Clinics in Pediatrics

Review Article
Published: 05 Nov, 2020

Impact of Maternal Gestational Diabetes on Neonatal Outcome of Late Preterm Infants

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Abstract

Late-preterm birth, defined as delivery between 34 to 36 weeks, comprises of over 70% of all preterm deliveries, and has a prevalence of 4.4% to 16% worldwide. Compared to term infants, late preterm infants are well known to be at risk for neonatal complications like respiratory distress syndrome, transient tachypnea of newborn, hypoglycemia, hyperbilirubinemia, feeding difficulties etc… Recent studies have shown that in addition to neonatal problems, late preterm infants are also associated with long-term complications including learning difficulties, cognitive problems and developmental delay. Meanwhile, maternal Gestational Diabetes Mellitus (GDM) or Diabetes Mellitus (DM) are also associated with preterm delivery as well as multiple obstetric and neonatal complications. Although late preterm delivery with maternal GDM/DM is expected to be at increased risk for adverse outcome, there are not many studies on this topic, and the actual impact on the mother and infant is not well delineated.

With the advancement of knowledge on late preterm births, both obstetric and neonatal care had evolved to optimize management and to improve both short and long-term outcome. This paper will analyze the implications of maternal GDM/DM on late preterm deliveries and review the latest knowledge and updated recommendations on management of late-preterm deliveries. Management of late preterm birth is a challenging topic and an interesting area for further research.

Keywords: Prematurity; Late preterm; Gestational diabetes; Diabetes

Introduction

Late-Preterm Birth (late-PTB), previously labeled as "near term" births, is defined as birth at $34^{0/7}$ through $36^{6/7}$ weeks gestation [1-4]. Numerous studies have shown that these infants are at considerably higher risks of morbidity and mortality than term infants [2,4]. For instance, in a population with a relatively low rate of PTB such as the 6.5% in Hong Kong, the corrected perinatal mortality rate was 3.5/1000 deliveries and 0.5/1000 deliveries for late-PTB and term births respectively [5]. Late-PTB is a significant factor for adverse neonatal outcome. Neonatal mortality was increased by 6 to 8 times [6]. Compared to term infants at 39 weeks, the adjusted Odds Ratio (aOR) of Respiratory Distress Syndrome (RDS) for late-preterm infants was 40.1 at 34 weeks and 9.1 at 36 weeks; whilst that of Transient Tachypnea of Newborn (TTN) was 14.7 at 34 weeks and 6.1 at 36 weeks [7]. The incidence of both short and long term complications [8-10], were increased in late-preterm infants.

Meanwhile, Gestational Diabetes Mellitus (GDM) is on an increasing trend globally [11], and is especially prevalent in the Asian population [12], with significant perinatal morbidities for both the mother and fetus [13]. Infants of mothers with GDM are at increased risk of neonatal morbidities such as preterm delivery [14], respiratory complications, hypoglycemia, polycythemia, neonatal jaundice, and congenital malformations [15,16].

As a consequence, late-preterm neonates with maternal GDM would be at increased risk for adverse outcome. In this review, we will present some of the problems encountered in late-preterm deliveries with maternal DM from both Obstetrics and Neonatal aspects.

Obstetrics Aspects of Late Preterm Births

Prevalence of late-preterm birth

Overall prevalence of late-PTB ranged from 4.4% to 16% [17], and is usually 3.0% to 6.0% among singleton live births [18]. Late-PTB accounts for the majority of PTBs, but the proportion

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Received Date: *11 Oct 2020*
Accepted Date: *02 Nov 2020*
Published Date: *05 Nov 2020*

Citation:
G.P.G. Fung, T.T.Lao. Impact of Maternal Gestational Diabetes on Neonatal Outcome of Late Preterm Infants. Clin Pediatri. 2020; 3: 1023.

of late- *vs.* early-PTB is influenced by the overall prevalence of PTB. In Hong Kong, the prevalence of early- and late-PTB was 1.8% and 4.7% respectively, with a ratio of 1:2.6 [5]. In a developed country such as USA, PTB had increased from 9.4% in 1981 to 12.3% in 2003, with most of the increase due to births between 32 and 36 weeks [4]. A review in 2010 confirmed a continued increase in PTB, due largely to a dramatic rise in late-PTB which has become the fastest growing subset of neonates and accounting for 74% of all PTB and 8% of total births [2]. Nevertheless, PTB rate, based on obstetric estimates, had dropped from 10.44% in 2007 to 9.56% in 2014, probably attributable to heightened understanding of the increased neonatal risks at these gestational ages [4].

