

Effects of Pregnancy Analgesic Use on Stillbirth: A Review

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Abstract

A dreadful pregnancy condition that is linked to emotional, social, and financial problems is stillbirth. Many risks are there can all contribute to stillbirth. Despite the fact that there are many possible causes of stillbirth, the use of analgesics makes the likelihood of stillbirth more likely. Each medication has advantages and disadvantages that impact the foetus. The incidence of stillbirth during pregnancy increased twofold when exposed to drugs. There is a lack of strong evidence that links the administration of analgesics during gestation to stillbirth, thus their usage is not strictly regulated. Thus, the current research review highlights the possibility of analgesic-induced stillbirth. Analgesics used improperly as OTC medications are well-known. Analgesics are frequently used for self-medication without a doctor's supervision. Some of these medications have a propensity to penetrate the placental barrier and may be harmful to the foetus. A pregnant woman may utilise analgesics for a variety of reasons, including pain brought on by the body's adaptation to the pregnancy-related changes. Owing to accessibility and ignorance of the risks to the foetus, analgesics are frequently used irrationally, which can result in pregnancy-related issues like stillbirth.

Keywords: Stillbirth, Opioid, NSAID, Analgesic, Pregnancy

INTRODUCTION

Of the estimated 33 lakh stillbirths that take place each year, with all most all occurring in developing nations.¹ The majority of underdeveloped countries have stillbirth rates that are ten times greater than those of many wealthy countries, which have rates as low as 3-5 per thousand births.² Decreases in intrapartum stillbirth rates are mostly to blame for the declines in stillbirth rates observed in developed nations. These drops in stillbirth appear to be related to increased access to obstetric services, especially better intrapartum foetal monitoring, and caesarean sections. In poor nations, foetal hypoxia, trauma, congenital abnormalities, fetal-maternal bleeding, and a range of maternal illnesses are among the reasons of stillbirth. These factors are largely comparable across areas. Because there isn't one international definition for what constitutes a stillbirth, making comparisons across time and space is difficult. Even with the usage of the classification schemes now in use, the majority of stillbirths still have unidentified causes.³⁻⁶

GLOBAL STILLBIRTH RATES

Where data are available, the majority of nations do not report stillbirth rates in their vital statistics systems, and when they do, they are frequently underreported for a variety of reasons.^{7,8} This is especially true for birth weights or gestational ages that are lower. Comparisons between countries, and particularly comparisons between developed and poor countries, are challenging even when stillbirth registration is excellent due to differences in the lower birthweight and gestational age cutoffs used to determine stillbirth. State laws in the US, for instance, often set the maximum gestational age at 20 weeks, or around 350g. Although gestational age dating is frequently unreliable, many poor nations define stillbirth using a birthweight limit, furthermore, considering that even live-born babies weigh. In 2021, there were around 1.9 million stillbirths globally, defined as births of infants that show no signs of life at 28 weeks or later.⁹⁻¹²

Women in South Asia and sub-Saharan Africa experience more stillbirths than any other region in the globe. These two areas accounted for more than 75% of projected stillbirths in 2021, with South Asia

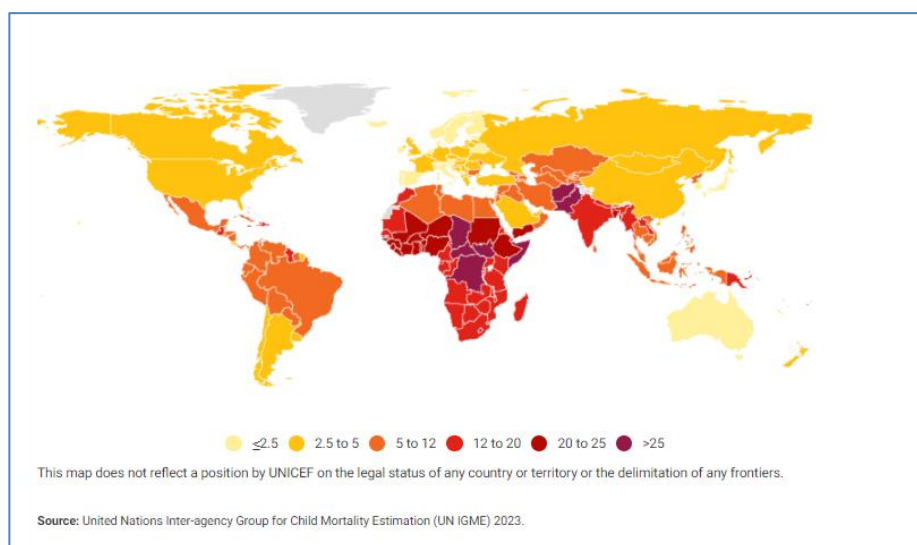
accounting for 32% and sub-Saharan Africa for 47% of the global total, respectively. The estimated stillbirth rate in sub-Saharan Africa, which was 21.1 per 1,000 live births, was eight times higher than the lowest regional average stillbirth rate, which was 2.6 in Western Europe. With 17.0 stillbirths per 1,000 live births, South Asia had the second-highest rate of stillbirths.^{1-6,12-15}

