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Early respiratory distress in full term newborns

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Abstract
Background: One of the most common reasons for admission of term neonates to a neonatal care unit is Respiratory Distress. The cause of respiratory distress could be respiratory and non respiratory with multiple predisposing factors to its occurrence.
Aim of the study: To study the frequency, causes, possible risk factors and early outcome of respiratory distress in full term newborn.
Patients and methods: A prospective case control study was conducted at the neonatal intensive care unit at Al-Yarmook teaching hospital in Baghdad over a period of 6 months that extends from January 1st 2016 to June 30th 2016. A questionnaire was designed to gather information from mothers of participants in both groups after obtaining their written consent to participate in the study. These information's include their age, parity, antenatal care, chronic diseases including diabetes and/or asthma, mode of delivery whether by normal vaginal delivery or by cesarean section (whether emergency or elective). Data were collected about possible neonatal risk factors, this include sex, birth weight and gestational age for the purpose of including or excluding from the study.
Results: During the 6 months study period, 2173 neonates were delivered at the delivery rooms of Al-Yarmook teaching hospital, out of these, sixty full term neonates were admitted to the neonatal intensive care unit with respiratory distress representing (2.76%) of the total live births. The majority of full term neonates who had presented with respiratory distress were diagnosed as transient tachypnea of newborn that accounted for (70%) of total cases with respiratory distress and (1.9%) of the total neonates delivered during the study period followed by meconium aspiration syndrome, respiratory distress syndrome and congenital pneumonia and congenital heart disease in (10%, 8%, 5% and 3%) of total cases with respiratory distress, respectively. Congenital diaphragmatic hernia and choanal Artesia had been diagnosed in only 2% from the total cases with respiratory distress for each. Gender distribution of respiratory distress cases shows a statically significant male predominance with a male: female ratio of 1.8:1. Age of mother, maternal asthma and smoking, mother with absent antenatal care and finally delivery by cesarean section particularly elective one was found to be risk factors for full term respiratory distress. From the total 60 cases with respiratory distress, three cases (5%) had died representing (0.13%) of total live birth.
Conclusions: Respiratory distress is still an important cause for admission of full term newborns to neonatal care unit. Transient tachypnea of the newborn is the commonest cause of respiratory distress in full term, while surgical conditions as choanal Artesia and congenital diaphragmatic hernia are rare causes of Cesarean section, mother with absent antenatal care and maternal diabetes are risk factors for respiratory distress.

Keywords: Cesarean, section, syndrome

Introduction
Respiratory distress (RD) is a common presenting feature requiring admission to neonatal intensive care unit (NICU) among newborn infants with many of its underlying causes are unique to this age group [1]. Fifteen percent of term infants and 29% of late preterm infants admitted to NICU develop significant respiratory morbidity [2]. Neonatal respiratory conditions can arise for several reasons: delayed adaptation or maladaptation to extra-uterine life, existing conditions such as surgical or congenital anomalies or from acquired conditions such as pulmonary infections occurring either pre- or post-delivery [1]. Hence, the cause of RD could be related to the respiratory system or to a cardiac, renal, metabolic, gastrointestinal, or neurological pathological process [3]. Respiratory conditions are the most common reason for admission to a neonatal unit in both term and preterm infants [4]. Evidence exists of rising rates of neonatal admissions in full term neonates due to respiratory conditions, possibly due to the effect of increased rates of caesarean section delivery [5]. RD in the newborn is recognized as one or more signs of increased work of breathing, such as tachypnea, nasal flaring, chest

