Gestational age at delivery, circumstances at parturition, and prenatal risk factors affect outcomes of late preterm newborns: results from an area-based, prospective cohort study.

Francesca Monari[1], Giuseppe Chiossi[1], Giancarlo Gargano[2], Michela Ballarini[1], Dante Baronciani[3], Alessandra Coscia[4], and Fabio Facchinetti[5]

[1]Policlinico di Modena
[2]Arcispedale S Maria Nuova
[3]Affiliation not available
[4]Ospedale Sant'Anna
[5]Università degli Studi di Modena e Reggio Emilia

June 23, 2020

Abstract

Objective: To identify pregnancies at risk for adverse outcomes in the late preterm (LP) period, we investigated how gestational age (GA) at delivery, circumstances at parturition, and specific prenatal risk factors may affect neonatal outcomes. Study design: Prospective, area-based cohort study of neonatal morbidity and mortality among singleton infants born between 34+0 and 36+6 weeks, at 21 L&D units in Emilia Romagna county, Italy, during 2013-15. The primary neonatal outcome was a composite of Apgar 5' [?] 3, umbilical-cord-blood arterial pH $<$ 7.0, RDS, TTN, hypoglycemia, sepsis, confirmed seizures, stroke, IVH, cardiopulmonary resuscitation, invasive respiratory support and hospitalization [?] 5 days. Multivariate logistic regression models were used to respectively investigate the effects on study outcomes of 1) GA at delivery and circumstances at parturition 2) GA at delivery and prenatal risk factors, after controlling for confounding Results: Among 1867 births, 302, 504 and 1061 infants were born at 34, 35 and 36 weeks, respectively. There were no neonatal deaths. When studying circumstances at parturition, an increased risk of composite neonatal outcome was observed among 34 weeks births, 35 weeks deliveries, and indicated deliveries. When studying prenatal risk factors, neonatal morbidity was associated with delivery 34 weeks, birth at 35 weeks, pregestational diabetes, pPROM, maternal BMI, bleeding and polyhidramnios; instead, preeclampsia had a protective effect. Conclusion: LP with indicated deliveries at 34 or 35 weeks, or with specific prenatal risk factors have worse neonatal outcome when compared to 36. Such differences should be considered when counseling patients and planning interventions.

BACKGROUND

Preterm birth is defined as delivery prior to 37 weeks' gestation. Although infants born toward the end of this period were traditionally assumed to be 'low risk,' research has unequivocally demonstrated increased rates of adverse neonatal outcomes associated with LP births (34^{+0}–36^{+6} weeks). Compared with term infants, LP infants are more frequently admitted to the neonatal intensive care unit (NICU), and have longer hospital stay, due respiratory morbidities, temperature instability, hypoglycaemia, and hyperbilirubinaemia. Such population is also at higher mortality risk and it is more susceptible to sepsis, necrotizing enterocolitis, and neurological morbidities [1, 2, 3].

The LP rate in Western countries represents 3.3-5.7% of all births, accounting for about two thirds of the entire preterm population [4]. Despite the LP period is restricted to just 21 days of intrauterine development, perinatal well-being may vary [5]. The primary determinant of neonatal outcomes is gestational age at

delivery; however, race, fetal gender, and administration of antenatal corticosteroids are also important factors affecting both survival and intact survival [6]. Recent research suggests that also indication for delivery significantly impacts neonatal outcomes [7, 8]: studies on both preterm [7] as well as LP births [9] showed worse outcomes among medically indicated as opposed to spontaneous preterm deliveries. Furthermore, among births prior to 34 weeks, intrauterine growth restriction (IUGR) was found to have increased neonatal risks [10, 11] , while fetal or obstetric indications for delivery lead to higher neonatal morbidity when compared to maternal indications [12]. However, the role of specific maternal (such as hypertensive disorders, diabetes mellitus) or fetal risk factors (such as IUGR, amniotic fluid abnormalities) on neonatal outcomes is still a matter of debate, when they are not directly responsible for LP deliveries. Moreover, the outcomes of late LP premature rupture of membranes have not been compared to other delivery indications.

With this study we sought to expand our understanding of how neonatal risks in the LP period may vary according to the timing and the indication for delivery, in order to personalize prenatal counseling, as well as obstetric care for individual mothers and their newborns. Therefore, we investigated a large prospective cohort of LP neonates to determine:

1) if neonatal outcomes differ according to the specific gestational age at delivery (34 vs 35 vs 36 weeks' births), as gestational age does not affect management of pregnancies when delivery is anticipated between 34^{+0} and 36^{+6} weeks

2) if neonatal morbidity varies based on the circumstances at parturition (spontaneous preterm labor (PTL), preterm premature rupture of membranes (pPROM), or indicated delivery)

3) if complications at birth are affected by specific maternal, fetal and obstetric conditions, even if they may not represent the indication for delivery.

MATERIALS AND METHODS

We conducted a prospective, multicenter, area-based cohort study of all the LP deliveries from December 1st 2013 to December 1st 2015 in Emilia Romagna, a region in Northern Italy with nearly 4.5 million people organized in 9 counties.