Late-preterm birth as an adverse obstetric outcome

Overall, PTB is related to adverse maternal factors and obstetric complications, including maternal socio-demographic, lifestyle characteristics and environmental factors [18], nulliparity status [18], inflammation [18], advanced age [17,19] and teenage [17], decreasing and low body mass index [20], short stature [21], and multifetal pregnancy [17]. Some factors could exert different and opposite effects on PTB. For instance, increasing BMI progressively reduced spontaneous PTB at <37 weeks, with the lowest rate at the BMI of 35 kg/m^2, but increased indicated PTB at the same time [20]. Other factors which increase PTB include medical practices such as provider-initiated delivery and assisted reproduction [18], and specific complications including Gestational Diabetes Mellitus (GDM) [17], eclampsia or pre-eclampsia [17], placenta previa [17], placental abruption [17], and pre-labor rupture of membranes [17], many of which impact mainly on late-PTB [17], as well as increased in pregnancies complicated by GDM [22,23]. Even a history of the aforementioned complications and neonatal death and small-for-gestational age infant in a previous term pregnancy [17], would increase the risk of PTB in a subsequent pregnancy by 2.0 fold with one previous term complication, and by 3.5-fold with two or more complications, even after excluding recurrence of the specific complication in the second pregnancy. Hence current and previous obstetric complications should all be regarded as risk factors for PTB in the current pregnancy.

Maternal hyperglycaemia as a cause of late-preterm birth: Apart from frank GDM [17], sub-threshold hyperglycemia also affects the length of gestation as a continuum. Among women who underwent the 75 g Oral Glucose Tolerance Test (OGTT), the 2-h glucose level from normal values up to the category of GDM was positively correlated with the incidence of spontaneous labor before 37 weeks gestation and inversely with the mean gestational age [24]. Similarly, using the 3-h 100 g OGTT following a positive 50 g glucose challenge test, the mean gestation age at delivery was inversely correlated with increasing number of abnormal glucose values, including the fasting and up to the 3-h values, while the risk of PTB and admission to the Neonatal Intensive Care Unit (NICU) was significantly and progressively increased from the group with two abnormal value to reach a peak in the group with all abnormal values [25]. When analyzed according to the categories of glucose response, the risk of spontaneous PTB increased significantly from 4.0% in the normal screening, 5.0% in the abnormal screening, to 6.7% in the GDM categories [12]. It is therefore not surprising that the rates of PTB and NICU admission were significantly higher and increased progressively from mild gestational hyperglycemia, to GDM, and finally to pre-existing diabetes [26]. In addition to PTB, even only elevation in the 1-h glucose level of the 100 g OGTT at 28 to 32 weeks was associated with increased fetal distress, low fifth minute Apgar score, hypoglycemia, respiratory distress syndrome, and perinatal death [27]. Thus, gravidae who have undergone the OGTT should be screened for sub-threshold hyperglycaemia to identify those with increased risk of PTB. As well, the synergistic effects of and mutual interactions between risk factors warranting antenatal OGTT and a diagnosis of GDM on perinatal outcome must be appreciated, such as the increasing maternal age and BMI on incidence of GDM as well as the independent effect of these factors on the need of the infants for NICU care [28].

Impact of maternal hyperglycaemia and GDM on perinatal outcome of late-PTB: As a group, women with GDM had a lower rate of spontaneous vaginal delivery and higher rate of caesarean delivery, and the neonates of GDM mothers had higher mean birth weight and birth weight percentile, including a higher rate of large-for-gestational age infants, for late-PTB infants as compared with late-PTB infants born to mothers without GDM [29]. For GDM, the degree of glycemia control is an important factor not only in the risk of PTB, but also impacts the in-utero fetal development and maturation. Using mean glucose level of 6.7 mmol/L as the criterion of adequate glycemic control, fetal lung maturation rates as reflected by amniocentesis was higher at term than at preterm for adequate but not inadequate glycemia control [30]. In fact, poor glycemic control was more frequently found in pregnancies with spontaneous PTB [11]. However, paradoxically, insulin treatment during pregnancy is an independent risk factor for respiratory distress in term and near-term newborns [31]. Therefore, regardless of glycemic control, infants from late-PTB in women with insulin-treated GDM should be considered high risk for respiratory distress.

