dogs shown that NSAIDs caused congenital malformations, involving nervous systems,[13-15] cardiovascular development (ventricular septal defect), midline closure (omphalocele and gastroschisis), diaphragmatic hernia,[16] skeletal and vascular defects.[3] Study in rats also shown that NSAIDs also caused maternal toxicity, which could lead to harmful effects for the offspring.[17]

HUMAN STUDIES

Preconception

NSAIDs consumption during child-bearing age has effects in human fertility. This effect could be caused by inhibition of prostaglandins that are important in ovulation. The mechanism related to inhibition of COX-2, resulting in inhibition of prostaglandin which generates proteolytic enzymes for follicular rupture, without prostaglandin follicle in ovary will persist and no ovulation occur.[18]

First Trimester

The administration of NSAIDs during the early pregnancy was proven to increase the risk of spontaneous abortion.[19-21] The possible mechanism of action why NSAIDs caused miscarriage had already mentioned above, related to its action to inhibit prostaglandins biosynthesis in most organ systems through inhibition of COX-1 and COX-2. Studies in animal have shown that prostaglandins are important for implantation of embryo in uterus wall. They also have roles in ovulation and implantation in human, through interaction with platelet activating factors and cytokines in uterus and embryo. NSAIDs also caused imbalance of prostanoids which are essential for maintaining normal blood pressure throughout pregnancy and have adverse effects on perfusion and circulation of placenta.[20] Meta-analysis done by Kozer at al shown that low-dose aspirin (75 mg/day or less) in first trimester do not increase risk of spontaneous abortion, but this study did not analyze the effect of higher dose aspirin and could not conclude the effect of higher dose of aspirin (more than 75 mg/day) in early pregnancy.[22]

Although animal studies demonstrated that NSAIDs caused congenital anomalies in animals,[13-16] in human the safety of their use in early pregnancy in is still controversial, some of the studies shown that there is increased risk of congenital anomalies, like cardiac septal defect and midline defects[23-25] but some studies did not show any association between consumption these drugs and the risk of congenital anomalies in human. [28-35]

A nested case-control study done by Ofori et al done in Canada, which included 36.387 participants shown that NSAIDs give a greater risk of structural congenital anomalies, especially cardiac septal defect. These effects can be explained by the understanding that prostaglandins may have roles in angiogenesis and vascular functions, to deliver oxygen and nutrients to tissue and endothelial cells, and COX inhibition can caused vascular disruption.[23] This study had a different result from a prospective cohort study done by Nielsen et al that concluded that there was no association between NSAIDs administration and congenital anomalies,[19] but because the size of participants in this study was almost of twice of Nielsen's, so their result would be more reliable. The confounding factor of this study would be the lack of information about the mother's lifestyle (marijuana or cigarette smoking, alcohol consumption, folic acid intake) that also had already known can cause these effects.[26] Case control studies done by Bateman et al, Werler et al, Banhidy et al confirmed that NSAIDs can cause congenital malformations (cardiac septal defect, gastroschisis, diaphragmatic hernia).[24,25,27] But case control study done by Cleves et al[28], Hernandez et al[4] and cohort studies done by van Gelder et al[29], Cassina et al[30], Ericson et al[31], Henriksen et al[32], Kallen et al[33] and Daniel et al[34] has a contradictory results.

Second Trimester

The use of NSAIDs in the second trimester is considerably safe, but a prospective cohort study in Denmark shown that high-dose ibuprofen, aspirin and paracetamol may associated with congenital cryptorchidism,[35] that could result in male reproductive disorders (poor semen quality and testicular cancer) on male offspring in the future life. The mechanism could result from antiandrogenic effects of prostaglandin inhibition.[3]

Third Trimester

The unfavorable effects of NSAIDs in late pregnancy is already established, as many studies showed that they cause contraction of ductus arteriosus, resulting in right ventricular hypertrophy and pulmonary hypertension in foetus when given in this period.[37-39] A meta-analysis study done by Koren et al had also confirmed this finding.[38] NSAIDs also related to fetal renal injury when consumed in the midgestation during the nephrogenesis (fifth to 36th week of gestation until term), causing impairment in renal function and oligohydramnios.[3,40,41]

Lactation Period

Most of NSAIDs are excreted in breast milk and can cause toxic effects in infants if the concentration is >10% infant dose. The non-selective COX inhibitors are considered safe and COX-2 selective inhibitors are probably safe

when given during in lactation period, because their amount in breast milk is not exceed this amount (Table 1), but aspirin should be used with caution or avoided since its concentration in breast milk is relatively high (9-21% of infant dose).[3,41]

