BMJ Open

Reduction in stillbirths at term after new birth induction paradigm. Results of a national intervention

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005785
Article Type:	Research
Date Submitted by the Author:	26-May-2014
Complete List of Authors:	Hedegaard, Mette; Rigshospitalet, Dept. of Gynaecology Lidegaard, Øjvind; Rigshospitalet, University of Copenhagen, DK-2100 Copenhagen, Denmark, Gynecological Clinic 4232, DK-2100 Skovlung, Charlotte; Rigshospitalet, University of Copenhagen, DK-2100 Copenhagen, Denmark, Gynecological Clinic 4232, DK-2100 Mørch, Lina; Rigshospitalet, University of Copenhagen, DK-2100 Copenhagen, Denmark, Gynecological Clinic 4232, DK-2100 Hedegaard, Morten; Rigshospitalet, University of Copenhagen, Dept. of Obstetrics
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Epidemiology, Evidence based practice, Public health
Keywords:	EPIDEMIOLOGY, Fetal medicine < OBSTETRICS, OBSTETRICS

May 24, 2014

Reduction in stillbirths at term after new birth induction paradigm.

Results of a national intervention

Mette Hedegaard[1], scholar researcher

Øjvind Lidegaard[1], professor in Obstetrics and Gynaecology,

Charlotte Wessel Skovlund[1], data manager

Lina Steinrud Mørch, epidemiologist, and

Morten Hedegaard[2], head of dept, of obstetrics,

Word counts: *Title: 15 words, 102 characters including space*

Abstract: 300 words

Text: 3,054 words (excl, abstract, references, tables and figures)

Tables: 2

Figures: 4

Supplementary online appendix: One with one table

1) *Department of Gynecology, Rigshospitalet, Faculty of Health Science, University of Copenhagen*

2) *Department of Obstetrics, Rigshospitalet, Faculty of Health Science, University of Copenhagen*

Correspondence: Oejvind.Lidegaard@regionh.dk

Abstract

Objective. Fetal deaths are still a key challenge for obstetricians worldwide. The risk of fetal death increases steeply after 42 gestational weeks. From 2009, Danish national guidelines recommended pregnant women to be offered induction to ensure delivery before 42 weeks. The aim of this study was to describe the development in fetal deaths with this more proactive birth induction practice, and to identify and quantify contributing factors for this development.

Design. National cohort study.

Setting. Denmark

Participants. Delivering women in Denmark, January 1, 2000 to December 31, 2012.

Outcome measures. Stillbirths per 1,000 women at risk (prospective risk of stillbirth) and per 1,000 new-born from 37 and 40 gestational weeks, respectively, through the study period.

Results. During the study period, 829,165 children were live-born and 3,770 (0.45%) stillborn. Induction of labour increased from 12.4 % in year 2000 to 25.1 % in 2012 (p<0.001), and the per cent of children born at or after 42 weeks decreased from 8.0 % to 1.5 % (p<0.001).

Through the same period, the prospective risk of stillbirth after 37 weeks fell from 0.70 to 0.41 per 1,000 ongoing pregnancies (p<0.001), and from 2.4 to 1.4 per 1,000 new-born (p<0.001).

The regression analysis confirmed the inverse association between year of birth and risk of stillbirth. The lowest risk was observed in the years 2011-2012 as compared to years 2000-2002 with a fully adjusted hazard ratio of 0.69 (95% CI 0.57-0.83). The general earlier induction, the focused earlier induction of women with body mass index >30, twins, and of women above 40 years, and a halving of smoking pregnant women were all independent contributing factors for the decrease.

Conclusion. A gradually more proactive and a differential earlier labour induction practice are likely to have the main responsibility for the substantial reduction in stillbirths in Denmark.

Key words: Birth induction, fetal death, stillbirth, misoprostol

Abbreviations: None.

Strengths and limitations

Strengths

- Complete national data through a 13-year long study period
- Data analysed for all births after 37 weeks and after 40 weeks, respectively
- Access to important confounders
- Complete follow-up on all children born during the study period
- Advanced regression analysis
- A clear clinical message

Limitations

- Several clinical improvements have been undertaken during the study period
-

Introduction

Fetal death is still a dreaded complication of pregnancy, not least when occurring at term. The worldwide number of stillborn infants is estimated to 2.6 million per year, and the causes of a substantial part of these deaths are still unknown.[1] Identified risk factors include high maternal age, adiposity, fetal asphyxia, infections, and different maternal medical diseases.[2-5] Randomised studies have suggested a potential for prevention of fetal deaths by earlier induction of deliveries.[6]

Over the last two decades, the discussion of induction of labour versus expectant management has been prevalent among obstetricians.[7] A national Danish guideline in 2009 recommended induction of pregnant women ensuring delivery before 42 weeks.[8] Generally, pregnant women have since been offered labour induction at 41+3-5, while women at risk (body mass index >30 or age >40 years) have been offered induction at 41 weeks. Lastly, women at a high risk such as women with multiple pregnancies, preeclampsia or intrauterine growth restriction are often recommended induction before term.

The aim of this study was to describe birth induction practice in Denmark since year 2000, the corresponding development in post-term deliveries, and the stillbirth rates from 37 and 40 weeks of gestation (prospective stillbirth rate) and per 1,000 new-born. Secondly, to adjust these trends in rates of stillbirth for important risk factors of stillbirth.

Methods

Design and setting

In a historical cohort design data were collected from the Danish Birth Register, covering the period January 2000 through December 2012. The Registry is considered complete through this period. In order to reduce random variation, the 13-year study period was subdivided into five sub-periods of three, three, three, two, and two years length, respectively.

Participants

All live births and stillbirths during the study period were included. For each gestational day after 37 weeks, the number and distribution of all new-born and stillbirths were assessed. The gestational ages were generally assessed from first trimester ultrasound examinations. For few women not attending this routine offer to all pregnant women in Denmark, the last menstrual period was used.

Outcome measures

Rates of stillbirth per 1,000 ongoing pregnancies, also called the prospective risk of stillbirth, were calculated with a daily update from 37 weeks of gestation, accounting for the rapidly declining denominator especially after term. [9] The proportion of deliveries and of stillbirths after 37, 40, 41,

and 42 weeks per 1,000 new-born were calculated annually from year 2000 through 2012, and in different sub-periods within this study period.

The gestational age was recorded in 99.4 % of all new-born during the study period. Of 146 missing gestational ages among stillborn infants, we sought in medical charts and local registers and achieved this information in 42 women, all of whom had ended their pregnancy before 37 weeks. Therefore, all with a missing gestational age were allocated to the premature group. Gestational ages were however achieved for all stillbirths in 2011 and 2012.

From 2004 a birth has in Denmark been defined as any pregnancy that ends after 22 weeks of gestation, and live-born before 22 weeks. Before 2004 only live-births between 22 and 28 weeks were considered as births, while delivery of dead fetuses before 28 weeks and live-born before 22 weeks were considered as abortions. This technicality explains a minor increase in stillbirths before 37 weeks of gestation from 2003 to 2004.