Contribution of other obstetric conditions and factors on perinatal complications in late-preterm births: The increased morbidity in late-PTB infants involves nearly every organ system, in addition to the higher risk of mortality [30]. Even in the absence of any identifiable maternal or fetal risks, there are increased risks of perinatal and neonatal complications. These will be discussed in detail below under the section "Neonatal aspects of late-preterm births". In view of the increased obstetric complications associated with GDM, it is often difficult to dissect out the attributable impact of GDM from that of other associated complications. For instance, one study which examined the impact of eight maternal medical conditions, including hypertensive disorders of pregnancy, diabetes, antepartum hemorrhage, lung disease, infection, cardiac disease, renal disease, and genital herpes, on neonatal morbidity in late-PTB infants found 7-times higher morbidity (22% *vs.* 3%) than term infants, with the morbidity rate doubling for each gestational week earlier than 38 weeks, and the late-PTB infants exposed to antepartum hemorrhage and hypertensive disorders were especially vulnerable [32]. Thus, the successful prevention and optimal management of other associated complications could significantly improve the perinatal outcome of GDM pregnancies.

Antenatal interventions and measures to reduce neonatal morbidity in late-preterm birth: Owing to the increased neonatal complications, especially respiratory complications in late-PTB and even early term infants, there has been recommendation for Antenatal Corticosteroid (ACS) administered to women at risk of both spontaneous and especially indicated late-PTB [33]. A multicenter randomized control trial comparing two injections of betamethasone 12 mg with matching placebo administered 24

h apart on neonatal composite of treatment (various respiratory interventions), or stillbirth, or neonatal death, within 72 h of birth, and the results demonstrated a 20% reduction in primary outcome and other respiratory complications without differences in incidence of chorioamnionitis or neonatal sepsis, but the betamethasone group had 60% increased neonatal hypoglycemia [34]. Furthermore, the reduction was significant only for Transient Tachypnea of Newborn (TTN) and Bronchopulmonary dysplasia on secondary analysis. In 2017, the American College of Obstetricians & Gynecologists has recommended steroid treatment in women with imminent late-PTB who have not received prior steroid treatment, the contraindications to this treatment include pre-gestational diabetes and chorioamnionitis, and there are concerns and caution raised regarding the administration of antenatal steroid for threatened late-PTB, especially for diabetic pregnancy [33]. Antenatal steroid for GDM therefore should not be recommended [35]. It is important to appreciate that it is not recommended to use tocolytic treatment to delay birth with threatened preterm labor occurring after 34 weeks gestation, and amniocentesis to determine fetal lung maturity should not be held as a valid reason to delay delivery at gestation from 34 weeks onwards if there is clearly maternal and/or fetal benefit or indications for terminating the pregnancy at that point in time [35]. While the decision for preterm delivery is usually a compromise between maternal *vs.* fetal interests, it should also be appreciated that it is important to deliver a preterm infant in an as optimal condition as possible under the circumstance and at the expense of several days of additional maturity, instead of gaining a few more days of maturity at the expense of worsened fetal condition which would jeopardize the neonatal course and chance of ultimate survival.

Neonatal Aspects of Late Preterm Births

Earlier studies on neonatal aspects of late preterm births and impact of GDM had focused on perinatal and neonatal complications. However, there is accumulating evidence in recent years that these infants are also at risk of long-term complications, especially in respiratory and neurodevelopmental aspects. This can be attributed to the fact that both pulmonary and central nervous system development is still ongoing in-utero at 34 to 36 weeks, and any insult during this period can lead to long lasting consequences. In the discussion below, neonatal management aspects will be divided into "short term" (indicating perinatal and neonatal period) and "long term" (childhood and adolescent) categories. A summary of these outcomes is shown in Table 1.

