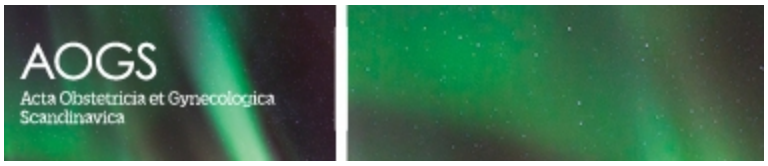

Obstetric strategies to reduce blindness from retinopathy of prematurity in infants born preterm

Journal:	*Acta Obstetricia et Gynecologica Scandinavica*
Manuscript ID	AOGS-18-0879.R2
Wiley - Manuscript type:	Guest Editorial (by invitation only)
Date Submitted by the Author:	26-Jun-2019
Complete List of Authors:	Gilbert, Clare; London School of Hygiene & Tropical Medicine, Clinical Research Dawes, Lisa; University of Auckland, Obstetrics & Gynaecology Wise, Michelle; University of Auckland, Obstetrics & Gynaecology Darlow, Brian; University of Otago, Paediatrics
Keywords:	Preterm Birth

TITLE PAGE

PUBLICATION TYPE: Guest Editorial

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Running title: Preventing blindness from retinopathy of prematurity

Disclosure Interests

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Retinopathy of prematurity

Retinopathy of prematurity (ROP) is a potentially blinding condition of preterm infants who have received neonatal care.[1] The blindness is usually bilateral and irreversible. The first epidemic of blindness from ROP (then called retrolental fibroplasia) occurred in the USA and Western Europe in the 1940s/1950s as neonatal intensive care became established. The epidemic came to an end after it was realized that 100% supplemental oxygen is highly toxic to immature retinal blood vessels. Blindness from ROP is now largely controlled in highly resourced countries where neonatal care is generally of high quality, and preterm infants are screened for ROP and treated if necessary. However, a further epidemic of ROP blindness is now occurring in middle income countries and in urban settings of low income countries as services for preterm infants expand, but where neonatal care is suboptimal and coverage of ROP screening and treatment is low.[2] A recent meta-analysis estimated that 32,300 preterm infants become blind or visually impaired from ROP every year, with the highest incidence in South East Asia.[3]

In ROP the developing retinal blood vessels initially stop growing and then proliferate abnormally. There is an international classification for ROP, the natural history is well described and the pathogenesis has been elucidated.[1] The initial stages (Stages 1 and 2) often regress spontaneously, but if more advanced disease develops (Stage 3), particularly if there are signs of active proliferation (plus disease), there is a high risk of progression to blinding retinal detachment (Stage 5). The purpose of screening, which should start within a few weeks of life, is to identify and treat vision-threatening ROP (VT-ROP). The gold standard treatment is laser photocoagulation of the peripheral, avascular retina, which must be delivered within 48-72 hours. Intraocular injection of anti-vascular endothelial growth factors holds promise, but the short and long-term ocular and systemic safety of these agents is not known.

The risk of VT-ROP is inversely related to the degree of prematurity and smaller size at each gestation, and can affect ≥10% of infants with birthweights <1500g in resource poor settings[4] Although a direct link between chorioamnionitis and ROP has not been proven, there is good evidence that perinatal inflammation, associated with factors such as severe pre-eclampsia and chorioamnionitis, play a role.[1] Other risk factors during the first few weeks of life include hyperoxia or fluctuating hypo-hyperoxia as a result of exposure to poorly regulated supplemental oxygen, sepsis, red blood cell transfusion and poor weight gain.

Much is now known about how blindness from ROP can be prevented – the challenge is to scale up these interventions, particularly in middle and low income settings. In this paper we describe strategies for the primary prevention of ROP where obstetricians, gynaecologists and midwives can play a critical role. Although there are currently no obstetric interventions which directly reduce ROP, there are aspects of care likely to have an impact. These include strategies to reduce the risk of preterm birth (PTB), appropriate management in pregnancy, and when mothers present with threatened or established preterm labour, ~~during labour of mothers threatening preterm delivery~~, and the care of preterm babies at birth.

Prevention of preterm birth

Despite global efforts to reduce PTB, rates are increasing in most countries where data are available, with 1 in 10 babies born prematurely in 2010.[5] Increasing rates of multiple pregnancies and medically-indicated PTBs are the main reasons for the increase.[6] Babies born extremely preterm and at very low birthweight have the highest risk of lifelong disability, including ROP.[5]

The causes of PTB are varied and multi-factorial. Risk factors include multiple pregnancy, previous preterm birth or cervical surgery, extremes of maternal age and body mass index, infection, underlying maternal chronic medical conditions, and lifestyle factors such as smoking and recreational drug use.[6]