Deaths within the first week after delivery was assessed for all included live-born, and rates of death were calculated in each study year.

In the analytical assessment, analyses of the cumulative risk of stillbirth with increasing gestational age per 1,000 ongoing pregnancies was estimated using Nielson Aalen estimator with gestational age (in days) as the time scale.[10] By cox regression analyses, the hazard ratios of stillbirth by year of birth were estimated using year 2000-2002 as the reference group. Gestational age was underlying time scale in these analyses. The following potential confounders were included in the model: Plurality, parity, maternal age, year, smoking, and body mass index. The regression model aimed to quantify the contribution from each of the potential confounders for the association between calendar year and rates of stillbirth.[10] Hazard ratios with 95% confidence limits were calculated, and p-values below 0.05 were considered significant. Logistic regression was used to generate crude odds ratios.

The main analysis was done on all deliveries from 37 weeks of gestation. As body mass index was not routinely recorded in the birth registry until 2004, additional sensitivity analyses were done for the sub-period 2004-2012, in order to quantify specifically the influence of body mass index on the decreasing stillborn rate. Finally, sensitivity analyses were conducted restricted to singletons.

Results

During the study period, 832,935 children were born. Of these were 3,770 (0.45 %) stillbirths and 829,165 (99.55 %) live-born. The distribution of new-born and stillborn infants in different pregnancy weeks, the crude rate of stillborn per 1,000 ongoing pregnancies and per 1,000 new-born in different gestational weeks, from different gestational ages and in different periods are shown in Table 1.

The frequency of birth induction increased from 12.4 % in year 2000 to 25.1 % in 2012, with a steep increase after 2010 (**Figure 1**). The earlier birth induction reduced the per cent of children born from 42 weeks of gestation from 8.0 % in year 2000 to 1.5 % in 2012 (**Figure 1**). The increasing induction rate and fall in deliveries from 42 weeks was, however, already observable from 2001.

Stillbirths with increasing gestational age.

The background for the new induction paradigm in Denmark is illustrated for the period 2000-2008 in **Figure 2**. With increasing gestational age the risk of fetal death rises, peaking after 43 weeks of gestation with more than 14 deaths per 1,000 ongoing pregnancies, a risk more than ten times higher than in the weeks before term.

During the period 2009-2012, the stillborn rates were reduced 21-39%, and from 41+3 stillbirths were eliminated (**Figure 2**).

Comment [KA1]: Jeg er lidt usikker på hvad du mener med sidste halvdel af sætningen?

The crude rates of fetal deaths with increasing gestational age were reduced by 30-66% when adjusting for age, year, parity, plurality, and smoking (**Figure 3**). Adjustment for body mass index did not change the estimates significantly.

Stillbirths by time.

The rate of stillborn infants from 37 weeks of gestation decreased from 0.70 (95% confidence interval 0.64-0.77) per 1,000 ongoing pregnancies (prospective stillbirth rate) during the period 2000-2002 to 0.41 (0.35-0.48) during the period 2011-2012 (**Figure 4**). The corresponding rate of stillborn infants from 40 weeks fell from 1.8 (1.6-2.1) during the period 2000-2002 to 0.74 (0.56-0.98) during 2011-2012, a reduction of 60 % ($p<0.001$). The fall was steepest from 2009-10 to 2011-12.

The rate of stillborn infants per 1,000 new-born after 37 weeks demonstrated a similar decrease from 2.4 (2.2-2.6) during the period 2000-2002 to 1.4 (1.2-1.6) during 2011-2012, a fall of 43% (**Figure 4**). Among children born from 40 weeks, the corresponding stillborn rates fell from 2.1 (1.9-2.4) per 1,000 new-born to 0.77 (0.58-1.0) or by 63% ($p<0.001$) (**Figure 4**).

Regression analysis

Several conditions, which may have influenced the risk of fetal death, changed during the study period (**Table 2**), The mean age of delivering women after 37 weeks of gestation increased from 30.1 years in 2000-2002 to 30.9 years in 2011-12, and the proportion of delivering women ≥40 years increased from 2.0 % to 3.5 % ($p<0.001$).

The mean body mass index increased from 24.1 kg/m^2 in 2003-2005 to 24.4 kg/m^2 during 2011-2012, and delivering women with a body mass index above 25 kg/m^2 increased from 32.0 % to 34.4 % through the same period ($p<0.001$).

While these changes are expected to increase the risk of fetal death, the proportion of pregnant smokers decreased from 20.5 % in 2000-2002 to 11.5 % in 2011-2012, almost a halving ($p<0.001$).

The proportion of primiparous increased slightly from 43.0 % to 44.5 % through the study period, while the proportion of multiple pregnancies after 37 weeks was almost stable; 2.4 % in 2000-2002, 2.6 % in 2006-2008, and 2.5 % in 2011-12 (**Table 2**). The proportion of multiple deliveries after 40 weeks of gestation from already low 0.12 % decreased to 0.04 %. Thereby, post term multiple deliveries almost disappeared through the study period.

In the fully adjusted model the following hazard ratios of fetal death were demonstrated: Smoking 1.4 (1.2-1.6), body mass index >25 kg/m^2; 1.5 (1.3-1.7), decreasing from 1.7 (1.4-2.0) during the period 2004-2008 to 1.3 (1.0-1.6) in 2009-2012. Primiparous had a relative risk of stillbirth of 1.2 (1.1-1.3), and multiple pregnancy of 51.5 (44.4-59.6).

With adjustment for gestational age at delivery, the decline in stillbirths was reduced from -41.5 % to -35.5 % suggesting that the general earlier induction in it self accounted for about 15 % of the reduction. Further adjustment for smoking, age at delivery, and parity increased the fall from -35.5 % to -37.6 %, because the decrease in smoking counterbalanced the influence of the slightly increasing age and proportion of primiparous by time. By additional adjustment for plurality, the relative risk of stillbirth by time was reduced from -37.6 % to -31.4 %, suggesting that the changes in the management of twin pregnancies accounted for approximately 16 % of the decrease.

In the sub-analysis covering the period 2004-2012, during which information about body mass index was available, the decreasing risk of stillbirth among women with high body mass index by time implied a further non significant four per cent reduction in overall stillbirth rates by time.

The rest of the reduction in stillbirths is thus apparently due to the differential induction practice, where women with high-risk pregnancies are induced more proactively (earlier) than low-risk pregnancies,

The risk of fetal death in the week after term was reduced by 33-38 % ($p<0.01$), in the week after 41 weeks by 30-33 % ($p<0.01$), and after 42 weeks by 30-33 % ($p<0.05$)(**Figure 2**). Thus, the new

induction paradigm firstly moved deliveries from late weeks with a high risk of stillbirth to earlier weeks with a lower risk. Secondly, in particular moved high-risk pregnancies to earlier induction, but thirdly, also reduced the risk of fetal death in each post term week.