retractions, or grunting [6, 7]. Normally, the newborn's respiratory rate is 30 to 60 breaths per minute. Tachypnea is defined as a respiratory rate greater than 60 breaths per minute [7]. Tachypnea is a compensatory mechanism for hypercarbia, hypoxemia, or acidosis (both metabolic and respiratory) [8]. Increased work of breathing results from mismatched pulmonary mechanics from increased airway resistance, decreased lung compliance, or both. Airway resistance increases when there is obstruction of air flow. The underlying cause of RD in a newborn varies and does not always lie within the lungs [6]. Thus, after initial resuscitation and stabilization, it is important to use a detailed history, physical examination, and radiographic and laboratory findings to determine a more specific diagnosis and appropriately tailor management. A thorough history may guide in identifying risk factors associated with common causes of neonatal RD. A detailed physical examination should focus beyond the lungs to identify non pulmonary causes, such as airway obstruction, abnormalities of the chest wall, cardiovascular disease, or neuromuscular disease that may initially present as RD in a newborn. Radiographic findings can identify diaphragmatic paralysis, congenital pulmonary malformations, and intrathoracic space occupying lesions, such as pneumothorax, mediastinal mass, and congenital diaphragmatic hernia, that can compromise lung expansion. Significant tachypnea without increased work of breathing should prompt additional laboratory investigation to identify metabolic acidosis or sepsis. Hypoglycemia, hypomagnesaemia, and hematologic abnormalities may result in a depressed ventilatory drive or impaired oxygen transport to the peripheral tissues, so laboratory evaluation should also be considered with these clinical findings. Hypermagnesemia may contribute to RD and affect a newborn's capacity to respond to resuscitation due to hypotonia and a depressed respiratory drive or even apnea [8]. Thorough clinical assessment of the newborn infant is the most important aspect of accurately diagnosing the underlying cause for RD. An infant with breathing difficulties displays classic clinical signs of RD regardless of the underlying cause. First line investigations in the assessment of a neonate with RD should include pulse oximetry, chest radiograph and blood tests (full blood count, C-reactive protein, blood culture and arterial blood gas) [6]. Echo cardiogram is indicated to exclude cardiovascular conditions. The chest radiograph remains the most common and most useful imaging tool in the diagnosis of conditions that contribute to RD in the newborn period, in particular those which cause lung parenchymal disease [9]. Computed tomography (CT) scan may be useful in confirming the presence of the lung lesions, determining the extent of the lesion, and defining the associated abnormalities [10].

Common conditions presented as RD in term infants

1. Transient tachypnea of the newborn (TTN) [11, 12].
2. Meconium aspiration syndrome (MAS|) [13, 6].
3. Congenital pneumonia (Cong.Pn.) [14, 15].
4. Respiratory distress syndromes (RDS) [16, 17].
5. Persistent pulmonary hypertension of the newborn (PPHN) [18, 19].
6. Congenital heart disease (CHD) [20].
7. Pneumothorax [21, 22].
8. Surgical and congenital anomalies: Choanal Artesia (CA) [23], Tracheo-oesophageal fistul (TOF) [24, 1], Congenital diaphragmatic hernia (CDH) [25, 11].

Treatment of RD in general

Whatever the cause, the cornerstone of treatment of neonatal RD is provision of adequate supplemental oxygen to maintain a PaO2 of 60–70 mm Hg and a saturation by pulse oximetry (SpO2) of 92–96%. PaO2 levels less than 50 mm Hg are associated with pulmonary vasoconstriction, which can exacerbate hypoxemia, whereas those greater than 100 mm Hg may increase the risk of oxygen toxicity without additional benefit. Oxygen should be warmed, humidified, and delivered through an air blender. Concentration should be measured with a calibrated oxygen analyzer. An umbilical or peripheral arterial line should be placed in any infant requiring more than 45% FIO2 by 4–6 hours of life to allow frequent blood gas determinations. Noninvasive monitoring with pulse oximeter should be used [26]. Other supportive treatment includes intravenous provision of glucose and water. Unless infection can be unequivocally ruled out, blood cultures should be obtained and broad-spectrum antibiotics started. Volume expansion (normal saline; 5% albumin) can be given in infusions of 10 mL/kg over 30 minutes for low blood pressure, poor perfusion, and metabolic acidosis. Sodium bicarbonate (1–2 mEq/kg) is indicated for treatment of documented metabolic acidosis that has not responded to oxygen, ventilation, and volume. Specific workup should be pursued as indicated by the history and physical findings. In most cases, a chest x-ray study, blood gas measurements, complete blood count, and blood glucose allow a diagnosis [26]. Intubation and ventilation should be undertaken for signs of respiratory failure (PaO2 ≤ 60 mm Hg). Peak pressures should be adequate to produce chest wall expansion and audible breath sounds (usually 18–24 cm H2O). Positive end-expiratory pressure (4–6 cm H2O) should also be used. Ventilation rates of 20–50 breaths per minute are usually required. The goal is to maintain a PaO2 of 60–70 mm Hg and a PaCO2 of 40–50 mmHg [26].

