

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The burden of early term birth on adverse infant outcomes: a population-based cohort study in Brazil
AUTHORS	Leal, Maria; Esteves-Pereira, Ana Paula; Nakamura-Pereira, Marcos; Domingues, Rosa; Dias, Marcos Augusto; Moreira, Maria; Filha, Mariza; da Gama, Silvana

VERSION 1 – REVIEW

REVIEWER	Julie Glavind, MD, PhD Dep. of Obstetrics and Gynecology & Perinatal Epidemiological Research Unit, Aarhus University Hospital, Aarhus, Denmark
REVIEW RETURNED	11-Jun-2017

GENERAL COMMENTS	<p>Thank you for this opportunity to read the paper by Leal et al. on the association between early term birth and adverse neonatal outcomes. The presented results support several previous studies that early term birth increases the risk of neonatal adverse outcomes. As the majority (>91%) of provider initiated births were caesareans, studies by Tita (2009) and Wilmink (2010) with more clearly defined outcomes, already provided observational evidence of the association between elective early term delivery and neonatal adverse outcomes. It is not surprising that provider initiated early term birth with no maternal or fetal indication were associated with higher risks of adverse neonatal outcomes than those with an indication (Brown 2014).</p> <p>The risk of confounding by indication for delivery remains in this study as well as in other studies on this topic, which should be recognized as an important weakness to the study. Further, the authors need to adjust their estimates for mode of delivery. I also find it methodologically incorrect to group singleton and multiple pregnancies when studying gestational age as exposure on neonatal outcomes – rather, multiples should be excluded from the cohort. The introduction and the discussion should be shortened and more stringently written. Throughout the paper, the language needs improvement and several wordings like “reanimation”, “the lowest rate of prevalence”, “treatment of missing data” should be rephrased.</p> <p>In Table 2, wrong numbers are given for breastfeeding outcomes in column 8 or 9.</p> <p>Several page & line referrals from the STROBE statement are inaccurate.</p>
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REVIEWER	Elaine Boyle University of Leicester, UK
REVIEW RETURNED	19-Jul-2017

GENERAL COMMENTS	<p>This study aims to determine the rate of early term births in Brazil using national data and to evaluate the impact of early term birth on neonatal outcomes. This is an important issue. previous studies have highlighted worse outcomes in infants born early term compared with those born at full term. It is not known how much of this increase in adverse outcomes is related to immaturity per se, obstetric intervention for clinical reasons, how different types of maternal and/or fetal problems influence neonatal outcomes or how much is associated with socio-demographic factors. This study will be of particular interest in Brazil, where it appears that rates of early term birth, especially by caesarean section are very high.</p> <p>The study compares births at 37 and 38 weeks with those at 39 and 40 weeks. Since gestational age has been further sub-categorised, full term is now generally regarded as 39-41 weeks, so comparison with results of some other studies may not be possible.</p> <p>The sample size is large and this is a strength of the study. Methods and statistical analysis seem generally appropriate, though as a non-statistician I am unable to assess the statistics in great detail.</p> <p>The findings of the study are broadly in line with others studies, showing an increase in adverse outcomes among early term births, with increasing morbidity noted at 37 compared with 38 weeks. Other studies have shown a similar gradient of risk for both early and longer-term outcomes.</p> <p>Outcomes in babies where delivery has been "provider-initiated" are compared with those where the onset was spontaneous. A number of maternal and fetal conditions were looked at together. Multiple birth was included as a fetal condition - I believe it may have been more appropriate to exclude or adjust for multiple births, as deliveries tend to be earlier in multiples and this is likely to be a normal phenomenon. It is unclear as to whether the maternal and fetal conditions were actually the indication for delivery, or simply present during pregnancy or at the time of delivery. This should be specified as it is difficult to know without this information whether the provider-initiated group represents a "sick" group of mothers and babies where the pregnancy is at risk (ie. medically indicated delivery) and for whom outcomes may be expected to be worse. I would like to see analysis exploring differences, within the provider-initiated group between medically indicated deliveries and those where delivery was not because of a medical indication. Similarly, if data are available, it would be interesting to try to tease out whether any particular maternal or fetal morbidity is more relevant.</p> <p>The plan for follow-up interview is not clear and it does not appear to have been standardised in any way. There is a wide range of times at which mother were contacted post discharge (45 to 119 days), and it would be helpful to know whether there was an intention for the interviews to be conducted at a particular number of days after birth or whether these were opportunistic communications. This discrepancy might lead to recall bias. Although the follow-up data collection included hospitalisation after discharge and reasons for this, this does not appear to be reported in the manuscript.</p>
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	<p>However, given the differences in timing of interviews, comparisons of this may not be valid.</p> <p>General comments: There is a large number of typographical and grammatical errors in the manuscript, particularly in the tables (eg. oxigenotherapy, hipoglicemia, taquypnea) and these require correction. Some terminology is not widely used and should be changed for an international audience (eg. reanimation would usually be referred to as resuscitation or resuscitation and stabilisation</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Julie Glavind, MD, PhD

