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Review Article

Management of Premature Labor

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Abstract

Introduction: Preterm birth is defined as a delivery before 37 weeks of gestation. It affects about 5 - 18% of pregnancies. Preterm birth is a leading cause of neonatal death, it is also the second most common cause of death in children below 5 years of age. Preterm infants have a higher risk of short-term complications (due to the immaturity of their organ systems) and neuro-developmental disorders such as intellectual disability, vision and/or hearing impairment and also cerebral palsy. Disability-adjusted life years, which is the number of years of life lost due to illness, disability or an early death, has preterm birth as its leading cause. The cost of health care related to this in the United States is about $26.2 billion annually. Most common cause of preterm births is idiopathic. Other causes include fetal factors, placental and uterine factors and maternal chronic diseases. 70% of preterm births in the US are idiopathic and the remaining are mostly related to pre-eclampsia (50%), fetal distress (25%) or placental abruption (25%).

Objectives: In this review, we will discuss the recent advances in management of premature labor.

Methodology: We did a systematic search for management of preterm labor using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

Conclusion: Preterm labor is a multifactorial condition accompanied with a great risk of morbidity and mortality. direction towards Prevention is by identifying women at risk and comprises screening and treatment for bacterial vaginosis, introducing cerclage in appropriate women and giving progesterone prophylaxis. The management of established preterm labor must be directed towards identifying those women in whom a delay in delivery is likely to be helpful and those in whom it may be harmful in terms of the outcome in neonates or infants.

Keywords: *Preterm Labor; Premature Birth; Intrauterine Infection; Premature Rupture of Birth*

Introduction

Preterm birth (PTB) is defined as a delivery before 37 weeks of gestation. It affects about 5 - 18% of pregnancies. PTB is a leading cause of neonatal death, it is also the second most common cause of death in children below 5 years of age. Around 15 million neonates are born preterm every year. Highest rates occur in North America and Africa [1]. Preterm infants have a higher risk of short-term complications (due to the immaturity of their organ systems) and neuro-developmental disorders such as intellectual disability, vision and/or hearing impairment and also cerebral palsy [2]. Disability-adjusted life years, which is the number of years of life lost due to illness, disability or an early death, has preterm birth as its leading cause. The cost of health care related to this in the United States is about $26.2 billion annually. Most common cause of PTB is idiopathic. Other causes include fetal factors, placental and uterine factors and maternal chronic diseases. 70% of preterm births in the US are idiopathic and the remaining are mostly related to pre-eclampsia (50%), fetal distress (25%) or placental abruption (25%). Preterm multiple fetal pregnancy as well as hypertension have been listed by one study as the major factors linked to preterm birth [3].

Methodology

We did a systematic search for management of premature labor using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used for search were preterm labor, premature birth, intrauterine infection, premature rupture of birth.

Causes

Infection, placental abruption/previa, substance abuse, preterm birth or abortion history, poor prenatal care, stress, smoking, maternal age less than 18 or greater than 40, inadequate nutrition, low BMI, fetal chromosomal anomalies, fetal intra uterine growth restriction, Poly or oligohydramnios, preterm premature rupture of membrane (PPROM), vaginal bleeding, and environmental factors are some of the most common factors that can lead to preterm labor [4].

The main concern with PPROM is prematurity. PPROM affects about 3% of all of the gestation in the United States. Most common cause of PPROM is intra-amniotic infection specially when it occurs at an earlier gestational age. Other causes are short length of cervix, bleeding occurring in the second or third trimester, underweight mother, low socioeconomic status, illicit drug use and smoking. Half of the mothers who have PPROM go into labor within a week's time. Respiratory distress is the most common complication of preterm birth, with sepsis, necrotizing enterocolitis and intraventricular hemorrhage being the others. Early gestation membrane rupture is also associated with an increased risk of white matter damage in the neonate. Accidents related to injury of the umbilical cord and intrauterine infections contribute to 1 - 2% of the total risk of fetal death after preterm rupture of membranes [5].

