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(REVIEW ARTICLE)

A systematic review of therapeutic trends in preterm Labour

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Abstract

Premature birth, occurring before 37 weeks of pregnancy, is a significant health concern. It can lead to various complications for both the mother and the baby, contributing to neonatal morbidity and mortality. The risk of long-term neurological and developmental disorders increases with the degree of prematurity. There are several risk factors for preterm labour and premature birth such as antepartum heamorrhage, Urinary tract infections (UTI), certain vaginal infections etc. Certain lifestyle and environmental factors including: Late or no health care during pregnancy, Smoking, Drinking alcohol, Using illegal drugs etc. Premature birth can result in various health issues for preemie babies. Common health conditions include respiratory distress syndrome, intraventricular hemorrhage, patent ductus arteriosus (heart issues), and necrotizing enterocolitis etc. Symptoms of Preterm Labor include Contractions**,** Cramping or pain in the lower abdomen, fluid leaking from the vagina, increase in vaginal discharge, increased pressure in the vagina or the pelvis. Tocolytics are the drug of choice to delay the uterine contractions for atleast 48 hours.

Keywords: Premature birth; Neonatal; Mortality and Morbidity; Tocolytics

1. Introduction

According to the world health organization (WHO) the term preterm birth (PTB) is defined as babies born before completing 37 weeks of gestational age. Indeed, premature birth, occurring before 37 weeks of pregnancy, is a significant health concern[1]. It can lead to various complications for both the mother and the baby, contributing to neonatal morbidity and mortality. The risk of long-term neurological and developmental disorders increases with the degree of prematurity. Early and comprehensive prenatal care is crucial in addressing and mitigating these risks[2]. In addition, preterm birth can also increase the risk of death from other neonatal diseases. A newborn can be:

- Late preterm: born between 34 and 36 completed weeks of pregnancy.
- Moderately preterm: born between 32 and 34 weeks of pregnancy.
- Very preterm: born between 28 and 32 weeks of pregnancy.
- Extremely preterm: born before 28 weeks of pregnancy.

1.1. Risk factors

There are several risk factors for preterm labor and premature birth. Some of these risk factors are "modifiable," . Other factors cannot be changed. Some of the risk factors of preterm birth are idiopathic. These are the following factors that put women at high risk for preterm labor or birth[3] such as, women who have experienced preterm labor before, are considered to be at high risk for preterm labor and birth, being pregnant with twins, triplets, or more, antepartum hemorrhage, urinary tract infections (UTI), Sexually transmitted infections, Certain vaginal infections, such as bacterial vaginosis and trichomoniasis, Hypertensive disorders of pregnancy, Vaginal bleeding, Certain developmental anomalies in the fetus, being underweight or obese before pregnancy, Short time period between pregnancies (less than 6 months

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between a birth and the beginning of the next pregnancy), Placenta previa, a condition in which the placenta grows in the lowest part of the uterus and covers all or part of the opening to the cervix, Premature preterm rupture of membrane(PPROM), Diabetes and gestational diabetes, Blood clotting problems, Uterine over distension, Maternal stress, intra uterine growth restriction (IUGR). Women younger than age 18 are more likely to have a preterm delivery or women older than age 35 are also at risk of having preterm deliveries. Certain lifestyle and environmental factors, including: Late or no health care during pregnancy, Smoking, Drinking alcohol, Using illegal drugs, Domestic violence, including physical, sexual, or emotional abuse, Lack of social support, Long working hours with long periods of standing, Exposure to certain environmental pollutants.[4]

1.2. Complications

Premature birth can result in various health issues for preemie babies. Common health conditions include respiratory distress syndrome, intraventricular hemorrhage (brain issues), patent ductus arteriosus and necrotizing enterocolitis. These challenges often require specialized medical care to support the premature baby's development and well-being[5]. These challenges include, apnea**, Bronchopulmonary dysplasia,** or underdeveloped lungs, Intraventricular heamorrhage or bleeding in the brain, Necrotizing enterocolitis or inflammation of the intestines, Neonatal sepsis and abnormal blood flow in the heart, underdeveloped blood vessels in the eye, Low birth weight, Breathing difficulties, Vision problems, Underdeveloped organs, especially the lungs and the stomach, Cerebral palsy, Hearing and vision problems, Learning disabilities, Poor growth. Babies born prematurely also have a higher risk of being born with learning disabilities, cerebral palsy, behavioral problems, and attention deficit hyperactivity disorder (ADHD)[6].