The decrease in the rate of stillbirth corresponds to a reduction in absolute numbers of stillborn infants after 37 weeks from 136 stillbirths per year to now about 75 per year, a reduction of approximately 60 per year ($p<0.001$), corresponding to one saved stillborn infant per 1,000 new-born.

During gestational weeks 37 to 40, the annual number of stillbirths fell from around 80 per year during the period 2000-2008 to 50 per year during 2009-2012. This reduction coincided with an increase in second trimester induced abortions on fetal indication from annually 292 during the period 2000-2008 to 410 per year during the period 2009-2012, an increase of 118 induced abortions per year.[11]

The risk of dying during the first week of life was reduced among children born after 37 weeks from 1.7 (1.4-2.0) per 1,000 new-born in 2000 to 0.8 (0.6-1.0) per 1,000 live-born in 2012.[12]

The Caesarean section rate in Denmark has after a steady increase over more than 40 years been stable throughout the last ten years at about 20 % of all deliveries, even with a slight reduction from 20.4 % in 2009 to 19.8 % in 2012 ($p<0.01$).[12]

The sensitivity analysis excluding women with unknown gestational age did not change anything after 37 weeks, but decreased slightly the risk of fetal deaths before 37 weeks (data not shown).

Sensitivity analyses restricted to singletons enhanced the fall in stillbirth rates by time. For all deliveries, the adjusted fall by time was -31% and for singletons -43%,

Discussion

We report a decrease in risk of fetal death after 37 weeks to 0.14 % on a national level, which is the lowest risk ever reported in Denmark. Nor have any similar rate to our knowledge been published elsewhere.

Ever since the 1990´s, there has been an ongoing discussion of induction of labour versus expectant management of women after term.[7] Through the last ten years, a gradually more proactive induction practice has gained ground over expectant management in several countries, including Denmark. The decision to make a Danish guideline in 2009 was stimulated by the NICE-guideline on induction of labour published in 2008 and the ACOG practice bulletin from 2009.[13, 14]

Before 2009, many women were still not offered induction until after they passed 42 weeks of gestation. From 2009, the recommended induction regimen prevented many pregnancies from reaching post term gestational weeks of a high risk of fetal death. This change reduced the number of fetal deaths after term, but should in principle not influence the rate of deaths per 1,000 ongoing pregnancies in a certain post term week. The gestational age specific stillbirth rate after 41 weeks was, however, also reduced. This reduction could not be explained by the general earlier induction practice, but is according to our analyses a result of an even more proactive induction practice in women at an increased risk of stillbirth, such as women with body mass index >30, and women over 40 years. An increased fetal monitoring after term by time may also have influenced the decrease.

Through the last ten years, the majority of Danish units have used misoprostol for induction of labour, either applied vaginally or orally. It has been questioned, if induction by misoprostol could increase the risk of uterine hyperstimulation, asphyxia, and ultimately of neonatal death. In theory, an initiative to reduce the risk of fetal death could lead to neonatal complications and neonatal death. It is therefore important that the reduction in stillbirths was not associated with an increase in early neonatal deaths. On the contrary, the early neonatal deaths were halved during the study period, a circumstance, which undoubtedly was also influenced by an improved neonatal care through the study period.

It has been discussed, if induction of labour causes more Caesarean sections.[15] Some have argued that expectant management of labour increases the Caesarean section rate due to the risks associated with prolonged pregnancy.[16] The slight reduction in Caesarean sections with the new induction paradigm demonstrates that a proactive induction practice not necessarily increases the frequency of surgical interventions.

The offer of first trimester combined screening (double test and nuchal translucency scan), has in Denmark been widened to all pregnant women from year 2005-2006.[17] Before then, only women at 35 years or older were routinely offered first trimester screening. With the new routine, a majority of chromosomal abnormalities are detected and pregnancy most often terminated, accounting for the increase of approximately 118 annual second trimester induced abortions. Before the general screening was fully implemented, some fetuses with undetected abnormalities died later in pregnancy. From 20 weeks of gestation until term, 13 % of trisomy 21, 75 % of trisomy 18, and 35 % of trisomy 13 experience fetal death [18], a majority of these before 37 gestational weeks. This circumstance may explain a reduction of about 15 fetal deaths per year, but only about seven after 37 weeks corresponding to 12 % (7/60) of the observed reduction in stillborn infants.

During the study period, the quality of screening for structural abnormalities (offered in general throughout the period) and Doppler ultrasound both improved the monitoring of fetuses in utero,

making it easier to detect threatened fetuses and to intervene to avoid further complications including fetal death. However, these circumstances are probably of minor importance for the decrease in stillbirths, as other countries with the same technical improvement have not observed a similar decrease in stillbirths. In Sweden, the proportion of deliveries after 42 weeks was 7.5 % in year 2000 and 6.5 % in 2011. During the same period, the stillbirth rate after 37 gestational weeks was stable between 1.6 and 1.9 per 1,000 new-born.[19] In Norway, 4.8 % of deliveries occurred at 42 weeks or later, and the stillbirth rate after 37 weeks was 1.47 per 1,000 new-born [20], figures close to Danish figures in 2010.

The earlier induction of multiple pregnancies explained about 15 % of the reduction in stillbirths. The selective early induction of high-risk pregnancies such as pregnancies in women with high body mass index, women above 40 years, and women with multiple pregnancies explains, why the impact of these risk factors decreased by time. Worldwide, maternal age at delivery has increased over the last five decades, and Denmark is no exception.[21] As high maternal age is associated with stillbirth, this increase should have increased the stillbirth rates slightly by time.[5, 22, 23]

Determining the optimal time to deliver necessarily involves balancing induction risks and benefits. According to earlier studies, the risks of post-term deliveries include an increased perinatal mortality, meconium aspiration, macrosomnia, low umbilical cord artery pH, and low Apgar score at five minutes.[24] Inducing labour too early, on the other hand, may cause iatrogenic prematurity and respiratory complications.[25, 26]

When considering the overall risk of either fetal or infant death, previous studies have suggested the risk of expectant management to be lower than the risk of delivery until about 38 weeks. Passing 38 weeks, the risk of expectant management was found to be higher than the risk of delivery, and the risk difference increases substantially after 40 and 41 weeks of gestation, favouring delivery over expectant management.[27]

Among the strengths of this study are the almost complete coverage of deliveries [28], and access to data making an evaluation of circumstances, which might have influenced the stillbirth rates possible. The main limitation is the observational design, and the difficulty to account effectively for all potential confounders. The significant reduction in fetal deaths seen in Denmark has not been observed in Sweden, where the handling of post term pregnancies has undergone less change.[19]

In conclusion, the striking decrease in risk of late fetal deaths through recent years is likely primarily to be due to the earlier and increased induction rate. The additional health costs to save these lives were low, and the reduction was obtained without an increase in surgical interventions.

An important issue, which needs further studies, is the morbidity in new-born through the same study period, to confirm that the reduced mortality is not at the expense of an increased morbidity in new-born.

