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Neonatal respiratory distress syndrome: are risk factors the same in preterm and term infants?

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Neonatal respiratory distress syndrome: are risk factors the same in preterm and term infants?

Objective: to analyze respiratory distress syndrome (RDS) incidence and risk factors at different gestational age.

Methods: we considered data from 321,327 infants born in Lombardy, a Northern Italian Region. We computed multivariate analysis to identify risk factors for RDS by dividing infants in early and moderate preterm, late preterm and term infants.

Results: Low birth weight is the main risk factor for RDS, with higher odds ratio in term births. The risk was higher in infants delivered by cesarean section and in male, for all gestational age. Pathological course of pregnancy resulted to increase the risk only in late preterm and term infants. Maternal age and multiple birth were not associated with increased risk in any group. Babies born at term after assisted conception were at higher risk of RDS.

Conclusion: Our analysis suggests as some risk factors do not influence RDS incidence in the same way at different gestational age.

Keywords: neonatal respiratory distress syndrome (RDS); late preterm infants; RDS risk factors

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INTRODUCTION

Overall preterm birth rate increased by about one third in the last 25 years [1]; this trend is mainly due to the rise in 34-36 gestational week births [2]. Factors affecting an early birth are temporal changes in maternal age, infertility treatments, multiple birth prevalence and obstetric interventions.

In the last decade, interest focused on these infants, defined as late preterm. A recent study estimated that late preterm infants represent almost a third of ventilated infants; about 30% of late preterm infants required intensive care, and 15% presented with respiratory failure [3].

Moreover, several studies showed an increased risk of RDS in babies born between the 34 and the 37 week of gestation in comparison with born at term [2, 4, 5].

All these evidences are in contrast with the lacking of large data-bases about epidemiological characteristics and outcomes of such infants.

Published data are generally based on clinical series, but few population-based data have been reported [5]. Some studies suggested that male gender is associated with higher risk of RDS, but it is not understood if gender steadily affects RDS risk through gestational ages (GA) [6, 7, 8].

The purpose of this study was to evaluate frequencies and risk factors for RDS at different GA in a large population database of babies born in Lombardy, a Northern Italian Region with a population of about 10 millions inhabitants [9] using data routinely collected in the Regional data base [10]. A specific interest of this study is the opportunity of analyzing a large data set from a single region, with similar assistance level through hospitals. We particularly focused on the risk factors for RDS among late preterm births in comparison with the risk factors of RDS among early and moderate preterm births and births at term.

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MATERIALS AND METHODS

This is a population-based study using data from a regional database.

We analyzed data of all newborn infants who were born in Lombardy, between 1st January 2010 and 30th June 2013.

Data were obtained from a regional standardized form, used to register all discharges from public and private hospitals: Scheda Dimissione Ospedaliera (SDO, Hospital Discharge Form). For all deliveries, information is available for maternal age, maternal country of birth and reason for admission. Neonatal information includes live birth/stillbirth status, sex, any diagnosis detected at birth or within the period of hospital admission. All admissions, discharges and diagnosis are coded according to the International Classification of Diseases 9th edition – Clinical Modification (ICD-9-CM), Italian version.

Further, at delivery, a specific form (Certificato Assistenza al Parto, Delivery Care Certificate, CedAP) is filled by midwifes including information on maternal characteristics, type of conception, course of pregnancy, delivery and maternal outcome at birth.

Data from the CedAP database have been linked with the SDO database in order to obtain detailed information on obstetric and neonatal data.

Diagnostic criteria for RDS were considered the presence of clinical sign of RDS, such as grunting, flaring, tachypnea, retractions, requiring a respiratory support (supplemental oxygen requirement and/or non invasive or invasive ventilation) and admission to a neonatal intensive care unit (NICU) for respiratory support. Typical radiological findings were reticulogranular patterns, air bronchograms and ground glass appearance.

Risk factors for RDS were analyzed in three groups: early and moderate preterm infants (23-33 weeks of pregnancy), late preterm infants (34-36 weeks of pregnancy) and term infants (≥37 weeks of pregnancy) [(R)].

