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## An analysis of the relationship between analgesic use during pregnancy and stillbirth

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### Abstract

Stillbirth is a tragic pregnancy complication associated with emotional, social, and economic disruptions. Stillbirth may be caused by advanced maternal age, smoking, obesity, comorbid conditions, low socioeconomic status, substance use during pregnancy, and other factors. Although evidence suggests a number of factors that contribute to stillbirth, the use of analgesics increases the risk of stillbirth. Each drug has its own set of advantages and disadvantages, which may have direct or indirect effects on fetal health. Drug exposure was associated with a twofold increase in the risk of pregnancy-related stillbirth. Control over the use of analgesics during pregnancy is not well-established due to a lack of substantial evidence implicating stillbirth as a consequence of analgesic use. In light of this, the risk of analgesic-induced stillbirth is highlighted in the present literature review. Widespread knowledge exists regarding the abuse of analgesics as over-the-counter medications. Painkillers are frequently used for self-medication without the supervision of a physician. Some of these medications tend to cross the placental barrier and can have harmful effects on the developing fetus. A pregnant woman may be compelled to take analgesics for a variety of reasons, including the discomfort associated with the mother's body adjusting to the changes that occur during pregnancy. Analgesics are ingested irrationally, resulting in pregnancy-related complications such as miscarriage, due to their accessibility and lack of knowledge regarding embryonic risk.

**Keywords:** Stillbirth, advanced maternal age, smoking, obesity, comorbid conditions

### Introduction

World Health Organization (WHO) defines stillbirth as foetal death after 28 weeks of pregnancy, but before or during birth.<sup>1</sup> Stillbirth is a tragic complication of the pregnancy which is associated with emotional, social and economic disturbances which is crucial to address the issue prior and to assess at each step of the pregnancy to avoid this complication.

Stillbirth can be a result of many causes like obesity, smoking, advanced maternal age (over 40), multiparity, hypertensive disorders of pregnancy (HDP), gestational diabetes, some ethnic race especially black women (because of no proper perinatal care) and others like inappropriate gestational periods, infections, thrombophilia etc.<sup>[2-8]</sup>. But in recent years' usage of drugs in pregnancy has been increased dramatically, globally it is estimated that 23%–85% of women use one or more types of prescribed medications during pregnancy<sup>[9, 10]</sup>. Prior to a new medicine being released into the market, the company seldom ever conducts studies on pregnant mothers to ascertain the drug's effects on the foetus<sup>[11]</sup>. As a result, safety profile for most of the drugs are poorly established.

The most recent statistics showed that there were 13.9 stillbirths per 1,000 live births worldwide in 2019<sup>[12]</sup>. This translates to one stillborn child every 16 seconds, or one in every 72 births overall. However, given that stillbirths are frequently underreported, this figure may be misinterpreted. The perinatal mortality rate in India currently is 36 deaths per 1,000 pregnancies.<sup>[13]</sup> According to Government's Annual report on the registration of Birth and Death reports act, 1969 stated that, Andhra Pradesh and Telangana 3.42% is the stillbirth rate in 2017<sup>[14]</sup>. In order to alleviate the burden of stillbirth, Government of India initiated 'The India Newborn Action Plan' in 2014, with the goal of lowering the rate of stillbirth by one-third nearing to 2025<sup>[15]</sup>.

As a thumb rule, each prescription has its own set of advantages and hazards, which may directly or indirectly affect the foetal health. Drugs like anticancer drugs, antiepileptic drugs, antipsychotics, analgesics cause stillbirth. In general, drug exposure was associated with the two-fold increased risk of stillbirth in pregnancy<sup>[16]</sup>. Usage of OTC during pregnancy has been increased,<sup>[17]</sup> which risks the foetus health. Painkillers are often used to self-medicate without the supervision of a medical professional<sup>[18]</sup>. In the current review, the risk of stillbirth on usage of analgesics during pregnancy is underlined.

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## Discussion

### Factors influencing the risk of stillbirth

Stillbirth can be caused by a variety of factors, which account for foeto-maternal mortality; nevertheless, documenting the reason for stillbirth is a stumbling block that leads to the notion that the cause of stillbirth is unclear [19]. Some of the factors are discussed hereafter.

