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REVIEW

PREVENTIVE ANTENATAL INTERVENTIONS TO REDUCE PREMATURE BIRTHS

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Abstract

Prematurity is the leading cause of neonatal mortality and one of the most challenging public health issues through the high and complex long-term morbidity and socio-financial burden of neonatal rehabilitation. Given the risks of preterm birth, multiple antenatal interventions were supposed avoiding prematurity (or at least the avoidance of very low- weight premature): tocolysis, corticotherapy, periventricular hemorrhages prophylaxis, antibiotherapy and also providing a safety delivery environment for the mother. The main objective of our paper was to evaluate the role of antenatal interventions in preventing premature births and their complications. Our paper is a narrative review and we selected studies from PubMed database from January 2000 to January 2021 using the following Medical Subject Headings: tocolysis, antibiotherapy, corticosteroids, prematurity, vitamin K, latency period. The results of the studies show there is an improvement of fetal and maternal outcomes when certain drugs are used such as tocolytic agents, antibiotherapy or corticosteroids. Every class of drug we presented in our paper aim to reduce the mortality and morbidity of

Résumé

Interventions anténatales préventives pour réduire les naissances prématurées

La prématurité est la principale cause de mortalité néonatale et l'un des problèmes de santé publique les plus difficiles en raison de la morbidité à long terme élevée et complexe et du fardeau socio-financier de la réadaptation néonatale. Compte tenu des risques d'accouchement prématuré, de multiples interventions prénatales ont été imaginées afin d'éviter la prématurité (ou du moins l'évitement des prématurés de très faible poids): tocolyse, corticothérapie, prophylaxie des hémorragies périventriculaires, antibiothérapie et aussi assurer un environnement d'accouchement sécuritaire pour la mère. L'objectif principal de notre article était d'évaluer le rôle des interventions prénatales dans la prévention des naissances prématurées et de leurs complications et nous avons sélectionné des études à l'aide de la base de données PubMed en utilisant les rubriques médicales suivantes : tocolyse, antibiothérapie, corticostéroïdes, prématurité, vitamine K, période de latence. Les résultats des études que nous

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the neonates and administrated in a rigorous manner, they prevent most of the unlikely outcomes. The data that support these strategies are limited in terms of the number of published studies, however, all the studies we included support the administration of tocolytic agents, antibiotherapy and corticosteroids as well as vitamin K.

Keywords: prematurity, antenatal, tocolysis, antibiotherapy, corticotherapy.

List of abbreviations:
AMP – adenosine monophosphate
NSAIDs – nonsteroidal anti-inflammatory drugs
CCBs – calcium channel blockers
WHO – World Health Organization
PPROM – preterm premature rupture of membranes
PO – per os
PVH – periventricular hemorrhages

avons présentées montrent qu'il y a une amélioration des résultats fœtaux et maternels lorsque ces médicaments sont utilisés. Toutes les interventions présentées dans notre article visent à réduire la mortalité et la morbidité des nouveau-nés et administrées de manière rigoureuse, elles préviennent la plupart des issues improbables. Les données qui soutiennent ces stratégies sont limitées en termes de nombre d'études publiées, cependant, toutes les études que nous avons incluses soutiennent l'administration de ces médicaments

Mots-clés: prématurité, anténatal, tocolyse, antibiothérapie, corticothérapie.

Introduction

Prematurity is the leading cause of neonatal mortality and one of the most challenging public health issues through high and complex long-term morbidity and socio-financial burden of neonatal final rehabilitation. Worldwide, preterm birth accounts for 965,000 deaths in the neonatal period and an additional 125,000 deaths in children aged one to five years[1]. In Romania, the rate of preterm birth is around 10% of all deliveries[2]. Preterm birth is a multifactorial medical condition which can be classified as spontaneous or iatrogenic, in case of acute pregnancy-associated conditions. Given the risks of preterm birth, multiple antenatal interventions were imagined avoiding the prematurity (or at least the very low weight premature): tocolysis, corticotherapy, periventricular hemorrhages prophylaxis, antibiotherapy and also providing a safety delivery environment for the mother.

