Effect of late prematurity on LCI and respiratory physiology in school age children

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Background-1

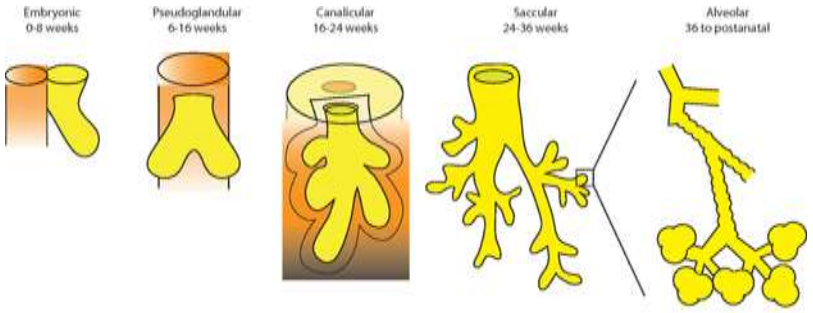
- Late preterm (LP) - born at 34-0/7 to 36-6/7 GA.
- Growing subset of neonates: ~74% of all preterm births & ~8-9% of total births in US.
- Factors contributing to ↑ incidence:
  - ↑women becoming pregnant later in life
  - ↑assisted reproductive technology & multiple gestation pregnancies
  - ↑induction of labor and caesarean sections

Kugelman & Colin. Pediatrics. 2013; 132:741-51.
Curr Probl Pediatr Adolesc Health Care 2010; 40:218-33.

Background-2

- LP - interrupts in utero lung development at the most rapid period of lung maturation.

- Associated with maternal and early life factors which adversely affect the developing respiratory system.



Am Rev Respir Dis. 1984; 129: 607–13.
Paediatr Respir Rev. 2015; 16:182-8.

Background-3

- Controversy exists whether LP birth history is independently associated with childhood asthma [J Allergy Clin Immunol Pract. 2015;3:905-10. Pediatrics. 2011; 127:e913-20].

- LP infants had higher risks for respiratory problems and asthma health service utilization during the neonatal period through adolescence, and the magnitude of the differences decreased with age [Pediatrics. 2017 Jul;140]

Background-4

- Lung clearance index (LCI), a global measurement of ventilation inhomogeneity, calculated from Multiple Breath Washout (MBW) technique, may detect early peripheral airways disease [Paediatr Respir Rev. 2011; 12].

- Few studies have examined LCI of preterm at school age, none in LP (In early premature [Eur Respir J. 2011;37. Eur Respir J. 2016; 47] or in adult survivors of BPD [Ann Am Thorac Soc 2016; 13]).

- There is lack of studies assessing physiological impairment in LP during childhood (6 min walk, exercise questionnaires).

- Aim: To examine the function of peripheral lung regions in former LP children at school age using spirometry & MBW measurement.

- Hypothesis: Due to the premature disruption of normal lung development, former LP children may present an abnormal ventilation distribution and abnormal pulmonary physiologic parameters.

Methods

- A prospective study evaluating children between 6-12 years old former LP births as compared to term controls.
- The participants were recruited from the hospital database or from local area using an advertisement.
- Each participant was assessed during one clinical visit in the Pediatric Pulmonology Institute, and a parent signed a formed consent.

Inclusion criteria

1) Children born between 1/2005 - 12/2010.
2) Ability to perform PFTs and MBW.
3) LP group - infants 34-0/7 to 36-6/7
4) Control group – healthy children, term born with AGA birth weight (>2500g in all cases).

Exclusion criteria

1) Preterm children with congenital bronchopulmonary malformations, CDH, thoracic-abdominal surgery or CHD.
2) Term-born children with current asthma or other chronic respiratory diseases.
3) Respiratory infections within the last 3 weeks.
4) Using systemic steroids or anti-inflammatory drugs in the previous 2 weeks.
5) Using bronchodilators in the previous 24 hours.

Outcome parameters

- MBW measurements: Easy-One Pro, MBW Module (NDD Medical Technologies, Zurich, Switzerland).
- Spirometry: a KoKo spirometer (n-Spire Healthcare, Inc., Longmont CO), pre and post bronchodilator when FEV_1<80%.
- 6 minute walking test (with pre and post vital signs).
- Questionnaires:
  - Symptoms related to asthma and allergy
  - Godin Leisure-Time Exercise Questionnaire
- A review of the medical record.