### Advanced maternal age

In most industrialized nations, the average mother age during delivery has increased in recent decades [20]. The risk of stillbirth during pregnancy is three times higher in women of advanced maternal age i.e. beyond the age of 40, with or without any medical issues [21]. The combination of age and gestational week results in strain on expectant mothers. Conventionally, stillbirth rates are high during the early gestational week (20-23 weeks), decline between 39 and 41 weeks of gestation and then subsequently rises at 42 weeks and beyond [22].

Studies showed that placental abnormal phenotype was prevalent in women aged 40 and above, in addition to the reduction in food intake that comes with aging in women. Ageing is also related with increased risk of elevated reactive oxygen species, inflammatory markers that cause oxidative stress, and tissue dysfunction that may be a factor in placental abnormalities, which exhibits as increased placental weight, altered utero-placental vascular function and decreased placental efficiency attributing to increased risk of stillbirth [23].

### Obesity

Women who are pregnant should look for both themselves and the developing foetus. High Body Mass Index (BMI) adds significantly to any medical problem; bearing a child will be a health burden for those with excessive body mass. Obesity defined as BMI > 30kg/m<sup>2</sup>, doubles the chance of stillbirth [24]. Corpulence increases the length of the umbilical cord accounting to hyper coiling, which increases the risk of cord entanglement, clogging of the umbilical cord, and umbilical knot around the foetus, reducing the blood flow and resulting in placental insufficiency, which causes foetal growth restriction and stillbirth [25].

Increased BMI may be a result of inheritance or a sedentary lifestyle. In order to minimize stillbirth, pregnant women should maintain a good height to body weight ratio.

### Social habits

Physical and emotional stress along with lack of education and social awareness would make one dependent on social vices like chewing tobacco, smoking and drinking alcohol.

Smoking and chewing tobacco increases the incidence of stillbirth by 14% and has its own impact on the health of the mother and developing foetus before, after, and even during pregnancy [26, 27]. Cigarette smoking and alcohol consumption causes narrowing of placental vessels and consequently impairing blood supply to foetus, in addition to this, reduces foetal oxygenation causing complex cascade resulting in shock and foetal death [26, 28].

### Socio-economic status

According to National Institute for Transforming India (NITI) Aayog, 23.01% of India's population are considered as multidimensionally poor in 2016, [29] which contributes to one-fourth of Indian population suggesting lack of education, awareness, poor antenatal care contributing to majority of pregnancy-related complications. A comprehensive evaluation of research from developing nations found that poor socioeconomic position of pregnant women was strongly related with stillbirth, with an attributable percentage ranging from 2%

to 75% of the population [30]. In addition to all these, lack of woman's autonomy in terms of decision making may majorly affect the health of the mother and foetus contributing to maternal and foetal complications including stillbirth [31].

### Comorbidities

Age, low educational attainment, and socioeconomic standing all have an effect on an individual's overall health, leading to several chronic conditions that can end in miscarriage.

Hypertensive disorders of pregnancy (HDP) like preeclampsia and eclampsia have resulted in 15% of perinatal foetal mortality, similarly pre-gestational diabetes and Gestational diabetes mellitus increases the risk of stillbirth by 4-5 folds by causing foetal anaerobic respiration, shock and death. India being the World Diabetes Capital, Indian pregnant women are at high risk of stillbirth [32-36]. In addition to this, anaemia by default reduces placental oxygenation resulting in hypoxic environment attributing to stillbirth [37].

Conditions like Polycystic Ovarian Disorder (PCOD), Placenta Previa, Abruptio Placentae, oligohydramnios, infections etc causes morphological or pathological changes leading to malformed placenta which results in abnormal implantation, foetal growth restriction, placental insufficiency, necrotic placenta contributing to stillbirth [38-41].

### Drug use during pregnancy

Pregnancy is a unique physiological and psychological state, where the pharmacology of drugs is affected by changes in body physiology throughout time, which is of primary concern [42]. Some of the drugs can cross placenta and reach developing foetus which can cause potential harm due to physiological adaptation in pregnant women. The drugs, by default, possesses inbuilt harm in pregnancy which was witnessed by the thalidomide and diethylstilboestrol catastrophe [43]. These tragedies have led to more serious concerns, the Food and Drug Administration (FDA) established stringent norms on the use of drugs during pregnancy. Thereby, FDA classifies the drugs based on their teratogenic activity [42].