The study steering committee (consisting in 2 obstetricians, 2 neonatologists and 1 epidemiologist) defined the information to collect on pregnancies resulting in LP deliveries, and on neonates' hospital course. Standardized chart abstraction forms were designed to obtain anonymized data on mothers (i.e maternal demographics, maternal medical and obstetrical complications, labor and delivery details) and their newborns (i.e birthweight, gender, Apgar scores, admission to the NICU or Intermediate/Step Down Unit, and length of stay, neonatal morbidities and mortality). In Emilia Romagna, inpatient obstetric and pediatric care was provided at that time by 28 hospitals within the National Health System. Recruitment occurred only at the 21 hospitals with at least 500 deliveries/year, equipped with NICUs or Intermediate/Step Down Units, that could care for LP infants: one obstetrician and one neonatologist/pediatrician from each study site approached mothers delivering at 34^{+0}-36^{+6} weeks for written informed consent, and respectively completed the maternal and the neonatal data collection forms, as they interviewed the patients and consulted the medical records. Five trained research associates visited the study sites on a monthly basis to review the maternal and neonatal data collection forms with the physicians that had filled them. At the Data Managing Center (Modena Policlinico Hospital, University of Modena and Reggio Emilia) research associates used optical character recognition technology (Flexi Capture, Abbyy ®, Germany) to scan the data collection sheets, extract pertinent data, and organize it in a password protected database. If automated data extraction failed (approximately 5% of the times), research associates reviewed the forms and manually entered the missing data in the database. Approval from the Institution Review Board of the 9 Emilia Romagna Counties was obtained. The study was financed by the Emilia Romagna County Grent (n 417149 _ 2014).

Study population

Women with a singleton viable pregnancy (antenatal stillbirth were excluded) were classified according to the circumstances at delivery as spontaneous PTL, pPROM or indicated delivery. The diagnosis of preterm

labor was based on clinical criteria of regular uterine contractions accompanied by progressive changes in cervical dilation and effacement [13]. As preterm labor occurred [?] 34 weeks, tocolytic therapy was not administered. Women presenting with pPROM between 34^{+0} and 36^{+6} weeks' gestation, who were not in labor within 24 hours after rupture of membranes and had no indication for immediate delivery, were expectantly managed as detailed in the PPROMEXIL trial [14]. Women in whom pPROM was diagnosed after 24^{+0} weeks, but who had not delivered by 34^{+0} weeks' gestation, could also be managed expectantly. The diagnosis of membrane rupture was confirmed by visualization of amniotic fluid passing from the cervical canal and pooling in the vagina, a basic pH test of vaginal fluid, or arborization (ferning) of dried vaginal fluid, which is identified under microscopic evaluation. When needed, commercially available test for amniotic proteins (Amnioquick (r) Biosynex) were utilized to confirm pPROM according to local protocols. A course of therapy with a combination of a beta lactam and a macrolide antibiotic was left at the discretion of each study site even when pPROM occurred after 34 weeks, as a preliminary inquiry had found such practice to be common. Rupture of membranes was considered as the delivery indication only when spontaneous labor occurred during expectant management, or if the patient and/or her obstetrician opted for an elective delivery. Instead, if onset of labor occurred within 24 hours of rupture of membranes, spontaneous PTL was the delivery indication. We defined indicated births as those occurring after labor induction or cesarean delivery without labor due to maternal, fetal or obstetric complications.

No specific recommendations were given concerning administration of antenatal corticosteroids, as the study was conducted prior to the publication of the ALPS trial [15].

The timing of delivery was determined in completed weeks of gestation such that 34 weeks (for example) included deliveries at 34^{+0} – 34^{+6} weeks. Gestational age was based either on first trimester ultrasound scan or, in women with a regular cycle, on the first day of the last menstrual period if the expected date of delivery differed less than 7 days from that estimated by ultrasound.

Outcome measures

The study outcomes were composite. Composite adverse neonatal outcome included neonatal death, adverse respiratory outcomes (RDS,TTN), hypoglycemia, newborn sepsis, confirmed seizures, stroke, IVH, cardiopulmonary resuscitation, mechanical ventilation, umbilical-cord-blood arterial pH $<$ 7.0 or base excess $<$ -12.5, a 5-minute Apgar score [?] 3, and prolonged hospitalization ([?] 5 days). As indicated by previous studies, these outcomes were chosen as they are associated with significant risks of neonatal mortality or long-standing neonatal morbidities, including hypoxic ischemic encephalopathy [16, 12]. Secondary outcomes included neonatal resuscitation (metabolic acidosis and/or resuscitation at birth), metabolic complications (hypoglycemia and/or difficulties feeding), and respiratory support (both invasive and non-invasive).

Non reassuring fetal status was defined as catergory III [17] or persistent category II fetal heart rate pattern with abnormal labor progress [18], non-reactive NST associated with recurrent decelerations among non-laboring women [19], absent or reverse umbilical artery end diastolic flow in the setting of IUGR [20]. Clinical chorioamnionitis included maternal fever in association with uterine fundal tenderness, maternal tachycardia, fetal tachycardia, purulent or foul amniotic fluid [21]. Mild metabolic acidosis was defined as pH= 7.20 – 7.30 and BE = -6 - -12, moderate acidosis consisted in pH= 7 – 7.19 and BE = -12 - -16, while severe acidosis was pH $<$ 7 and BE $<$ -16. CPAP and oxygen administration represented non-invasive respiratory support, as opposed to mechanical ventilation, the invasive respiratory support. Neonatal sepsis was defined as a clinical syndrome prompting antibiotic treatment, with or without positive cultures. Cerebral lesions were suspected clinically, screened by neonatal brain ultrasound, and confirmed on MRI. (For details about specific definitions of outcomes please see Table S1) .

Statistical analysis

As we stratified neonatal outcomes according to timing of delivery, we also compared how maternal characteristics, obstetric features, fetal characteristics, and circumstances at parturition varied with each completed week of gestation at the time of delivery. Categorical variables were presented as n (%) and tested with Chi square test or Fisher's exact test as appropriate. Normally distributed continuous variables were presented

as mean +- SD and compared with One Way ANOVA. Non-normally distributed continuous variables were presented as median (IQR) and tested with One Way ANOVA on ranks. A level of statistical significance of P [?] 0.05 was considered

Multivariate logistic regression analysis was used to investigate if gestational age and circumstances at delivery (spontaneous PTL, pPROM or indicated delivery) independently affected the risk of adverse neonatal outcomes. The following variables were tested as potential confounders: maternal age, parity, history of spontaneous preterm birth, race, low education, smoking, maternal BMI, excessive weight gain, utilization of assisted reproductive technologies (ART), treatment with antenatal corticosteroids, ASA, LMWH, or progesterone. Maternal medical disorders, obstetric or fetal complications, type of labor other than spontaneous (i.e induced or no labor), and route of delivery were not included in the models as they were considered on the same causal pathway of circumstances at delivery. Finally, a potential interaction between gestational age at delivery and circumstances at delivery was investigated.