Short Term Neonatal Complications and Management

Respiratory outcome (neonatal period)

Respiratory distress syndrome: The pathophysiology of RDS is surfactant deficiency. Surfactant, consisting of 90% phospholipids and 10% proteins, is synthesized in the Type 2 alveolar cells. It decreases the surface tension of alveoli, preventing atelectasis, and results in improved lung compliance. During the embryological development of the respiratory system, respiratory bronchioles are formed at 16 to 25 weeks' gestation (canalicular phase); alveolar ducts at 24 to 34 weeks (saccular phase); and alveolar sacs at 34 to 38 weeks (alveolar phase). Surfactant mRNA is expressed at 20 weeks' gestation and surfactant level rises at 36 to 38 weeks. Meanwhile, maternal GDM is associated with delayed surfactant synthesis due to hyperinsulinism, which interferes with induction of lung maturation by glucocorticoids [36,37]. Therefore, both late-preterm delivery and maternal diabetes are associated with increased risk of RDS.

Epidemiological studies have shown that compared to term infants, late preterm infants have a higher incidence of RDS, which increases with decreasing gestation. The USA Consortium on Safe Labor [7], with data from records of 233,844 deliveries, including 19,334 late preterm births from 2002 and 2008 reported that the incidence of RDS increased from 1% for infants born at gestation 37 weeks to 2.8%, 6% and 10.5% at 36, 35 and 34 weeks. Compared to term infants at 39 weeks, the adjusted Odds Ratio (aOR) for RDS was 40.1 at 34 weeks; 21.9 at 35 weeks and 11.1 at 36 weeks [7]. A systematic review of 22 studies involving 29,375,675 infants yielded similar results, showing Relative Risk (RR) of RDS as 48.4, 28.8, 10.9 at 34, 35 and 36 weeks respectively [6]. In contrast, studies on relationship between maternal GDM and RDS show conflicting results. Some studies [38,39], revealed maternal GDM as a significant risk factor for RDS in late preterm [38] and term neonates [39], whilst others showed no association between RDS and GDM [40]. One study [31] showed that maternal GDM on insulin is a significant risk factor for RDS, but maternal GDM not requiring insulin is not. One postulated reason for the discrepancy is that maternal glycemic control plays an important role in RDS development. In mothers with well-controlled diabetes, the incidence of RDS in neonates approaches that of mothers without diabetes at a similar gestational age [41], thus illustrating the need for close monitoring and good glycemic control in cases of maternal GDM.

RDS presents clinically within a few hours of life with tachypnea, nasal flaring, subcostal recessions, expiratory grunting, cyanosis and reticulogranular pattern, air bronchogram or white-out lung fields on Chest Radiograph (CXR). Many studies, including a randomized controlled trial comparing use of antenatal steroids or placebo in anticipated late-preterm delivery, showed significantly lower incidence of respiratory complications and need for ventilatory support in the group treated with antenatal steroids [34] (severe respiratory complications 8.1% *vs.* 12.1%, RR 0.67, $p<0.001$; surfactant use 1.8% *vs.* 3.1%, RR 0.59, $p=0.03$). Another study showed improved lung compliance in late-preterm neonates who had received antenatal steroids [42]. In 2017, the American College of Obstetrics and Gynecology has recommended a course of antenatal steroids for anticipated preterm delivery. Neonates presenting with RDS are treated with surfactant therapy and ventilatory support as appropriate. Nowadays, with the use of non-invasive ventilation and newer modalities of surfactant administration, the incidence of long-term respiratory complications (bronchopulmonary dysplasia) in late-preterm infants can be further decreased.

Transient tachypnea of the newborn (TTN): TTN is caused by delayed clearance of alveolar fluid. The fetal lung is filled with alveolar fluid, which is important for lung growth and development. After delivery, alveolar fluid is cleared rapidly by Epithelial Sodium Channels (ENaC) and cyclic nucleotide gated channels to facilitate gaseous exchange. Increases in sodium content in cells stimulates Na-L-ATPase activity, which creates an osmotic gradient and allows water transport [43,44]. ENaC channels increases in the perinatal period, and peak expression of ENaC occurs at term. Late preterm infants have a lower expression of ENaC, which reduces their ability to clear lung fluid. The incidence of TTN is increased in late-preterm infants, with incidence of 6.3%, 4.6%, 2.5% and 1% at 34, 35 and 36 and 37 weeks respectively. Compared to full term infants (gestation 39 weeks), the relative risk of TTN increases from 5.7 at 36 weeks to 15.4 at 34 weeks.

Table 1: Complications associated with late preterm and GDM.