Denmark already had a low stillbirth rate a decade ago.[1] With the further reduction in stillbirths, we may now have achieved the lowest stillbirth rate ever reported. We see no reason why a similar more proactive induction paradigm could not be implemented in other countries, with a succeeding further reduction in late stillbirths worldwide.

Acknowledgements

The study was approved by the Danish Data Protection Agency (J.no: 2013-41-2063) and the National Board of Health (J.no, FSEID 00000579). Ethical approval is not requested for registry based studies in Denmark

Contributions

Hedegaard, Hedegaard and Lidegaard planned the study, Skovlund retrieved data from the National Birth Registry and National Health Registry. Mørch, Lidegaard, and Skovlund analysed the data. Hedegaard and Lidegaard wrote the manuscript. All authors revised the manuscript and accepted the final version. Morten Hedegaard is the guarantor.

Funding

The study was supported by a scholar grant from Rigshospitalet. Other expenses were covered by Department of Gynaecology, Rigshospitalet, University of Copenhagen.

Conflict of interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that Lidegaard within the last three years received honoraria for speeches in pharmacoepidemiological issues. Hedegaard, Hedegaard, Mørch and Skovlund did not declare any conflicts.

Data Sharing Statement

No additional data available

References

1. Cousens S, Blencowe H, Stanton C, et al. National, regional, and worldwide estimates of stillbirth rates in 2009 with trends since 1995: a systematic analysis. *Lancet* 2011; **377**: 1319-30. doi: 10.1016/S0140-6736(10)62310-0
2. The Stillbirth Collaborative Research Network Writing Group. Causes of death among stillbirths. *JAMA*. 2011; **306**:2459-68
3. Page JM, Snowden JM, Cheng YW, Doss AE, Rosenstein MG, Caughey AB. The risk of stillbirth and infant death by each additional week of expectant management stratified by maternal age. *Am J Obstet Gynecol* 2013; **209**: xx-xx. http://dx.doi.org/10.1016/j.ajog.2013.05.045.
4. Flenady V, Koopmans L, Middleton P, et al. Major risk factors for stillbirth in high-income countries: A systematic review and meta-analysis. Lancet 2011; 377: 1331-40.
5. Flenady V, Middleton P, Smith GC, et al. Stillbirths: The way forward in high-income countries. Lancet 2011; 377: 1703-17.
6. Gülmezoglu AM, Crowther CA, Middelton P, Heatley E. Induction of labour for improving birth outcomes at or beyond term (Review). *Cochrane Database* of Systematic Reviews 2012, Issue 6.
7. Hannah ME, Hannah WJ, Hellmann J, et al. Induction of labor as compared with serial antenatal monitoring in post-term pregnancy. A randomized controlled trial. *N Engl J Med* 1992; **326**: 1587-92.
8. Sandbjerg guidelines[internet]. Graviditas prolongata [Danish]. Available from: http://clin.au.dk/fileadmin/www.ki.au.dk/forskning/forskningsenheder/gyn_kologisk-obstetrisk_afd__y/logistics/sandbjerg_m__der/sandbjerg_2011/Graviditas_prolongata2011_1.pdf Visited March 13, 2014.
9. Yudkin PL, Wood L, Redman CW. Risk of unexplained stillbirth at different gestational ages. *Lancet* 1987; **1**: 1192-1194.
10. Smith GCS. Estimating risks of perinatal death. Am J Obstet Gynecol 2005; 192: 17-22.
11. Lidegaard Ø. Early pregnancy and abortions. Annual report for year 2012 [Danish]. National Quality Database for Early Pregnancy and Abortions. 2013. Online www.tigrab.dk. Visited March 13, 2014.
12. Danish birth registry online. http://www.ssi.dk/Sundhedsdataogit/Dataformidling/Sundhedsdata/Fodsler/Fodte%201973.aspx. Visited August 7, 2013.
13. Induction of Labour. NICE Guideline (CG70), July 2008. http://guidance.nice.org.uk/CG70. Visited March 13, 2014.
14. Clinical management guidelines for obstetrician-gynecologists. Induction of labor. ACOG Practice bulletin (107), August 2009. http://www.pqcnc.org/documents/sivbdoc/sivbeb/2ACOG2009PracticeBulletin107InductionofLabor.pdf Visited March 13, 2014.

15. Heffner LJ, Elkin E, Fretts RC. Impact of labor induction, gestational age, and maternal age on caesarean delivery rates. *Obstet Gynecol* 2003; **102**: 287-93.

16. Caughey AB. Perinatal outcomes related to induction of labor: a call for randomized trials. *Am J Obstet Gynecol* 2013; http://dx.doi.org/10.1016/j.ajog.2013.07.011. Visited February 24, 2014

17. Ekelund CK, Jørgensen FS, Petersen OB, Sundberg K, Tabor A. Impact of new national screening policy for Down's syndrome in Denmark: population based cohort study. BMJ 2008; 337: a2547.

18. Nicolaides KH. Nuchal translucency and other first-trimester sonographic markers of chromosomal abnormalities. Am J Obstet Gynecol 2004; 191: 45-67.

19. Socialstyrelsen. Pregnancies, deliveries and newborn. Medical Birth Registry 1973-2011. Assisted reproduction 1991-2010. [Swedish]. National Board of Health [Hälso- och Sjukvård] 2013. http://www.socialstyrelsen.se/publikationer2013/2013-2-7. Visited March 13, 2014.

20. Ebbing M, Klungsøyr K. Deliveries in Norway 2011. [Norweigian]. Folkehelseinstituttet 2013. http://www.fhi.no/dokumenter/2a92108f4f.pdf. Visited January 24, 2014.

21. Statistics of Denmark. http://www.statistikbanken.dk/statbank5a/default.asp?w=1024. Visited March 13, 2014.

22. Fretts RC, Schmittdiel J, McLean FH, Usher RH, Goldman MB. Increased maternal age and the risk of fetal death. *N Engl J Med* 1995; **333**: 953-7.

23. Reddy UM, Ko CW, Willinger M. Maternal age and the risk of stillbirth throughout pregnancy in the United States. *Am J Obstet Gynecol* 2006;**195**:764-70.

24. Kaimal AJ, Little SE, Odibo AO et al. Cost-effectiveness of elective induction of labor at 41 weeks in nulliparous women. *Am J Obstet Gynecol* 2011; **204**: 137. e1-9.

25. Clark SL, Frye DR, Meyers JA, Belfort MA, Dildy GA, Kofford S, et al. Reduction in elective delivery at <39 weeks of gestation: comparative effectiveness of 3 approaches to change and the impact on neonatal intensive care admission and stillbirth. Am J Obstet Gynecol 2003:449.e1-6. doi: 10.1016/j.ajog.2010.05.036. Epub 2010 Jul 8.

26. Agency for Healthcare Research and Quality [internet]. Evidence report number 176: Maternal and Neonatal Outcomes of Elective Induction of Labor. Available from: http://www.ahrq.gov/research/findings/evidence-based-reports/eil-evidence-report.pdf Visited March 13, 2014.