This paper is a literature narrative review of studies related to the role of these interventions in the prevention of preterm birth.

The objective of the study

We aimed to evaluate the role of antenatal interventions in preventing premature births and their complications.

Materials and methods

We selected studies from Google Academic and PubMed databases and reviewed recent original articles from the literature, aiming to evaluate the impact of drug therapy on antenatal prevention of prematurity. We included articles published between January 2000 – January 2021, using the following Medical Subject Headings: tocolysis, antibiotherapy, corticosteroids, prematurity, vitamin K, latency period. The including criteria are the following: studies published in English, free full articles, systematic reviews, meta-analyses, and clinical trials. We excluded the studies published in other languages than English and clinical trials on animals.

Results

Tocolysis

Tocolytics are a class of drugs that inhibit myometrial contractions of the uterus, hence, preterm birth. Their main role is to delay the delivery for at least 48 hours, to administrate antenatal corticosteroids for enhancing fetal lung maturity.

Uterine contractions involve the interaction between actin and myosin with myometrial cells, mediated by myosin light-chain kinase[2,3]. The mechanism of action of tocolytic agents involves the regulation of the myosin light-chain kinase activity: calcium and cyclic adenosine monophosphate (AMP).

Many agents are used to inhibit these contractions, including magnesium sulphate, calcium channel blockers, oxytocin antagonists, nonsteroidal anti-inflammatory drugs (NSAIDs) and beta-adrenergic receptor agonists. No evidence exists that tocolytic therapy has any direct favorable effect on neonatal outcomes or that any prolongation of pregnancy afforded by tocolytics is translated to significant

neonatal benefit[2]. According to the American College of Obstetricians and Gynecologists, Table 1 summarizes the main tocolytic agents, their side effects, and contraindications.

Calcium channel blockers (CCBs) act as tocolytics by inhibiting calcium flow trough cell membranes and the release of intracellular calcium ions from the sarcoplasmic reticulum[3]. The most used drug for tocolysis is nifedipine. A meta-analysis of 38 studies published in 2014, involving 3550 women, compared betamimetics and CCBs and concluded that CCBs offer an additional delay of delivery of 4.4 days and fewer maternal adverse effects, such as hypotension and tachycardia[3]. The same study also concludes that nifedipine is superior to betamimetics in arresting birth within 48 hours when administrated for 7 days and before 34 weeks of gestation[4].

Several studies compared multiple classes of tocolytics and compared with placebo. The probability of delaying delivery by 48 hours was the highest with NSAIDSs, followed by CCBs and betamimetics. One study included 301 women in preterm labour, at 24 to 32 weeks of gestation, and compared the outcomes of nifedipine and indomethacin. Neonatal morbidity and mortality did not differ among the groups[5].

Oxytocin receptor antagonists compete with the peptide hormone, oxytocin, at binding sites located in the myometrium and decidua[2,3], preventing the increase in intracellular unbound calcium, that occurs when oxytocin binds to its receptor[2,3]. Atosiban is commonly used in Europe, but it has not been approved by U.S Food and Drug Administration because of its fetal effects[3]. A study randomized women with preterm labour to oral nifedipine versus intravenous atosiban for 48 hours, and the results showed that both medications resulted in similar perinatal outcomes[6].

Corticosteroids

The most beneficial intervention for improvement of neonatal outcomes among patients who give birth preterm is the administration of antenatal corticosteroids[7]. For pregnant women starting at 23 weeks of pregnancy who are at risk of premature delivery within 7 days, a single course of corticosteroids is indicated[7]. A recent study shows its beneficial role and concludes that corticotherapy should be considered routine for all preterm deliveries. Neonates whose mothers receive antenatal corticosteroids have significantly lower severity, frequency, or both of respiratory distress syndrome. Betamethasone and dexamethasone, two corticosteroids that vary in the orientation of the methyl substituent at position 16, have been demonstrated to be effective in fetal lung development[7]. They are both synthetic fluorinated steroids with a high affinity for the glucocorticoid receptor, but little mineralocorticoid action, and both cross the placenta.

