ORIGINAL ARTICLE

# Maternal Factors and Neonatal Mortality and Morbidity Associated with Late Preterm Birth

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Submission: 10 Aug. 2015
Accepted: 15 Sep. 2015

**Citation**
Al-Wassia HK. Maternal factors and neonatal mortality and morbidity associated with late preterm birth. JKAU Med Sci 2015; 22 (4): 1-8.
DOI: 10.4197/Med. 22.4.1

## Abstract

The objective of this study is to ascertain risk factors and outcomes associated with late preterm birth. A 1:1 matched case-control study of mothers who delivered at $34^{+0}$ to $36^{+6}$ weeks gestation (cases) and at term (controls) at King Abdulaziz University Hospital, Jeddah, Saudi Arabia between June 1st, 2014 and March 30th, 2015. We enrolled 53 cases and 53 controls. Mothers of late preterm infants were older ($p = 0.03$), with higher parity ($p = 0.04$), body mass index ($p = 0.01$) and multiple pregnancies ($p = < 0.001$) compared to mothers of infants born at term. A higher proportion of hypertension and ($p = 0.01$) and premature rupture of membrane ($p = < 0.001$) preceded late preterm deliveries. Cesarean section frequency was greater in late preterm infants ($p = 0.002$). Late preterm infants were admitted to the neonatal intensive care unit more frequently than their term counterparts ($p = < 0.001$), had more respiratory adverse outcomes ($p = 0.006$) and longer hospital stay ($p = 0.001$). Late preterm birth is a substantial perinatal health problem warranting a closer look at efforts to improve prenatal care strategies to reduce risk factors associated with it and prevent non-medically indicated premature birth.

## Keywords

Late preterm; Risk factors; Morbidity

## Introduction

The rate of late preterm delivery, described as labor occurring between $34^{+0}$ to $36^{+6}$ completed gestational weeks has risen worldwide[1-3]. Late preterm birth has a substantial impact on perinatal health because of its associated mortality[4,5], early-life and enduring morbidities and financial implications for the health care-system[6-9].

Controversies exist over the rate of inevitable late preterm delivery. While Holland *et al.*[10] demonstrated that more than 80% of deliveries of late preterm infants were inexorable, Reddy *et al.*[11] reported that 23% of late preterm births were iatrogenic. Iatrogenic delivery at $34^{+0}$ to $36^{+6}$ weeks is medically indicated when the risk of associated morbidity and mortality is less than that of expectant management. Moreover, obstetricians reported inconsistencies in the management of late preterm pregnancies in that 71%, 69% and 33% will proceed with delivery of cases with severe preeclampsia, early rupture of membranes and placenta previa, respectively[12].

Risk variables related to late preterm delivery reported in the literature includes very young and advanced maternal age[13,14], assisted reproductive technology (ART) and the resultant multiple

pregnancy[15,16], previous preterm birth[17], obesity[18], hypertension[13], smoking[19], positive urine and/or vaginal culture[13] and preterm premature rupture of membrane (PROM).

The purpose of our study is to ascertain risk factors and outcomes related to late preterm birth in women who gave birth at King Abdulaziz University Hospital.

Primary Objective: To study the risk factors in the population of women giving birth at King Abdulaziz University Hospital associated with late preterm delivery.

Secondary Objectives: To establish the effect of late preterm delivery on neonatal mortality and morbidity.

## Materials and Methods

### Study Design

Case control study

### Population

Cases were women who gave birth at King Abdulaziz University (KAU) hospital at $34^{+0}$ to $36^{+6}$ weeks gestation between June 1st, 2014 and March 30th, 2015. Controls were mothers who delivered at term (37 or more gestation). Controls were matched 1:1 to cases by delivery date (within 2 days). Only women whose pregnancy was established by ultrasound in the first or early second trimester were included. Infants with major congenital anomalies were excluded from the study. King Abdulaziz University Hospital Conjoint Research Ethics Board reviewed and approved the study.

### Maternal Factors

The effect of the following maternal factors on the incidence of late preterm birth was explored: maternal age, educational background (number of years), parity, history of previous preterm delivery, invasive procedures during pregnancy (chorionic villous sampling and amniocentesis), prenatal care status, body mass index (BMI), maternal smoking, diabetes[15], hypertension (HTN), vaginal and urine culture during the third trimester, the use of ART, PROM and mode of delivery.

The total number of prenatal visits defined prenatal care[20]. Body mass index is estimated from information on height and weight at the first prenatal visit. Maternal smoking habits during pregnancy included both cigarette and/or sheisha smoking during pregnancy. Diabetes in pregnancy was either pre-gestational or gestational diabetes diagnosed according to the World Health Organization's diagnostic criteria for gestational diabetes[21]. Maternal hypertension is defined by the Committee on Terminology of American College of Obstetrics and Gynecology[22] and included both chronic hypertension foregoing pregnancy and pregnancy-induced hypertension. Leakage of amniotic fluid before 37 weeks of gestational age was used to define preterm premature rupture of the membranes[23].