Aims of the study

The study aimed to study:

1. The incidence of RD in full term newborn from the total live birth at the same time and place of delivery.
2. The possible risk factors for RD in full term newborn.
3. Outcome of full term babies presented with RD and admitted to NICU of Al-Yarmook teaching hospital.

Patients and Methods

A prospective case control study was conducted at the NICU at Al_Yarmook teaching hospital in Baghdad over a period of 6 months that extends from January 1st 2015 to June 30th 2016. Eligible cases were 60 full term neonates (gesational ages between 37 weeks to completed 41 week) presented with RD in the first 24 hour of life who had delivered at the delivery room at Al-Yarmook teaching hospital, whereas; the control group consist of a similar number of a full term babies whom had delivered at the same time and at the same place with no RD. Gestational age was calculated by fetal sonography and confirmed by the mother's estimated date of her last menstrual period and physical examination of the neonate by the new Ballard scoring system [27]. A questionnaire was designed to gather information from mothers of participants in both groups after obtaining their written consent to participate in the study. These informations include their age, parity, antenatal care (ANC), smoking, chronic diseases including diabetes and/or asthma, mode of delivery whether by normal vaginal delivery or by cesarean

section (whether emergency or elective). Data were collected about possible neonatal risk factors, this include sex, birth weight and gestational age for the purpose of including or excluding from the study. Exclusion criteria were the babies who were delivered at preterm and post term neonates. Newborns with RD were investigated by (Random blood sugar, complete blood count, C-reactive protein, Blood culture, and Chest x-ray). The causes and outcome of RD cases were recorded. Echocardiography was done to suspected cardiac cases.

Case diagnosis

- RDS is suspected clinically and supported by chest roentgenogram showing a reticular granularity appearance and air bronchograms, which is characteristic but not pathognomonic appearance, and a negative blood culture [28].
- TTN is characterized by the early onset of tachypnea, sometimes with retractions, or expiratory grunting and, occasionally, cyanosis that is relieved by minimal oxygen supplementation (<40%). Most infants recover rapidly, usually within 3 days the chest radiograph shows prominent pulmonary vascular markings, fluid in the intralobar fissures, overaeration, flat diaphragms [28].
- MAS is defined as meconium stained amniotic fluid with the presence of meconium in the trachea supported by chest roentgenogram appearance of over inflation, coarse opacities and flattening of the diaphragm [13].
- Congenital pneumonia: in which the infant typically suffers progressive RD and has signs of systemic sepsis, which develop within a few hours of birth. The appearance is varied; there can be lobar or segmental consolidation, atelectasis, diffuse haziness or opacification. This is accompanied by positive blood culture and/or elevated inflammatory indices [28].
- CHDs were supported by clinical features, CXR and echo study of the heart.
- Choanal Artesia: Diagnosis is established by the inability to pass a firm catheter through each nostril 3-4 cm into the nasopharynx [29].
- TOF is usually diagnosed with a CXR confirming a coiled nasogastric tube in the upper pouch of the oesophagus.
- Congenital DH is usually diagnosed by CXR which reveals herniation of abdominal content to the chest after their birth.

Results

During the 6 months study period, 2173 neonates were delivered at the delivery rooms of Al-Yarmook teaching hospital, out of these sixty full term neonates were admitted to the NICU with RD representing (2.76%) of the total live births.

The majority of full term neonates who had presented with RD were diagnosed as TTN that accounted for (70%) of total cases with RD and (1.9%) of the total neonates delivered during the study period, MAS was the cause of RD in 6 neonates representing (10%) of the RD cases and (0.27%) of the total; whereas RDS was diagnosed in 5 cases representing (8.3%) of RD cases and (0.23%) of the total. The incidence of other less frequent causes of RD are shown in table 1.

Table 1: Distribution of RD cases according to the cause:

Cause of RD	TTN	MAS	RDS	Cong.Pn.	CHD	CDH	CA (Choanal Atresia)
No. of cases	42	6	5	3	2	1	1
% of RD cases	70%	10%	8%	5%	3%	2%	2%
% of total delivered	1.933%	0.276%	0.230%	0.138%	0.092%	0.0465	0.0465%

Gender distribution of RD cases shows a significant male predominance that 39 (65%) of cases were males and 21 (35%) were females in a ratio of 1.8:1, beside that male gender predominate in all case groups of RD as shown in table 2.