**Table 1:** FDA classification of drugs used during pregnancy

Categories	Description	Example
A	Adequate studies on pregnant women indicated no foetal risk	Vitamin B, C, D, E and folic acid, thyroxin etc.
B	Animal studies have showed no evidence of harm to the foetus, but lack of studies in pregnant women	Acetaminophen, Phenacetin etc.
C	Animal studies have shown adverse effect or no animal studies are conducted and no adequate studies in pregnant women	Aspirin, Gentamicin, antimalarial etc.
D	Studies showed risk to foetus, but benefit may outweigh the risk	Streptomycin, Tetracycline etc.
X	Studies showed evident risk to the foetus and use of the drug is contraindicated in pregnant women.	Estrogen, Norethindrone Etc

Some women become pregnant with pre-existing medical issues and few others develop novel medical conditions during the course of pregnancy that necessitate therapeutic intervention. Failure to address these issues has an impact on the health of both the expectant mother and the growing baby [44]. According to a study conducted by Sharma R and co-authors, around 8% of awaiting mothers require therapeutic intervention because of prevailing medical issues and pregnancy-related complications.

45 Considering the mother and foetal health; vitamins, minerals, iron and other dietary supplements are essential.

Drug use during pregnancy plays a pivotal role in ameliorating the mother's health and well being; nevertheless, for drug used to be successful, it must be non-toxic, effective, and should be rationally used. Primary factors of irrational medication usage include ease of access, feelings of improvement, underestimation of drug toxicity, unethical advertising, cost-driven attitude, incorrect perceptions of drug side effects, lack of adequate drug education by the prescriber, a lack of regulatory control system, etc. 46 The outcome of irrational use of drugs is exhibited as maternal and foetal complications owing to maternal as well as foetal death.

As cited previously, the safety of pharmaceuticals in pregnancy is not well established, and data indicates that Over-The-Counter (OTC) and prescription drug usage is widespread throughout pregnancy, with 2-3% of drug use resulting in birth abnormalities. 42 OTC medications are cheap, provide accentuated symptomatic relief which makes a pregnant woman to rely on OTC, thus promoting self- medication without being aware of risk. This had promoted pregnant women to go beyond OTC range that includes 'Schedule H' drugs being dispensed irrationally which are categorised under prescription drugs [47, 48].

The majority of antibiotics belong within the schedule H group of medications that are arbitrarily prescribed and used during pregnancy which could attack the mother's host cells, endangering her health and forcing her to ingest more and more drugs, perhaps leading to stillbirth.

Pregnancy-related irrational medication use has grown in developing nations like India as a result of drug dispensing without a prescription, distributing by non-pharmacists, and dispensing through a third party [49]. Analgesics, antipyretics, cough and nasal decongestants, antihistamines, and other drugs are available over-the-counter. Antibiotics, opioid analgesics,

antihypertensive, antianginal, antipsychotic, and other medications on prescription are included.