Institution and Country: Dep. of Obstetrics and Gynecology & Perinatal Epidemiological Research Unit, Aarhus University Hospital, Aarhus, Denmark

Competing Interests: None declared

Comments: Thank you for this opportunity to read the paper by Leal et al. on the association between early term birth and adverse neonatal outcomes. The presented results support several previous studies that early term birth increases the risk of neonatal adverse outcomes. As the majority (>91%) of provider initiated births were caesareans, studies by Tita (2009) and Wilmink (2010) with more clearly defined outcomes, already provided observational evidence of the association between elective early term delivery and neonatal adverse outcomes. It is not surprising that provider initiated early term birth with no maternal or fetal indication were associated with higher risks of adverse neonatal outcomes than those with an indication (Brown 2014).

Comment 1- The risk of confounding by indication for delivery remains in this study as well as in other studies on this topic, which should be recognized as an important weakness to the study. Further, the authors need to adjust their estimates for mode of delivery.

Answer: This aspect of confounding by indication for delivery was cited in the discussion section in lines 310 to 315: "CS was not classified according to clinical indication, which limited the analysis of specific conditions on neonatal outcomes. We also used data of clinical and obstetric conditions collected at the hospital from medical records as evidence of the presence of these conditions. This criterion influenced results, making them more sensitive but less specific classification, which may have led to an overestimation of the presence of complications".

We performed a new analysis where we also the adjusted for mode of delivery according to the reviewer's suggestion. The methods and results sections within the manuscript, as well as the tables, were updated in accordance with this new analysis.

Comment 2- I also find it methodologically incorrect to group singleton and multiple pregnancies when studying gestational age as exposure on neonatal outcomes – rather, multiples should be excluded from the cohort.

Answer: We agree with the reviewer and excluded twins from the analysis. We also excluded newborns with foetal malformations potentially related to indication for CS and/or prematurity, including anencephaly, hydrocephaly, spina bifida, gastrosquisis and other abdominal wall defects, cardiac malformations and multiple malformations. We have updated the methods and results sections within the manuscript, as well as the tables, in accordance with this new analysis.

Comment 3- The introduction and the discussion should be shortened and more stringently written.

Answer: We shortened the introduction and discussion as the reviewer suggested.

Comment 4- Throughout the paper, the language needs improvement and several wordings like “reanimation”, “the lowest rate of prevalence”, “treatment of missing data” should be rephrased.

Answer: We carry out a general review of the text language and modify the terms indicated by the reviewer.

Comment 5- In Table 2, wrong numbers are given for breastfeeding outcomes in column 8 or 9.

Answer: We reviewed the numbers of this table.

Comment 6-Several page & line referrals from the STROBE statement are inaccurate.

Answer: We reviewed the STROBE statement.

Reviewer: 2

Reviewer Name: Elaine Boyle

Institution and Country: University of Leicester, UK

Competing Interests: None declared

Comments: This study aims to determine the rate of early term births in Brazil using national data and to evaluate the impact of early term birth on neonatal outcomes. This is an important issue. previous studies have highlighted worse outcomes in infants born early term compared with those born at full term. It is not known how much of this increase in adverse outcomes is related to immaturity per se, obstetric intervention for clinical reasons, how different types of maternal and/or fetal problems influence neonatal outcomes or how much is associated with socio-demographic factors. This study will be of particular interest in Brazil, where it appears that rates of early term birth, especially by caesarean section are very high.

The sample size is large and this is a strength of the study. Methods and statistical analysis seem generally appropriate, though as a non-statistician I am unable to assess the statistics in great detail.

The findings of the study are broadly in line with others studies, showing an increase in adverse outcomes among early term births, with increasing morbidity noted at 37 compared with 38 weeks. Other studies have shown a similar gradient of risk for both early and longer-term outcomes.

General comments:

There is a large number of typographical and grammatical errors in the manuscript, particularly in the tables (eg. oxigenotherapy, hipoglicemia, taquypnea) and these require correction. Some terminology is not widely used and should be changed for an international audience (eg. reanimation would usually be referred to as resuscitation or resuscitation and stabilization).

Answer: We carry out a general review of the text language and modify the terms indicated by the reviewer.

Comment: The study compares births at 37 and 38 weeks with those at 39 and 40 weeks. Since gestational age has been further sub-categorised, full term is now generally regarded as 39-41 weeks, so comparison with results of some other studies may not be possible.

Answer: We agree with the reviewer. However, we decided to use the ACOG definition, which defines as full term newborns the ones from 39 0/7 weeks of gestation to 40 6/7 weeks of gestation. We also opted for this reference category because recent studies have shown increased neonatal risks for late term newborns (41 0/7 weeks of gestation through 41 6/7 weeks of gestation) when compared to full term newborns.

REF: ACOG (2013) Committee Opinion No 579: Definition of term pregnancy. *Obstet Gynecol* 122: 1139-1140.

Comment 1- Multiple birth was included as a fetal condition - I believe it may have been more appropriate to exclude or adjust for multiple births, as deliveries tend to be earlier in multiples and this is likely to be a normal phenomenon.