A Cochrane review which compared antenatal administration of dexamethasone and betamethasone

Table 1. Common tocolytic agents (Adapted from: Practice Bulletin No. 159: Management of Preterm Labour. *Obstet Gynecol.* 2016;127(1))

Agent or class	*Maternal side effect*	*Fetal/Newborn adverse effects*	*Contraindications*
Calcium channel blockers	Dizziness Hypotension Suppression of heart rate Cardiac lesions (aortic and left ventricular systolic pressure insufficiency) Elevation of hepatic aminotransferases	-	Hypotension Cardiac lesions
NSAIDs	Nausea Esophageal reflux Gastritis Platelet dysfunction	Necrotizing enterocolitis	Platelet dysfunction Hepatic dysfunction Gastrointestinal ulcerative disease Renal dysfunction Asthma
Beta adrenergic receptor agonists	Tachycardia Hypotension Palpitation Shortness of breath Hypokalemia Hyperglycemia	Fetal tachycardia	Tachycardia
Magnesium sulfate	Nausea Loss of deep tendon reflexes Respiratory depression Neuromuscular blockade (when used with calcium-channel blockers)	Neonatal depression	Myasthenia gravis

Legend: NSAIDs – non-steroidal anti-inflammatory drugs

Table 2. International guidelines of expectant management of preterm premature rupture of membranes (PPROM)

Organization	*Antibiotics used and dosage*
ACOG (USA)	Penicillin Ampicillin (alternative) Erythromycin Clindamycin
DGGG (Germany)	Penicillin G Mezlocillin Piperacillin Clindamycin Ampicillin Erythromycin or Cefazolin (alternative)
RCOG (UK)	Penicillin Erythromycin –10 days Benzylpenicillin (3g IV and 1.5g 4h until delivery) or Clindamycin (900 mg IV for 8 hours) Vancomycin (if resistant)
SOGC (Canada)	Ampicillin (2g IV every 6h for 48h) and/or Erythromycin (250mg IV every 6h for 48h, followed by 333mg PO every 8h for 5 days)

Legend:
ACOG – American College of Obstetricians and Gynecologists (United States of America); DGGG – Deutsche Gesellschaft fur Gynakologie und Geburtshilfe; RCOG – Royal College of Obstetricians and Gynecologists (United Kingdom); SOGC – Society of Obstetricians and Gynecologists of Canada

evaluated the results of 10 trials including 1159 women and 1213 infants. Dexamethasone showed increased risk of interventricular hemorrhage compared to betamethasone, but there are no differences related to other pathologies, such as patent ductus arteriosus, periventricular leukomalacia or neonatal death[8].

The administration of corticosteroids is controversial: the World Health Organization guidelines do not recommend them after 34 weeks of pregnancy, the Royal College of Obstetricians and Gynecologists also does not recommend late preterm use of steroids[9], but according to American College of Obstetricians and Gynecologists recommendations, pregnant women between 34 and 36 weeks of pregnancy, who are at risk of preterm delivery within 7 days and who have not previously taken prenatal corticosteroids, should get a single course of betamethasone[10].

Regarding caesarean deliveries, the Royal College of Obstetricians and Gynecologists recommend the use of steroids for all women prior to 39 weeks of gestation[9], but American College of Obstetricians and Gynecologists does not recommend them for term births, regardless of planned mode of delivery[10]. The pathophysiology of respiratory morbidity in term infants is different than that of preterm infants: in term infants, the respiratory complications are thought to be caused by increased fluid retention in the lungs and the lack of cathecolamine surge that normally occurs with labour[2]. Also, labour activates sodium channels in epithelial cells of the lungs, that promote drainage of alveolar fluid. In absence of labour, glucocorticoids increase the activity of sodium channels, which represents a benefit of antenatal corticosteroids of caesarean deliveries[2].

Women with multiple gestations are six times more likely to give preterm birth than women with singleton gestations[12]. Neonates from multiple pregnancies are at increased risk of prematurity complications, including interventricular hemorrhage.

