Evidence to support key Antenatal Optimisation measures

These references provide the evidence for antenatal optimisation interventions and can be used to persuade your team of the rationale.

Prediction of preterm birth

1. QUiPP app:

Watson HA, Carter J, Seed PT, et al. The QUiPP App: a safe alternative to a treat-all strategy for threatened preterm labor. *Ultrasound in Obstetrics & Gynecology* 2017;50(3):342-46. doi: 10.1002/uog.17499

Brief summary: The authors evaluated the impact of triaging women at risk of spontaneous preterm birth (sPTB) using the QUiPP App as compared to a treat-all policy in women presenting with threatened preterm labour before 30 weeks gestation. The QUiPP App incorporates a predictive model combining history of sPTB, gestational age and quantitative measurements of fetal fibronectin. In this prospective observational secondary analysis study the authors collected data of pregnant women presenting with symptoms of preterm labor at 24-34 weeks' gestation from the research databases of the EQUIPP and PETRA studies. Each episode of threatened preterm labor was retrospectively assigned a risk for sPTB within 7 days using the QUiPP App. A primary outcome of delivery within 7 days was used to model the performance accuracy of the QUiPP App compared with a treat-all policy.

A total of 188 cases were compared. The study found that using a 5% risk of delivery within 7 days according to the QUiPP App as the threshold for intervention, 9/9 women who presented with threatened preterm labor <34 weeks would have been treated correctly, giving a sensitivity of 100% and a negative predictive value of 100%. If this 5% threshold had been used to triage women presenting between 24+0 and 29+6 weeks, 89.4% (n = 168) of admissions could have been safely avoided, compared with 0% for a treat-all strategy. No true case of preterm labor would have been missed using this criteria.

Based on present and similar previous studies, therefore, the authors concluded that for women with threatened preterm labor, the QUiPP App can accurately guide management at risk thresholds for sPTB of 1%, 5% and 10%, allowing outpatient management in the vast majority of cases. The authors recommended that the prediction of sPTB should be performed routinely before 30 weeks to determine appropriate management to prevent unnecessary hospitalisation.

Other key references:

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- Cerdeira AS, O'Sullivan J, Ohuma EO, et al. Randomized Interventional Study on Prediction of Preeclampsia/Eclampsia in Women With Suspected Preeclampsia: INSPIRE. *Hypertension* 2019;74(4):983-90. doi: 10.1161/hypertensionaha.119.12739 [published Online First: 2019/08/14]
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- Kuhrt K, Hezelgrave-Elliott N, Stock SJ, et al. Quantitative fetal fibronectin for prediction of preterm birth in asymptomatic twin pregnancy. *Acta Obstet Gynecol Scand* 2020 doi: 10.1111/aogs.13861 [published Online First: 2020/04/07]
- Sotiriadis A, Papatheodorou S, Kavvadias A, et al. Transvaginal cervical length measurement for prediction of preterm birth in women with threatened preterm labor: a meta-analysis. *Ultrasound Obstet Gynecol* 2010;35(1):54-64. doi: 10.1002/uog.7457 [published Online First: 2009/12/17]
- Stock SJ, Wotherspoon LM, Boyd KA, et al. Quantitative fibronectin to help decision-making in women with symptoms of preterm labour (QUIDS) part 1: Individual participant data meta-analysis and health economic analysis. *BMJ Open* 2018;8(4):e020796. doi: 10.1136/bmjopen-2017-020796
- van Baaren GJ, Vis JY, Grobman WA, et al. Cost-effectiveness analysis of cervical length measurement and fibronectin testing in women with threatened preterm labor. *Am J Obstet Gynecol* 2013;209(5):436.e1-8. doi: 10.1016/j.ajog.2013.06.029 [published Online First: 2013/06/25]
- Watson HA, Carlisle N, Kuhrt K, et al. EQUIPTT: The Evaluation of the QUiPP app for Triage and Transfer protocol for a cluster randomised trial to evaluate the impact of the QUiPP app on inappropriate management for threatened preterm labour. *BMC Pregnancy and Childbirth* 2019;19(1):68. doi: 10.1186/s12884-019-2210-1

Antenatal Steroids

1. Antenatal steroids in extreme preterm infants:

Norberg H, Kowalski J, Maršál K, et al. Timing of antenatal corticosteroid administration and survival in extremely preterm infants: a national population-based cohort study. *BJOG: An International Journal of Obstetrics & Gynaecology* 2017;124(10):1567-74. doi: 10.1111/1471-0528.14545

Brief Summary: In this population-based prospective cohort study, the authors explored the association between administration-to-birth interval of antenatal corticosteroids (ACS) and survival in extremely preterm infants. The data of all live-born infants (*n* = 707) born at 22–26 completed weeks of gestation across Sweden during April 2004 to March 2007 was analysed. The relationship between time from first administration of ACS to delivery and survival was investigated.