Pathophysiology

Labor has 3 main components: cervical changes, recurrent uterine contractions, and the activation of the membranes and the decidua. While labor with occurs at term is physiological, preterm labor is pathological. The cause of preterm labor can be physiological as well as pathological. Some processes by which it occurs are acute while some take several weeks. The main events in preterm labor is the fetal inflammatory response syndrome (FIRS). This involves systemic inflammation and fetal plasma elevation of Interleukin-6 levels in response to some trigger such as chorioamnionitis. Fetal hypothalamus signals secretion of CRH and ultimately the release of ACTH causing cortisol production by adrenal glands of the fetus which activates the parturition pathway. Inflammatory cells release cytokines that stimulate the cervical stroma and lead to cytokine and prostaglandin release which in turn stimulates cervical ripening. This leads to increases collagen and glycosaminoglycans production. Estrogen induces collagen degradation whereas progesterone inhibits it. Progesterone is hence used to stop ripening. Both hormones regulate gap junction formation and cause the upregulation proteins called connexin 43 that contribute to labor. In addition, uterine contractions are an important contributor to labor. Uncoordinated myometrial contractions to coordinated

ones is occurs due to neural control and oxytocin has an essential role in this. Fetal fibronectin is a marker for apoptosis of extracellular matrix and its presence in the cervicovaginal secretions is part of labor. If it is detected between 22 and 37 weeks of gestation, then it indicates disruption of the placenta and increased risk of preterm labor. Evidence implicates that this apoptosis is a critical factor that leads to the above process. Recent advances in prevention of preterm birth (PTB) [6].

Cervical length screening

In mid-pregnancy transvaginal ultrasound is used to measure length of cervix and it is able to predict PTB with reliability. For predicting preterm birth, a cervical length of < 25 mm with a singleton gestation (no prior PTB) is ~40% sensitive (negative predictive value of 97%) with a history of PTB, this sensitivity reaches 70% [7]. Risk increases as the cervical length decreases; a cervix length of < 15 mm increases the risk to 50%. Screening for shortened cervix is limited by its low prevalence (0.9 to 2.3%) depending on the prevalence in the population and the cut-off used (< 15, 20 or 25 mm). It has been calculated that screening 10,000 asymptomatic pregnancies followed by progesterone therapy would likely prevent only 60 cases of PTB and 16 deliveries at < 33 weeks. In places where PTB rates are lower, there is a greater likelihood of getting less benefit of screening and treatment. However, keeping in mind the potential mortality and morbidity, an investment in preventing these cases may actually be warranted [8].

Some new ultrasound approaches to screening of cervical measurements appear promising, however. Dziadosz., *et al.* [9] recently suggested uterocervical angle measurement at 16 - 23 weeks' gestation as a way of screening. They suggest that an angle of ≥ 95° was associated with significantly number of PTB at age < 37 weeks, with a sensitivity of about 80% and an overall negative predictive value of about 95%, whereas an angle of more than or equal to 105° of the predicted PTB at < 34 weeks will have sensitivity of 81% and a negative predictive value of 99%. This has outperformed the standard transvaginal cervical length measurement.

The use of cervical ultrasound elastography to predict PTB has been investigated vastly with and without the assessment of the overall cervical length. Two approaches have been developed for the quantitative determination of the physical properties of the cervix during pregnancy: strain and shear wave elastography. In a pilot study, strain elastography ratio and cervical length measurement combination was seen to greatly increase predictive performance, scoring an AUC of 0.88. These advancements lead to significant improvements in risk prediction and also the response to treatment, but they are likely to predict only a small fraction of women who deliver preterm [10].

Preventing and treating intrauterine infections

A major cause of early PTB is an ascending intrauterine infection and it is also an important preventable cause for all of the PTBs. Preterm deliveries caused by infections are most likely to be associated with a) unresponsiveness to tocolysis, b) FIRS, c) severe chorioamnionitis and funisitis and d) poorer neonatal outcomes. Most of the bacteria that are involved in the infection related PTB are the common bacteria that are frequently found in the female reproductive tract and some are abnormal vaginal microbiota (e.g. bacterial vaginosis [BV]) and/or the bacteria associated with reproductive tract infections [11,12].