Neonatal outcomes included neonatal mortality prior to discharge from hospital, condition at birth (cord arterial pH, Apgar scores at one and five minutes and the need for resuscitation), respiratory adverse outcomes comprising respiratory distress syndrome, transient tachypnea of neonate, apnea of prematurity and persistent pulmonary hypertension, hypothermia, hypoglycemia, hyperbilirubinemia, sepsis, feeding difficulty and duration of hospital stay. Respiratory distress is defined by a constellation of clinical signs and symptoms that persist more than two hours[24]. Persistent pulmonary hypertension is defined by echocardiographic finding of right to left or bidirectional shunting at foramen ovale or ductus arteriosus and/or tricuspid regurgitation. Hypothermia is defined as temperature < 36.5°C that is persistent after standard warming measures. Hypoglycemia is defined as two-blood glucose less than 2.6[25]. Hyperbilirubinemia is defined as serum bilirubin level requiring phototherapy at any time during the neonatal period. Sepsis is defined as positive blood and /or central nervous system culture during hospital stay. Feeding difficulty is defined as feeding duration more than 30 minutes, difficulty waking the infant for feeding or fussiness, distress, breathing difficulty, lethargy, frequent coughs and chokes and decreased arousal during feeding[26]. We also studied the rate of readmission to the hospital and the reason for readmission by reviewing the charts of the discharged infants and calling the families 2 months after discharge to inquire about readmission in another hospital.

### Sample Size Calculation

Since we studied multiple risk factors we calculated our sample size based on neonatal admission rate to the neonatal intensive care unit (NICU). For a 30% admission rate of preterm infants to NICU[27] and 6.3 % for term infants[28], at 5% level of significance and 80% power, a total sample size of 96 neonates was required, 48 in each group. A 10% increase in the sample size was

entertained to account for attrition and missing data and that resulted in a total sample size of 106 neonates.

## Statistical Analysis

IBM SPSS Statistics for Windows, Version 20 (IBM Corp., Armonk, NY USA) was utilized for all statistical tests. For descriptive statistics, *t*-test and chi-square or Fisher's exact test were employed to compare continuous and categorical variables correspondingly. Statistical significance was set at 5% level.

## Results

A total of 106 infants were included, 53 infants in each group. Table 1 depicts maternal demographic and clinical features. Mothers of late preterm infants were older, had higher parity, BMI and increased number of multiple pregnancies. They did not vary from mothers of term infants in educational background, working status and smoking. Mothers in both groups had comparable number of antenatal visits and number of invasive procedures during pregnancy. Mothers in the late preterm group had increased use of antenatal steroid and cesarean delivery. Cesarean section (C/S) for unknown reason or electively was the mode of delivery in more than two third of late preterm infants (75.7%) compared to 57% of term infants (Table 2). Mothers of late preterm infants had significantly higher frequency of hypertension and PROM. More mothers in the late preterm infants group had encountered preterm labor and conceived using assisted reproductive technology, that did not reach statistical significance. Table 3 outlines infants' characteristics and rate of morbidities in both groups. Late preterm infants had significantly lower birth weight, needed more resuscitation, and

**Table 1.** Maternal characteristics.

| | Cases N = 53 | Controls N = 53 | p value |
|---|---|---|---|
| **Maternal Characteristics** | | | |
| Age | 33.0 (5.9) | 30.6 (5.7) | **0.03** |
| Body Mass Index | 30.1 (9.5) | 26.2 (5.4) | **0.01** |
| Parity | 3 (0, 6 ) | 2 (0, 9) | **0.04** |
| Educational Background (number of years) | 16 (6, 20) | 16 (6, 21) | NS |
| Working Mother | 22 (41.5) | 15 (28.3%) | NS |
| No. of Antenatal Visits | 6 (2, 15) | 6 (2, 18) | NS |
| Invasive Procedures during Pregnancy | 0 (0.00%) | 3 (5.67%) | NS |
| Multiple Pregnancy | 16 (30.19%) | 1(1.89%) | **<0.001** |
| Smoking | 4 (7.54%) | 0 (0.00%) | NS |
| Previous History of Preterm Birth | 13 (24.52%) | 6 (11.32%) | NS |
| Antenatal Steroids | 18 (33.96%) | 2 (3.77%) | **<0.001** |
| Cesarean Section | 37(69.81%) | 21 (39.62%) | **0.002** |
| Induction of Labor | 8 (15.09%) | 13 (24.52%) | NS |
| *Diabetes mellitus* | 10 (18.87%) | 7 (13.21%) | NS |
| Hypertension | 16 (30.19%) | 5 (9.43%) | **0.01** |
| Premature Rupture of Membrane | 18 (33.96%) | 1 (1.89%) | **<0.001** |
| Positive Vaginal/Urine Culture | 5 (9.43%) | 6 (11.32%) | NS |
| Assisted Reproductive Technology | 7 (13.21%) | 1 (1.89%) | NS |