Table 2: Gender distribution of RD cases

Cases	Male N. (%)	Female N. (%)	Total N.
TTN	27(64.3)	15(35.7)	42
MAS	4(66.7)	2(33.3)	6
RDS	3(60)	2(40)	5
Cong.Pn.	2(66.7)	1(33.3)	3
CHD	1(50)	1(50)	2
CDH	1(100)	0(0)	1
CA	1(100)	0(0)	1
Total	39(65)	21(35)	60
P.value 0.02			

When comparing the birth weight of patients with RD with that of the control group, there was no significant difference in their birth weight (table 3).

Table 3: Mean birth weight ± SD in RD and control groups:

	RD patients	Control	P. Value
Mean birth weight (Kg)	3.32	3.44	0.141
Standard deviation(Kg)	0.32	0.54	

There was no significant difference between the RD cases and control regarding the incidence of low birth weight; however a statically significant difference is noted when comparing the gender between the cases and control group that males constitute 61.9% versus 38.1% in cases and control group, respectively (Table 4). Age of the mothers of RD cases show

a significant risk factor as compared to the control group that 90% of cases had a mothers with their ages below 20 years as opposed to only 10% in the control group, beside77.7% of RD cases had a mother age above 40 years compared to only22.3% in the control group (Table 4). Despite that 52.5% of RD cases were delivered to multiparous mothers, this result was not shown to be statically different as opposed to the control group (p. value 0.353) as shown in Table 4. Maternal asthma was not shown to be a risk factor for RD (p. value 1.00); on the other hand, maternal diabetes and smoking was found to be a statically significant risk factor for RD that maternal diabetes was found in 88.8% of RD cases versus only 11.3% in the control group (p. value of 0.032) and maternal smoking was found in 100% of cases; whereas, none of the control group had a smoking mother (Table 4). Mother with absence of ANC was found to be a strong risk factor for RD (p. value of 0.009) (Table 4). Nearly 2/3 of RD cases were delivered by cesarean section opposed to 1/3 in the control group, thus delivery by cesarean section was found to be a strong risk factor for RD as shown in (Table 4).

Table 4: Possible risk factors for RD

Possible risk factor		Total N.	RD group N.(%)	Control group N.(%)	P.val.
Gender	Male	63	39(61.9)	24(38.1)	0.010
	Female	57	21(36.8)	36(63.2)	
Maternal age	Less than 20 yrs.	10	9(90)	1(10)	0.012
	20 -30 yrs.	64	28(43.7)	36(56.3)	
	Between 30 -40 yrs.	37	16(43.2)	21(56.8)	
	More than 40 yrs.	9	7(77.7)	2(22.3)	
Parity	Primiparous	23	9(39.1)	14(60.9)	0.353
	Multiparous	97	51(52.5)	46(47.5)	
Maternal asthma	Asthmatic	5	3(60)	2(40)	1.000
	Not	115	57(49.5)	58(50.5)	
Maternal diabetes	Diabetic	9	8(88.8)	1(11.2)	0.032
	Not	111	52(46.8)	59(53.2)	
Maternal smoker	Smoker	7	7(122)	0(0)	0.013
	Not	113	53(46.9)	60(53.1)	
Antenatal care	With ANC	49	17(34.6)	32(65.4)	0.009
	Without ANC	62	34(54.8)	28(45.2)	
Mode of delivery	NVD	64	21(32.8)	43(67.2)	0.0001
	C/S	56	39(69.6)	17(30.4)	

Of the 39 RD cases who had delivered by cesarean section, the majority (82.5%) were delivered electively versus only 7 cases (17.5%) were delivered by elective cesarean section in the control group. Hence elective cesarean section was found to be a risk factor for RD (Table 5).

Table 5: Elective C/S and RD relationship

Variable	Total	RD N.(%)	Control N.(%)	P.value
Elective C/S	40	33(82.5)	7(17.5)	0.002
Non elective C/S	16	6(37.5)	10(62.5)	
Total		39(100)	17(100)	

*C/S =Cesarean Section.

Early outcome of RD cases

Of the 60 RD cases, three cases (5%) had died representing (0.13) of total live birth, one with complex CHD, the other one with meconium aspiration. The third one was a patient with congenital pneumonia. The cases of Choanal Artesia and congenital DH were referred to specialized surgical wards.