Most commonly found organism is *Ureaplasma* spp. It is isolated from fetal membranes and the amniotic cavity in patients who have PTB. Rates of colonization of the vagina with *Ureaplasma* spp. in women who are pregnant ranges from 35 - 90%. There is a clear link seen between *Ureaplasma* spp. Colonization with a vigorous inflammatory response and preterm delivery and adverse neonatal outcomes. Two *Ureaplasma* have been found to colonize the human vagina, *Ureaplasma parvum* and *Ureaplasma urealyticum*. One study recently reported that around 40% of the pregnant women have *U. parvum and* 11% are positive for *U. urealyticum*. Also, *U. parvum* was detected in around 77% of women who went on to have a PTB compared to about 36% in those who were delivered at term. *U. parvum* genotype SV6 was seen to be 3.6-fold more common in preterm deliveries and can be detected in 54% of all sPTBs [13, 14].

It is not easy to identify women who are at risk of preterm delivery due to infection and it mainly relies of BV for the recruitment of women for trials of administration of prophylactic antibiotics. BV is still a less-than-optimal diagnostic criteria for the trail inclusion and risk prediction. There is an increased risk of PTB with BV in populations that have more African ethnicities. It is a weak risk predictor in

Caucasians (OR < 2) with a low rate of prevalence (< 10%). This method fails to identify many women with vaginal dysbiosis who do not have BV but may still be at high risk of infection-associated PTB. BV diagnosis also does not take into account *Ureaplasma* spp. status of colonization or allow the classification of *Ureaplasma*-positive women to either high or low risk. A diagnostic test (checking for the presence of *U. parvum* SV6 and other bacteria) is being developed it could considerably have a better performance than BV as a risk marker. Moreover, it identifies women who can benefit from therapy with antibiotics [15,16].

Several meta-analyses have taken place that show that antibiotic treatment of BV does not prevent PTB or generally improve neonatal outcomes, another meta-analysis of trials of clindamycin for women with BV before 22 weeks' gestation showed a significant reduction in the numbers of PTB at ≤ 37 weeks' gestation and also a reduction in the overall incidence of the late miscarriage [17]. *Ureaplasma* spp. colonization of the amniotic fluid occurs mainly after 20 weeks of pregnancy. The antibiotics commonly used to treat BV (e.g. clindamycin) demonstrate poor action against the *Ureaplasma* spp., with significant antibiotic resistance [18]. It has recently been demonstrated that a new antibiotic called solithromycin, a fourth-generation macrolide is superior to other drugs and have been developed to overcome macrolide resistance. It has high activity against *Ureaplasma* and *Mycoplasma* species and is effective against all of the bacteria that are known to cause infection (amniotic infection). Also, it can cross the placenta and treat the fetus. Solithromycin is not yet approved for sale. Its safety has to be tested before its antenatal applications can be evaluated in clinical trials [19].

Conventional treatment of BV results in relatively high recurrence and relapse rates. Probiotics (both vaginal and oral) have been shown to enhance the effectiveness of treatment of BV and candidiasis and markedly lower rates of recurrence. Probiotics are able to restore microbial homeostasis and exclude colonization by pathogens. It is likely, therefore, that probiotics administered after antibiotic therapy are likely to enhance treatment efficacy and reduce PTB rates; data from large randomized controlled trials to support this expectation are needed [20].

There is proven evidence that a trial of screening for vaginal infections then administering antimicrobial treatment can greatly reduce the rates of PTB and improve perinatal outcomes. Kiss., *et al.* [21] hired around 4,400 women in Vienna with singleton pregnancies ≤ 20 weeks of gestation. Women went through screening for BV and presence of *Candida* spp. and if turned out to be positive they were given antimicrobial treatment (clindamycin or clotrimazole as appropriate for six days), repeated if necessary, after re-screening at 24 - 27 weeks. Treatment regimen resulted in significant reductions in PTB at ≤ 37 weeks (43% reduction) and miscarriage (64% reduction). In women who went through screening and were positive, the overall PTB rate went down from 7.0 to 2.9% with management; in women with BV, the PTB rate went down by 38% (5.5 to 3.3%) and in women with *Candida* spp. it dropped by 66% (7.7 to 2.6%). The importance of the outcome observed is great in comparison to the results of other interventions, in particular bearing in mind the low risk prediction performance of the screening test (RR 1.3). The program was greatly cost-effective, with estimated costs ranging to only around 7% of the direct costs saved due to the reductions in prematurity (ratio of cost: benefit 1:14). As an outcome of the success of this trial, a voluntary antenatal infection "screen and treat" program was presented in Vienna, offered to women with great risk of PTB due to obstetric risk factors. Recurrent infections were stopped, and probiotics were given to women after treatment to prevent BV recurrence. Exceptionally, the outcomes actually exceeded the benefits of the actual trial, proving that the benefits could be attained in a routine clinical setting. More of obstetric care and reassurance to clinic patients may have been a major contributor to better outcomes, independent of any direct interventions [22].