Results
Neonatal Characteristics

	Study n=29	Control n=30	p
Multiple gestation pregnancy	16 (55%)	0	P<0.0001
Normal pregnancy	25 (86%)	30 (100%)	P=0.052
Maternal smoking during pregnancy	0	0	
Type of delivery (caesarian)	20 (69%)	5 (17%)	P<0.0001
GA, mean (range), wk	35.5 (34-36.86)	39.6 (37-42)	P<0.0001
Birth weight (gr)	2336.2±400	3386±485	P<0.0001
Antenatal steroids	5 (17%)	-	P=0.024
Admitted to NICU	19 (65.5%)	-	P<0.0001
Length of Hospitalization (days)	12±6.7	3.3±1.5	P<0.0001
Oxygen use	5 (17.2%)	1 (3.3%)	P=0.10
Non-invasive Ventilation	2 (6.9%)	0	P=0.24
Exclusive breastfeeding for 3m	11 (37.9%)	24 (80.0%)	P=0.001

Pulmonary symptoms & treatments

	Study n=29	Control n=30	p
Wheezing episodes ever	15 (51.7%)	4 (13.3%)	**P=0.002**
Wheezing episodes in the last 12m	2 (6.9%)	0	P=0.24
Known doctors' diagnosis of Asthma	6 (20.7%)	2 (6.7%)	P=0.15
Known allergies	6 (20.7%)	7 (23.3%)	P=1.00
Positive Skin tests	4 (13.8%)	1 (3.3%)	P=0.19
Treatments since birth			
Bronchodilators	18 (62.1%)	3 (10.0%)	**P<0.0001**
ICS	10 (34.5%)	1 (3.3%)	**P=0.002**
Oral corticosteroids	8 (27.6%)	2 (6.7%)	**P=0.042**
On preventing treatment in the last 12 m	3 (10.3%)	0	P=0.11
Family			
Familial history of Asthma	5 (17.2%)	6 (20.0%)	P=1.00
Familial history of allergy	6 (20.7%)	12 (40.0%)	P=0.16
Animals at home	12 (41.4%)	10 (33.3%)	P=0.59
Smokers at home	7 (24.1%)	2 (6.7%)	P=0.08

Pulmonary physiology

	Study n=29	Control n=30	p
Child age (yr)	8.2±1.7	8.8±1.8	P=0.14
BMI	16.5±2.5	17.7±2.9	P=0.08
FVC (L)	1.73±0.45	1.99±0.49	**P=0.009**
FVC %pred	85.9±10.7	92.9±8.7	**P=0.011**
FEV_1 (L)	1.59±0.48	1.80±0.39	**P=0.005**
FEV_1 %pred	86.6±12.2	92.7±7.8	**P=0.049**
FEF_{25-75} (L)	2.15±0.90	2.35±0.48	P=0.097
FEF_{25-75} %pred	91.1±26.9	98.9±19.5	P=0.25
LCI	7.10±0.79	6.96±0.75	P=0.50
LCI %	130.4±14.9	127.5±14.0	P=0.46
FRC LCI (L)	0.87±0.20	0.94±0.29	P=0.28
FRC LCI %	66.1±13.7	66.5±13.5	P=0.92
6MWT (M)	464.8±42.4	468.4±49.6	P=0.76
Weekly leisure activity score	53.0±30.4 [0-110]	47.8±22.7 [10-101]	P=0.73

PFTs

- In 5/8 and in 0/2 of the LP and control groups, there was ≥12% increase in FEV_1 after β_2 ($p=0.44$).
- A negative correlation exists between LCI and PFTs (FEV_1; FVC ; FEF_{25-75}) in the study group as expected.
- No correlation was found between GA (34-34+6 vs 35-35+6 vs 36-36+6) and PFTs or LCI.

Discussion-1 (LCI)

- ✓ This is the first study to evaluate ventilation inhomogeneity in selectively former LP at school aged children.

- ✓ In this specific cohort and sample size, there was no difference in LCI compared to term controls.

LCI in preterm

- ✓ A study evaluating children at 11 yrs of age, born extremely preterm (<26W GA) demonstrated mildly elevated LCI in 58% of them.
- ✓ Abnormalities of the lung periphery appeared to be mediated primarily through extreme preterm birth.
- ✓ Nevertheless, spirometry remained the most discriminative test in this population.