*Results are expressed as: mean ± SD, median, range or %.*

**Table 2.** Reason for cesarean delivery.

| Reason for Cesarean Section | C/S in Cases N = 37 | C/S in Controls N = 21 |
|---|---|---|
| Oligohydramnios | 0 (0.00%) | 1 (4.76%) |
| Chorioamnionitis | 1 (2.70%) | 0 (0.00%) |
| Hypertension/Eclampsia | 1 (2.70%) | 1 (4.76%) |
| Previous Cesarean Section | 4 (10.81%) | 5 (23.81%) |
| Placenta Previa | 1 (2.70%) | 0 (0.00%) |
| Position of Baby | 2 (5.40%) | 2 (9.52%) |
| Unknown/Elective | 28 (75.68%) | 12 (57.14%) |

*Abbr: C/S: Cesarean section.*

**Table 3.** Infant characteristics and rate of comorbidities.

| | Cases N = 53 | Controls N = 53 | p value |
|---|---|---|---|
| **Infant Characteristics** | | | |
| Birth weight (g) | 229.6 (37.6) | 323.3 (37.61) | **<0.001** |
| Gestational age (weeks) | 35.2 (0.85) | 38.9 (0.92) | **<0.001** |
| Apgar score 1 minute | 8 (3, 9) | 9 (1, 9) | **0.03** |
| Apgar score 5 minute | 10 (6, 10) | 10 (6, 10) | **0.007** |
| **Neonatal Morbidities** | | | |
| Need for resuscitation | 8 (15.09%) | 2 (3.77%) | **0.046** |
| NICU Admission | 17 (32.08%) | 1 (1.89%) | **<0.001** |
| Respiratory Distress Syndrome | 8 (15.09%) | 0 (0.00%) | **0.006** |
| Transient Tachypnea Of Neonate | 4 (7.54%) | 0 (0.00%) | NS |
| Apnea of Prematurity | 1 (1.89%) | 0 (0.00%) | NS |
| Need for Intubation | 2 (3.77%) | 1 (1.89%) | NS |
| Continuous Positive Airway Pressure | 8 (15.09%) | 0 (0.00%) | **0.006** |
| Hypoglycemia | 1 (1.89%) | 1 (1.89%) | NS |
| Hyperbilirubinemia | 1 (1.89%) | 0 (0.00%) | NS |
| Sepsis | 0 (0 %) | 1 (1.89%) | NS |
| Hospital Stay (days) | 4.4 (3.7) | 2.4 (2.1) | **0.001** |
| Readmission | 3/50 (6.00%) | 1/46 (2.17%) | NS |

*Abbreviations: NICU, neonatal intensive care unit; Results are expressed as: mean ± SD or median, range or %.*

exhibited lower one and five minutes Apgar scores compared to term infants. Significantly higher number of late preterm infants were admitted to the NICU, had respiratory distress syndrome (RDS), and needed to be supported with continuous positive airway pressure (CPAP). Moreover, late preterm infants exhibited significantly longer length of hospital stay than term infants. We did not discern a significant increase in the rate of other morbidities including hyperbilirubinemia, hypoglycemia, hypothermia, sepsis and feeding difficulty. Three infants in the late preterm group and one in the control group needed to be readmitted during the first month after discharge. Hyperbilirubinemia was the cause in two of the late preterm infants and sepsis was the cause of readmission in one infant of both groups.

## DISCUSSION

The maternal factors associated with late preterm delivery identified in our study were comparable to other studies[29,30]. Compared to term infants, mothers of late preterm infants were older and had higher BMI, parity and multiple pregnancies. Hypertension and PROM are proven contributors to late preterm delivery. The study did not have the power to detect disparities in secondary outcomes and that can explain the statistically insignificant difference between the two groups in the rate of use of ART. A number of published studies have documented the association between ART and the increased risk of premature delivery and multifetal pregnancies[31,32]. A greater proportion of late preterm in neonates in our population was born by C/S compared to term infants. Moreover, the motive for the greater number of C/S in late preterm infants was either elective or unknown medical indication. Recent published data suggest that the increasing use of elective cesarean delivery has influenced the upsurge in rate of late preterm birth[33,34]. 6-23% of late preterm deliveries resulting from elective or non-medically indicated deliveries could be potentially avoided[10,11].