Logistic regression models were performed to evaluate the association between potential risk/protective factors and RDS for each category of GA. In order to take into account main potential confounding factors, we estimated the odds ratio (OR) and 95% confidence interval (CI) using a multivariate model. The list of the terms included in the equation is indicated in the table footnotes. Statistical analyses were performed using SAS 9.2 software (SAS Institute Inc., Cary, NC, USA).

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RESULTS

Between 1st January 2010 and 30th June 2013, in Lombardy, a total of 327,039 births were registered in the CedAP database and 327,376 in the SDO database. The database obtained by linkage included information on 321,813 newborn: 98.4% and 98.3% of records were linked in SDO and CedAP database respectively.

After exclusion of 444 (0.14%) records with missing information about GA at birth and 92 (0.03%) records with GA less than 23 weeks, the analysis database included 321,327 births.

The mean maternal age at birth was 31.9 years (SD=5.5; range 14-54). In particular, it was 31.0 years at the first birth, 32.7 years at the second, 33.7 years at the third, and 34.7 years for ≥4th. In 7.0% of births, maternal age was ≥ 40 years. 92,567 deliveries (28.8%) occurred in non native Italian women. Assisted reproductive technique (ART) was reported in 8,367 (2.6%) deliveries.

A total of 4,894 (1.5%) multiple deliveries occurred (9,931 newborns, 3.1%). Of these, 4,753 (1.5%) were twin deliveries, 139 (0.04%) triplets and 2 (0.0006%) quadruplets.

The overall stillborn rate was 0.4/1000 births.

The mean duration of hospital admission was 4.3 days (standard deviation=7.2, median=3.0, range=1-419). Table 1 shows the frequency of RDS according to GA at birth in the total population and in strata of mode of delivery. RDS rate declined till the 40 weeks of gestation when leveled off at 0.1/100 live births. Considering late preterm births, the frequency of RDS was 9.9% among babies born at 34, 4.6% at 35 and 1.6% at 36 weeks of gestation.

The risk of RDS was higher in infants delivered by elective and emergency cesarean section, for all GA at birth.

Frequency of RDS, adjusted and unadjusted ORs, for early/moderate preterm, late preterm and at term births are shown in Table 2. Birth weight, mode of delivery and pathological pregnancy were the main factors associated with RDS.

Babies weighing 1000-1499 grams were at higher risk of RDS as compared to those weighing 1500-2499 in all GA groups. In the multivariate model, ORs (95% CI) were 3.0 (2.6-3.4), 2.5 (1.6-3.7) and 47.9 (29.4-78.0) in early/moderate and late preterm, and at term births respectively. For newborns weighing 2500-3999 grams, ORs (95% CI) were 0.2 (0.1-0.3), 0.5 (0.4-0.6) and 0.2 (0.1-0.2) respectively.

Elective cesarean section showed an increased risk in late preterm (OR 2.1; 95% CI 1.7-2.5) and at term infants (OR 4.1; 95% CI 3.3-5.2). In early/moderate preterm data

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showed an increased risk but the adjusted estimate was not statistically significant (OR 1.2, 95% CI 1.0-1.4). Emergency cesarean section and operative vaginal delivery were consistently associated with increased risk: ORs (95% CI) were 1.5 (1.2-1.7) in early/moderate preterm births, 2.2 (1.8-2.8) in late preterm, and 3.6 (2.7-4.6) in at term infants, for elective cesarean section, and 1.5 (1.1-2.1), 2.0 (1.3-3.2) and 1.5 (0.9-2.5) respectively for operative vaginal delivery.

Pathological pregnancy increased the risk of RDS in late preterm (OR 1.4, 95% CI 1.2-1.7) and at term infants (OR 1.7, 95% CI 1.3-2.2). Females were consistently at lower risk of RDS in all groups.

Maternal age and parity were not associated with RDS in all the analyses by category of GA.

DISCUSSION

Our findings showed that RDS frequency decreased with increasing GA, either considering the whole sample or stratifying by mode of delivery. Consistently in strata of early/moderate and late preterm, and at term delivery, we found that the main risk factors for RDS were low birth weight and cesarean delivery, either elective or unplanned. However, the estimates differed in different GA groups.

Overall, in late preterm infants the frequency of RDS was 9.9%, 4.6% and 1.6% in 34, 35 and 36 weeks of gestation respectively.