Disorders of the mother or the fetus may affect neonatal outcomes, even if they are not the primary indication for delivery. Therefore, we tested the independent effect on adverse neonatal outcomes of maternal medical conditions (diabetes mellitus, hypertensive disorders, liver disorders), fetal characteristics (non-reassuring fetal status, IUGR, prenatally diagnosed fetal anomalies or aneuploidies, and amniotic fluid disorders), pregnancy complications (pPROM, spontaneous PTL, chorioamnionitis, vaginal bleeding from placental abruption or abnormal placentation), and gestational age at delivery using multivariate logistic regression. Maternal age, parity, history of spontaneous preterm birth, race, low education, smoking, maternal BMI, excessive weight gain, utilization of ART, treatment with antenatal corticosteroids, ASA, LMWH, or progesterone were tested as potential confounders. Type of labor other than spontaneous (i.e induced or no labor), and route of delivery were not included in the models as they were considered on the same causal pathway of maternal, fetal, or obstetrics complications.

The strength of the association between the covariates and the dependent variable was estimated as area under the curve of a receiver operating characteristic (ROC) curve plotted with the true-positive rate compared with the false positive rate. Statistical analyses were performed using Stata 15 (StataCorp, College Station, TX).

RESULTS

Among the 1897 LP births, 302 (16.2%) occurred at 34 weeks', 504 (27%) at 35 weeks' and 1061 (56.8%) at 36 weeks' gestation. Spontaneous preterm labor accounted for 686 (36.7%) deliveries, pPROM for 398 (21.3%), while 783 (42%) were indicated LP births.

Table 1 summarizes the maternal and obstetrics characteristics of the study population presented by gestational age at delivery. Demographic features, socioeconomic attributes, medical complications (hypertensive and liver disorders, chorioamnionitis), prophylaxis with ASA or LMWH were similar across different gestational age groups. Only 4 patients developed pPROM $<$ 34 weeks' gestation. Diabetes mellitus was more common among mothers who delivered at 34 weeks' gestation ($p < 0.01$), pPROM was more prevalent among pregnancies resulting in 36 weeks deliveries ($p = 0.03$), while vaginal bleeding due to abruption or abnormal placentation was less frequent among gestations leading to 36 weeks as opposed to earlier births ($p < 0.01$). Antenatal corticosteroids and progesterone prophylaxes progressively decreased with gestational age ($p < 0.01$). The last (and for 605/634 the only course) of antenatal corticosteroids was administered to 237 (37.4%) patients $<$ 34 weeks' gestation, while 397 (62.6%) received the treatment later. Induction of labor was more common later in pregnancy, as opposed to CDs performed prior to labor onset ($p < 0.01$); the vaginal delivery rate increased with gestational age at delivery ($p < 0.01$).

Thirty-four women (4%) were diagnosed with pPROM prior to 34 weeks' gestation, while 809 (96%) later. The median interval from rupture of membranes to delivery was 4 days (95%CI 2 -5 days). Antibiotic treatment was administered to 699 (83%) women with pPROM; although details about the duration of treatment were available for only 634 women, the vast majority (i.e. 610, 96%) received a [?] 7 day-course.

Fetal characteristics are displayed in table 1. Non reassuring fetal status, prenatally diagnosed fetal anomalies, and amniotic fluid abnormalities were similar among study groups, while IUGR was significantly less common when delivery occurred closer to term ($p < 0.01$). Circumstances at parturition (spontaneous PTL, pPROM or indicated deliveries) did not differ according to timing of delivery (Table 2). Instead, most neonatal outcomes were affected by gestational age (Table 3). No cases of neonatal deaths were detected in our study population. The prevalence of metabolic acidosis and respiratory support dropped with gestational age at delivery ($p < 0.01$), while 5' Apgar score and cardiopulmonary resuscitation remained unaffected (Table 3). Later deliveries were associated with higher birthweights, higher proportions of SGA infants, as well as lower rates of jaundice, difficulty feeding, hypoglycemia and sepsis ($p < 0.01$).

The composite neonatal outcome was detected among 27.1% (82/302) of the 34 weeks deliveries, 17.7% (89/504) of the 35 weeks deliveries, and 8% (85/1061) of the 36 weeks births ($p < 0.01$). Similarly, the composite outcomes respectively summarizing metabolic complications, and respiratory support decreased when delivery occurred closer to term, while the risk of metabolic acidosis and/or neonatal resuscitation was unaffected by timing of delivery (Table 3).

Multivariate analysis showed that gestational age at delivery had the most significant impact on the composite neonatal outcome, metabolic complications, and the need for respiratory support. Table 4 summarizes the multivariate logistic regression models investigating the role of timing and circumstances at delivery. Neonatal morbidities decreased with gestational age at delivery ($p < 0.01$), and were associated with indicated births ($p < 0.01$); of note, outcomes of pregnancies delivered due to pPROM were similar to spontaneous PTLs (Table 4). Instead, timing of delivery did not affect neonatal resuscitation, that appeared to be uniquely associated to deliveries indicated by maternal, fetal or obstetric complications ($p < 0.01$). Table 5 illustrates the multivariate logistic regression models assessing the impact of maternal medical conditions, fetal characteristics, pregnancy complications, and gestational age at delivery on neonatal morbidities. As gestational age increased, the composite neonatal outcome, metabolic complications and the need for respiratory support dropped ($p < 0.01$). Considering the same outcome measures, pregestational diabetes was a significant risk factor for neonatal morbidities ($p = 0.02$, < 0.01, and < 0.01 respectively), while preeclampsia showed a protective effect ($p = 0.03$, < 0.01, and 0.04 respectively). Vaginal bleeding due to abruption or abnormal placentation ($p = 0.03$), increasing maternal BMI ($p = 0.03$, and 0.02 respectively), and polyhydramnios ($p = 0.045$, and < 0.01 respectively) were significantly associated with both the composite neonatal outcome and respiratory support, while pPROM ($p < 0.01$) was solely associated with the composite neonatal outcome. Non-reassuring fetal status was related to both metabolic complications ($p < 0.01$), and respiratory support ($p = 0.04$); instead, spontaneous PTL ($p < 0.01$) had a protective effect on the risk of metabolic complications, as opposed to IUGR ($p < 0.01$). Gestational age at delivery did not affect the risk of metabolic acidosis and/or neonatal resuscitation; the likelihood of such outcome was associated with bleeding due to placental abruption or abnormal placentation ($p < 0.01$), as well as with non-reassuring fetal status ($p < 0.01$).

