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Long-term childhood outcomes after interventions for prevention and management of preterm birth

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ABSTRACT

Globally, preterm birth rates are rising and have a significant impact on neonatal morbidity and mortality. Preterm birth remains difficult to prevent and a number of strategies for preterm birth prevention (progesterone, cervical pessaries, cervical cerclage, tocolytics, and antibiotics) have been identified. While some of these show more promise, there is a paucity of evidence regarding the long-term effects of these strategies on childhood outcomes. Strategies used to improve the health of babies if born preterm, such as antenatal magnesium sulfate for fetal neuroprotection and antenatal corticosteroids for fetal lung maturation, show evidence of short-term benefit but lack large-scale follow-up data of long-term childhood outcomes. Future research on preterm birth interventions should include long-term follow-up of the children, ideally with similar outcome measures to allow for future meta-analyses.

Introduction

Globally, preterm birth rates are rising with 10% of neonates born less than 37 weeks gestation.[1] Preterm birth is the most common single cause of perinatal and infant mortality.[2] For those infants who survive preterm delivery there is an increased risk of neurological disability. This risk increases with decreasing gestational age with extremely preterm babies (≤26 weeks) having the worst neurological outcomes.[3,4] The risk of having special educational need at school age also shows an inverse relationship with increasing need seen with decreasing gestational age.[5] However, the rate of survival without neurodevelopmental impairment, even at extreme prematurity, has increased in recent years.[6]

The aim of interventions to prevent preterm birth is to prolong pregnancy, which is presumed to improve the health of babies.[7] Methods of preterm birth prevention include cervical cerclage, vaginal and intramuscular progesterone, cervical pessaries, antibiotics, and tocolytics. Despite these interventions forming a crucial part of obstetric practice, a recent review of the evidence surrounding preterm birth prevention concluded that the best intervention is still unclear and that delaying delivery may not necessarily result in improved health in the children.[7]

In addition to methods of preterm birth prevention two interventions improve the health of the babies if born preterm—antenatal corticosteroids to promote fetal lung maturation and antenatal magnesium sulfate for fetal neuroprotection.[8–11] These interventions have been endorsed by National and International bodies including the Royal College of Obstetricians and Gynaecologists UK (RCOG) and UK National institute of Clinical Excellence (NICE) in the UK,

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the World Health Organisation (WHO), and the American College of Obstetricians and Gynecologists (ACOG).

Although the immediate outcomes of the interventions to prevent PTB and improve the outcome of babies born preterm are well researched, less is known about the long-term outcomes of these interventions. In this review long-term neurological outcomes of interventions to reduce preterm birth will be evaluated as well as long-term outcomes of interventions to improve the health of infants born preterm.

Long-term outcomes of progesterone for preterm birth prevention

Progesterone is available as an intramuscular injection of 17 α-hydroxyprogeterone caproate (only licensed in the USA) or a vaginal progesterone preparation (the only available progesterone product in the UK, but not licensed either in USA or Europe for preterm birth prevention). Progesterone is currently recommended for use for preterm birth prevention in the UK NICE guideline for certain specific categories of women (singleton pregnancies at high risk of preterm birth). Biological plausibility for the use of progesterone comes from the concept that uterine quiescence is maintained throughout pregnancy and labor is thought to occur as a result of a functional withdrawal of progesterone.[12] Some work has been done in recent years regarding the safety of the use of progesterone for the prevention of preterm birth.[13,14] The most recent review published in 2016 by O'Brien and Lewis[15] of the safety of 17 α-hydroxyprogestone caproate concludes that its use is contraindicated in multiple pregnancies because of the risk of adverse immediate neonatal events (RR = 1.21, 95% CI: 1.03–1.43 for a composite outcomes of death and severe morbidity) and that in singletons further research is needed to determine its safety. Studies investigating the effectiveness of progesterone in preventing preterm birth have conflicting results. A recently published Cochrane review and individual patient data (IPD) meta-analysis of the use of progesterone in singleton pregnancies demonstrated it was an effective agent in preventing preterm birth in women with previous preterm birth and a short cervix.[16,17] The recently published OPPTIMUM trial, the largest randomized controlled trial (RCT, $n = 1228$) to date of vaginal progesterone versus placebo for prevention of preterm birth demonstrated no difference in gestational age at delivery between the two groups.[18] Nevertheless, despite this controversy, progesterone is used widely throughout the world for preterm birth prevention and therefore information about the long-term childhood neurological outcomes is crucial for counseling women about its use.