Progesterone therapy

Few randomized controlled studies and meta-analyses have been conducted on two particular interventions made clinically for PTB prevention: progesterone management and cervical cerclage. Despite the controversy over the efficacy of these managements in the last years, some clarity is emerging. Jarde., *et al.* [23], conclusion was made that progesterone had greater efficacy than cerclage for primary prevention of PTB in high-risk women with a singleton pregnancy in a recently published network meta-analysis. Similar study is consistent with a recent patient-level meta-analysis, that concluded that cervical cerclage was deficient in demonstrable efficacy in women with

a shortened cervix (< 25 mm), although this can depend on prior PTB status. In contrast, progesterone management was found to greatly decrease rates of PTB at < 34 weeks (OR 0.44) and < 37 weeks (OR 0.58) and neonatal death (OR 0.50). Romero., *et al.* [24] had earlier come to the same outcomes following their own re-analysis of published studies, supporting prior analyses of benefits and risks. These two meta-analyses included the OPPTIMUM trial, which did not succeed to find a great benefit of progesterone, although it reported some useful trends. mainly, the longer-term benefits of progesterone management to the newborn still remain to be proven, and some authors have found some important concerns regarding side effects on the developing brain. This is still a major area of clinical confusion in need of solid, unambiguous data [25].

Progesterone's efficacy in women with a multiple pregnancy shows much lesser importance than in singleton pregnancies, although the evidence that it is deficient in the efficacy in this group has recently been brought up; consensus on this topic remains hidden. The outcome of countless studies, including a new published large trial, recommends that vaginal progesterone is greater in efficacy than intramuscular 17α-hydroxyprogesterone (17-OHP), although this can depend on a lot of risk factors and etiology. Vaginal progesterone is a less expensive option. There is only some proof of increased risk of developing gestational diabetes with 17-OHP management [26].

One side effect of progesterone management is that it is applicable to only a little percentage of pregnant women (mainly those with a shortened cervix and those with a history of previous PTB), so its overall benefits on a population basis are decreased. however, several trials have now confirmed the ability of conducting population-based cervical precheck programs and have concluded that the cost-effectiveness of such programs combined with progesterone therapy is beneficial, although they would clearly be enhanced if the efficacy of interventions could be increased [24].

Treatment

Preterm labor management should be directed towards looking for the cause, making sure delivery under utmost conditions, and considering the pros and cons of prolonging labor to increase gestational age. In clinical practice, this is to demonstrate that women that present to the hospital in threatened preterm labor must be appropriately examined to determine the best time for delivery. The presentation of fetal compromise or intrauterine infection can get worse prolonging the delivery, whereas early gestational age and uncomplicated preterm labor with present membranes can mitigate a prolongation in delivery. Deciding should be based on a risk-benefit analysis for all patient. The best pharmacological management are whether to give antibiotics, steroids or tocolytics.

Steroids

Great evidence suggest that antenatal steroids must be given to mothers who have threatened preterm labor to decrease the incidence of newborn respiratory distress syndrome, interventricular hemorrhage and perinatal death. Ongoing Discussion about whether they should be given at < 24 weeks or > 34 weeks and, although the RCOG advices up to 36 weeks, most babies born at > 34 weeks survive with no problems. The use of the time interval between administering and delivery being around 24h and 7 days have been exhibited, however, there could be a possibility that some advantage even outside these times. Current consensus is that steroids should be administered, although a better outcome has not been identified in multiple pregnancies. Most doctors give betamethasone, as a large observational trial showed a decreased incidence of periventricular leukomalacia compared with use of dexamethasone. Results of a randomized, controlled trial of dexamethasone and betamethasone are pending. Differences between oral and intramuscular administration has shown that, although there were no changes in the incidence of respiratory distress syndrome, the incidence of neonatal sepsis and intraventricular hemorrhage were higher in the neonates of mothers receiving oral steroids. Current guidelines are therefore to administer intramuscular betamethasone. A one course of maternal steroids is accompanied with a better neonatal prognosis, and detrimental outcome have not been shown in follow-up trials for up to 20 years. Nevertheless, there are greater concerns in regard to the effect of repeated courses on neurological development, neonatal or maternal infection, birth weight, adrenal suppression, maternal osteoporosis and deficient glucose tolerance. therefore, a one course of betamethasone must be given to almost all pregnant women in threatened preterm labor unless contraindicated or delivery is imminent [27,28].