System	Complications in late preterm infants	Complications in infants of mothers with GDM
Cardiovascular	PDA	Cardiac defects (3% to 9%) TGA, DORV, VSD, truncus, TA, PDA Hypertrophic cardiomyopathy
Respiratory	Respiratory distress syndrome Transient tachypnea of newborn Apnea of prematurity	Respiratory distress syndrome Transient tachypnea of newborn
GI	NEC Poor feeding	Congenital intestinal anomalies: Duodenal atresia, imperforate anus, anorectal atresia, small left colon syndrome, situs inversus, small L colon syndrome
Renal		Ureteral duplication, renal agenesis, hydronephrosis.
Metabolic	Hypoglycaemia Hyperbilirubinaemia	Hypoglycemia Hypocalcemia Hypomagnesemia Hyperbilirubinemia
Hematological	Polycythaemia	Polycythemia
CNS	Longterm: Cognitive impairment Poor school performance Motor deficits, cerebral palsy Psychological and behavioral disorders Sensorineural defects	Congenital: Anencephaly, arrhinencephaly, microcephaly, holoprosencephaly, neural tube defects Spina bifida, Hemivertebrae. Caudal regression syndrome
Congenital structural anomalies		Flexion contractures Vertebral anomalies Cleft palate
Growth	Failure to thrive	Obesity
Others	Hypothermia Increased risk of birth defects Risk of readmission after initial discharge	Macrosomia (LGA) + risk of birth injury Increased risk of birth defects

Abbreviations: TGA: Transposition of the Great Arteries; DORV: Double Outlet Right Ventricle; VSD: Ventricular Septal Defect; TA: Truncus Arteriosus; PDA: Patent Ductus Arteriosus

Although previous studies had reported increased risk of TTN in infants of diabetic mothers due to decreased alveolar fluid clearance [45,46], more recent studies have provided differing results. The higher incidence of caesarean section delivery in maternal GDM may contribute to the increased risk of TTN. Some studies [38,39], showed significant association between TTN in late-prematurity with maternal GDM, whilst others did not. However, the definition of TTN differs between studies. Larger scale studies would help to delineate the extent of the problem.

TTN typically presents as respiratory distress after delivery. As TTN is a diagnosis by exclusion, other pathology (e.g. cardiac disease, RDS, pneumonia, etc…) needs to be ruled out, and supportive management should be provided. Symptoms should resolve within 48 h. Antenatal steroids can significantly decrease the incidence of TTN from 9.9% to 6.7% (RR 0.68, p=0.002) [34].

Apnea of prematurity: Apnea of prematurity is defined as cessation of breathing for over 20 sec or a shorter respiratory pause associated with oxygen desaturation and/or bradycardia in infants less than 37 weeks gestation [47]. The pathogenesis in most cases is due to immaturity of respiratory responses at different levels, including central and peripheral chemosensitivity, and inhibitory pulmonary neuronal signal (central apnea). In a small proportion of cases, apnea may be caused by upper airway obstruction (obstructive apnea). A large systematic review shows that the incidence of apnea of prematurity increases from 0.1% at 37 weeks gestation to 0.65%, 0.74% and 2.1% at 36, 35 and 34 gestation weeks respectively [6]. Compared to term infants, the relative risk for apnea is increased 39-fold at 34 weeks; 14.9-fold at 35 weeks; and 7-fold at 36 weeks [6]. One study analyzing pulse oximetry recordings on neonates found that intermittent hypoxic events occurred more frequently in late-preterm infants at 2 to 3 days compared to term infants (2.5 ± 1.2 *vs.* 1.0 ± 1.2; P<0.0001) [48]. So far, there are no studies on whether these intermittent events are associated with long-term sequela.

After pathological causes (e.g. Sepsis, upper airway obstruction, and central nervous system abnormality) had been ruled out, management of apnea of prematurity is mainly supportive. Management includes head and neck positioning (to maintain open airway), airway support (CPAP, non-invasive ventilation, mechanical ventilation), as well as medications (e.g. Caffeine).