1.3. Symptoms of Preterm Labor[7,8]:

- Contractions that come every 10 minutes or closer together
- **Lower Backache which might be** constant or can be on and off.
- Cramping or pain in the lower abdomen.
- Vaginal fluid leaking
- Flu-like symptoms including nausea, vomiting, or diarrhea.
- increase in normal vaginal discharge
- increased pressure in vagina or the pelvis.

1.4. Diagnosis

Transvaginal ultrasound cervical length measurement is commonly recommended for women at risk of preterm labor between 16 and 34 weeks of gestation. Monitoring cervical length helps healthcare providers assess the risk of premature birth[9]. An abnormally short cervix during this period may indicate an increased likelihood of preterm delivery, allowing for timely interventions or preventive measures to be taken[10]. Identifying women at risk for preterm birth is difficult. Several decision tools and clinical nomograms for predicting the risks of preterm labor are available, but most lack accuracy and precision[11]. The most useful tools for predicting risk are[12]: ultrasonography to determine cervical length and fetal fibronectin testing, shortened cervix and vaginal secretions these are strong predictors of preterm labor and birth[13].

1.5. Prevention and Treatment

Cervical cerclage is one strategy used for prevention[19]. It is of two types:

- Prophylactic cerclage is used in women with a history of recurrent mid trimesterlosses and who are diagnosed with cervical insufficiency. Prophylactic cerclage for women identified during sonography examination to have a short cervix.
- Rescue cerclage, done emergently when cervical incompetence is recognised in women with threatened preterm labour.

Corticosteroids. Corticosteroids are often recommended during preterm labor to promote lung maturity in the baby. Woman with age between 23 and 34 weeks and at an increased risk of imminent delivery, corticosteroids may be administered to enhance the baby's lung development. This intervention can be beneficial in improving the newborn's respiratory function and reducing the risk of complications associated with premature birth [14].

Tocolytics. Certainly, tocolytics are medications that can temporarily slow contractions. They are often employed for up to 48 hours to delay preterm labor. This delay allows for the administration of corticosteroids, maximizing their effectiveness in promoting the baby's lung maturity. In some cases, it also provides time for the expectant mother to be

safely transferred to a hospital with specialized care for premature babies, ensuring optimal outcomes for both mother and child[16]. Tocolysis aims to delay and weaken uterine contractions, primarily targeting the activity of the myometrium, which is the smooth muscle in the uterus. While the American College of Obstetricians and Gynecologists (ACOG) doesn't designate a definitive first-line tocolytic agent, commonly used medications for preterm labor include magnesium sulfate (MgSO4), indomethacin, and nifedipine. Each of these agents works through different mechanisms to achieve the goal of inhibiting premature contractions and potentially delaying labor[20].

The different medications currently used are:

- Beta-Adrenergic receptor agonists : terbutaline, Salbutamol, Ritodrine
- Calcium channel blockers : nifedipine, nicardipine
- Magnesium Sulfate
- Nonsteroidal anti inflammatories :indomethacin, celecoxib
- Oxytocin inhibitors : Atosiban, Ritosiban, barusiban
- Nitroglycerine : Nitroglycerin, nitric oxide

Beta-adrenergic receptor agonists: like hexoprenaline and ritodrine medications are used internationally for tocolysis. These drugs lead to potential maternal cardiac complications, including cardiac arrhythmias, tachycardia, hypotension, nausea, and vomiting. Fetal risks, such as tachycardia, are also considered. This emphasizes the importance of careful consideration and monitoring when using these medications in certain situations[22]. In the past, beta-mimetic agents like terbutaline or ritodrine were commonly used for tocolysis. In current practice, the approach has shifted towards avoiding beta-mimetic agents and considering combination tocolytic therapy, as it might be more effective in delaying preterm labor. This involves using a combination of different tocolytic medications with distinct mechanisms of action to achieve better results while minimizing side effects[21].