The cost of stillbirths is not shared equally among all nations. From 1.6 stillbirths per 1,000 live births in 2021 to 31.2 stillbirths per 1,000 live births in that same year. The chance of a stillbirth was around 20 times higher in the nation with the highest rate than it was in the nation with the lowest rate. The majority of the 26 nations with an estimated rate exceeding 20 are in sub-Saharan Africa, with the remaining five being in South Asia, the Middle East, or Northern Africa. In contrast, the predicted stillbirth rate for 20 nations, mostly in Europe, was under 2.5 stillbirths per 1,000 live births. This significant disparity between nations both within and between areas shows how much stillbirths that could have been prevented may be reduced.^{12,15}

As long as tested therapies that enhance the health of mothers and their babies along the continuum of care are accessible and used, the majority of stillbirths can be avoided. In 2021, it was anticipated that 45% of stillbirths worldwide occurred during pregnancy (i.e., the baby died during labour). In comparison to 8% of stillbirths in Western Europe, around 50% of stillbirths occur intrapartum in West and Central Africa, Eastern and Southern Africa, and South Asia. 91% of all intrapartum stillbirths globally occurred in sub-Saharan Africa and South Asia in 2021, when an estimated 741,700 newborns died during labour. A critical indicator of the effectiveness and timeliness of intrapartum care is intrapartum stillbirth. In both of these areas, immediate action is required to give life-saving measures.^{1,2,15}

Moreover, stillbirths decreased overall by 35%, from 2.9 million in 2000 to 1.9 million in 2021. It is noteworthy that these decreases have not kept up with the improvement in under-five mortality. Stillbirths increased in several sub-Saharan African countries due to population growth surpassing stillbirth rate reductions. Fig 1

Figure 1: still birth data¹



DEFINITION AND MISUSE OF THE ANALGESICS

The WHO describes stillbirth as foetal death beyond 28 weeks but before or during birth. To avoid stillbirth, which can cause emotional, social, and economic problems, it's important to treat the issue before and during pregnancy.¹

Incorrect gestational periods, smoking, advanced maternal age (over 40), multiparity, “hypertensive

disorders of pregnancy (HDP)”, gestational diabetes, some ethnic groups, particularly black women (due to inadequate perinatal care), infections, thrombophilia, and other conditions may result in stillbirth. In recent years, drug use during pregnancy has increased considerably, with 23%–85% of women worldwide using one or more prescription pharmaceuticals. The business rarely tests a new drug on pregnant women before releasing it. Most medications have poor safety profiles.¹⁵

Each prescription has pros and cons that may affect foetal health. Anticancer, antiepileptic, antipsychotic, and analgesic medications cause stillbirth. Drug use generally raised stillbirth risk by two-fold.¹⁶ OTC use during pregnancy has increased, risking the foetus. Self-medication with painkillers is common. Analgesics during pregnancy increase the risk of stillbirth, according to this review.

RISK FACTORS STILLBIRTH

Stillbirth can be caused by many circumstances, including foeto-maternal death, however documenting the cause is difficult, leading to the belief that the cause is unknown. Risk factors for stillbirth include advanced maternal age.¹⁷ Stillbirth is more likely in women without professional delivery and emergency obstetrical care. One-third or more of labouring women in underdeveloped nations deliver at home with experienced delivery attendants. A trained birth attendant is important since delivery difficulties are a leading cause of stillbirth. Intrapartum stillbirth rates were more closely connected with obstetric care measures, specifically c-section rates, than antepartum rates, showing that medical care availability is more closely related to intrapartum stillbirth. Prolonged and obstructed labour and hypoxia because many stillbirths in developing nations, therefore this relationship was expected.^{15,17}

Timely delivery and caesarean section can minimise stillbirth from preeclampsia/eclampsia and other disorders. Essential obstetric services include caesarean section, parenteral antibiotics, blood transfusion, oxytocic medications, anticonvulsants, and manual placenta and retained products of conception removal. In developing nations, trained delivery attendants do not guarantee critical obstetric treatments, especially caesarean section. A skillful attendant may be a nurse without caesarean section training or surgery equipment. So, while critical obstetric services may include a qualified attendant, this measure does not include the life-saving caesarean section or other life-saving procedures. Finally, unfavourable pregnancy outcomes, prior stillbirths, and short interpregnancy intervals, increase stillbirth risk.¹⁸⁻²¹

Still births and the drug usage

Pregnancy is a unique physiological and psychological situation that affects medication pharmacology.¹⁶⁻²² Due to physiological adaptation, some medications can pass the placenta and harm the growing embryo. The thalidomide and

diethylstilboestrol disasters showed that medications inherently endanger pregnant women. After these tragedies, the FDA tightened medication use during pregnancy. FDA classifies medications by teratogenicity.^{15,23-26}

