Determinants of Neonatal Blood Pressure

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Abstract Blood pressure (BP) measurements have been increasingly used across neonatal intensive care units to determine and monitor hemodynamic status in neonates. A number of studies have attempted to derive normative blood pressure data in both preterm and term infants. However, this still remains a complex process, as several maternal and neonatal factors influence neonatal blood pressure. Maternal conditions, including hypertension and preeclampsia, seem to have some impact on neonatal BP, while maternal drugs, in particular antenatal steroids, seem to have a strong influence. Among the neonatal factors, gestational age, post-conceptual age and weight seem to have the strongest influence. The paucity of data on the short and long term effects of maternal conditions and medication on neonatal BP requires further research.

Keywords Blood pressure · BP · Pregnancy · Hypertension · Neonate · Preeclampsia · Maternal factors · Neonatal factors · Antenatal steroids · Magnesium sulfate · Antihypertensive agents

Introduction

BP measurement is still the mainstay of monitoring haemodynamics, especially in the early neonatal period, despite echocardiographic evidence that it may not always be an accurate representation of circulation [1]. However, it is still the easiest and quickest measurement to obtain, and thus accurate BP measurement and reliable normative data are

essential. Uncertainty continues to exist in many aspects of BP management in the neonatal period, including treatment of hypotension and hypertension [2–4]. As a consequence, knowledge of maternal and neonatal factors which may influence BP in the neonatal period are essential to assist the clinician in guiding their responses to BP measurements in the first days and weeks of life. Evidence is also required on the implications of these maternal and neonatal factors on long term cardiovascular health. In this review we will discuss important maternal and neonatal determinants of BP in the neonatal period, along with areas for future research.

Maternal Factors Affecting Blood Pressure (BP) in the Neonate

Hypertension during pregnancy has numerous implications on the neonate including in-utero growth restriction (IUGR), microcephaly, thrombocytopenia, leucopenia, neutropenia, low Apgar scores, delayed adaptation, patent ductus arteriosus, hypotonia and gastrointestinal motility [5, 6]. Neonatal morbidity is generally increased as a consequence of IUGR and prematurity, rather than the maternal hypertension itself [7]. However, a recent study has suggested that neonatal outcomes do differ depending on cause of preterm birth depending upon gestation [8•]. This section of the review will examine the available literature assessing the effects of maternal factors, including hypertension on neonatal BP in the early and later neonatal period.

Maternal Age, Anaesthesia, and Mode of Delivery

There are numerous factors that may affect BP in the early neonatal period. Maternal age is implicated in a number of adverse pregnancy outcomes, including reduced fertility, preterm birth, IUGR, multiple births, congenital anomalies and more importantly diabetes and hypertension [9–16]. There is a paucity of data assessing the impact of maternal

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age on neonatal BP. Gillman et al. in their study found that advancing maternal age was associated with higher newborn systolic BP, however these findings were not supported in the studies by Sedaghat et al. [17] and Morrison et al. [18••]. The differences between the studies by Gillman et al. and Sedaghat et al. may be due to the different techniques utilized for BP assessment and the women and neonates sampled [16, 17]. Sedaghat et al. also excluded all women with possible confounding variables such as hypertension and diabetes, which may in itself account for the difference [17]. Morrison et al. assessed influence of multiple maternal and pregnancy characteristics on offspring cardiometabolic traits at birth [18••]. They did not identify any influence of maternal age on neonatal blood pressure. The patient characteristics and BP assessment techniques were similar to those in the study by Gilman et al. [16].

There is also a paucity of literature on the effects of maternal anaesthesia and neonatal BP. Studies by Mattingly et al. and Lundell et al. reported that mode of anaesthetic had no effect on the neonate [19, 20]. However, other authors have noted that mode of anaesthesia can affect the Apgar score, pH balance and left ventricular ejection time [21, 22]. Sedaghat et al. showed that spinal anaesthesia was associated with a lower systolic BP on the first day of life compared to epidural, general or no anaesthesia, which was not evident on future BP readings on day 2 and 3 [17]. The sample population in this study is one of the largest reported, utilized modern oscillometric techniques and as previously discussed, excluded women with possible confounding factors including hypertension and diabetes.

Neonates born by caesarean section have been reported to have a lower systolic BP and other neonatal complications than with other modes of delivery [23–25]. However, these findings have not been found by other investigators [26, 27]. In the study by Sedaghat et al., caesarean section was found to be associated with a lower systolic BP, however, when placed in a dummy variable ordinary least squares regression analysis the factor that was found to be significant was type of anaesthesia, not the route of delivery [17].

Maternal Hypertension and Early Neonatal Blood Pressure

Maternal hypertension and preeclampsia have the capacity to influence neonatal BP, along with the medications that may be utilized to manage the condition as well as administration of corticosteroids in the situation where preterm delivery is required. In early studies of infants of preeclamptic mothers there were conflicting results on the effects on neonatal blood pressure [24, 28, 29]. The paucity of current literature in this area with only few recent studies leaves this question unanswered. Swarup et al. reported infants of preeclamptic mothers born at > 29 weeks gestation had a higher BP on the first day of life and during the first week of life [30]. However, Teng et al. have shown that premature neonates of

preeclamptic mothers are more likely to have early neonatal hypotension requiring treatment than controls [31].