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Eur Respir J. 2011; 37: 1199-1207.

LCI

- ✓ A recent study evaluated the structural and functional lung impairment in adult survivors of BPD.
- ✓ LCI scores were significantly higher in BPD than in non-BPD subjects and term controls.
- ✓ 30% of subjects with BPD with normal FEV_1 (>80%) had abnormal LCI measurements.

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Ann Am Thorac Soc 2016; 13: 1262-70.

LCI

- ✓ 86 school-aged children born between 24-35W GA vs. 49 terms.
- ✓ LCI and Sacin did not differ between groups.
- ✓ Scond was significantly elevated in 54% of former preterms.
- ✓ Scond showed no significant difference between extremely low GA (<28W) and ≥28W of gestation.

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Eur Respir J. 2016; 47: 147-155.

Discussion-2 (PFTs)

- ✓ In this prospective study, we found that subjects born LP had lower FEV_1 and FVC as measured by spirometry at school age compared with children born term.

- ✓ There was no maternal smoking during pregnancy in both groups; a known risk factor for asthma in LP [Allergy Asthma Proc. 2017 ;38:152-156].

Pediatrics. 2016 Apr;137(4). pii: e20152056. doi: 10.1542/peds.2015-2056. Epub 2016 Mar 23.

Lung Function at 8 and 16 Years After Moderate-to-Late Preterm Birth: A Prospective Cohort Study.

Thunqvist P[1], Gustafsson PM[2], Schultz ES[3], Bellander T[4], Berggren-Broström E[5], Norman M[6], Wickman M[7], Melén E[7], Hallberg J[7].

- ✓ Swedish prospective birth cohort.
- ✓ 4.8% moderate to LP birth defined as a GA of 32 - 36 W.
- ✓ Participants underwent spirometry at ages 8 and 16 years, and impulse oscillometry additionally at age 16 years.
- ✓ At age 8 yrs, adjusted FEV_1 was lower in preterm female subjects compared with term females.
- ✓ At age 16 yrs, both genders in the preterm group demonstrated lower FEV_1.

Thorax. 2012 Jan;67(1):54-61. doi: 10.1136/thoraxjnl-2011-200329. Epub 2011 Sep 27.

Effect of late preterm birth on longitudinal lung spirometry in school age children and adolescents.

Kotecha SJ[1], Watkins WJ, Paranjothy S, Dunstan FD, Henderson AJ, Kotecha S.

- ✓ At 8-9 yrs of age, all spirometry measures were lower in children born at 33–34W GA than in term controls and were similar to the spirometry decrements observed in the extremely preterm infants.
- ✓ Infants born at 35–36W GA had the same PFTs as term infants.
- ✓ By 14–17 yrs, FEV_1 and FVC in children born at 33–34W GA were similar to those in children born at term with the exception of FEV_1/FVC and $FEF_{25-75\%}$ which remained significantly lower than term controls.

Discussion-3

- ✓ Despite no difference in familial history of asthma or allergy or smoking, former LP children have more episodes of ever wheezing and more treatments, but not current asthma diagnosis or preventive treatment.

- ✓ LP- More caesarean, low birth weight , multiple pregnancy, NICU and low breast feeding – all may contribute to ↑respiratory problems.

Discussion-4

- In this study we found no difference with respect to 6MWT, self-rated exercise and weekly leisure activity score as measured by Godin Questionnaire between LP and terms.

- One study examined physical fitness in young adults (23y) born LP, and found no difference in cardiorespiratory fitness, measured by heart rate at the end of a 4M step test, and self-rated fitness vs controls [Pediatrics. 2016 Jan;137(1)].

Limitations

- Limited sample size and hence lower power with which subgroup analyses could be reliably undertaken.
- Selection bias.
- No longitudinal follow-up to adolescence or adulthood.
- Reversibility after bronchodilation was not performed in all children.
- S_{cond} & S_{acin} were not determined.
- No Cardiopulmonary exercise test.

Conclusions
In selective LP birth

- More wheezing episodes and use of medication.
- FEV_1 & FVC were reduced.
- No difference in LCI & FEF_{25-75}.
- No difference in 6MWT & leisure activity score.
- Further larger studies are required to assess the medium and long term respiratory consequences of LP birth, and implications regarding follow-up.

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