CONCLUSIONS

Although births at 34^{+0} – 36^{+6} are usually considered as a homogeneous population under the definition of LP, this large prospective, observational study demonstrated significant differences in neonatal outcomes based on gestational age at delivery. We found that approximately one third of newborns at 34 weeks experienced neonatal morbidities, when compared to $< 10\%$ of the 36 weeks births (Table 4). Moreover, after controlling for confounding, adverse outcomes were 2-4 folds more common when delivery took place at 34 instead of 36 weeks' gestation (Tables 5, 6). As also shown by the Consortium on Safe Labor [22], we identified a continuum of neonatal morbidities that inversely correlated with timing of delivery; therefore, when maternal, fetal or obstetric complications develop between 34^{+0} and 36^{+6} weeks' gestation, obstetricians need to carefully balance the risks and benefits of birth at a specific gestational age with the consequences of pregnancy continuation beyond that time point [23].

As metabolic acidosis and the need for neonatal resuscitation reflect the fetus' exposure to hypoxia and increased metabolic demands, we found an association with pregnancy complications rather than gestational

age at delivery (Table 5, 6). De Almeida et al. [24] initially demonstrated that LP babies were at substantially increased risk for neonatal resuscitation when compared to term counterparts. Our multivariate analyses confirmed among LP newborns known risk factors for resuscitation at birth, such as delivery prompted by maternal or fetal disorders (i.e. indicated deliveries, Table 5), vaginal bleeding from placenta abruption/abnormal placentation, and non-reassuring fetal status (Table 6) [25]. These findings may help develop strategies to prepare for circumstances requiring advanced neonatal resuscitation skills, and to organize in utero transfer to Tertiary Care Centers.

In our cohort, indicated deliveries were associated with worse immediate neonatal outcomes when compared with spontaneous LP labor (Table 5), as also indicated in previous reports [8, 9]. The process of labor itself likely facilitates fetal lung maturation and improves clearance of pulmonary fluid, reducing the risk of neonatal respiratory morbidities and the need for resuscitation [26], while the underlying condition that prompted delivery may also account for poorer outcomes. Interestingly, expectantly managed pPROM had outcomes similar to spontaneous LP labor, suggesting that prompt induction of labor may not represent the only option available when rupture of membranes complicates LP gestations, as also stated in the PPROMEXIL [14] and PPROMEXIL2 [27] trials.

Our study also showed that an adverse intrauterine environment may significantly contribute to neonatal morbidity. The association between infection, inflammation and adverse neonatal outcomes may be explained by the ability of pro-inflammatory cytokines to produce the "fetal inflammatory response" [28]. Intrauterine inflammation has been demonstrated in pregnancies complicated by preeclampsia [29], maternal obesity [30], polyhydramnios [31], rupture of membranes, and chorioamnionitis [32]. Diabetes mellitus not only creates a pro-inflammatory intrauterine environment [33], but it also accounts for the damaging effects of fetal hyperglycaemia and hypoxia [34]. Accordingly, our multivariate analyses confirmed the correlation between pregestational diabetes and increasing maternal BMI with both the composite adverse neonatal outcome, and the need for respiratory support, while polyhydramnios was linked to both the composite adverse neonatal outcome and resuscitation at birth. We also showed how pregestational diabetes relates to neonatal metabolic complications, while pPROM was confirmed as a risk factor for the composite of neonatal morbidities (Table 6). Surprisingly, preeclampsia had a protective effect on neonatal complications (Table 6), suggesting that the increased antepartum surveillance once preeclampsia is diagnosed may counterbalance the risks associated with an adverse intrauterine environment

Placental ischemia and hypoxia are characterized by impairment of placental blood flow, which results in reduced delivery of oxygen and nutrients to the fetus [35]. According to our multivariate analyses, placental abruption or bleeding from abnormal placentation were associated with the composite adverse neonatal outcome, with metabolic acidosis and/or resuscitation at birth, and respiratory support as they may compromise fetal supply of oxygen and nutrients to the fetus (Table 6). Similarly, increased metabolic demands may lead to non-reassuring fetal status, that was also correlated with resuscitation at birth, the composite metabolic outcome, and respiratory support (Table 6). Insufficient intrauterine growth has been attributed to hypoxemia from placental under perfusion [36, 37], and it was found to have increased neonatal risks among preterm births [10, 11]. Our multivariate analyses confirmed such finding also in the LP population, since IUGR babies had more metabolic complications (Table 6).

It has been speculated that spontaneous onset of preterm labor may be a consequence of an earlier idiopathic activation of the normal labor process in an attempt to protect the fetus. Therefore, labor may enable the fetus to exit a potentially "hostile" in-utero environment [38]. Accordingly, our multivariate analysis showed a protective effect of spontaneous preterm labor on the risk of developing the composite metabolic outcome, as opposed to other maternal, fetal or obstetric complications.