Late preterm infants are born in the late saccular stage of development, when surfactant and antioxidant systems are still immature. The immature lung structure may be functionally associated with delayed intrapulmonary fluid absorption, surfactant inefficiency and inefficient gas exchange. Moreover, during the last 6 weeks of gestation, the fetus begins to develop synchrony and control over breathing, so that preterm delivery increases the risk of apnea [3] .

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Incidence of RDS

Overall, in early/moderate preterm infants RDS occurred in about 45% of cases, whereas this figure reduced to 4% and less than 1% in late preterm and at term newborns, respectively. The lowest frequency was observed in babies born at 40-42 weeks of gestation. This finding was consistently observed in strata of mode of delivery. Our results were consistent with previous large population based studies conducted in different countries.

In a retrospective study conducted in Manitoba (Canada) and including 25,312 infants, the frequency of RDS was 12.3% at 34, 6% at 35 and 2.2% at 36 weeks of gestation [11]. These estimates are largely consistent with our findings.

Likewise, in an American retrospective cohort study including 175,000 neonates, babies born at 35 weeks, compared with neonates born between 37 and 40 weeks, were at increased risk of surfactant use (adjusted OR 3.74, 95% CI 3.21-4.22) and ventilation use >6 hours (adjusted OR 5.53, 95% CI 5.11-5.99). Neonates born at 36 weeks remained at higher risk of morbidity compared with those born at 37-40 weeks of gestation [12].

Late preterm infants had a significantly higher incidence of respiratory morbidity and a significantly longer hospital stay in the analysis of the British Columbia Perinatal Database [13]. In this study, RDS, which had a relatively low absolute risk at late gestation, had as a gradient crossing term 2.3% at 36 weeks, 1.2% at 37 weeks and 0.6% at 38 weeks.

In a large retrospective study conducted in the US [14], RDS incidence decreased from 10.5% at 34 weeks to 0.3% at 38 weeks: ORs of RDS declined until 38 weeks, as compared to 39-40 weeks.

Risk factors for RDS

In our study, the main risk factors for RDS were low birth weight and cesarean delivery, either elective or unplanned. Even if risk factors were consistent and their ORs were similar among early/moderate, late preterm and term births, some differences have to be underlined.

Low birth weight was the main risk factor for RDS, with OR estimates largely similar in early/moderate and late preterm births. In at term births, low birth weight was associated with higher ORs. This can be explained by the fact that a bigger proportion of such infants are small for GA.

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As regards mode of delivery, most studies have consistently shown that babies born by cesarean section were at increased risk of developing RDS [1, 15, 16].

Neonates born by caesarean section have a larger residual volume of lung fluid, secrete less surfactant to the alveolar surface and have a delayed clearance of lung fluid [17]; thus, they are at higher risk of developing RDS.

Melamed and collegues [6] found a two-fold increased risk of RDS in babies born by cesarean section, in cases of low-risk, singleton late preterm deliveries. More recently, Ghartey et al. [18] evaluated the risk of respiratory morbidity in neonates delivered at "early term" (37-38 weeks) compared with those delivered at 39 weeks. Infants delivered at 37-38 weeks had a 2-fold increased risk of respiratory distress syndrome, oxygen use, continuous positive airway pressure use, and composite respiratory morbidity.

Confirming these findings, in our analyses the RDS risk was higher in babies delivered by elective and emergency cesarean section and operative vaginal delivery, in comparison to spontaneous delivery. We found higher ORs in late preterm and at term infants than in early/moderate preterm infants. This difference may be explained by the fact that in late preterm and at term infants RDS is due more frequently to a delay in lung fluid reabsorption, whereas in early/moderate preterm infants respiratory distress is due to lung immaturity.

In our analysis, pathological pregnancy (including gestational diabetes and hypertension) was associated to RDS risk in late preterm and at term births, but not in early/moderate preterm births. This finding could be explained by the fact that chronic intrauterine stress and choriamnionitis, frequently associated to early preterm labor, stimulate surfactant protein synthesis and accelerate fetal lung maturity.

Anyway, as pathological pregnancy included different maternal diseases, it is difficult to properly discuss this result.