Discussion

One of the most common reasons for admission of term neonates to a NICU is RD. The cause may be of pulmonary or non pulmonary origin. This study focuses on the major causes and predisposing factors for RD in term infants. In this study, sixty full term neonates were admitted to the NICU with RD representing 2.76% of the total live births, this is close to the result of the incidence of RD in a similar study conducted in Baghdad by Numan Nafie *et al* in which 50 full term neonates had developed RD from 2312 total birth, constituting 2.1% the total live births [30]. A nearly similar result was obtained by Kari Horowitz *et al* whom had examined 9580 neonates with gestational age between 37-40 weeks, of which 201 infants were admitted to the NICU with respiratory morbidity (2.1%) [31]. However, this is lower than that of another study conducted by Eman F. badran *et al* in Amman, Jordan, in which the incidence of RD in full term neonates was found to be 3.7% [32]. Which is higher than that obtained in this study. This could be attributed to the different study design and different incidence of RD risk factors. In this study, TTN accounted for the majority (70%) of full term RD, this is in accordance with Numan Nafie *et al* study that showed that 79% of full term RD cases had TTN [30]. Similarly, Keerti Swarnkar *et al* study showed that TTN ranked first as a cause of RD in both full term and preterm newborns [33]. On the other hand, Falah Diab Salih *et al* study showed that TTN was the most common cause of full term RD but with a percentage lower than that obtained in our study (41.8%) [34]. MAS and RDS ranked second and third as the cause of full term RD in this study with a nearly similar percentage of 10% and 8.3%, respectively. Similarly, Falah Diab Salih *et al* found that the RDS and MAS occur with a similar percentage of 13% of full term RD [34]; however, in Numan Nafie *et al* study, RDS and MAS accounted for 12% and 4% of full term RD respectively [30]. Congenital peumonia was diagnosed in three neonates (5%) out of the 60 full term neonates in this study, which is higher than that of Numan Nafie *et al* study (2%) [30]; however, this percentage is significantly lower than that the 17.8% of congenital peumonia in Falah Diab study [34]. The percentage of CHD presented with RD in this study and in Keerti Swarnkar *et al* was close (3% and 3.5% of all RD cases, respectively [33]. Only one case was diagnosed for both congenital DH and choanal atresia accounted for only 2% of cases for each. Available data for comparison of these frequencies is scarce, this could be related to the rare occurrence of these surgical conditions. Although the