27. Rosenstein MG, Cheng YW, Snowden JM, Nicholson JM, Caughey AB. Risk of Stillbirth and Infant Death Stratified by Gestational Age. *Obstet Gynecol* 2012; **120**: 76-82. doi: 10.1097/AOG.0b013e31825bd286

28. Blenstrup LT, Knudsen LB. Danish registers on aspects of reproduction. *Scand J Public Health*. 2011; 39: Suppl 7: 79-82.

Legends for tables and figures

Table 1

Rates of born and stillborn in and from different gestational weeks and periods in Denmark 2000-2012.

Table 2

Characteristics of women giving birth at term and relative risk of stillbirth by time.

Figure 1

Proportion (%) of induced deliveries and of children born from 41 weeks and 42 weeks, respectively, in Denmark from 2000 through 2012, Number of children born: 832,935.

Figure 2

Fetal deaths per 1,000 ongoing pregnancies according to gestational age during the periods 2000-2008 and 2009-2012. Number of weeks: 3,406,615. Number of fetal deaths: 3,770. Lower part the same in a semi-logarithmic plot

Figure 3

Crude fetal deaths per 1,000 ongoing pregnancies according to gestational age during the period 2000-2012 and after adjustment for different confounders. Lower part the same in a semi-logarithmic plot.*

Figure 4

Fetal deaths per 1,000 ongoing pregnancies (upper), and per 1,000 new-born (lower) after 37 and 40 gestational weeks, respectively, in different sub-periods from year 2000 through 2012. 95% confidence limits indicated,

Supplementary online appendix (optional)

Table 1S

Number of born and stillborn in and from different gestational weeks and periods in Denmark 2000-2012.

Table 1

Rates of born and stillborn in and from different gestational weeks and periods in Denmark 2000-2012.*

	2000-02	2003-05	2006-08	2009-10	2011-12	2000-08	2009-12	2000-12
Number of born and stillborn infants								
Born (n)	197,222	194,774	196,023	127,165	117,751	588,019	244,916	832,935
Stillborn (n)	835	915	992	539	489	2,742	1,028	3,770
Stillbirths per 1,000 ongoing pregnancy weeks (prospective risk of stillbirth)								
<37	0.22	0.20	0.21	0.17	0.17	0.21	0.17	0.20
37+0-6	0.39	0.46	0.39	0.27	0.23	0.41	0.25	0.37
38+0-6	0.36	0.51	0.46	0.41	0.34	0.44	0.38	0.42
39+0-6	0.56	0.54	0.63	0.44	0.46	0.57	0.45	0.54
40+0-6	1.20	0.95	0.97	0.93	0.76	1.04	0.85	0.98
41+0-6	2.29	2.40	1.73	1.35	0.54	2.15	0.98	1.82
42+	15.55	6.09	11.16	6.60	7.83	11.60	6.96	10.86
Total	0.35	0.29	0.28	0.23	0.21	0.30	0.22	0.27
From 37 w	0.70	0.67	0.63	0.50	0.41	0.67	0.46	0.61
From 40 w	1.84	1.43	1.30	1.10	0.74	1.54	0.93	1.36
From 41 w	3.12	2.46	2.09	1.51	0.69	2.60	1.14	2.21
Stillborn per 1.000 new-born								
From 37 w	2.39	2.21	2.07	1.68	1.36	2.23	1.52	2.02
From 40 w	2.11	1.59	1.41	1.20	0.77	1.71	0.99	1.50
From 41 w	2.43	1.82	1.46	1.04	0.41	1.93	0.73	1.57
From 42 w	3.16	1.05	1.55	0.82	0.95	2.04	0.86	1.79

**) Absolute numbers given in supplementary appendix Table 1S.*

Table 2

Characteristics of women giving birth at term and relative risk of stillbirth by time.

	2000-02	2003-05	2006-08	2009-10	2011-12
Mean age	30.1	30.6	30.8	30.9	30.9
Mother ≥40 yrs	3,584	4,366	5,436	3,740	3,777
% ≥40 years	2.0	2.4	3.0	3.2	3.5
BMI recorded (n)	na	112,635	167,962	111,972	106,201
Mean BMI	na	24.1	24.2	24.3	24.4
BMI >25	na	36,076	54,903	37,616	36,528
% BMI >25	na	32.0	32.7	33.6	34.4
BMI >30	na	12,480	19,683	13,946	13,720
% BMI >30	na	11.1	11.7	12.5	12.9
BMI >35	na	4,032	6,813	4,880	4,689
% BMI >35	na	3.6	4.1	4.4	4.4
Smoker	37,540	30,782	25,656	14,891	12,527
% smokers	20.5	17.1	14.2	12.6	11.5
Multiple pregnancies	4,353	4,617	4,727	3,116	2,747
% multiples	2.4	2.6	2.6	2.6	2.5
Stillborn multiples	51	111	61	40	29
% stillborn multiples	1.2	2.4	1.3	1.3	1.1
Para 0	78,718	77,231	77,685	51,675	48,584
% Para 0	43.0	42.9	43.0	43.8	44.5

Regression analysis	**Hazard ratio[§] of stillborn (2000-2002 reference)**				
Crude[#]	1	0.95	0.89	0.72	0.59
Adjusted for GA[¤]	1	1.02	0.98	0.78	0.65
95% confidence intervals		0.89-1.17	0.85-1.12	0.66-0.92	0.53-0.78
Adjusted excpt, Plurality*[¤]	1	1.03	0.89	0.73	0.62
95% confidence intervals		0.90-1.18	0.78-1.03	0.61-0.86	0.52-0.75
Fully Adjusted[¤]**	1	1.07	0.96	0.78	0.69
95% confidence intervals		0.93-1.23	0.83-1.11	0.65-0.92	0.57-0.83

*) Adjusted only for age, smoking, and parity **) Additionally adjusted for plurality
[§]) Hazard ratios by cox regression. The crude estimates were calculated by logistic regression, and the risk estimates were odds ratios

Figure 1

Proportion (%) of induced deliveries and of children born from 41 weeks and 42 weeks, respectively, in Denmark from 2000 through 2012, Number of children born: 832,935.

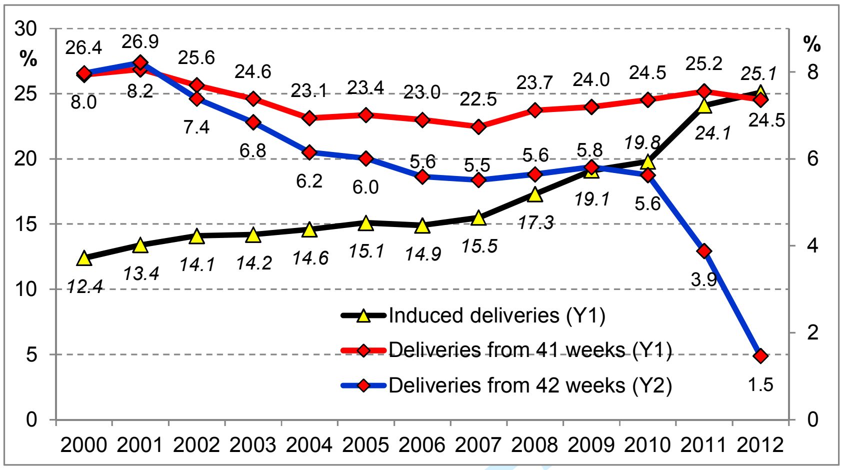


Figure 2

Fetal deaths per 1,000 ongoing pregnancies according to gestational age during the periods 2000-2008 and 2009-2012.