Even fewer studies have evaluated the effect of primary maternal hypertension on newborn BP. Amini et al. investigated the association between maternal blood pressure disorders and neonatal blood pressure within the first hours of birth. They reported higher systolic and diastolic blood pressures in newborns whose mothers had preeclampsia or chronic hypertension in comparison to normotensive mothers [32]. Morrison et al. [18••] in their study did not find any association between maternal hypertension and newborn BP.

Maternal Treatments

Antenatal Corticosteroids

BP in the early neonatal period in premature infants is linked to the development of intraventricular haemorrhages, ischaemic cerebral lesions, adverse neurodevelopmental outcome and neonatal mortality [33–42]. The introduction of antenatal corticosteroid treatment in women at risk of delivering preterm has reduced neonatal morbidity and mortality and has become a mainstay of treatment [43]. Four studies have shown that the administration of antenatal steroids results in increased neonatal BP during the first 24–48 hours of life and is associated with a decreased requirement for BP support [37, 44–47].

Magnesium Sulfate

Severe preeclampsia is associated with the development of eclampsia and other maternal morbidities such as placental abruption. Anti-epileptic medications and magnesium sulfate have been utilized to reduce the incidence of eclamptic seizures. Magnesium sulfate is thought to act by causing cerebral vasodilation, reducing cerebral ischaemia considered to be the underlying cause of eclamptic seizures. The Cochrane review by Duley et al. reported that magnesium sulfate reduced significantly the risk of eclamptic seizures in comparison to other anti-epileptic medications, reduced the risk of placental abruption and potentially reduced maternal mortality [48]. Magnesium sulfate has now become standard management in the treatment of severe preeclampsia [49, 50]. Several studies have reported that magnesium sulfate is associated with decreased cerebral perfusion in the neonate [51, 52, 53•]. It is speculated that magnesium sulfate decreases the reactivity of the cerebral arteries in the neonate and as a consequence conveys the neuroprotection reported in the recent metaanalysis when magnesium sulfate is used prior to preterm delivery [54]. However, the systemic haemodynamic effects of magnesium sulfate on neonatal BP in the early neonatal period are unknown.

Antihypertensive Agents

β-Blockers

The administration of β -blockers in pregnancy does not appear to be associated with an increased teratogenic risk [55]. Long-term administration of atenolol throughout pregnancy appears to be associated with an increased risk of small for gestational age infants, and thus is not recommended [56–60]. β -blockers administered for hypertension in pregnancy do reduce the risk of severe hypertension and the requirement for other additional medications without appearing to increase perinatal morbidity or mortality [61]. β -blockers have been shown to cause neonatal bradycardia which does generally not require any intervention [62–64]. A randomized clinical trial comparing hydralazine to labetalol reported lower BP in those neonates exposed to maternal labetalol [65]. A recent study also showed that hypotension was more common in babies' whose mother received labetalol for preeclampsia regardless of dosage or route [66•].

Centrally Acting α -2 Adrenergic Agonists

Although methyldopa may have been replaced in the routine management of hypertension by agents with better tolerated profiles, it is still a recommended agent in the management of hypertension in pregnancy [50]. The distribution of methyldopa in the neonate at delivery appears to be similar to that of the mother and takes several days to disappear [67]. Evidence on the effect of methyldopa on neonatal BP is limited and conflicted. Sulyok et al. found that there was no effect on neonatal BP, whereas Whitelaw found that the systolic BP in the first two days of life was lower than controls [68, 69].

Calcium Antagonists

Nifedipine has been used for the acute treatment of severe hypertension in pregnancy as well as a tocolytic agent. As with other anti-hypertensive agents used in severe hypertension nifedipine can be associated with maternal hypotension and resultant fetal distress. These effects may be potentiated with concomitant use of magnesium sulfate and hydralazine [62, 70, 71]. A recent metaanalysis has shown that there are increased adverse maternal events when women received more than 60 mg of nifedipine [72]. There are no reports in the literature on the effects of nifedipine on neonatal BP.

Direct Vasodilators

Oral vasodilators have generally been replaced by other anti-hypertensive agents, but parenteral hydralazine may be used for the acute management of severe hypertension. Due to concerns regarding maternal hypotension and fetal distress

with intravenous hydralazine, oral nifedipine or labetalol may be better tolerated, although there appears to be no significant differences in early neonatal morbidity with hydralazine than other anti-hypertensives [62, 73]. However, labetalol did appear to be associated with lower BP in the early neonatal period in one randomized controlled trial [65].

There is a significant paucity of evidence on the effects of maternal anti-hypertensives on the neonate, both in the early neonatal period and long-term. Further research is required to determine whether there are clinically relevant effects in the early neonatal period on BP, and whether there are any long-term cardiovascular risks.