Strengths of this study include the large sample size and multicenter nature of the cohort: both characteristics increase the generalizability of our findings. The prospective design of the survey, along with predefinition of standardized chart abstraction forms completed by Obstetricians and Pediatricians, and periodically audited by research associates, limit misclassification bias and assures data validity. We acknowledge also some limitations. The study did not classify neonatal complications according to specific obstetric, maternal or fetal

indications for delivery. We deliberately chose to analyze together the outcomes of all indicated deliveries, as some disease processes such as hypertensive disorders, diabetes mellitus or intraamniotic infections may affect both mothers and babies. Moreover, we focused on specific disorders, rather than delivery indications, as those may be indirectly responsible for LP deliveries; for example, IUGR may account for non-reassuring fetal status that prompts emergent delivery, or also preeclampsia may cause placental abruption that then leads to delivery. Although inconsistencies in antenatal corticosteroids administration may reflect different opinion leaders' viewpoints prior to the publication of the ALPS trial, we considered bethamethasone treatment among the potential confounders in our multivariate analyses.

In conclusion, gestational age at delivery, circumstances at parturition, and specific maternal, fetal, as well as obstetric complications have a significant impact on neonatal outcomes. Therefore, the decision to deliver or not during LP period should be based on the underlying conditions affecting the mother and/or the fetus, and a careful assessment of the risks of preterm delivery versus the potential benefits of expectant management should be performed. Our findings can be helpful when counselling mothers at risk of LP delivery, and can be used to plan interventions for their newborns.

DISCLOSURE OF INTERESTS : Each author declares to have no conflicts of interest.

CONTRIBUTION TO AUTHORSHIP: each author contributed significantly: FM and MB in writing paper and collecting data, GC in statistical analysis and writing paper, GG, DB, AC in the conception of the study and FF in scientific conception and principal investigator of the study.

DETAILS OF ETHICS APPROVAL: The study was approved from the Institution Review Board of the 9 Emilia Romagna Counties (n 24512 _ 25/9/2014)

FOUNDING: The study was financed by the Emilia Romagna County Grent (n 417149 _ 2014)

* ***Late Preterm Emilia Romagna Group:*** *Vittorio Basevi (Health facilities, Emilia-Romagna Region, Bologna, Italy), Frusca Tiziana (Obstetrics and Gynaecology Unit, University of Parma, Parma, Italy), Giuseppe Battagliarin (Health facilities, Emilia-Romagna Region, Bologna, Italy) , Marinella Lenzi (Maternal and Pediatrics Department, Maggiore Hospital, Bologna, Italy)., Gina Ancora (Neonatal Intensive Care Unit, Azienda Sanitaria Romagna, Infermi Hospital Rimini, Rimini, Italy), Luigi Corvaglia (Pediatric unit, Ospedale S. Orsola- Malpighi di Bologna).*

Acknowledgments: we are indebted to all collegues and research fellows for their contributions to data collection:

Group of Bologna: Maria Bisulli (Obstetric Unit), Nicola Rizzo (Obstetric Unit), Elisa Moro (Obstetric Unit), Silvia Vandini (Neonatal Unit) from Ospedale S. Orsola- Malpighi di Bologna; Francesco Giura (Neonatal Unit), Fabrizio Sandri (Neonatal Unit), Paola Murano (Obstetric Unit), Barbara Di Marcobernardino (Obstetric Unit), Giorgio Scagliarini (Obstetric Unit) from Ospedale Maggiore of Bologna.

Group of Romagna: Elena Baudassi (Neonatal Unit) from Ospedale Infermi of Rimini

Group of Parma and Piacenza : Federica Tamarri (Neonatal Unit), Cinzia Magnani (Neonatal Unit), Alice Suprani (Obstetric Unit), from the Department of Medicine and Surgery, University of Parma ;

Bruno Mandelli (Obstetric Unit), Melissa Bellini (Pediatric Unit), Luca Le Pera (Pediatric Unit) from the Ospedale of Piacenza; Maria Luisa Bidetti (Pediatric Unit), Giuseppe Crovini (Obstetric Unit) from Ospedale of Fidenza; Salvatore Anfuso (Obstetric Unit), Antonio Albarelli (Obstetric Unit) from Ospedale of Borgotaro.

Group of Modena: Petrella Elisabetta (Obstetric Unit), Isotta Guidotti (Neonatal Unit), Fabrizio Ferrari (Neonatal Unit), Mariamaddalena Carbone (Obstetric Unit), from Mother-Infant and Adult Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia, Modena.

Group of Reggio Emilia: Marina Palmieri (neonatal Unit), Flavio Vanacore (Obstetric Unit) from Arcispedale Santa Maria Nuova, IRCCS, Reggio Emilia, Lisa Melandri (Pediatric Unit) from Ospedale of

Montecchio and Ospedale of Scandiano, Marcella Palmisano (Obstetric Unit) from Ospedale of Guastalla.

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Legend:

LP: late preterm

RDS: Respiratory Distress Syndrome,

GA: gestational age

TTN: transient tachypnea of neonate

IVH: Intraventricular Hemorrage

PPROM: preterm premature rupture of membranes

NICU: Neonatal Intensive Care Unit

BMI: Body mass index

IUGR: intrauterine growth restriction

CNS: Central nervous system

SGA: small for gestational age

AGA: adeguate for gestational age

LGA: large for gestational age

ART: assisted reproductive technologies

ASA: Cardioapirin

LMWH: Low molecular weight heparin

CD: caesarean delivery

HTN: hypertension

IOM guidelines: Institute of Medicine Weight Gain Recommendations for Pregnancy

PTB: Preterm birth

PTL: preterm labour

CPAP: Continuous Positive Airway Pressure

MRI: Magnetic Resonance Imaging

A1 GDM: Gestational Diabetes under diet control

A2 GDM: Gestational Diabetes under drugs control (subcutaneous insulin or medication)