Number of weeks: 3,406,615, Number of fetal deaths: 3,770.

Lower part the same in a semi-logarithmic plot.

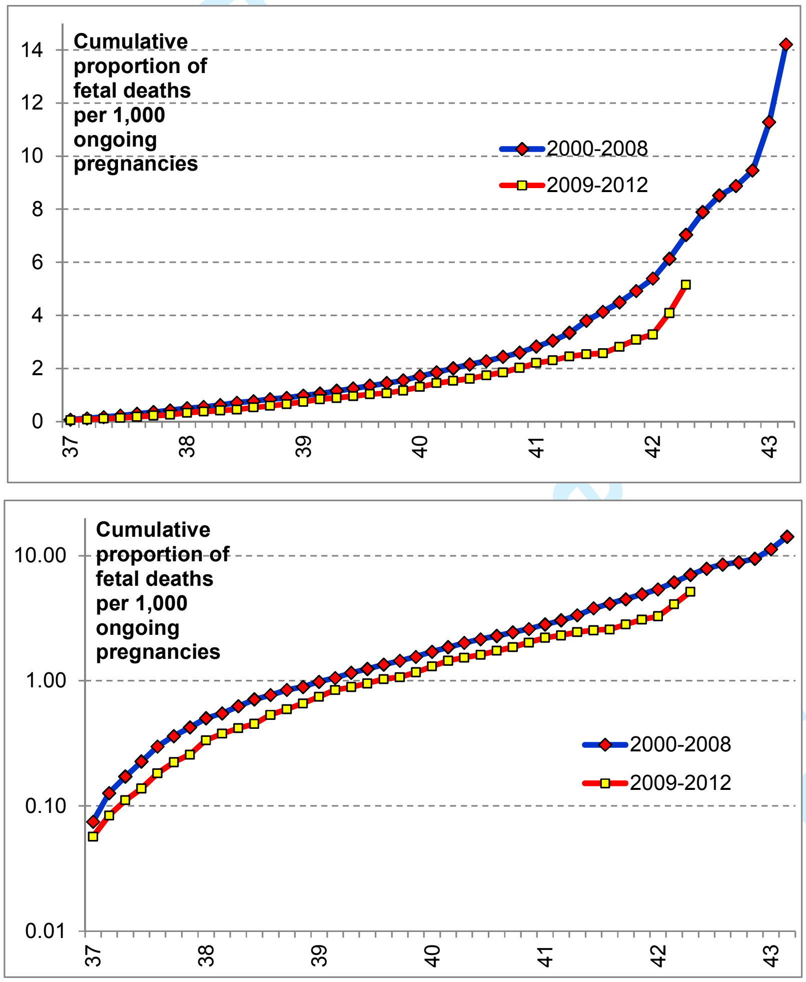
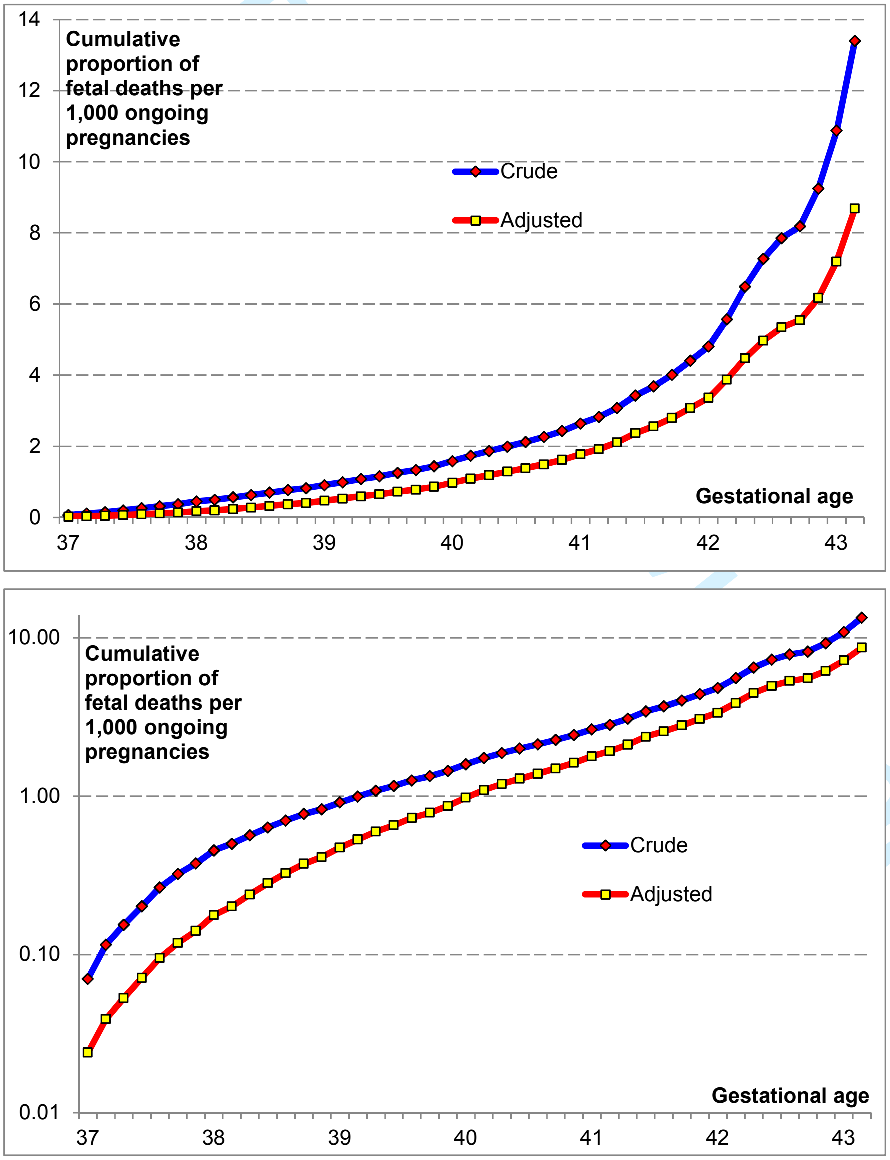