Long-Term Implications of Maternal Hypertension

Barker and Osmond first postulated in 1986 that intrauterine and early nutrition may be associated with ischaemic heart disease [74]. This hypothesis has instigated much research and the findings and hypotheses are well represented in the literature [75•, 76•, 77•, 78•, 79•]. Recent studies have provided normative BP values using modern oscillometric techniques in premature and term neonates and infants in the first year of life of women without any potential confounders of hypertension and diabetes [80–82]. These values can be used to compare neonates of women who have hypertension in pregnancy, diabetes and obesity to determine whether there are possible effects of maternal disease on BP in the early neonatal period. Recent studies indicate that exposure to maternal hypertension and diabetes influences BP in the first month of life and increases the risk of neonatal hypertension [83, 84].

Maternal hypertension and its clinical management does have implications for BP in the early neonatal period, however, the literature available is limited. Further research is required to determine whether there are clinically relevant impacts on the neonatal circulation both in the early neonatal period and then long-term into childhood and adulthood.

Neonatal Factors Affecting Blood Pressure in the Neonate

Advances in neonatal practice have led to generation of normative data on neonatal BP [80, 85, 86]. The most important determinants of BP in newborns are gestational age, postconceptual age, and birth weight [80, 85, 86].

Gestational Age and Blood Pressure

The cardiovascular system of the human fetus undergoes both structural and functional maturation during the intrauterine period. Hence, gestational age is expected to play a role in determining neonatal BP [87]. Zubrow et al. measured systolic and diastolic BP in 608 newborns admitted to 14 NICUs in

the Philadelphia area from 1 to 99 days after delivery [85]. They found that the systolic and diastolic BP strongly correlated with the gestational age on day 1. However, their study included a heterogeneous sample including infants ventilated and on ionotropes. Pejovic et al. measured arterial BP in a stable group of premature babies admitted to their NICU in the first week and at 1 month of life [86]. They classified the infants in groups as per their birth weight and gestational age, showing that BP was significantly higher in the group with higher gestational age in the first week of life. Gestational age continued to be significant predictor of BP even on day 30 of life. In the most recent study by Kent et al., BP was measured in stable premature neonates between 28–36 weeks gestation [80]. They also showed that the younger gestation age group tended to have lower average blood pressures over 28 days.

Postmenstrual Age and Blood Pressure

Postmenstrual age seems to be a primary determinant of BP in preterm babies after day 1. In the study by Zubrow et al., during the first 5 days of life there was a rapid rise in systolic and diastolic BP regardless of gestational age or weight at birth. After day 5, there was a more gradual rise in the daily systolic and diastolic BP's [85]. Pejovic et al. showed a similar pattern, with BPs in each gestational group increasing at a faster rate over the first week of life, and slowly thereafter until day 28. BP also increased at a faster rate in preterm infants compared to full-term infants [86]. The most recent data from Kent et al. showed a progressive increase in BP over 2 weeks in stable infants less than 31 weeks gestation. Thereafter their BP was similar to that of term infants. In infants over 31 weeks of age, the BP increased significantly over first 7 days, but remained stable thereafter [80].

Healthy term infants have a somewhat different pattern of BP rise. One of the largest studies by Kent et al. on BP measurements in normal term infants showed a significant increase in BP in these infants from day 1 to day 2, but no difference thereafter, suggesting an earlier leveling off of BP in comparison to preterm infants [81].

Birth Weight and Blood Pressure

In the study by Zubrow et al., the systolic and diastolic BP in infants correlated strongly with their birth weight on day 1 of life [85]. The findings were similar in the study by Pejovic et al., which also showed that the BP was higher in groups with higher birth weight [86]. In yet another study, Smal et al. compared BP between small-for-gestational-age (SGA) and appropriate-for-gestational-age (AGA) infants in preterm infants less than 36 weeks in the first week of life. Both the SGA and AGA groups had similar BP values and similar rates of

rise during the first week of life. However, while the BP in AGA infants correlated positively with their birth weight, the BP in SGA infants had an inverse correlation with their birth weight where the SGA infants with the lowest birth weight had the highest BP [88].

In term infants, the data on birth weight and BP is conflicting. In a recent study from Nigeria, Sadoh et al. measured mean systolic BP in 473 babies in the first 4 days of life. They showed that the birth weight was the most important determinant of newborn systolic BP, with an average of 3.61 mm rise in systolic BP with every 0.5 kg rise in birth weight [89]. A Spanish study demonstrated that small-for-gestational-age infants had lower BPs compared to appropriate-for-gestation infants at birth. However, by 1 month all term infants had similar BP values [90]. This is in contrast to the data from Kent et al. who found no significant difference in BP readings with respect to birth weight [81]. In view of these differences, further larger multicenter studies are needed.

Conclusions

Neonatal BP has been poorly studied in the past, but the cardiovascular changes that occur in the first hours and days of life is now being increasingly examined by a number of researchers. However, the effect of maternal disease states and drugs on the neonate is largely unknown in both the short and long term and requires further research.

Compliance with Ethics Guidelines

Conflict of Interest Alison L. Kent and Tejasvi Chaudhari declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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