There is moderate evidence that prevention of adolescent pregnancy and promotion of optimal birth spacing can reduce the risk of PTB and improve perinatal outcomes.[5] Thus provision of contraception should be prioritized, especially in low resource settings. Around 40% of twin pregnancies and nearly all higher-order multiples will result in spontaneous preterm labour or preterm premature rupture of membranes. The increased risk of multiple pregnancy from in vitro fertilization can be significantly reduced if a universal policy of single embryo transfer (SET) is adopted by fertility specialists. A meta-analysis has shown a reduction in multiple pregnancy from 32% to 1% with elective SET, without significant reduction in live birth rate when combined with a second frozen SET cycle.[7]

Women who receive regular antenatal care have a lower risk of PTB.[8] Smoking cessation programmes and treatment of sexually transmitted infections in pregnancy have shown a modest reduction in PTB rates.[5,8] Vaginal progesterone and cervical cerclage have a role, but evidence supports use only in women with multiple previous PTBs or those who develop a short cervix in the mid-trimester.[9]

Reducing rates of medically-indicated PTB is likely to reduce neonatal morbidity including ROP, although direct evidence is not available. For women at risk of preeclampsia or fetal growth

restriction, early use of low-dose aspirin provides an 8% risk reduction of PTB and a 10% lower risk of small-for-gestational-age (SGA) babies.[8] If severe early-onset SGA is diagnosed, umbilical artery doppler monitoring should be used to support prolongation of pregnancy as long as clinically safe to do so.

Care during threatened or established preterm labour

Few women who present with symptoms of threatened preterm labour deliver preterm; 3.9% within 14 days of presentation and 21% before 37 weeks gestation[10]. Transvaginal ultrasound cervical length and vaginal biomarkers are more accurate predictors of who will deliver within the next 14 days than symptoms alone and should be used when available.[9]

Tocolysis can provide a short-term delay for women with threatened or established preterm labour to allow for interventions that improve perinatal outcomes,[8] such as (1) antenatal corticosteroids, (2) magnesium sulphate to reduce cerebral palsy, and (3) in utero transfer to ensure birth occurs in a hospital with appropriate level neonatal services.[5]

The World Health Organization strongly recommends a course of antenatal corticosteroids for women at risk of preterm birth at 24^{+0} to 34^{+6} weeks ~~gestation before 35 weeks~~ when gestational age is known, preterm birth is imminent, there is no clinical evidence of maternal infection, and obstetric and newborn care are available.[11] The overall benefits of reducing neonatal mortality and respiratory distress syndrome (RDS) are well established. The evidence for reduction in ROP is less well known. A prospective cohort study of 117,941 babies showed that infants exposed to antenatal corticosteroids had lower rates of severe ROP or death than unexposed infants at all gestations (adjusted odds ratios ranging from 0.33-0.67 from 23 to 34 weeks gestation).[12] Additionally, exposed infants born <30 weeks had lower rates of the composite outcome of death, severe intraventricular hemorrhage (IVH), severe necrotizing enterocolitis (NEC) and severe ROP than unexposed infants.[12]

Labour ward care

It is vital that all health professionals recognize the importance of the first minutes and hour of life (“the golden hour”). Newborn stabilization and resuscitation requires a team approach and it is essential that all personnel are familiar with the equipment and protocols.

There is strong evidence that delaying cord clamping by 30-60 seconds reduces hospital mortality, increases the infant’s hematocrit and reduces blood transfusions,[13] which have been associated with ROP in other studies. Delayed cord clamping has also been associated with

reductions in IVH, NEC and sepsis. Current recommendations are that cord clamping is delayed by 30 seconds or longer in vigorous preterm infants.

Preterm infants rapidly lose heat but this can be effectively prevented by placing the infant's body in a plastic bag or using occlusive wrapping.[14] As well as reducing hypothermia there is some evidence that major morbidities, including ROP, are also reduced.[14]

Informed by experimental and clinical evidence, neonatal stabilization and resuscitation guidelines have embraced a more gentle approach than formerly, avoiding 100% inspired oxygen and maneuvers that over distend the lung.[11] Internationally agreed guidelines can be modified for national or local use. Piped air and 100% oxygen should be available in the labour ward together with blenders and ideally pulse oximeters. If respiratory support is required, recommendations suggest providing continuous positive airways pressure via an appropriate facemask with 21%-30% oxygen initially and before bagging. If air is not available, start with 100% oxygen but reduce the inspired concentration as soon as possible. Following resuscitation, very preterm infants who are not born in a hospital with a neonatal special or intensive care unit should be transported to such a facility at an early stage.

Summary

Preventing preterm birth and its complications, including blindness from ROP, requires a multi-disciplinary approach before and during pregnancy and immediately after PTB. Meticulous care, team work and the engagement of mothers are required, underpinned by policies, regulatory frameworks and protocols. Obstetricians, gynecologists and midwives can plat an ~~very~~ important role in reducing blindness from ROP which can lead to developmental delay and ~~promoting child development and preventing the~~ emotional, economic and social costs to affected children and their families.[15]

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