In this study 591 (84%) infants were exposed to ACS. In the final adjusted model, infant survival was lower in infants unexposed to ACS, in infants born <24 h and >7 days after ACS but not in infants born 24–47 h after ACS, as compared with infants born 48 h to 7 days after administration. The findings were similar for neonatal survival. Survival without major neonatal morbidity among live-born infants was 14% in unexposed infants and 30–39% in steroid-exposed groups, indicating that any ACS exposure was valuable.

The authors concluded that the administration of ACS 24 h to 7 days before extremely preterm birth was associated with significantly higher survival than in unexposed infants and in infants exposed to ACS at shorter or longer administration-to-birth intervals. Thus the authors emphasise that the timing of antenatal corticosteroids is important for extremely preterm infants' survival.

2. Timing of antenatal steroids:

Norman M, Piedvache A, Børch K, et al. Association of Short Antenatal Corticosteroid Administration-to-Birth Intervals With Survival and Morbidity Among Very Preterm Infants: Results From the EPICE Cohort. *JAMA Pediatr* 2017;171(7):678-86. doi: 10.1001/jamapediatrics.2017.0602 [published Online First: 2017/05/16]

Brief summary: The Effective Perinatal Intensive Care in Europe (EPICE) study, a population-based prospective cohort study, gathered data from 19 regions in 11 European countries in 2011 and 2012 on 4594 singleton infants with gestational ages between 24 and 31 weeks, without severe anomalies and unexposed to repeated courses of ANS. The authors explored the associations between ANS administration-to-birth interval and survival and morbidity among very preterm infants.

Time from first injection of ANS to delivery in hours and days were noted. Main outcomes studied were in-hospital mortality; a composite of mortality or severe neonatal morbidity, defined as an IVH grade of 3 or greater, cystic periventricular leukomalacia, surgical necrotizing enterocolitis, or stage 3 or greater retinopathy of prematurity; and severe neonatal brain injury, defined as an IVH grade of 3 or greater or cystic periventricular leukomalacia. Total 4594 infants were included in the cohort.

The study found that administration of ANS was associated with an immediate and rapid decline in mortality, reaching a plateau with more than 50% risk reduction after an administration-to-birth interval of 18 to 36 hours. A simulation of ANS administered 3 hours before delivery to infants who did not receive ANS showed that their estimated decline in mortality would be 26%. The authors concluded that antenatal corticosteroids may be effective even if given only hours before delivery.

Other key references

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- Crowther CA, Middleton PF, Voysey M, et al. Effects of repeat prenatal corticosteroids given to women at risk of preterm birth: An individual participant data meta-analysis. *PLOS Medicine* 2019;16(4):e1002771. doi: 10.1371/journal.pmed.1002771
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Antenatal Magnesium

1. Evidence for benefit and safety

Crowther CA, Middleton PF, Voysey M, et al. Assessing the neuroprotective benefits for babies of antenatal magnesium sulphate: An individual participant data meta-analysis. *PLOS Medicine* 2017;14(10):e1002398. doi: 10.1371/journal.pmed.1002398

Brief summary: The aims of the AMICABLE (Antenatal magnesium sulphate individual participant data international collaboration: Assessing the benefits for babies using the best level of evidence) individual participant data meta-analysis (IPD-MA) were to assess the effect of antenatal magnesium sulphate when given to women at risk of preterm birth on important clinical outcomes and whether treatment effects varied depending on participant and treatment factors. The study included five randomised trials with 5,493 women and 6,131 babies comparing antenatal magnesium sulphate versus control treatment on neonatal neurological outcomes.

The study found that antenatal magnesium sulphate given to women at imminent risk of preterm birth prevents cerebral palsy and reduces the combined risk of fetal/infant death or cerebral palsy. Benefit was seen regardless of the reason for preterm birth, across a range of preterm gestational ages, and with minimal variation in outcomes related to time prior to birth or dosage given.

Therefore, the authors recommended that antenatal magnesium sulphate should be given close to planned or expected preterm birth using the smallest effective dose of 4 g with or without a 1 g/hour maintenance dose to minimise chances of death or cerebral palsy.

Other key references:

- Brookfield K, Su F, Elkomy M, et al. Pharmacokinetics and Placental Transfer of Magnesium Sulfate in Pregnant Women. *American Journal of Obstetrics and Gynecology* 2016;214 doi: 10.1016/j.ajog.2015.12.060
- Doyle LW, Crowther CA, Middleton P, et al. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. *Cochrane Database Syst Rev* 2009(1):Cd004661. doi: 10.1002/14651858.CD004661.pub3 [published Online First: 2009/01/23]
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Intrapartum Antibiotics

1. Evidence for benefit in GBS positive pregnancies:

Fairlie T, Zell ER, Schrag S. Effectiveness of intrapartum antibiotic prophylaxis for prevention of early-onset group B streptococcal disease. *Obstet Gynecol* 2013;121(3):570-7. doi: 10.1097/AOG.0b013e318280d4f6 [published Online First: 2013/05/03]

Brief summary: The authors estimated the effectiveness against early-onset group B streptococcal (GBS) disease of intrapartum antibiotic prophylaxis among term and preterm deliveries, deliveries with fewer than 4 hours of antibiotics, and deliveries receiving clindamycin regimens. They performed a secondary analysis of the Birthnet cohort, a survey of 7,691 births to residents of the Active Bacterial Core surveillance system from 2003 to 2004.