commonest causes of RD in the different studies are similar, yet their arrangement in frequency is different. These differences between this study and other studies could be attributed to the differences in the sample size and the frequency of RD risk factors. Gender distribution of RD cases shows a statically significant male predominance; a similar result was obtained by Numan Nafie *et al.* [30] and Qian L *et al.* [35], this could be related to the fact that male gender is a risk factor for RDS [28], TTN [36] and sepsis [37] who are the major risk factors for RD in this study. There was no significant difference in the birth weight of newborn with RD and the control group, beside low birth weight was not considered to be a risk factor for RD, this is in accordance with a Turkish study conducted by Mervan Bekdas *et al.* [38]; however, in another study conducted Numan Nafie *et al* whom had studied 100 TTN cases in children welfare hospital in Baghdad had found that there was a highly significant correlation between the neonates' weight and the incidence of TTN, that the incidence much decrease with the larger weight [39]. This could be related to the small number of cases with LBW (only 3 cases) in the RD group. In this study, maternal age was found to be a significant Risk factor for RD, that women with their ages below 20 years and more than 40 years were considered as a risk factor for RD, Maternal age older than 29 years was found to had an impact on the incidence of TTN in a study conducted by Esengül Keleş *et al* in Turkey [40]; on the other hand, Masahiro Fukushima *et al.* [41] and Mervan Bekdas *et al.* [38] shows no significant role of maternal age in the incidence of RD. However; the role of maternal age as a risk factor for RD seems to be unclear. Maternal parity was not considered as a risk factors for RD in our study, this agree with Numan Nafie *et al.* [30] Mervan Bekdas *et al.* [38] and Shamel Mustafa *et al.* [42] studies whom had found that parity was not considered as a risk factor for RD. Schatz*et al* studied a group of 294 pregnant women with asthma and a group of 294 pregnant women without asthma. TTN was found in 11 infants (3.7%) of mothers with asthma and in 1 infant (0.3%) of a mother from the control group, thus asthma was considered as a strong risk factor for TTN [43]. However, in the current study and in Numan Nafie *et al* study [30], maternal asthma was not shown to be a risk factor for RD, this could be related to the small number of asthmatic mothers in both studies. Infants of diabetic mother in this study were more prone to develop RD as opposed to the control group. This could be attributed to the fact that infants of diabetic mothers had increased rates of premature birth, CHD, TTN and diaphragmatic paralysis from a brachial plexus injury beside RDS requiring admission to a NICU occurs almost 6 times as frequently in infants of diabetic mothers as in infants of non diabetic one [44]. History of smoking was found in 7 (11.7%) mothers in RD group while none of the mothers in the control group where smokers; thus maternal smoking was considered as a risk factor for RD in agreement with Numan Nafie *et al.* [30]. Smoking affect the intrauterine lung development in the way that fetal breathing movements are essential for normal growth and structural maturation of the fetal lungs [45], it had found that lung function tests in infants born to smoking mothers confirm reduced airway patency [46] and the effect of prenatal smoke exposure most likely plays a greater role on lung function in childhood than postnatal and childhood exposure [47]. Mother with no ANC was found to be a strong risk factor for development of RD in their full term babies. This is in accordance with a study conducted by Assel Mohammed Wadi and Aida Abdul Kareem on 167 full term neonates who were admitted to the NICU in Basra Maternity and Children Hospital with signs of RD, in which 27% of patients had no ANC [48]. The association of absent ANC and RD could be related to the absence of anticipatory guidance, diagnosis and treatment of the mothers' co-morbid conditions during the pregnancy. Delivery by C/S was found to be a strong risk factor for RD development (p. value of 0.0001) and in particular in those delivered by elective C/S (p. value of 0.002), this is in agreement with many other studies such as Eman F. Badran *et al.* [32], Numan Nafie *et al.* [30, 39] and Erol Tutdibi *et al* studies [49]. The effect of labor in those delivered by normal vaginal delivery and emergency C/S enhances the release of catecholamine in maternal and fetal circulation, resulting in β-adrenergic receptor mediated up regulation of surfactant synthesis and transepithelial sodium ion transport, with subsequent fluid reabsorption, in the neonatal lung. Infants delivered through Elective C/S often are deprived of this labor-related physiological stress response pattern at birth and consequently experience failure of postnatal respiratory transition [49]. TTN is characterized by relatively mild symptoms that resolve naturally over time with most infants recover rapidly, usually within 3 days [28]; that is why patients with TTN had the lowest Down's score as well as the shortest admission period in our study and in Numan Nafie *et al* study [30]. On the other hand patients with congenital pneumonia had the longest period of admission as congenital and neonatal pneumonias are often a difficult disease to identify and treat with an estimated 750000-1.2 million neonatal deaths annually, accounting for 10% of global child mortality [49].

Death occurs in 3 patients with RD which accounted for 5% of total neonates presented with RD and 0.13% of total live birth representing the case fatality rate of this study. This is close to case fatality rate of 0.17% and 0.2% of total live birth in Numan Nafie [50] and Eman F. Badran *et al.* [51] studies, respectively.

Conclusions

1. RD is still an important cause for full term newborn admission to NICU.
2. TTN is the commonest cause of RD in full term newborn while surgical conditions such as choanal atresia and congenital DH are the lowest.
3. Male gender, maternal diabetes and mothers with absent ANC was considered to be risk factors for RD development.
4. Delivery by C/S particularly elective C/S was found to be a strong risk factor for RD development.
5. TTN patients had the shortest admission period of admission while patients with congenital pneumonia had the longest period of admission.

Recommendations

1. Provision of effective ANC to prevent, alleviate and/or treat health problems and diseases (including those directly related to the pregnancy) that are known to have unfavorable outcome on pregnancy and childbirth.
2. Possible reduction of the risk factors associated with full term RD such as elective C/S.
3. The responsible obstetrician should collaborate with the responsible neonatologist to identify the risk factors for adverse neonatal respiratory outcome such as maternal illness and maternal age.
4. Current study is a study from single maternity hospital NICU, larger study from multiple NICU in Iraq is required to delineate the incidence and risk factors of RD.

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