Some women have pre-existing medical disorders and others develop new ones during pregnancy that require treatment. These concerns affect the expectant mother and her baby's health. Sharma R found that 8% of expecting moms need therapy due to medical concerns and pregnancy difficulties. Micronutrients are needed for mother and foetal health.²⁷⁻³⁰

The mother's health is improved by drug use during pregnancy, but the drug must be safe, useful, and used responsibly. Accessibility, feelings of improvement, underestimation of drug toxicity, unethical advertising, a focus on costs, incorrect perceptions of drug side effects, a lack of prescriber drug education, a lack of regulatory control system, etc. are all factors that contribute to irrational pharmaceutical use. Drug addiction results in issues for the mother and the foetus as well as death.^{15,31}

As mentioned, the safety of medications in pregnancy is unclear, and research shows that OTC and prescription drug use is ubiquitous throughout pregnancy, with 2-3% of drug use causing birth defects. OTC drugs are inexpensive and provide symptom alleviation, encouraging pregnant women to self-medicate without knowing the risks. This encouraged pregnant women to use "Category H" prescription medications that were dispensed arbitrarily. The majority of antibiotics are schedule H pharmaceuticals that are arbitrarily prescribed and used throughout pregnancy. This puts the mother's health at risk, forces her to take more drugs, and could result in a stillbirth. Pregnancy-related irrational pharmaceutical use has risen in developing countries like India due to the growing availability of drugs without a prescription, non-pharmacist distribution, and third-party dispensing. Over-the-counter medications include analgesics, antipyretics, nasal decongestants, antihistamines, and others. Drug use during pregnancy can hurt, stunt, or kill the foetus. They also cause placental insufficiency and preterm uterine contraction, which injures the foetus and leads to pregnancy issues like stillbirth.^{15,32}

Analgesic use in pregnancy

Pregnant women may utilise analgesics due to dramatic physiologic changes that cause discomfort, which they perceive as pain. Aspirin, ibuprofen,

diclofenac, naproxen, and paracetamol are non-opioid analgesics. These analgesics can be bought over-the-counter and used arbitrarily. Pregnant women often take a lot of over-the-counter medicines to alleviate their discomfort, jeopardising their unborn child. NSAIDs as analgesics should be avoided after 30 weeks of pregnancy unless prescribed by a doctor to reduce pregnancy-related risks. Pregnancy-safe analgesics include paracetamol (acetaminophen). Opioid analgesics were used in 2-4% of US pregnancies, posing a serious health risk. Opioids' teratogenic effects endanger the mother and foetus and cause pregnancy problems. Opioid analgesics include methadone, buprenorphine, fentanyl, and morphine.³³

Stillbirth and its association to analgesics

Opioid analgesic

Opioids during pregnancy can cause obstetric and perinatal issues. Stillbirth is more likely in first- and second-trimester opioid-exposed pregnancies. Opioid dependency is the highest risk, and women hide their use for many reasons, including a sense of improvement. Opioid painkiller "usage" and "abuse" debates continue.^{33,34}

Opioids enter the growing foetus through the placenta and breach the "*Blood Brain Barrier*", causing respiratory discomfort, growth restriction, and mortality. Hypoxia and placental bed vasoconstriction cause placental abruption. Cocaine can cause early uterine contraction and foetal damage or death. Brogly et al., found a statistically significant link between opiate exposure and stillbirth.^{33,34}

Non-opioid analgesic.

Many factor related to the mothers physiology may affect the drug metabolism. Low molecular weight and lipid solubility make it easy for these free drugs to cross the placenta and enter foetal circulation, which can have harmful effects. Aspirin, ibuprofen, naproxen, and acetaminophen are examples.³⁴ 19% of the population uses NSAIDs, cyclooxygenase enzyme inhibitors that are analgesic, antipyretic, and anti-inflammatory. Due to side effects, NSAIDs are usually avoided after the first trimester.³⁵

As the embryo develops, the body adjusts, making the last three months the most vulnerable. NSAIDs rapidly cross the placenta, and prostanoid inhibition may cause miscarriage. They enter the foetal circulation after crossing the placental barrier, injuring the developing kidneys. This causes oligohydramnios, which can cause two cord damage

and foetal mortality due to nutritional deficiency.²⁶ Aikaterini Zafeiri et al. found 405 stillbirths in 43998 pregnant women who took at least one OTC painkiller in a cohort study on singleton pregnancies.³²

CONCLUSION

Although analgesics are typically considered safe for use during pregnancy, there is a chance that they could cause a stillbirth, especially if they are used in the second and third trimesters. India has a high rate of irrational analgesic use during pregnancy without awareness of the risks associated with the medications. Thus, it is crucial to encourage the sensible use of analgesics. This can be done by either educating pregnant women about the hazards to their unborn children or by hiring a qualified chemist who can ensure that analgesics are only dispensed with prior medical authorization.

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