Another topic of interest is the role of gender in the risk of RDS. Males have been suggested to be at increased risk of RDS or respiratory diseases [1, 6, 7, 8], and our data confirmed this finding, for all classes of GA. The rationale of this association is not yet completely understood. It is believed that female fetal lung produces pulmonary surfactant earlier in gestation than the male lung, probably due to different hormonal profile of male infants [19, 20].

Androgens delay lung fibroblast secretion of fibroblast-pneumocyte factor, which can delay the development of alveolar type II cells; furthermore, they reduce the release of

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surfactant. Androgens slow fetal lung development by adjusting the signaling pathways of epidermal growth factor and transforming growth factor-beta. On the contrary, estrogens promote the synthesis of surfactant, including phospholipids, lecithin, and surfactant proteins A and B, and improve fetal lung development by increasing the number of alveolar type II cells and the synthesis of lamellar bodies [20].

The association of parity with respiratory complications was reported in a study conducted in Israel. Infants born by multiparous women were at increased risk of RDS [6]. Our data did not confirm this finding. Consistently through GA groups, nulliparous women showed a slight, not significant increased risk of RDS in comparison to parous women.

Advanced maternal age and multiple gestation have been suggested to be associated with increased risk of RDS, both in preterm and at term infants [15]. In our study, only at term infants had an increased RDS risk for maternal age higher than 40 years and for multiple births, but the relation disappeared when adjusting for confounding factors. It is likely that RDS is associated to preterm birth in older mothers and multiple gestations, rather than directly to maternal age and number of fetuses.

Assisted conceptions showed an increased risk of RDS in at term infants, and the association remained significant after adjustment for confounding factors.

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Limitations and strength of the study

Potential strengths and limitations of the study should be considered.

Analyses based on large databases may suffer from some limitations in accuracy. The diagnosis of RDS was based on standardized criteria. Even if some center may have used slightly different criteria, it is unlikely that different criteria were used in the same center in different GA infants.

A second limitation is that we have no information on the quality of GA determination. However, in Italy, less than 4% of pregnant women undergo the first examination after the 12 week of gestation [21].

As regards pathological course of pregnancy, in this analysis we could not differentiate the wide range of diseases that such definition included.

Among the strength we have to consider the large sample size and the population based design.

Further, in order to take into account the main potential confounding factors, we adjusted our results in a multivariate analysis including the main determinants of RDS.

Conclusion

Our analysis, based on two large population databases, suggests that well known RDS risk factors, such as birth weight and pathological course of pregnancy, act differently in early/ moderate and late preterm, and at term infants.

Further studies are needed to better investigate such aspects, defining in a more homogeneous way the different risk factors and analyzing other potential cofactors.

Conflict of interest

There is no conflict of interest to declare.

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Table 1. Frequency of RDS in strata of gestational age at birth and mode of delivery. Lombardy, Italy, 1st January 2010 – 30th June 2013.

Gestational age at birth	Total		Spontaneous delivery		Elective cesarean section		Emergency cesarean section		Operative vaginal delivery	
	%*	N**	%*	N**	%*	N**	%*	N**	%*	N**
23	75.0	75	71.2	47	78.6	11	84.2	16	100.0	1
24	86.8	138	81.8	72	91.3	21	97.8	45	0.0.	0
25	85.3	133	81.3	39	85.4	35	87.7	57	100.0	2
26	85.7	210	78.2	43	87.5	77	88.0	81	90.0	9
27	82.9	214	66.7	42	91.2	83	86.4	76	81.3	13
28	80.7	309	60.6	40	84.8	134	85.6	125	76.9	10
29	73.1	312	59.5	50	75.5	139	77.8	105	75.0	18
30	51.2	312	30.8	45	57.7	135	57.8	122	55.6	10
31	46.0	373	27.7	52	50.8	189	51.8	113	59.4	19
32	33.1	365	19.9	53	37.9	191	38.6	115	17.6	6
33	18.2	325	15.0	70	21.6	155	15.6	85	28.8	15
34	9.9	295	7.0	68	11.6	142	10.3	74	14.1	11
35	4.6	229	3.1	63	5.6	102	5.6	59	3.9	5
36	1.6	155	0.9	41	2.1	70	2.2	37	2.4	7
37	0.5	102	0.2	26	0.9	61	0.5	13	0.3	2
38	0.2	128	0.1	25	0.3	75	0.4	24	0.2	4
39	0.2	158	0.1	42	0.5	73	0.6	35	0.2	8
40	0.1	75	0.1	43	0.3	9	0.2	18	0.1	5
41	0.1	43	0.1	27	0.1	2	0.2	13	0.0	1
42	0.0	1	0.0	0	0.0	0	0.2	1	0.0	0
Total	1.2	3952	0.4	888	2.9	1704	3.5	1214	1.0	146

*Percent of RDS by strata of mode of delivery.
**The sum does not add up the total due to missing values.