The OPPTIMUM trial reported on childhood outcomes at age 2 ($n = 869$) using the Bayley Score of Infant Development (BSID). There were no statistically significant differences in the scores between the progesterone and placebo group reported with a difference in means of −0.48 [95% Confidence intervals (CI): −2.77 to 1.81]. Analysis of secondary outcomes showed (nonstatistically significant) higher rates of death from trial entry to age of 2 in the progesterone group (3% compared with 4%, OR = 1.28 (95% CI: 0.66–2.51), $p = 0.48$) and a (nonstatistically significant) higher incidence of moderate to severe neurodevelopment disability (9% compared with 12%, OR = 1.48 (95% CI: 0.98–2.33), $p = 0.087$]. A study by Northen et al.[19] performed the longest follow-up study to be done in singletons with a mean age at follow-up of 48 months ($n = 270$). This was a follow-up of the National Institute of Child Health and Human Development Maternal-Fetal Networks Study of 17 α-hydroxyprogesterone caproate as part of a multicenter placebo-controlled trial.[20] The initial study demonstrated a significant reduction in the rate of spontaneous preterm birth but the follow-up study reported that, despite 17 α-hydroxyprogesterone caproate apparently preventing preterm birth, scores of the 'Ages and Stages' questionnaire (ASQ) did not differ significantly between the progesterone and the placebo groups being within normal ranges in both (ASQ score below cut-off on at least one area 27.5% in the progesterone group compared with 28% in the placebo group, $p = 0.92$).

In multiple pregnancies a placebo-controlled RCT of vaginal progesterone published by Rode et al.,[21] the PREDICT trial, reported on long-term infant follow-up. The infants were assessed by ASQ at 6 and 18 months after the expected date of delivery ($n = 1050$). There were no statistically significant differences found in the mean scores between the progesterone group and the placebo group (ASQ mean score at 6 months 215 compared with 218, $p = 0.45$ and mean ASQ score at 18 months 193 compared with 194, $p = 0.89$). The STOPPIT[22] RCT also compared vaginal progesterone with placebo in twin pregnancies and a follow-up study published in 2015 investigated the effect of vaginal progesterone on childhood outcome.[23] The mean age at follow-up was 55.5 months and the 'Child Development Inventory' was used to measure childhood outcome ($n = 759$). There was no evidence of difference between the progesterone-exposed and the placebo-exposed twins (Child Development Inventory score below cut-off on at least one area 30% compared with 35%, $p = 0.66$), equally there was no difference in the overall health index of the groups (Health Utilities Index rating 'excellent' 88% compared with 90%, $p = 0.51$). A further follow-up of the PREDICT babies has recently been published by Vedel et al.[24] providing the longest follow-up to date of children aged 8 years ($n = 989$). The primary outcomes investigated by this study were neurophysiological development of the children assessed by the ASQ and admissions and diagnoses up to 8 years of age using medical records of the children. The study did not report any harmful effect of exposure to progesterone in terms of diagnoses and admissions ($n = 989$). A statistically significantly higher mean ASQ score in the progesterone group compared to the placebo group was reported [mean total score 269, (Standard deviation SD = 28.2) compared with 261.7 (SD = 31.4), $p = 0.03$] but of note the scores were only received on 437 of the children (45.8% response rate but no differences found on maternal characteristics of responders and nonresponders).

As well as a putative effect on delaying the onset of labor, it has been proposed that progesterone may have a direct beneficial effect on the fetal brain. Progesterone has recently been investigated because of its potential therapeutic use in acute traumatic brain injury in adults. Biologically beneficial effects are thought to be feasible because progesterone is widely distributed throughout the central nervous