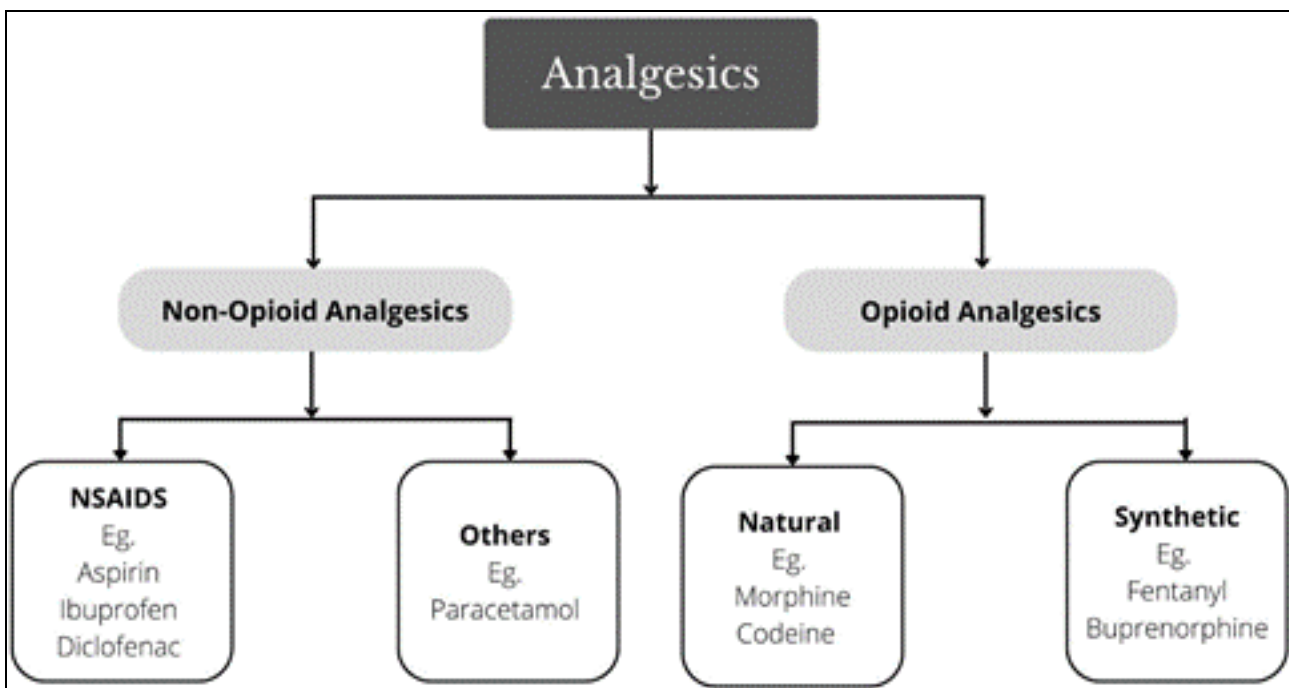
Drug use during pregnancy will have an impact on the foetus, either directly or indirectly, causing harm, aberrant development, and even death. They also impair the placental function by causing placental insufficiency, and few results in preterm uterine contraction injuring the foetus contributing to various pregnancy-related complications including stillbirth [42].

**Analgesic use in pregnancy**

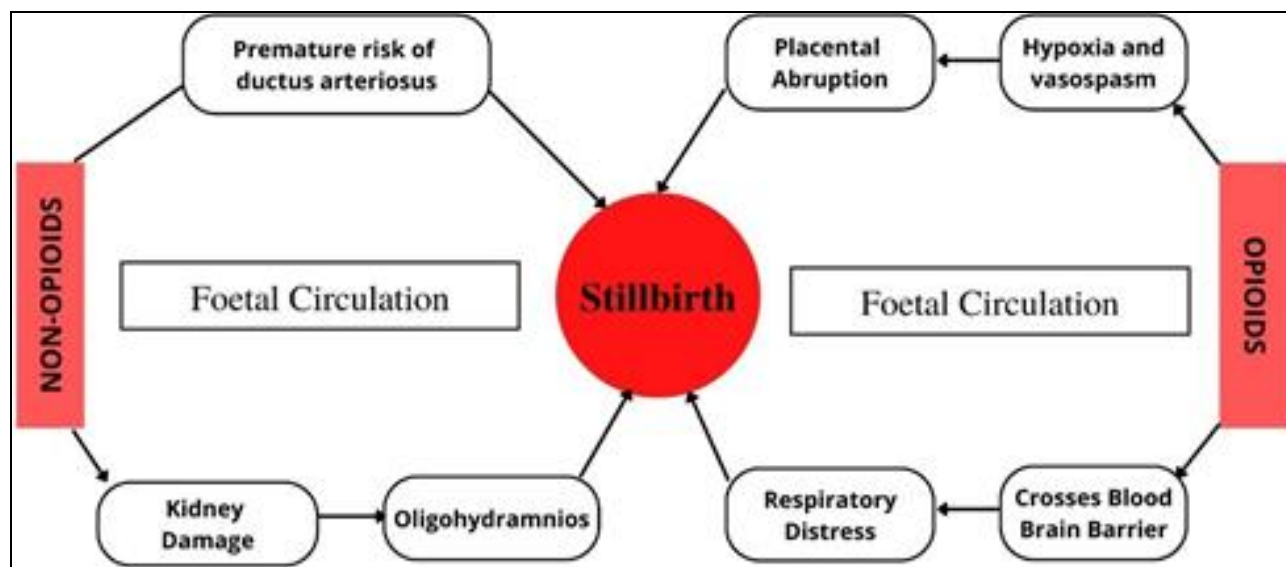
Many circumstances might drive a pregnant woman to use analgesics; for example, drastic changes in human physiology during pregnancy produce discomfort, which is majorly perceived as pain.