Antibiotics

There are three mechanisms by which antibiotics reduce the incidence of preterm birth, including prematurity complications: first, in PPROM, secondly, prophylactically in women at risk because of abnormal genital tract flora in early pregnancy, and finally in the inhibition of spontaneous preterm labour in women with intact membranes at risk of preterm birth.

Regarding the preterm rupture of the membranes, the treatment is needed to prolong the latency period of pregnancy, hence the international guidelines recommend the options presented in Table 2.

Lee et al found that the combination of ceftriaxone, clarithromycin and metronidazole prolonged the latency period, reduced acute chorioamnionitis and improved neonatal outcomes in patients with PPROM, especially with intraamniotic infection[13,14]. Also, this antibiotic combination was associated with a more successful eradication of intraamniotic

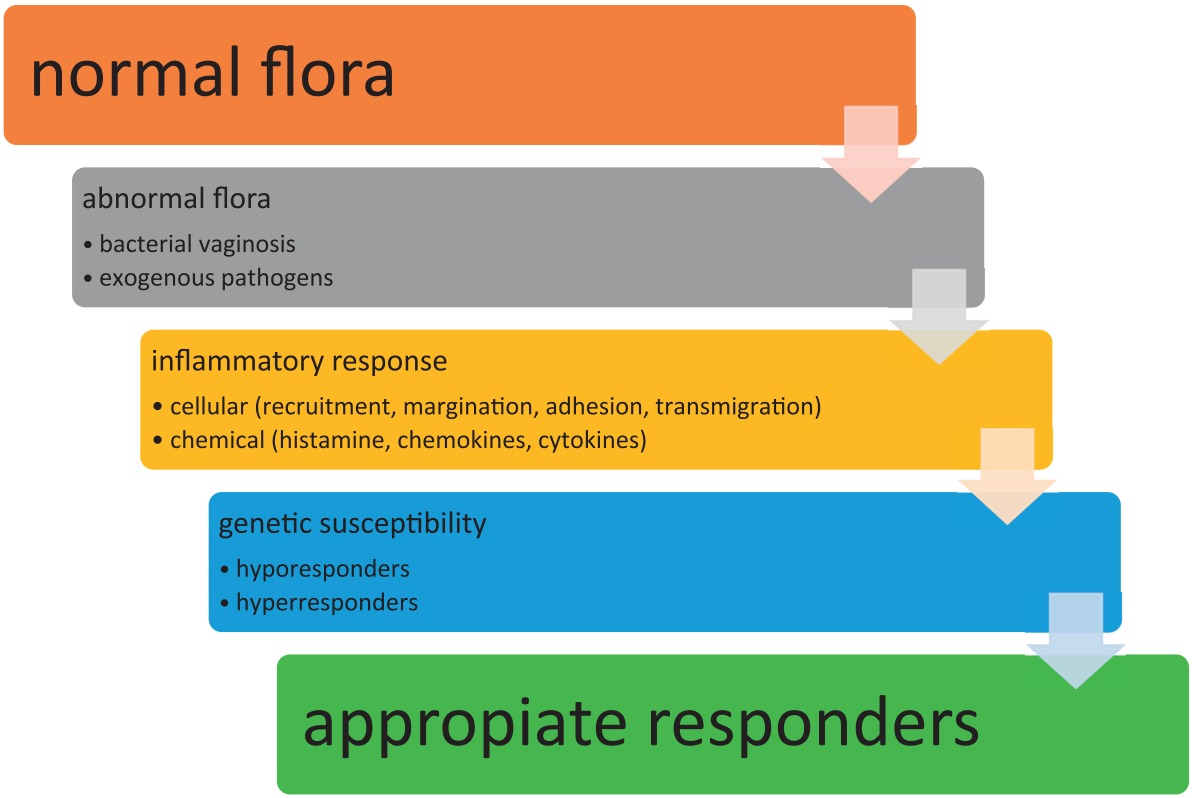

Figure 1. The host inflammatory response to abnormal genital tract flora (Adapted from: Lamont RF. Can antibiotics prevent preterm birth-the pro and con debate. *BJOG.* 2005;112 Suppl 1:67-73)