Table 1: Maternal and fetal characteristics

	34 w (n: 302)	**35 w (n: 504)**	**36 w (n: 1061)**	**Total (n: 1867)**	**Total (n: 1867)**	**P**
Mean age	32.8 ± 5.8	32.3 ± 5.6	32.5 ± 5.6	1867	1867	NS+
Primiparity	117 (38.7%)	193 (38.2%)	419 (39.5%)	729 (39%)	729 (39%)	NS*
Previous PTB	25 (8.3%)	48 (9.5%)	84 (7.9%)	157 (8.4%)	157 (8.4%)	NS*
Race	233 (77.1%) 41	390 (77.4%) 61	832 (78.4%)	1455 (77.9%)	1455 (77.9%)	NS*
Caucasian	(13.6%) 16	(12.1%) 20	122 (11.5%) 37	224 (12%) 73	224 (12%) 73	
African South	(5.3%) 12	(4%) 33	(3.5%) 70	(3.9%) 115	(3.9%) 115	
East Asian	(4%)	(6.5%)	(6.6%)	(6.2%)	(6.2%)	
Other						

	34 w (n: 302)	**35 w (n: 504)**	**36 w (n: 1061)**	**Total (n: 1867)**	**Total (n: 1867)**	**P**
Low education (< 8 years)	101 (33.4%)	153 (30.4%)	294 (27.7%)	548 (29.3%)	548 (29.3%)	NS*
BMI	22.5 (20.7-25.9)	22.5 (20.2-25.9)	23.4 (20.2-25.4)	1867	1867	NS§
Excessive Weight Gain (IOM)	124 (60.8%)	221 (62.6%)	434 (56%)	779 (58.8%)	779 (58.8%)	NS*
Smoking habit *Smoking* *Stopped in pregnancy* *Stopped prior to pregnancy* *No smoking*	30 (10.%) 17 (6%) 8 (2.8%) 229 (80.6%)	54 (10.9%) 25 (5%) 16 (3.2%) 400 (80.9%)	89 (9%) 45 (4.5%) 45 (4.5%) 809 (82%)	173 (9.8%) 87 (4.9%) 69 (3.9%) 1438 (81.4%)	173 (9.8%) 87 (4.9%) 69 (3.9%) 1438 (81.4%)	NS*
Assisted reproductive technologies	21 (6.9%)	23 (4.5%)	41 (3.8%)	85 (4.5%)	85 (4.5%)	0.08*
Diabetes *Pregestational diabetes Class A2 GDM* *Class A1 GDM No diabetes*	8 (2.6%) 15 (5%) 26 (8.6%) 253 (83.8%)	13 (2.6%) 14 (2.8%) 28 (5.6%) 449 (89%)	14 (1.3%) 20 (1.9%) 90 (8.5%) 937 (88.3%)	35 (1.9%) 49 (2.6%) 144 (7.7%) 1639 (87.8%)	35 (1.9%) 49 (2.6%) 144 (7.7%) 1639 (87.8%)	**0.01***
Hypertensive disorders *Chronic Hypertension* *Chronic Hypertension superimposed Preeclampsia* *Gestational Hypertension Preeclampsia* *Normotensive*	9 (3%) 0 16 (5.3%) 14 (4.6%) 263 (87.1%)	9 (1.8%) 0 30 (5.9%) 23 (4.6%) 442 (87.7%)	15 (1.4%) 0 74 (7%) 29 (2.7%) 943 (88.9%)	33 (1.8%) 0 120 (6.4%) 66 (3.5%) 1648 (88.3%)	33 (1.8%) 0 120 (6.4%) 66 (3.5%) 1648 (88.3%)	NS**
Vaginal bleeding (Abruption/Placenta previa)	29 (9.6%)	55 (10.9%)	60 (5.7%)	144 (7.7%)	144 (7.7%)	<**0.01***
Liver disorders	10 (3.3%)	14 (2.8%)	40 (3.8%)	64 (3.4%)	64 (3.4%)	NS*
pPROM	133 (44%)	205 (40.7%)	505 (47.6%)	843 (45.1%)	843 (45.1%)	**0.03***

	34 w (n: 302)	**35 w (n: 504)**	**36 w (n: 1061)**	**Total (n: 1867)**	**Total (n: 1867)**	**P**
Clinical chorioamnionitis	1 (0.3%9	2 (0.4%)	7 (0.7%)	10 (0.5%)	10 (0.5%)	0.7
Type of labor *No labour*	106 (35.1%)	176 (35%)	270 (25.5%)	552 (29.6%)	552 (29.6%)	$<$ **0.01***
Induced labour	41 (13.6%)	99 (19.7%)	226 (21.3%)	366 (19.6%)	366 (19.6%)	
Spontaneous labour	155 (51.3%)	228 (45.3%)	563 (53.2%)	946 (50.8%)	946 (50.8%)	
Mode of delivery *Vaginal delivery (spontaneous and operative)*	157 (52%)	257 (51.1%)	642 (60.6%)	1056 (50.6%)	1056 (50.6%)	$<$ **0.01***
Cesarean in labor	39 (12.9%)	70 (13.9%)	147 (13.9%)	256 (13.7%)	256 (13.7%)	
Cesarean not in labor	106 (35.1%)	176 (35%)	270 (25.5%)	552 (29.7%)	552 (29.7%)	
Antenatal corticosteroids *No steroids*	111(36.7%)	305 (60.5%)	817 (77%)	1233 (66%)	1233 (66%)	$<$ **0.01***
1 course	178 (58.9%)	195 (38.7%)	232 (21.9%)	605 (32.4%)	605 (32.4%)	
2 courses	13 (4.4%)	4 (0.8%)	12 (1.1%)	29 (1.6%)	29 (1.6%)	
ASA prophylaxis	10 (3.3%)	11 (2.2%)	23 (2.2%)	44 (2.3%)	44 (2.3%)	NS*
LMWH prophylaxis	3 (1%)	8 (1.6%)	13 (1.2%)	24 (1.3%)	24 (1.3%)	NS**
Progesterone Prophylaxis	23 (7.6%)	26 (5.2)	31 (2.9%)	80 (4.3%)	80 (4.3%)	$<$ **0.01***
Non ressuring fetal monitoring (category III sec ACOG)	18 (6%)	32 (6.3%)	51 (4.8%)	51 (4.8%)	101 (5.4%)	NS*
Growth restriction (IUGR)	41 (13.6%)	68 (13.5%)	88 (8.3%)	88 (8.3%)	197 (10.5%)	**0.01***
Diagnosis of fetal anomaly *None*	295 (97.7%)	496 (98.4%)	1039 (97.9%)	1039 (97.9%)	1830 (98%)	0.7**
Cardiovascular	3 (1%)	0	6 (0.6%)	6 (0.6%)	9 (0.5%)	