Calcium channel blockers, such as nifedipine, work by inhibiting T-type calcium channels, which decreases the entry of calcium into uterine smooth muscle. This action affects the activation of myosin light chain kinases, leading to muscle relaxation[23]. By blocking calcium, these medications promote the relaxation and opening of blood vessels. Maternal risks associated with calcium channel blockers like nifedipine include flushing, headache, dizziness, nausea, and hypotension. Importantly, studies have indicated no significant fetal risks with the use of nifedipine for managing preterm labor. Recent literature suggests that nifedipine may be considered the preferred tocolytic agent due to better neonatal outcomes and fewer side effects when compared to some other options. However, the choice of tocolytic therapy is often tailored to individual patient circumstances and medical considerations[24].

Magnesium sulfate: It works by reducing the amount of calcium in the uterine smooth muscles, which results in relaxation and decreased contractions[25]. The magnesium sulfate is used for neuroprotection. Several observational studies have reported an association of antenatal treatment with magnesium sulfate for preterm labor or preeclampsia with a decreased risk of cerebral palsy in low birth weight or preterm infants[26]. There are risks of magnesium toxicity and the side effects include flushing, nausea, reduced deep tendon reflexes, blurred vision, and reduced cardiac contractility. Calcium gluconate and fluids are used to manage the side effects of magnesium toxicity. Magnesium sulfate is often considered for women at high risk of delivering between weeks 24 and 32 of pregnancy. Research suggests that it may reduce the risk of cerebral palsy, a type of brain damage, in babies born prematurely. This medication is administered to provide neuroprotection and minimize the potential complications associated with early birth during this critical gestational period[15].

A nonsteroidal anti-inflammatory (NSAID) used for symptomatic management of chronic musculoskeletal pain conditions and to induce closure of a hemodynamically significant patent ductus arteriosus in premature infants. NSAID'S work through inhibiting cyclooxygenases (COX)[27].These enzymes are responsible for the production of prostaglandins from arachidonic acid. The most commonly used medication is Indomethasin. Indomethacin is also contraindicated after 32 weeks of gestational age because of premature closure of the ductus arteriosus[28].Other fetal effects from indomethacin include oligohydramnios, gastric perforation, and pulmonary hypertension. The initial recommended dose is 100 mg per rectum followed by 50 mg orally every 6 hours for 8 doses.

Oxytocin inhibitors work by competitively acting at the oxytocin receptor site. The medications currently in this class are atosiban and retosiban[29].**Atosiban** An inhibitor of oxytocin and vasopressin used to delay imminent preterm birth in pregnant adult women displaying specific clinical observations.

Intravenous nitroglycerine works by relaxing smooth muscle cells by releasing nitric oxide thus causing prompt cervico-uterine relaxation. Though the side effect profile is better when compared to beta-adrenergic receptor agonists,

transdermal nitroglycerine isn´t recommended for tocolysis[30]. This competes with other literature that shows that transdermal nitroglycerine is more effective at delaying birth compared with nifedipine[31].

1.6. Management[17]:

Preterm infants often need specialized medical care in a neonatal intensive care unit (NICU). This is a specific part of the hospital for babies in critical condition. Some babies stay in the NICU for weeks or months.

- Life style modifications[18]:
- Avoid tobacco, alcohol or drugs while pregnant.
- Eat a healthy, balanced diet.
- Get thorough prenatal care throughout pregnancy.
- Reduce stress level.
- Maintain the gap of at least 18 months between pregnancies.

2. Conclusion

Preterm birth before 37 weeks of gestation poses significant health risks for both mothers and infants, with potential long-term consequences. Various risk factors, both modifiable and non-modifiable, contribute to preterm labour. Complications for preterm infants include respiratory distress syndrome, intraventricular hemorrhage, and other developmental issues. Early diagnosis through methods like transvaginal ultrasound and prompt treatment, including tocolytics and corticosteroids, are crucial in managing preterm labor. Specialized care in neonatal intensive care units is often necessary for preterm infants. While there is no foolproof method to prevent premature birth completely but their incidence can be minimized by giving tocolytics. Neonatal mortality and morbidity can be improved by giving corticosteroids and thereby fetal life can be improved.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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