Answer: We agree with the reviewer and excluded twins from the analysis. We also excluded newborns with foetal malformations potentially related to indication for CS and/or prematurity, including anencephaly, hydrocephaly, spina bifida, gastrosquisis and other abdominal wall defects, cardiac malformations and multiple malformations. We have updated the methods and results sections within the manuscript, as well as the tables, in accordance with this new analysis.

Comment 2- It is unclear as to whether the maternal and fetal conditions were actually the indication for delivery, or simply present during pregnancy or at the time of delivery. This should be specified as it is difficult to know without this information whether the provider-initiated group represents a "sick" group of mothers and babies where the pregnancy is at risk (ie. medically indicated delivery) and for whom outcomes may be expected to be worse. I would like to see analysis exploring differences, within the provider-initiated group between medically indicated deliveries and those where delivery was not because of a medical indication. Similarly, if data are available, it would be interesting to try to tease out whether any particular maternal or fetal morbidity is more relevant.

Answer: In this study, we cannot sort if the delivery indication was appropriate. Instead, we used data of clinical/obstetric conditions as a proxy of the CS indication and stratified the women according to this criterion. The rationale of this strategy was to have a group clear of any clinical/obstetric condition and, therefore, very unlikely to have had a CS or induction of labour for a medical reason. We focused in discussing differences in neonatal risks associated with to 37 and 38 weeks/gestation in this specific group (of women without clinical/obstetric conditions). However, we cannot rule out the bias that the birth has had an indication. We mention this in the limitations of the study in lines 310 to 315: "CS was not classified according to clinical indication, which limited the analysis of specific conditions on neonatal outcomes. We also used data of clinical and obstetric conditions collected at the hospital from medical records as evidence of the presence of these conditions. This criterion influenced results, making them more sensitive but less specific classification, which may have led to an overestimation of the presence of complications".

Comment 3- The plan for follow-up interview is not clear and it does not appear to have been standardised in any way. There is a wide range of times at which mother were contacted post discharge (45 to 119 days), and it would be helpful to know whether there was an intention for the interviews to be conducted at a particular number of days after birth or whether these were opportunistic communications. This discrepancy might lead to recall bias. Although the follow-up data collection included hospitalisation after discharge and reasons for this, this does not appear to be reported in the manuscript. However, given the differences in timing of interviews, comparisons of this may not be valid.

Answer: In relation to exclusive breastfeeding at the follow-up interview, we agree with the reviewer and excluded the variable from the analysis.

In relation to phototherapy after hospital discharge, we believe that recall bias is very unlikely because such procedure needs to be performed inside a health facility. We also believe that the range of 43 to 119 days would not be enough to differentiate mothers regarding their ability to remember such incident. Notwithstanding, we have adjusted for the age of the infant at the time of the follow-up interview.

As other reasons for hospitalization after discharge was not included in the current analysis, we excluded the statement from the methods section.

VERSION 2 – REVIEW

REVIEWER	Elaine Boyle University of Leicester United Kingdom
REVIEW RETURNED	06-Sep-2017

GENERAL COMMENTS	<p>Thank you for responding to my previous comments. I believe that you have addressed the comments and concerns appropriately, and the manuscript is much improved and is much easier to read. The discussion is more succinct and readable than in the previous version. There are still a few minor typographical errors that will require correction:</p> <p>Page 40, line 44 should read "have demonstrated a clear benefit" Page 5, line 59 should read "early term birth via" Page 11, line 205 should read "birth at 39/40"</p> <p>All relevant tables: "Single live births" should read "singleton live births" Page 21, line 248 should read "the rate of provider-initiated" Page 22, line 272 should read "early term infants born at 37 weeks" There is some inconsistency in the spelling of hypoglycemia/hypoglycaemia throughout the manuscript.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: Elaine Boyle

Institution and Country: University of Leicester, United Kingdom

Competing Interests: None declared

Thank you for responding to my previous comments. I believe that you have addressed the comments and concerns appropriately, and the manuscript is much improved and is much easier to read. The discussion is more succinct and readable than in the previous version. There are still a few minor typographical errors that will require correction:

Comment: Page 40, line 44 should read "have demonstrated a clear benefit"

Answer: The sentence was corrected as suggested.

Comment: Page 5, line 59 should read "early term birth via"

Answer: The sentence was corrected as suggested.

Comment: Page 11, line 205 should read "birth at 39/40"

Answer: The sentence was corrected as suggested.

All relevant tables: "Single live births" should read "singleton live births"

Answer: The tables were corrected as suggested.

Comment: Page 21, line 248 should read "the rate of provider-initiated"

Answer: The sentence was corrected as suggested.

Comment: Page 22, line 272 should read "early term infants born at 37 weeks"

Answer: The sentence was corrected as suggested.

Comment: There is some inconsistency in the spelling of hypoglycemia/hypoglycaemia throughout the manuscript.

Answer: We have standardized to "hypoglycaemia".