The study found that beta-lactam prophylaxis given 4 or more hours before delivery is highly effective for prevention of early-onset GBS disease. Prophylaxis of shorter durations or with clindamycin is less effective, reinforcing the need for health care providers to adhere to prevention recommendations, particularly for preterm deliveries, penicillin-allergic women, and neonates exposed to fewer than 4 hours of prophylaxis.

Other key reference:

- Group B Streptococcal Disease, Early-onset (Green-top Guideline No. 36): Royal College of Obstetricians & Gynaecologists; 2017 [Available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg36/.

Place of birth

1. Birth outside a tertiary hospital and harm

Helenius K, Longford N, Lehtonen L, et al. Association of early postnatal transfer and birth outside a tertiary hospital with mortality and severe brain injury in extremely preterm infants: observational cohort study with propensity score matching. *BMJ* 2019;367:l5678. doi: 10.1136/bmj.l5678

Brief Summary: In this retrospective observational cohort study with propensity score matching, the authors aimed to determine if postnatal transfer or birth in a non-tertiary hospital is associated with adverse outcomes in preterm infants. Data was collected from the UK National Neonatal Research Database.

A large cohort (n=17 577) of extremely preterm infants born at less than 28 gestational weeks between 2008 and 2015 were grouped based on birth hospital and transfer within 48 hours of birth. The three groups consisted of upward transfer (non-tertiary to tertiary hospital, n=2158), non-tertiary care (born in non-tertiary hospital; not transferred, n=2668), and controls (born in tertiary hospital; not transferred, n=10 866). Infants were matched on propensity scores and predefined background variables to form subgroups with near identical distributions of confounders.

The authors identified main outcome measures as death, severe brain injury, and survival without severe brain injury. The study found that compared with controls, infants in the upward transfer group had no significant difference in the odds of death before discharge (odds ratio 1.22, 95% confidence interval 0.92 to 1.61) but significantly higher odds of severe brain injury (2.32, 1.78 to 3.06) and significantly lower odds of survival without severe brain injury (0.60, 0.47 to 0.76). Compared with controls, infants in the non-tertiary care group had significantly higher odds of death (1.34, 1.02 to 1.77) but no significant difference in the odds of severe brain injury (0.95, 0.70 to 1.30) or survival without severe brain injury (0.82, 0.64 to 1.05). Compared with infants in the upward transfer group, infants in the non-tertiary care group had no significant difference in death before discharge (1.10, 0.84 to 1.44) but significantly lower odds of severe brain injury (0.41, 0.31 to 0.53) and significantly higher odds of survival without severe brain injury (1.37, 1.09 to 1.73).

The authors concluded that in extremely preterm infants, births in a non-tertiary hospital and transfer within 48 hours are associated with poorer outcomes. They recommended that perinatal services should be organised to facilitate delivery of extremely preterm infants in tertiary hospitals in preference to postnatal transfer.

2. In utero transfer of mother vs ex utero transfer of baby

Shah KP, deRegnier RO, Grobman WA, et al. Neonatal Mortality After Interhospital Transfer of Pregnant Women for Imminent Very Preterm Birth in Illinois. *JAMA Pediatr* 2020;174(4):358-65. doi: 10.1001/jamapediatrics.2019.6055 [published Online First: 2020/02/18]

Brief summary: This population-based cross-sectional study assessed whether antenatal transfer to a level III hospital is associated with neonatal mortality in infants who are very preterm. The study included 4817 infants born at gestational age of 22-31 completed weeks to Illinois residents and were followed up for 28 days after birth during 2015-16.

The authors looked at the neonatal mortality based on place of birth - at a level III hospital after maternal presentation at that hospital, at a level III hospital after in- utero transfer from another hospital, and at a non-level III hospital.

The study found that the risk of neonatal mortality was similar for very preterm infants whether women initially presented at a level III hospital or were transferred to a level III hospital before delivery. This suggests that the increased risk of mortality associated with delivery at a non-level III hospital may be mitigated by optimizing opportunities for early maternal transfer to a level III hospital.

Other key references:

- Boland RA, Davis PG, Dawson JA, et al. Outcomes of infants born at 22-27 weeks' gestation in Victoria according to outborn/inborn birth status. *Arch Dis Child Fetal Neonatal Ed* 2017;102(2):F153-f61. doi: 10.1136/archdischild-2015-310313 [published Online First: 2016/08/18]
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