Antibiotics

Preterm delivery is somewhat accompanied with evidence of chorioamnionitis, and the early gestational age at delivery, the higher the risk. Nevertheless, it is somewhat not clear whether infection or inflammation is the origin or the outcome of preterm delivery. In women with uncomplicated preterm labor with no ruptured membranes, the ORACLE trial did not succeed to show a better neonatal prognosis with antibiotic use. As this study recruited over 6000 women, it covers the subsequent meta-analysis and the final outcome from the latter are therefore the same. For the time being, antibiotics cannot be used for the management of preterm labor in the absence of prelabor rupture of the membranes. nevertheless, both ORACLE and the subsequent meta-analysis advise that, if rupture of the membranes happens preterm prior to the onset of labor, giving erythromycin is accompanied with prolongation of pregnancy and a better neonatal outcome. As a side effect of Augmentin on neonatal necrotizing enterocolitis was found, erythromycin seems the best first-choice antibiotic [29].

Tocolysis

A great number of authorities believe that tocolysis is beneficial in uncomplicated preterm labor, although this was never shown true in clinical trials. Meta-analysis of tocolysis compared with placebo or no treatment has shown to postpone delivery and maternal complication associated with tocolysis but with no improved perinatal outcome. The truth behind the maternal complications is concerning and could be patient selection (those with the potential for a complication may not have been identified). The time that was taken was not made used to undertake measures that would help the outcome (e.g. the rate of steroid administration was little at around 36%). Patients were incorporated at a gestational age at which postponing delivery was unlikely to help in measurable improvement in outcome. There are not enough large studies available to demonstrate an effect on the outcome. Such studies have led to the publication of guidelines that do not necessitate tocolysis to postpone delivery in uncomplicated preterm labor. Despite such guidance, most authorities give tocolytics either to postpone delivery long enough to let steroids to have an effect or to instigate other measures that are most likely to improve the prognosis, such as transfer to a unit with newborn intensive care facilities. If tocolysis is given, the question then becomes which drug should be administered [30].

Nifedipine

Calcium influx is important for myometrial cell contraction which is blocked by nifedipine. It is commonly used to relax vascular smooth muscle for the treatment of hypertension but not specific for uterine smooth muscle. improved neonatal outcome have been reported in women given nifedipine rather than ritodrine with less maternal side effects Although there are neither placebo nor double-blind controlled studies of nifedipine for the management of preterm labor. Meta-analysis of the clinical trials in which compares nifedipine with other tocolytic (usually ritodrine) also postpones delivery, reducing deliveries at < 34 weeks and improved neonatal prognosis. However, the singular studies which was found in the analysis have been considerably discussed as: (1) high comparator concentrations of ritodrine could have been administered, leading to patient withdrawal due to complications; (2) none were double blind; (3) a lot were small; or (4) individuals could have been given ritodrine prior to the study and rescue tocolysis used [31].

Conclusion

Preterm labor is a multifactorial condition accompanied with a great risk of morbidity and mortality. It can be prevented by identifying women at risk and comprises screening and treatment for bacterial vaginosis, introducing cerclage in appropriate women, and giving progesterone prophylaxis. The management of established preterm labor must be directed towards identifying those women in whom a delay in delivery is likely to be helpful and those in whom it may be harmful in terms of the outcome in neonates or infants. most obstetricians manage threatened uncomplicated preterm labor, although there is little evidence that tocolysis improves the prognosis for the baby, in order to give steroids or transfer the mother to an appropriate hospital. Nifedipine or atosiban are supported current guidelines treatment, both of which have their advocates. It is recommended to treat threatened, uncomplicated preterm labor with an oxytocin blocker to postpone delivery for steroid administration or transfer to an appropriate unit for delivery. When a single course of steroids should be given, it is believed that there is no indication for subsequent retreatment.

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