infection and prevented secondary intraamniotic inflammation more frequently than a regimen including ampicillin and/ or cephalosporins in patients with PPROM[14]. Cousens et al. showed that antibiotic treatment would decrease the complications of prematurity and post-natal infection in high-income settings. In low-income settings, where access to other interventions (antenatal steroids, surfactant therapy, ventilation, and antibiotic therapy) does not exist or is insufficient, antibiotics for PPROM could prevent 4% of neonatal deaths due to complications of prematurity and 8% of those due to infection[15]. Some studies show that children born by mothers without PPROM, who received erythromycin or amoxicillin-clavulanic acid during pregnancy, developed cerebral palsy or epilepsy compared to mothers who did not receive these antibiotics[16,17].

Genital tract flora can be graded as I, II or III by using a Gram stain of vaginal secretions. In contrast to normal flora (grade I), grades II (intermediate) and III (bacterial vaginosis) are considered abnormal flora[18]. Normal flora becomes abnormal either due to an endogenous imbalance because of a condition such as bacterial vaginosis, or alternatively by introduction of an exogenous pathogen[18]. This results in an acute inflammatory response involving hyperemia, tissue permeability and oedema from a combination of cellular and chemical immune response. The host response is shown in Figure 1. If antibiotics are used before abnormal flora results in infection, adhesion, invasion, and inflammation, it is expected that spontaneous preterm labour and preterm birth to occur[18]. If antibiotics are used when inflammation and tissue damage have already occurred, it may be impossible to reverse the process. The initial intervention in high-risk pregnancies using systemic antibiotics suggested that treatment reduced the risk of preterm delivery and infectious morbidity.

In a study, 80 bacterial-vaginosis-positive pregnant women at high-risk of preterm birth were randomly assigned to take oral metronidazole or placebo. Compared to placebo, women in the treatment group had fewer admissions for preterm labour, preterm births and PPROM[19]. In other trial, 624 pregnant women at high-risk of preterm birth were randomly assigned to take metronidazole and erythromycin or placebo. In the 258 women with bacterial vaginosis, antibiotic treatment reduced the preterm birth rate compared to placebo[20]. In two studies[21,22], administration of oral metronidazole late in the second trimester (23-24 weeks of gestation) did not reduce the risk of preterm delivery in women with bacterial vaginosis who were at a low risk of preterm birth. Carey at al. used 2g doses of metronidazole administered

48h apart at 23 weeks and two further doses between 24 and 30 weeks of gestation, while McDonald et al. used oral metronidazole 400mg twice a day for two days. In the first study, persistent bacterial vaginosis was present, and 60% of cases required repeated therapy[21], whereas efficacy was approximately 75% in the latter study[22].

Antenatal administration of vitamin K for preventing neonatal periventricular hemorrhages (PVH)

Infants born prematurely are at significant risk of developing brain injuries, which are associated with periventricular hemorrhages. Later neurodevelopmental abnormalities, such as cerebral palsy, can occur because of these damages. The main cause of PVH is unknown, however, the most plausible explanation is brain ischaemia, followed by bleeding in the subependymal matrix[23]. In addition, coagulation disorders have been reported in most infants with PVH. Preterm newborns have low levels of clotting factors, some of which require vitamin K for activation. It has been stated that prophylactic antenatal rather than postnatal treatment is preferable, due to the arising time of the hemorrhages, which usually are thought to be close to the time of birth[2,23]. Besides the benefits for the neonates, antenatal administration of vitamin K in pregnant women has benefits for improving maternal outcomes. Vitamin K supplementation has been suggested to improve prothrombin and partial thromboplastin activities[23].