Figure 3

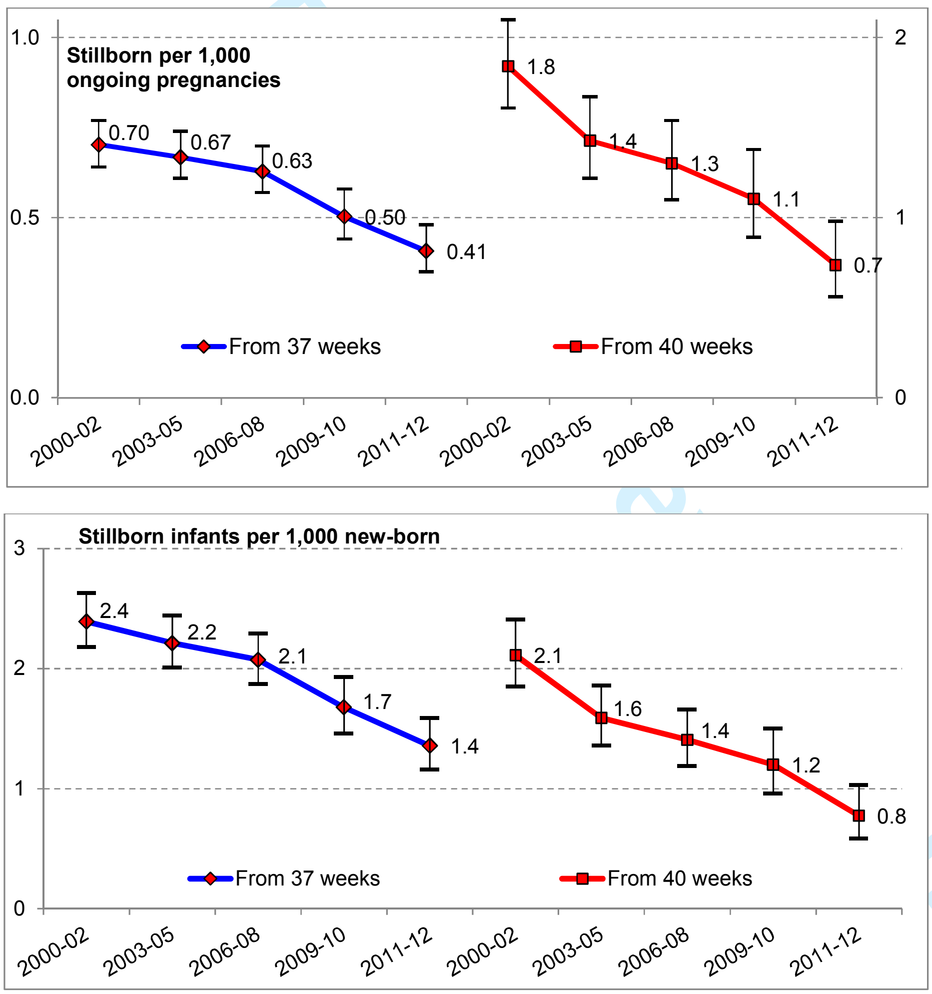
Crude fetal deaths per 1,000 ongoing pregnancies according to gestational age during the period 2000-2012 and after adjustment for different confounders. Number of weeks: 3,406,615. Number of fetal deaths: 3,770. Lower part the same in a semi-logarithmic plot*



*) Adjusted for age, calendar year, parity, plurality, and smoking

Figure 4

Fetal deaths per 1,000 ongoing pregnancies (upper), and per 1,000 new born (lower) after 37 and 40 gestational weeks, respectively, in different sub-periods from year 2000 through 2012. 95% confidence limits indicated.



Online supplement

Table 1S

Number of born and stillborn in and from different gestational weeks and periods in Denmark 2000-2012.

	2000-02	2003-05	2006-08	2009-10	2011-12	2000-08	2009-12	2000-12
New-born								
<37	14,127	14,806	15,171	9,212	8,693	44,104	17,905	62,009
37+0-6	10,964	12,129	11,533	7,066	6,369	34,626	13,435	48,061
38+0-6	24,807	27,976	28,521	17,757	16,121	81,304	33,878	115,182
39+0-6	42,212	42,303	42,711	27,282	24,523	127,226	51,805	179,031
40+0-6	53,193	51,410	52,874	35,005	32,777	157,477	67,782	225,259
41+0-6	36,415	33,813	34,267	23,570	26,106	104,495	49,676	154,171
42+	15,504	12,337	10,946	7,273	3,162	38,787	10,435	49,222
Total	197,222	194,774	196,023	127,165	117,751	588,019	244,916	832,935
37+	183,095	179,968	180,852	117,953	109,058	543,915	227,011	770,926
40+	105,112	97,560	98,087	65,848	62,045	300,759	127,893	428,652
41+	51,919	46,150	45,213	30,843	29,268	143,282	60,111	203,393
Number of stillborn infants								
<37	397	517	617	341	341	1,531	682	2,213
37+0-6	72	83	70	32	25	225	57	282
38+0-6	62	85	78	46	35	225	81	306
39+0-6	82	75	89	41	40	246	81	327
40+0-6	96	71	72	47	36	239	83	322
41+0-6	77	71	49	26	9	197	35	232
42+	49	13	17	6	3	79	9	88
Total	835	915	992	539	489	2,742	1,028	3,770
37+	438	398	375	198	148	1211	346	1557
40+	222	155	138	79	48	515	127	642
41+	126	84	66	32	12	276	44	320

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract: *Line 35*
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found: *Line 38-43*
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported: *Line 66-76*
Objectives	3	State specific objectives, including any prespecified hypotheses: *Line 73-76*
Methods		
Study design	4	Present key elements of study design early in the paper: *Page 3 line 79*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection: *Line 79-80*
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up: *Line 81-86*
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed: *This study was not matched*
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable: *Line 88-93*
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group: *Line 79-87*
Bias	9	Describe any efforts to address potential sources of bias: *Line 106-119*
Study size	10	Explain how the study size was arrived at: *Line 84*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why: *Line 88-119*
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding: *Line 106-119*
		(*b*) Describe any methods used to examine subgroups and interactions 116-119
		(*c*) Explain how missing data were addressed: *Line 94-98*
		(*d*) If applicable, explain how loss to follow-up was addressed: *Line 94-98*
		(*e*) Describe any sensitivity analyses: *Line 119*
Results		
Participants	13*	(a) Report numbers of individuals included in the study, completing follow-up, and analysed: *Line 94-98, 123-127*
		(b) Give reasons for non-participation at each stage: *Not relevant*
		(c) Consider use of a flow diagram: *Not relevant in this case*
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders: *Table 1*
		(b) Indicate number of participants with missing data for each variable of interest: *Line 94-98*
		(c) Summarise follow-up time (eg, average and total amount): *Not relevant*
Outcome data	15*	Report numbers of outcome events or summary measures over time: *Table 1, Table 2 and Table 1S, Line 133-152*

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included: *Fig. 2 and Fig. 3*
		(*b*) Report category boundaries when continuous variables were categorized: *Line Table 1*
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period: *Line 144-152, 191-193*
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses: *Line 206-207*
Discussion		
Key results	18	Summarise key results with reference to study objectives: *Line 211-2123*
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. *Line 280-283*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. *Line 252-261*
Generalisability	21	Discuss the generalisability (external validity) of the study results: *Line 239-242*
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based: *Line 299-306*

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

23.05.14

Adverse perinatal outcomes following an earlier post-term labour induction policy: a historical cohort study.