Table 1. Suitability of Short-Term Nonsteroidal Anti-Inflammatory Drugs During Early Postpartum Breastfeeding.[3]

Drug	RID	Safety recommendation
Aspirin	9%–21%	Potential toxicity Should be given to nursing mothers with caution. Low dose (<150 mg/d) may be indicated
Celecoxib	0.3%	Usually compatible
Diclofenac	1%	Usually compatible
Fenoprofen	NA	Probably compatible
Flufenamic acid	2%	Usually compatible
Flurbiprofen	0.1%	Compatible
Ibuprofen	0.6%	Usually compatible
Indomethacin	0.4%	Probably compatible Usually compatible
Ketoprofen	0.3%	Compatible
Ketorolac	0.2%–0.4%	Probably compatible Usually compatible
Mefenamic acid	0.3%	Probably compatible Usually compatible
Naproxen	1%–3%	Probably compatible Usually compatible
Parecoxib and Valdecoxib	0.6%	Probably compatible
Piroxicam	1%	Probably compatible Usually compatible
Tenoxicam	NA	NA
Lornoxicam	NA	NA
Tolmetin	0.4%	Probably compatible Usually compatible

RID = relative infant dose in breastmilk; i.e., estimated absolute infant dose (drug concentration in milk [mg/L] × estimated volume of milk ingested in 24 h in L/kg) divided by the maternal dose (mg/kg) and expressed as a percentage; NA = no data available

DICLOFENAC

Diclofenac is a phenylacetic acid derivative that is relatively nonselective COX inhibitor,[4] grouped in class C in FDA drug classification in pregnancy.[31] Diclofenac passes through human placenta to the embryo/foetus[7] and can cause congenital malformation.[37,39] It is also excreted in the breast milk with low concentration (Table 1) and usually compatible for breastfeeding mothers.[3]

Animal study in rats showed that offspring of a mother given diclofenac during pregnancy has abnormal liver structures and there was also prolong in pregnancy and delivering period because the effect of this drug.[42] Other studies had shown that diclofenac also has a toxic effect in nervous systems: central nervous system (optic nerve[12]), cervical spinal cords[13] and peripheral nervous system.[14] Diclofenac also caused caudal neural tube and hind

limbs malformations in rats.[43] The mechanism of this teratogenicity effects may result from the inhibition of angiogenesis that important for organogenesis.[44]

A study using zebra fish model suggested that diclofenac has toxic effect during myogenesis that lead to impairment of myofibril alignment and actin polymerization. The mechanism of diclofenac toxicity is not only through inhibition of COX, but also through its role in DNA synthesis and inhibition of voltage-dependent potassium channel which important to regulate immunoactivity and neuron function. It also inhibited voltagegated sodium channel in muscle tissue and disturbed inward movement of sodium and or calcium current.[45]

A study done by Cassina et al suggested that use in first trimester is safe, but this study should be confirmed further by more studies to establish its safety, as over-the-counter drug. Some cases reported premature closure of ductus arteriosus in infants whose mother ingested diclofenac at the last trimester of pregnancy. The mechanism could be related to inhibition of prostaglandin that cause vasodilatation, which results in vasoconstriction of ductus arteriosus.[37,39]

CONCLUSION

The use of these drugs in pregnancy is best avoided, but the consideration to use these drugs still can be done if there is no other option for the disorder in the pregnant women needed these drugs, or the benefit outweighs the risk, and with the consent of the patient. The use should be done under strict supervision, and if there is adverse outcome, it should be reported for future safety. Since most of NSAIDs are easily obtained as over-the-counter drugs, the potential hazards for women taking these drugs during pregnancy should be well known. Patient leaflet information of these drugs not recommends their use in the first and second trimester, unless given by a physician and the benefit outweighs the risk, but the warning for patients should be made known more clearly in the leaflet, so those who are taking these drugs are well informed about the risks. Acetaminophen could be a better option for analgesic and antipyretic during the early pregnancy, since it was not associated with increased risk of miscarriage.[20]

Studies in human were epidemiological studies as cohort and case-control studies which have their own weaknesses and strength. The retrospective cohort studies and case control studies that were done by giving questionnaires to mothers whose infants were having birth defects may have information bias/recall bias (since these women might had forgotten what drugs they had taken more than 9 months before). Prospective cohort studies were better, but usually had smaller number of participants included in these studies, so the statistical power also lower. The

other difficulties found in these studies were the confounding factors that could also cause reproductive toxicities, like diseases (as viral infections), other drugs and lifestyle (smoking, diet, alcohol).

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