Non-opioid analgesics include Non-Steroidal Anti-Inflammatory Drugs (NSAIDS), such as aspirin, ibuprofen, diclofenac, and naproxen, as well as paracetamol. These analgesics are available over-the-counter, allowing easy access owing to arbitrary use. Due to unavoidable stressful commitments, pregnant women frequently use a lot of over-the-counter painkillers to manage their discomfort, unknowingly endangering the unborn child's health. To minimise pregnancy-related issues, the use of NSAIDS as analgesics is not suggested in pregnancy unless required and prescribed by a medical practitioner, and should be avoided beyond the gestational age of 30 weeks. While certain analgesics, such as acetaminophen (paracetamol), are safe to take throughout pregnancy [50].

In the US, 2-4% of pregnancies involved at least one opioid analgesic for pain, making the use of opioids during pregnancy a severe health risk [51]. Opioids are renowned for their teratogenic effects, which pose serious health risks to both the mother and the foetus and result in issues with pregnancy. Morphine, pethidine, codeine, methadone, buprenorphine, and fentanyl are few examples of opioid analgesics [51].



**Fig 1:** Classification of analgesics

**Mechanism of analgesics causing stillbirth****Fig 2:** Mechanism involved in analgesic-induced stillbirth

Non-opioid analgesic. During pregnancy, the increased plasma volume, cardiac output and glomerular filtration rate changes the pattern of drug absorption, thus increasing the bioavailability of free drug flowing in the circulation of mother with features of lipid solubility and low molecular weight making it simple for these free drugs to cross the placenta allowing the entry into foetal circulation which exhibits some hazardous effects. Drugs that belongs to the above category are aspirin, ibuprofen, naproxen and acetaminophen<sup>[52]</sup>.

NSAIDs are cyclooxygenase enzyme inhibitors that are widely used by 19% of the population for their analgesic, antipyretic, and anti-inflammatory properties. NSAIDs are often used in the first trimester and are generally avoided in the third trimester owing to adverse effects<sup>[53]</sup>.

The last three months of pregnancy are the most susceptible period, as the body gradually adapts to the change as the foetus develops. NSAIDs easily pass through the placenta, and inhibition of prostanoid action may result in miscarriage. After passing through the placental barrier, they enter the foetal circulation, causing kidney injury since the developing kidneys are unable to handle the foreign substance. This causes the placenta to have very little amniotic fluid, which leads to oligohydramnios, which can cause 2 cord injuries and foetal mortality due to insufficient nutritional supply<sup>[54]</sup>. (Figure 2) According a cohort study conducted by Aikaterini Zafeiri *et al.*, on singleton pregnancies showed 405 stillbirths out of 43998 pregnant women who have consumed at least one over-the-counter analgesics<sup>[50]</sup>.

**Opioid analgesic**

Opioid use during pregnancy has been connected to a number of obstetric and perinatal problems. Pregnancies exposed to prenatal opioid in the first and second trimesters have an increased risk of stillbirth<sup>[51]</sup> The biggest danger with opioid usage is dependency, and most women hide their opioid use for a variety of reasons, one of which is a sense of improvement. In the idea of opioid analgesics, the debate between "usage" and "abuse" persists.

When opioids are taken during pregnancy, they penetrate the placenta and enter the growing foetus's system, where they pass the blood brain barrier, causing respiratory distress, foetal

growth limitation, and foetal death<sup>[55]</sup> On the other hand, it also results in placental abruption by causing hypoxia and vasoconstriction of placental bed. Some of the opioid like cocaine can result in early uterine contraction leading to foetal injury and death<sup>[54]</sup>. A study conducted by Brogly *et al.* showed a statistically significant association between the occurrence of stillbirth and opioid exposure<sup>[51]</sup>.

**Conclusion**

Analgesics are usually blindfolded as safe for the use during pregnancy, but they do carry potential risk such as stillbirth, especially with the use in the second and third trimester. The irrational use of analgesics during pregnancy is high in India without the knowledge of risk attributed by the drugs. Hence, it is of paramount importance to promote the rational usage of analgesics, which can be attained either by educating the pregnant woman about foetal risks and/or by employing a registered pharmacist who can ensure dispensing of analgesics with prior medical authorization.

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