Respiratory infections: Recent studies have shown that late preterm infants are at risk for respiratory infections. A retrospective cohort study [49], reviewed a total of 599,535 children (1,216,382 person-years) enrolled in a health system, and showed that late-preterm infants accounted for 643 (8.5%) of infections by Respiratory Syncytial Virus (RSV). Late preterm infants with gestation 330/7 to 346/7 have a significantly higher adjusted risk for RSV hospitalizations (Hazard Ratio (HR) 2.45; 95% CI 1.96-3.07), whilst those of gestation 350/7+0 to 366/7 weeks have adjusted risk (HR 1.92, 95% CI 1.66-2.22). These infants are at higher risk of severe sequela including respiratory failure and need for ECMO.

Metabolic aspects

Hypoglycemia: In the neonate, glucose homeostasis to maintain normoglycemia relies on normal glucogenesis and ketogenesis [50]. Impaired glucogenesis/ketogenesis may occur due to hyperinsulinism, decreased counter-regulatory hormone production, or inadequate glycogen reserve [50,51]. Reviews on neonatal hypoglycemia have pointed out difficulties in correlation of plasma glucose levels with clinical signs in the neonatal period [50,52]. Correlation with long term neurological outcome is also difficult due to heterogeneity of studies and presence of confounding conditions [52,53].

Many studies have demonstrated late preterm and maternal GDM as risk factors for hypoglycemia [8]. A meta-analysis in 2011 [6], showed significantly increased risk of hypoglycemia in late-preterm

infants compared to term (OR 7.4, 95% CI 3-18.1). A study in 2012 showed that up to 50% of all at-risk infants developed hypoglycemia whilst those with multiple risk factors (e.g. Prematurity, maternal DM) have a higher risk of profound hypoglycemia [54]. This is likely the result of the combined effect of fetal hyperinsulinism due to GDM [55], together with inadequate neonatal glycogen reserves and inability to mount a ketogenic response due to prematurity [56].

For infants with hypoglycemia, feeding should be started early if possible, with support for breast feeding. Intravenous dextrose should be given if hypoglycemia persists after feeding to achieve normoglycemia. Higher Glucose Infusion Rate (GIR) may be required for infants with refractory hypoglycemia. In refractory hypoglycemia requiring GIR above 10 mg/kg/min, endocrinologist should be consulted to screen for hyperinsulinism and other metabolic causes. In the past decade, newer modalities of glucose supplementation are available, including oral dextrose gel [57], which is used increasingly in many Nurseries and Neonatal units. A Cochrane review [58] has shown that use of dextrose gel did not significantly decrease the need for intravenous dextrose, but did significantly reduce maternal-baby separation and improves the rate for successful breast feeding.

Feeding problems: Breast milk is the diet of choice for late-preterm infants. Breast-feeding for infants of GDM pregnancies leads to a slower body mass index growth trajectory up to late childhood, and is protective against childhood adiposity [59-63]. However, feeding problems is encountered in many late-preterm infants. A systematic review showed a 6.5-fold increased risk of feeding problems in late-preterm infants compared to term (34% *vs.* 6.7%, OR 6.5 95% CI 2.5-16.9) [6]. Another study showed that feeding problems is one of the leading causes for delayed discharge or unplanned readmissions [9]. Feeding assessment should be performed for early detection and management of feeding difficulties. Support from lactation nurse could facilitate feeding, consolidate mother-infant bonding, and prevent prolonged hospital stay.

Hyperbilirubinemia

Late-preterm infants are at risk of hyperbilirubinemia (neonatal jaundice) because of reduced hepatic uptake and decreased conjugation of bilirubin in the liver. One study reported a high incidence of hyperbilirubinemia in late preterm compared to term neonates (54% *vs.* 38%) [9]. Neonates with hyperbilirubinemia requiring phototherapy increases from 2.5% at 37 weeks to 13.4% at 36 weeks; 22.6% at 35 weeks and 27.7% at 34 weeks [8]. Maternal GDM is also known to be a risk factor for hyperbilirubinemia, occurring in 11% to 29% of infants [14]. However, most studies had not investigated the combined effect of maternal GDM and prematurity.

Late-preterm infants with hyperbilirubinemia are at risk of developing Bilirubin Induced Neurological Damage (BIND) due to their relatively immature central nervous system and blood brain barrier [64]. Therefore, bilirubin levels should be monitored, and treatment with phototherapy initiated as necessary for these infants. Threshold for phototherapy and exchange transfusions varies between different gestations, with a lower treatment threshold for preterm neonates. Bilirubin normograms, like the AAP and NICE guidelines are used for reference [65,66].