Respiratory morbidities had accounted significantly to NICU admissions as shown in other studies [14, 35]. Although several studies demonstrated that late preterm infants had increased risk of hypoglycemia, sepsis, hyperbilirubinemia requiring phototherapy and feeding difficulties compared to their term infants' counterparts, we failed to show similar findings in our study most likely because of the limited sample size to address all neonatal morbidities[36, 37]. Several articles have evaluated the hospital readmission rate of late preterm infants in the neonatal period. In a population based cohort study by Tomashek *et al.*[38], the admission rate for late preterm infants was reported to be 1.8 times higher than term infants in the first month after discharge. More recently, Kuzniewicz *et al.*[39] reported similar conclusions of increasing the likelihood of

readmission for late preterm infants compared with their matched term infants (RR 1.29; 95% CI, 1.13-1.47). The most common reasons for readmission included feeding problems, sepsis and hyperbilirubinemia[8,40]. We did not examine the neonatal cost relative to gestational age. Several studies have indicated that the overall average cost decreases with increasing gestational age at birth[30,41,42]. Moreover, we did not investigate maternal emotional impact of having a late preterm infant. Several published studies demonstrated that mothers of late preterm infants have greater emotional stress[43] and symptoms of depression and anxiety compared to mothers of full term infants[44].

Late preterm infants exhibit immaturity both developmentally and physiologically and endure more health co-morbidities than infants born at term. Recognizing maternal characteristics associated with late-preterm birth is important to help in implementing pre-pregnancy and prenatal care strategies aiming at modifying and reducing those factors. Furthermore, realizing mortality and morbidity risks among late-preterm infants is essential for supporting neonatal health care providers to develop guidelines and management plans adapted to the special requisites of late-preterm infants and to foresee conceivable morbidities that will prolong their hospital stay or bring them back to hospital after discharge. Further, for non-emergency obstetric decisions of late preterm birth, obstetricians ought to evaluate the potential increased maternal and perinatal morbidities of expectant management versus iatrogenic prematurity. Future studies should consider evaluating the effectiveness of methods to postpone late preterm deliveries and the impact of that on the reduction of neonatal adverse outcomes.

## Acknowledgement

We thank Dr. Hanan Bajunaid, Dr. Reem Al-Wassia and Ms. Rola Al-Malki for their contribution to data collection for this study. Dr. Heidi Al-Wassia had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

## Conflict of Interest

The author has no conflict of interest.

## Disclosure

The author did not received any type of commercial support either in forms of compensation or financial for this study. The author has no financial interest in any of the products or devices, or drugs mentioned in this article.

## Ethical Approval

Obtained.

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# العوامل الوالدية (الأمهات ) و الوفيات والأمراض في حديثي الولادة المرتبطة بولادة الخدج المتأخرة

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***المستخلص***. هدفت الدراسة الى تحديد عوامل الخطر والنتائج المرتبطة بالولادة المتأخرة للخدج. استخدم منهج الدراسة المقارنة (١:١) ، للنساء اللواتي ولدن في عمر حمل يقع بين ٣٤+٠ إلى ٣٦+٠أسبوع من الحمل (كمجموعة دراسة) وللنساء اللواتي أتممن فترة الحمل كاملة (كمجموعة ضابطة) في مستشفى جامعة الملك عبد العزيز، جدة، المملكة العربية السعودية من من يونيو ٢٠١٤ م الى مارس ٢٠١٥ م .
وقد شملت الدراسة ٥٣ حالة و ٥٣ ضابطة. تميزت أمهات الخدج المولدين متأخراً، بكبر السن (p=٠٣.٠) ، معدل عالي للإنجاب (p=٠٤.٠) مقارنة بأمهات الأطفال المولودين لفترة الحمل كاملة. سبقت حالات ولادة الخدج المتأخرة بنسبة عالية من حالات ارتفاع ضغط الدم (p=٠١.٠) و التمزق المبكر للأغشية (p<٠٠٠١.٠). كما كان هناك ارتفاع في معدل الولادة القيصرية للخدج المولودين متأخرا (p=٠٠٢.٠) مقارنة بالمولودين بعد اتمام فترة الحمل كاملة.
كما سجل الخدج المولودين متأخرا اعلى معدل للدخول إلى وحدة العناية المركزة للرضع (p<٠٠١.٠)، مضاعفات الجهاز التنفسي (p=٠٠٦.٠) وأطول فترة بقاء في المستشفى (p=٠٠١.٠).
تعتبر ولادة الخدج المتأخرة من المشاكل الصحية الكبيرة خلال الفترة المحيطة بالولادة ، والتي تستدعي نظرة فاحصة على الجهود المبذولة لتحسين استراتيجيات الرعاية خلال فترة ما قبل الولادة للتقليل من عوامل الخطر المرتبطة بها ، والحد من الولادات المبكرة غير المقررة طبياً.