	34 w (n: 302)	**35 w (n: 504)**	**36 w (n: 1061)**	**Total (n: 1867)**	**Total (n: 1867)**	**P**
CNS	0	2 (0.4%)	3 (0.3%)	3 (0.3%)	5 (0.2%)	
Gastrointestinal	1 (0.3%)	2 (0.4%)	3 (0.3%)	3 (0.3%)	6 (0.3%)	
Genito-urinary	0	0	2 (0.2%)	2 (0.2%)	2 (0.1%)	
Others	3 (1%)	4 (0.8%)	8 (0.7%)	8 (0.7%)	15 (0.9%)	
Amniotic fluid *Oligo/anidramnios* *Polidramnios* *Normal*	18 (6%) 7 (2.3%) 277 (91.7%)	31 (6.1%) 8 (1.6%) 465 (92.3%)	52 (4.9%) 16 (1.5%) 993 (93.6%)	52 (4.9%) 16 (1.5%) 993 (93.6%)	101 (5.4%) 31 (1.7%) 1735 (92.9%)	0.7

Low education: primary and secondary school; Excessive Weight Gain: above IOM guidelines per BMI category; Previous PTB: prior birth < 37 weeks; Class A1 GDM: diet, Class A2 GDM: Insulin therapy; Non reassuring fetal monitoring category III tracing according to ACOG.

* Chi square test, ** Fisher Exact test, § ANOVA on ranks, + ANOVA

Table 2: Circumstances at delivery

	34 w (n: 302)	**35 w (n: 504)**	**36 w (n: 1061)**	**Total (n: 1867)**	**P**
Mode of late preterm birth					0.06*
Spontaneous preterm labor	116 (38.4%)	170 (33.7%)	400 (37.7%)	686 (36.7%)	
pPROM	57 (18.9%)	98 (19.5%)	243 (22.9%)	398 (21.3%)	
Indicated	129 (42.7%)	236 (46.8%)	418 (39.4%)	783 (42%)	

* Chi square test

Table 3: Neonatal outcomes

	34 w (n: 302)	**35 w (n: 504)**	**36 w (n: 1061)**	**Total (n 1867)**	**P**
Male	168 (55.6%)	283 (56.1%)	604 (56.9%)	1055 (56.5%)	0.9*
Mean birth weight	2291.7 ± 411.1	2484.6 ± 422 g	2721 ± 423 g	1867	**< 0.01**+
Weight percentile *AGA*	239 (79.1%)	402 (79.8%)	853 (80.4%)	1494 (80%)	0.04*
LGA	42 (13.9%)	45 (8.9%)	97 (9.1%)	184 (9.9%)	
SGA	21 (7%)	57 (11.3%)	111 (10.5%)	189 (10.1%)	
Median NICU length of stay	7 d (5-12 d)	5 d (3-8 d)	3 d (3-5 d)	1867	**<0.01§**
NICU stay longer than 5 days	238 (78.8%)	279 (55.4%)	307 (28.9%)	824 (44.1%)	**<0.01§**
Metabolic acidosis at birth *No acidosis*	290 (96%)	488 (96.8%)	1039 (97.9%)	1817 (97.3%)	**0.01****

	34 w (n: 302)	**35 w (n: 504)**	**36 w (n: 1061)**	**Total (n 1867)**	**P**
Mild acidosis	2 (0.7%)	1 (0.2%)	6 (0.6%)	9 (0.5%)	
Moderate acidosis	1 (0.3%)	0	7 (0.7%)	8 (0.4%)	
Severe acidosis	9 (3%)	15 (3%)	9 (0.8%)	33 (1.8%)	
5' Apgar score < 3	1 (0.3%)	2 (0.4%)	2 (0.2%)	5 (0.3%)	0.7**
Cardiopulmonary resuscitation	20 (6.6%)	27 (5.4%)	48 (4.5%)	95 (5.1%)	0.3*
Respiratory support *No support*	208 (68.9%)	411 (81.5%)	971 (91.5%)	1590 (85.2%)	**< 0.01***
Invasive	5 (1.6%)	9 (1.8%)	13 (1.2%)	27 (1.4%)	
Non invasive	89 (29.5%)	84 (16.7%)	77 (7.3%)	250 (13.4%)	
Seizures	0	3 (0.6%)	0	3 (0.2%)	**0.02****
Therapeutic hypothermia	1 (0.3%)	2 (0.4%)	4 (0.4%)	7 (0.4%)	0.9 **
Jaundice	145 (48%)	188 (37.3%)	241 (22.7%)	574 (30.7%)	**<0.01***
Sepsis	22 (7.6%)	27 (5.4%)	23 (2.2%)	72 (3.9%)	**< 0.01***
Hypoglycemia	92 (30.5%)	126 (25%)	196 (18.5%)	414 (22.2%)	**< 0.01***
Difficulty feeding	57 (18.9%)	70 (13.9%)	65 (6.1%)	192 (10.3%)	**< 0.01***
Cerebral lesion *None*	*302 (100%)*	502 (99.6%)	1056 (99.5%)	1860 (99.6%)	0.9**
Stroke	0	1 (0.2%)	2 (0.2%)	3 (0.2%)	
Basal nuclei anomalies	0	1 (0.2%)	1 (0.1%)	2 (0.1%)	
IVH >=2	0	0	2 (0.2%)	2 (0.1%)	
Congenital anomalies none	267 (88.5%)	462 (91.6%)	990 (93.3%)	1719 (92.1%)	0.1**
Cardio vascular	10 (3.3%)	5 (1%)	21 (2%)	36 (1.9%)	
CNS	1 (0.3%)	1 (0.2%)	2 (0.2%)	4 (0.2%)	
Gastrointestinal	1 (0.3%)	4 (0.8%)	4 (0.4%)	9 (0.5%)	
Genito-urinary	1 (0.3%)	7 (1.4%)	3 (0.3%)	11 (0.6%)	
Others	22 (7.3%)	25 (5%)	41 (3.8%)	88 (4.7%)	
Chromosomal anomalies	1 (0.3%)	4 (0.8%)	4 (0.4%)	9 (0.5%)	0.5**
Adverse Composite Neonatal Outcome	82 (27.1%)	89 (17.7%)	85 (8%)	256 (13.7%)	**<0.01***
Hypoglycemia and difficulty feeding	129 (42.7%)	170 (33.7%)	239 (22.5%)	538 (28.8%)	**<0.01***