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Table 2. Risk factors of RDS in early preterm, late preterm and term births. Lombardy, Italy, 1st January 2010 – 30th June 2013.

	Gestational week at birth																							
	23-33								34-36								37+							
	No (3265)		Yes (2766)		Unadjusted		Adjusted**		No (17217		Yes (679)*		Unadjusted		Adjusted**		No (296893		Yes (507)*		Unadjusted		Adjusted**	
	N	%	N	%	OR	95% CI	OR	95% CI	N	%	N	%	OR	95 %C	OR	95% CI	N	%	N	%	OR	95 %	OR	95 %C
Multiple pregnancy																								
Single	2275	69.7	1863	67.4	1+		1+		13059	75.8	522	76.9	1+		1+		292963	98.7	461	90.9	1+		1+	
Multiple	990	30.3	903	32.6	1.1	1.0-1.2	1.1	1.0-1.3	4158	24.2	157	23.1	0.9	0.8-1.1	0.7	0.6-0.8	3930	1.3	46	9.1	7.4	5.5-10.1	1.0	0.7-1.5
Maternal age																								
≤24	283	8.7	224	8.2	1+		1+		1595	9.3	62	9.2	1+		1+		30952	10.5	46	9.1	1+		1+	
25-29	647	19.9	495	18.0	1.0	0.8-1.2	0.9	0.7-1.2	3240	18.9	139	20.5	1.1	0.8-1.5	1.0	0.7-1.3	64322	21.7	120	23.8	1.3	0.9-1.8	1.2	0.9-1.8
30-34	1055	32.5	828	30.2	1.0	0.8-1.2	0.9	0.7-1.2	5492	32.0	221	32.6	1.0	0.8-1.4	0.8	0.6-1.1	100945	34.1	146	28.9	1.0	0.7-1.4	0.9	0.6-1.3
35-39	959	29.5	864	31.5	1.1	0.9-1.4	1.0	0.7-1.2	5015	29.2	182	26.9	0.9	0.7-1.3	0.7	0.5-1.0	79619	26.9	150	29.7	1.3	0.9-1.8	1.0	0.7-1.5
40+	302	9.3	333	12.1	1.4	1.1-1.8	1.3	0.9-1.7	1809	10.5	73	10.8	1.0	0.7-1.5	0.8	0.5-1.1	19905	6.7	43	8.5	1.5	1.0-2.2	0.9	0.6-1.4

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Nulliparous																							
No	1303	40.4	1024	37.3	1+		1+		7793	46.0	312	46.5	1+		1+		145951	49.8	232	45.8	1+		1+	
Yes	1922	59.6	1723	62.7	1.1	1.0-1.3	1.1	1.0-1.2	9166	54.0	359	53.5	1.0	0.8-1.1	1.1	1.0-1.3	147276	50.2	274	54.2	1.2	1.0-1.4	0.9	0.8-1.2
Course of Phisiological	1768	54.5	1209	44.0	1+		1+		13460	78.5	442	65.4	1+		1+		280796	94.6	418	82.4	1+		1+	
Pathological	1475	45.5	1538	56.0	1.5	1.4-1.7	0.9	0.8-1.1	3695	21.5	234	34.6	1.9	1.6-2.3	1.4	1.2-1.7	15041	5.1	89	17.6	4.0	3.2-5.0	1.7	1.3-2.2
ART***																								
No	2856	87.5	2372	86.0	1+		1+		15521	90.5	628	92.9	1+		1+		288962	98.0	467	92.7	1+		1+	
Yes	407	12.5	385	14.0	1.1	1.0-1.3	0.9	0.8-1.1	1620	9.5	48	7.1	0.7	0.5-0.99	0.7	0.5-1.0	5870	2.0	37	7.3	3.9	2.8-5.5	2.0	1.3-3.0
Mode of delivery																								
Spontaneous	985	30.2	553	20.0	1+		1+		7386	42.9	172	25.3	1+		1+		203550	68.6	163	32.1	1+		1+	
Elective cesarean	1257	38.5	1170	42.3	1.7	1.5-1.9	1.2	1.0-1.4	6090	35.4	314	46.2	2.2	1.8-2.7	2.1	1.7-2.6	49414	16.6	220	43.4	5.6	4.5-6.8	4.1	3.3-5.2
Emergency/unplanned cesarean	922	28.2	940	34.0	1.8	1.6-2.1	1.5	1.2-1.7	3268	19.0	170	25.0	2.2	1.8-2.8	2.2	1.8-2.8	29664	10.0	104	20.5	4.4	3.4-5.6	3.6	2.7-4.6
Operative vaginal delivery	101	3.1	103	3.7	1.8	1.4-2.4	1.5	1.1-2.1	473	2.7	23	3.4	2.1	1.3-3.3	2.0	1.3-3.2	14265	4.8	20	3.9	1.8	1.1-2.8	1.5	0.9-2.5