Long-Term Neonatal Complications and Management

Respiratory outcome (childhood and adolescence)

Although respiratory outcome has been extensively studied in extremely preterm infants, there are not many studies on long-term respiratory outcome in late preterm neonates. A cross sectional study in 2019 [67], compared respiratory function assessment (spirometry, multiple breath washout, lung clearance index, 6 min walk test); as well as symptoms related to asthma/ allergy between former late preterm infants and term infants. Results showed significantly lower FEV1 and FVC in the late-preterm group, and increased symptoms related to asthma (number of wheezy episodes, use of bronchodilators and use of inhaled corticosteroids). Another group of infants from the UK Millenium Study also confirmed increased risk of asthmatic symptoms and wheeze, as well as increased use of bronchodilator therapy at age 5 years. Further large-scale studies on long-term respiratory outcome would provide more useful information on management of these infants.

Neurodevelopmental outcomes

Background: In the past 10 years, our understanding of neonatal brain structure and function has been revolutionalized by the use of Magnetic Resonance Imaging (MRI) [68]. Conventional MRI with diffusion imaging provides quantitative estimations of brain structure and volume, as well as microstructural development of the neonatal brain, whilst functional MRI investigates neuronal activity [69-71]. MRI measurements of brain volume have demonstrated that the preterm brain volume at 28 weeks' is only 13% of that of term neonates. Brain volume increases at a rate of 1.4% per week, and by 34 weeks' gestation, the brain volume is 65% of that of term neonates [72]. White matter volume increases 5-fold between 35 to 41 weeks' gestation. Meanwhile, the fetal brain undergoes structural maturation in the late preterm period with increased neuronal connectivity, dendritic arborization and synaptic junctions. Pre-oligodendrocytes differentiate into immature oligodendrocytes at term [72]. Different events in cerebral white and grey matter development: Oligodendrocyte differentiation, gyration, myelination, synaptogenesis, axonal elongation etc… follow different sequences of maturation in the human brain. Maturation of the white matter is not yet complete by late preterm; hence these infants are vulnerable to development of periventricular leukomalacia and are at risk of adverse neurodevelopmental outcome.

Late preterm and cerebral palsy: Extremely preterm infants are at risk for severe (Grade III/IV) intraventricular hemorrhage, which leads to cerebral palsy and adverse neurological outcome. Although the incidence of severe intraventricular hemorrhage is low in late-preterm infants (0.01%), long-term outcome data shows that these infants are also at increased risk of developing cerebral palsy in childhood [73,74]. This may be related to the fact that brain growth and neuronal development are still ongoing at 34 to 36 weeks gestation, and any hypoxic ischemic or inflammatory/ infective event may lead to injury in the developing brain with long-term sequela. One large scale National study [75], in Finland involving 48,273 late preterm and 1,096,283 term infants showed a higher incidence of cerebral palsy at age 7 years in the late preterm group as compared to term infants (0.6% *vs.* 0.1%) with odds ratio 2.35 (95% CI 1.99-2.77) at age 7 years. Associated risk factors for cerebral palsy are need for resuscitation at birth, 1 min Apgar score <7 and intracranial hemorrhage. Another epidemiological study in USA [76], comparing 8341 preterm and 131,059 term infants showed a significantly higher risk of cerebral palsy in late-preterm infants (HR 3.39 (95% CI 2.54-4.52)).

Cognitive delay: There are many studies in the literature

addressing the question of cognitive delay in late preterm infants. Some studies show a positive association between late-preterm infants and cognitive delay in childhood whilst others did not [74-77]. Of these, one large scale study [74] looked at MDI and PDI using the Bayley Scale of Infant Development in 1200 late preterm and 6300 term infants at 24 months. Results showed that late-preterm infants had significantly lower Mental Developmental Index (MDI) (85 *vs.* 89) and Psychomotor Developmental Index (PDI) (88 *vs.* 92), P<0.0001. Compared to term infants, a significantly larger proportion of late-preterm infants had MDI <70 (21% *vs.* 16%) and PDI <70 (6.1% *vs.* 6.5%, with AOR 1.52 (95% CI 1.62, 1.82). Another large-scale study involving 8341 late-preterm infants and 131,059 term infants [76], also showed increased risk of developmental delay in late-preterm infants with AOR=1.36 (95% CI: 1.11, 1.66). However, studies on cognitive function are heterogenous and different methods are used for different studies. For example, some studies use the Bayley Scale of infant Development, whilst others used the Griffith's Mental Developmental Scale; the revised Woodcock-Johnson Psycho-Educational Battery; the Wechsler Intelligence Scale for Children etc… The age of assessment is usually around 4 to 6 years, but studies can range from 24 months to 15 years [78-81].