	34 w (n: 302)	**35 w (n: 504)**	**36 w (n: 1061)**	**Total (n 1867)**	**P**
Metabolic acidosis/ resuscitation	20 (6.6%)	27 (5.4%)	48 (4.5%)	95 (5.1%)	0.3*
Respiratory support	94 (31.1%)	93 (18.4%)	90 (8.5%)	277 (14.8%)	**<0.01***

Maternal other indication: 1 case of severe asthma, 1 case of severe headache.

Fetal other indication: 1 case of Rh isoimmunization, 1 case of fetal arrhythmia.

Mild acidosis: BE between -6 e -12 or pH 7.20-7.30

Moderate acidosis: BE between -12 e -16 or pH 7.00-7.19

Severe acidosis: BE less than -16 or pH <7.00

* Chi square test, ** Fisher Exact test, § ANOVA on ranks, + ANOVA

For details about specific definitions please see table S1 .

Table 4: Multivariate analysis of the effect of gestational age and circumstances at delivery on neonatal outcomes

	Composite adverse neonatal outcomes	**Composite adverse neonatal outcomes**
	AOR (95%CI)	**P**
Gestational age		
34	**4.2 (3-6)**	**< 0.01**
35	**2.3 (1.7-3.2)**	**< 0.01**
36	§	
Circumstances at delivery		
Spontaneous PTL	§	
pPROM	0.9 (0.6 – 1.3)	0.5
Indicated	**1.7 (1.3- 2.3)**	**< 0.01**

Multivariate logistic regression models investigating the role of gestational age and circumstances at delivery on neonatal outcomes. The following variables were tested as potential confounders: maternal age, parity, previous preterm birth, race, education, BMI, excessive wait gain, smoking, utilization of assisted reproductive technologies, treatment with LDA, progesterone, or LMWH, antenatal corticosteroids

AOR: adjusted OR

The area under receiver operating characteristic (ROC) curve was respectively 0.68 for composite adverse neonatal outcomes, 0.65 for neonatal resuscitation, 0.66 for metabolic complications, and 0.69 for respiratory support.

For details about specific definitions please see table S1 .

Table 5: Multivariate analysis of the impact of maternal medical conditions, fetal characteristics, pregnancy complications, and gestational age at delivery on neonatal morbidities

	Composite adverse neonatal outcomes	**Composite adverse neonatal outcome**
	AOR (95%CI)	**P**

	Composite adverse neonatal outcomes	**Composite adverse neonatal outcome**
Gestational age		
34	**4.2 (3-6)**	**<0.01**
35	**2.2 (1.6-3.1)**	**<0.01**
36	§	
Diabetes		
No Diabetes	§	
Pregestational Diabetes	**2.6 (1.2-5.7)**	**0.02**
Class A1 GDM	0.6 (0.3-1.1)	0.3
Class A2 GDM	0.7 (0.3-1.6)	0.07
Hypertensive disorders		
Normotensive	§	
Cronic HTN	0.5 (0.2-1.7)	0.3
Gestational HTN	0.7 (0.3-1.3)	0.2
Preeclampsia	**0.3 (0.1-0.9)**	**0.03**
pPROM	**1.7 (1.3 – 2.3)**	**< 0.01**
BMI	**1.03 (1.003-1.06)**	**0.03**
Abruption/bleeding	**1.6 (1.05-2.5)**	**0.03**
Amniotic fluid		
Normal	$	
Oligohydramnios/anhydramnios	0.9 (0.5-1.7)	0.9
Polyhydramnios	**2.4 (1.02 – 5.8)**	**0.045**
Non reassuring fetal status		
Spontaneous PTL		
IUGR		

Multivariate logistic regression models investigating the role of maternal conditions (diabetes mellitus, hypertensive disorders, liver disorders), fetal characteristics (non-reassuring fetal status, IUGR, prenatally diagnosed fetal anomalies or aneuploidies, and amniotic fluid disorders), pregnancy complications (pPROM, spontaneous PTL, chorioamnionitis, vaginal bleeding from placental abruption or abnormal placentation) on neonatal outcomes. To control for confounding, the following variables were tested in each model: maternal age, parity, previous preterm birth, race, education, BMI, excessive wait gain, smoking, utilization of assisted reproductive technologies, treatment with LDA, progesterone, or LMWH, antenatal corticosteroids

The area under receiver operating characteristic (ROC) curve was respectively 0.71 for composite adverse neonatal outcomes, 0.62 for neonatal resuscitation, 0.64 for metabolic complications, and 0.72 for respiratory support.

AOR: adjusted OR

For details about specific definitions please see table S1 .