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Sex of the																								
Male	1670	51.1	1500	54.2	1+		1+		9055	52.6	409	60.2	1+		1+		15271	51.4	305	60.2	1+		1+	
Female	1595	48.9	1266	45.8	0.9	0.8-1.0	0.7	0.7-0.8	8162	47.4	270	39.8	0.7	0.6-0.9	0.7	0.6-0.8	14418	48.6	202	39.8	0.7	0.6-0.8	0.6	0.5-0.8
Birthweight																								
<1000	166	5.1	966	34.9	13.9	11.5-16.7	13.6	11.1-16.6	9	0.1	11	1.6	24.5	10.1-59.4	22.7	8.6-60.0	80	0.0	18	3.6	19.3	11.2-33.5	17.3	8.9-33.9
1000-1499	805	24.7	989	35.8	2.9	2.6-3.3	3.0	2.6-3.4	204	1.2	34	5.0	3.3	2.3-4.9	2.5	1.6-3.7	58	0.0	40	7.9	59.3	37.9-92.8	47.9	29.4-78.0
1500-2499	1865	57.1	782	28.3	1+		1+		8260	48.0	412	60.7	1+		1+		8685	2.9	101	19.9	1+		1+	
2500-3999	410	13.2	29	1.0	0.2¥	0.1-0.2	0.2¥	0.1-0.3	8691	50.3	222	32.7	0.5¥	0.4-0.6	0.5¥	0.4-0.6	2709	91.3	324	63.9	0.1	0.1-0.1	0.2	0.1-0.2
4000+	19	0.6	0	--	--	--	--	--	53	0.3	0	--	¥	--	¥	--	1713	5.8	24	4.7	0.1	0.1-0.2	--	--
Vitality/status of newborn																								
Alive	3190	97.7	2432	87.9	1+		1+		17187	99.8	657	96.8	1+		1+		296770	100.0	474	93.5	1+		1+	
Stillborn	39	1.2	66	2.4	2.2	1.5-3.3	1.8£	1.3-2.4	10	0.1	5	0.7	13.1	4.5-38.4	12.9£	7.0-23.8	17	0.0	6	1.2	252.£	166.6-381.4	82.4£	48.1-150.0
Neonatal death (1-28 days)	28	0.9	232	8.4	10.9	7.3-16.1	£		14	0.1	12	1.8	22.4	10.3-48.7	£		53	0.0	22	4.3	£		£	
Discharged dead at missing time	7	0.2	36	1.3	6.7	3.0-15.2	£		3	0.0	5	0.7	43.6	10.4-182.8	£		12	0.0	5	1.0	£		£	

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+Reference category
*In some cases the sum does not add the total because of missing values.
**All variable were considered in the model. We excluded record with missing values in “Maternal age”, “Native”, “Course of pregnancy”, “Sex of newborn”.
***ART=Assisted Reproductive Technology
¥In logistic analysis model cases with birthweight=”4000+” were included in “2500-3999” category.
£In logistic analysis adjusted model, variable “Vitality/status of newborn” was dichotomized (Alive/Dead).

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