A study published in 2006 analysed the combined antenatal corticosteroids and vitamin K therapy in reducing the frequency and the degree of PVH in premature new-born less than 35 weeks of gestation[24]. The study included four groups, the first one received vitamin K 10 mg per day for 2-7 days, the second dexamethasone 10 mg single dose, the third group received 10 mg dexamethasone, two days and the last one combined therapy of dexamethasone 10 mg single dose and vitamin K 10 mg for 2-7 days. The results showed that after antenatal treatment with combined dexamethasone and vitamin K, the incidence and frequency of PVH significantly decreased. There were no differences between the 2nd and the 3rd group in terms of the incidence. In another study, it has been shown that vitamin K-dependent coagulation factors II, VII, and X are deficient in preterm infants, and antenatal vitamin K administration resulted in a significant improvement in plasma activity of these factors, as well as a lower degree of hemorrhage in preterm infants[25].

In a Cochrane review, there were analysed 7 studies, concluding that the benefit of vitamin K in preventing severe periventricular hemorrhage is „unlikely to be a true effect of the drug“ and the apparent lack of effect of vitamin K could be explained by poor placental transfer of vitamin K, therefore a poor effect on fetal coagulation factors[26].

Latency period

Latency period refers to the time between membrane rupture and delivery and is an important factor for neonatal survival. It is not clear what influences the latency period, although several factors were linked with shortened latency, such as gestational age, intra-amniotic infection, placental abruption and fetal distress[2,27]. The risks that occur after preterm premature rupture of membranes are high in terms of infant mortality rates, especially before 30 weeks of gestation, pulmonary diseases being the major cause of death[2,28]. Also, the risk of chorioamnionitis increases directly with latency period, which worsens the neonatal outcomes, being one of the leading cause of brain damage.

One study published in 2020 evaluated the maternal and fetal outcomes of PPROM with different latency periods at 24-34 weeks of gestation [29]. The study group includes 206 patients who were divided in 3 subgroups by the duration of the latency period: 3-7 days, 8-13 days and ³ 14 days. The study revealed that as the latency period prolonged at 24-28 weeks of gestation, Apgar at 1“ <5 and at 5“ <7 and the number of new-born babies requiring resuscitation significantly decreased. In new-born babies, born at < 32 weeks, the rate of total complications was lower in the latency period ³ 14 days group compared to those in the latency period of 3-7 days and 8-13 day groups. There was no significant difference between the latency period and total complications after 32 weeks. Another study conducted on 303 pregnant women indicated that twin pregnancy and chorioamnionitis are factors that independently influence the prolongation period between rupture of membranes and delivery: the mean interval for singleton (5.5 days) is longer than for twin pregnancies (3.3 days)[30]. The same study concluded that the failure rate of delaying delivery for more than 48 hours after PPROM is higher in twin pregnancies (74.2%) than in singletons (51,5%). The study points on the fact that the association between twin pregnancy and short latency period is limited in cases under 30 weeks' gestation.

Available evidence shows that all the antenatal interventions are successful to delay the delivery and to create a safety environment for the new-born. Regarding tocolytics, the most promising one is nifedipine, being inexpensive and easy to administrate and could be further implemented worldwide, as most of the trials demonstrated its beneficial effects. Also, corticotherapy showed its undeniable

useful effect on neonatal outcomes in preventing respiratory tract diseases, and its implementation was analysed by the most important international guidelines. The debate is whether vitamin K and antibiotherapy should be administrated, when and how. One of the key factors which determine the maternal and fetal outcome is latency period and further investigation should be performed to establish the right medical conduct.

Conclusions

Premature rupture of membranes is more likely to be caused by a pathology that occurs earlier during pregnancy. All the presented strategies aim to reduce the mortality and morbidity of the neonates and applied in a rigorous manner they prevent most of the unfavourable outcomes. The data supporting these strategies are limited in terms of number of published studies, however all the studies we included in this review support them. Even if the treatment scheme differs between countries, the effect seems to be constant, and the statistics show the same result. More research is required to understand the actions of corticosteroids and vitamin K, including a clear decision-making pathway.

Author Contributions:

D.R.U. conceived the original draft preparation. D.R.U., M.A.M., S.I.B. and C.V.A. were responsible for conception and design of the review. D.R.U., S.C., and D.G.F were responsible for the data acquisition. D.R.U., M.A.M., C.V.A, S.C. and S.I.B. were responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

Compliance with Ethics Requirements:

The authors declare no conflict of interest regarding this article

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