Contrary to studies in late-preterm infants, there is not much data on long-term cognitive outcome in infants of diabetic mothers. A systematic review included 14 studies on effects of maternal GDM/ DM on neurodevelopmental outcome of infants [82]. 8 out of 14 studies comparing MDI and IQ between infants of diabetic mothers showed negative effect of maternal GDM on cognitive outcome. However, the effect size is heterogenous, varying from -1.30 to 0.54. Furthermore, the methodology, assessment tool and outcome measures differ between studies, so further analysis is not possible. One study showed socioeconomic status also plays a role in outcome [83], and maternal diabetes and low SES is significantly associated with lower IQ scores.

Congenital malformations

Both prematurity and maternal GDM are associated with increased risk of congenital malformations which may affect multiple systems. This is especially so with poorly controlled DM/ GDM during the antenatal period. Please refer to Table 1 for details

School performance: A number of large-scale studies have provided valuable insight on school performance in late preterm infants. The Millennium Cohort Study analyzed the outcome of a large group of children born in UK in 2000-2001. School performance assessed at 5 years old (1st year at school) by Foundation Stage Profile showed that compared to term infants, late-preterm infants had 12% increased risk of not reaching a good standard of overall achievement (59% *vs.* 51%) [84]. Repeat assessment at age 7 years (3rd year at school) by Key stage 1 showed that late-preterm infants had 36% increased risk of poor performance compared to term infants [85]. Lipkind et al. [86] from USA showed that late preterm children had lower Maths and English scores on 3rd grade tests, and 30% adjusted odds for special education. Another study from the Early Childhood Longitudinal Study Birth Cohort Preschool showed that late preterm infants have significantly lower developmental assessment scores at 9 months but catch up by 24 months [87]. However, late-preterm infants still have significantly lower scores for preschool reading and Math's when compared to term infants.

Management of late-preterm infants: Late-preterm infants are at risk of many short and long-term complications. As seen from above, there is growing evidence that some of these complications may be exacerbated in infants with maternal GDM. It is important for Pediatricians to anticipate and recognize the problems early so that appropriate management could be given. Complete and thorough physical examination should be performed after delivery to screen for congenital abnormalities. These infants' respiratory status should be monitored carefully, together with vital signs, temperature, and blood glucose. Timely respiratory support (with oxygen therapy, high flow nasal cannula, CPAP, non-invasive ventilation) may prevent further deterioration and decrease the need for mechanical ventilation. Feeding should be started early, and breast feeding encouraged with lactation consultant support as needed. For infants with persistent hypoglycemia, intravenous dextrose infusion should be started. Other means of glucose supplementation (e.g. oral dextrose gel) can also be considered. After discharge from hospital, family physician and community nurse could be enlisted for continuing support and advice to the family. Growth measurements should be performed during regular visits to the Family Physician or Maternal and Child Health Centre for vaccinations and well-baby check.

As long-term neurodevelopmental problems are more prevalent in these infants, regular developmental assessment could be performed so that subtle delays in development could be recognized. Early training with physiotherapy, occupational therapy and/or speech therapy would help these children to catch up with their peers. For those children with persistent learning difficulties, special arrangements on education should be discussed with the family.

Conclusion

Late-preterm infants are a vulnerable group of infants who may encounter multiple complications after delivery. Maternal diabetes has been shown to cause additional complications in late preterm infants with both short and long-term sequela. Close communication and collaboration between the obstetrics and neonatal teams are essential in the management of such high-risk deliveries. Good antenatal care with special attention to glycemic control and close intrapartum monitoring is important in minimizing both maternal and neonatal problems. Neonatologists should monitor these infants closely after birth, so that timely and appropriate management can be provided. Long-term complications, especially neurodevelopmental aspects are a challenging and interesting area for further research.

Author Contributions

All authors contributed equally to the writing of the draft and revisions.

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