Ms. Mette HEDEGAARD[1], MS

Dr. Øjvind LIDEGAARD[1], DMSc

Ms. Charlotte W. SKOVLUND[1], M. Sc.

Ms. Lina S. MØRCH[1], Ph. D.

Dr. Morten HEDEGAARD[2], Ph. D.

1) *Department of Gynaecology, Rigshospitalet, Faculty of Health Science, University of Copenhagen, Denmark.*

2) *Department of Obstetrics, Rigshospitalet, Faculty of Health Science, University of Copenhagen, Denmark.*

Correspondence:

Professor Øjvind Lidegaard, Rigshospitalet,

Blegdamsvej 9, Copenhagen, Denmark.

Mail: Oejvind.Lidegaard@regionh.dk,

Telephone no. +45 35450950, Mobile no. +45 40632268

Word counts: *Abstract: 258 words*

Text: 3,113 words (excl. abstract, ref., tables, figures)

Short title*: Perinatal outcomes with labour induction at 41+3-5 weeks (57 characters).*

Abstract

Objective. To assess the changes in adverse perinatal outcomes in children born from 37 weeks' gestation after implementing an earlier (41+3-5) post-term labour induction practice.

Design. Register-based cohort study.

Setting. Denmark, 2000-12.

Population. Newborns from 37 weeks' gestation.

Methods. Hazard ratios (HRs) of adverse perinatal outcomes were estimated using a Cox regression analysis with gestational age as the underlying time, and adjusted for maternal age, parity, plurality, smoking, and body mass index.

Outcome measures. Adverse perinatal outcomes.

Results. 770,926 infants were included in total. The use of labour induction increased from 9.7% in 2000-02 to 22.5% in 2011-12. From 2003-05 to 2011-12, the risk of umbilical cord pH <7.0 decreased by 23% (HR 0.77, 95% confidence interval (CI) 0.67-0.89), and the adjusted risk of Apgar score <7 at five minutes was stable. The risk of admission to neonatal intensive care units increased by 56% (HR 1.56, 95% CI 1.47-1.66), whereas the risk of neonatal deaths decreased by 44% (HR 0.56, 95% CI 0.45-0.70). The risk of cerebral palsy was reduced by 26% (HR 0.74, 95% CI 0.60-0.90) from 2000-02 to 2009-10. The proportion of infants born with fetal weight ≥4500 grams decreased by one-third (HR 0.68, 95% CI 0.65-0.71). However, the risk of shoulder dystocia increased by 32% (HR 1.32, 95% CI 1.21-1.44), and the risk of peripheral nerve injuries was reduced by 43% (HR 0.57, 95% CI 0.45-0.73).

Conclusion. The results suggest an overall improvement in perinatal outcomes as a result of a more proactive approach to post-term labour induction.

Keywords. Asphyxia, birth induction, misoprostol, perinatal outcome

Introduction

In 2008, the National Institute for Health and Clinical Excellence published a guideline on post-term labour induction, stating that uncomplicated pregnancies should be induced in weeks 41-42; this guideline was followed by a similar practice bulletin issued by the American Congress of Obstetricians and Gynaecologists in 2009.[1,2] The same year, the national Danish guidelines were changed accordingly to recommend induction at week 41+3-5 for low-risk pregnant women and even earlier for high-risk pregnant women (with a body mass index >30, age ≥40 years or certain medical conditions) even earlier.[3] The goal was to ensure delivery before 42 weeks.[4] In Denmark, no uncomplicated pregnancies are induced before gestational week 41+3-5, unless there is a clear medical indication for labour induction. This guideline on prolonged pregnancy led to an increase in post-term labour induction, which was followed by a significant reduction in the number of stillborn infants at term with no increase in operative intervention.[5] Studies have also suggested that maternal morbidity may be improved by a more proactive post-term induction practice.[6] However, recent meta-analyses found only a few studies that addressed the impact of different induction practices on neonatal mortality and morbidity;[4, 7, 8] thus, further studies are required.[9]

When examining rare outcomes, such as neonatal death, it is often difficult to achieve statistically significant correlations in clinical trials.[10] Under such circumstances, large observational studies may provide useful information.[11, 12]

This study aimed to investigate the national changes in different adverse perinatal outcomes over a period, during which a more proactive approach to post-term labour induction was implemented.

Methods

Design and setting

This historical cohort study included all newborns in Denmark delivered from January 1, 2000 to December 31, 2012. To reduce the random year-to-year variation, the 13-year study period was subdivided into five intervals of three, three, three, two and two years.

Data were retrieved in October 2013 from the Danish National Health Register and the Medical Birth Register, which contains information on all deliveries in Denmark since 1973.[13]

Approval was obtained from the Danish Data Protection Agency (J.no: 2013-41-2063) and the National Board of Health (J.no. FSEID 00000579). According to the Danish Research Ethics Committee Law (§ 8, section 3), ethical approval is not required for register-based studies in Denmark.

Participants

Infants born from 37 gestational weeks were included, irrespective of maternal parity or plurality, because Cox regression analyses demonstrated only limited confounding due to these factors. As the focus of this study was post-term labour induction, it seemed logical to set the limit for inclusion at >40 gestational weeks. After careful consideration, however, the limit was set at >37 gestational weeks to avoid excluding the outcomes of high-risk pregnancies, which are often induced before 40 weeks. Gestational age was generally calculated based on first-trimester ultrasound examinations. For the few women who did not attend this routine offer to all pregnant women in Denmark, the date of their last menstrual period was used.

Based on diagnostic and surgical codes, the study population was subdivided according to the intentional mode of delivery as follows: a) an induction of labour cohort, b) a planned spontaneous vaginal delivery cohort, and c) an elective Caesarean section cohort. The specific codes identifying the cohorts are listed in the supplementary appendix (Table 1S).

Outcomes

Eight outcomes were defined based on different criteria or clusters of diagnosis codes from the International Classification of Diseases (ICD 10). The outcomes were categorised into three groups (Appendix, Table 2S): asphyxia indicators (umbilical cord pH <7.0 and Apgar score <7 at five minutes), potential manifestations of asphyxia (admission to neonatal intensive care units within 28 days after birth, neonatal death, and cerebral palsy), and prevention of macrosomia (fetal weight ≥4500 grams, shoulder dystocia, and peripheral nerve injury). A neonate could potentially have more than one outcome.

Prior to 2003, umbilical cord pH was not routinely recorded in the register. In this study we intended to use arterial pH, but in the few cases where this information was not available, either venous or unspecified pH was used. All pH values not in the range of 6.6-7.9 were considered invalid, and were consequently excluded from the analysis.

There is often a long latency from birth until cerebral palsy is diagnosed. Therefore, a follow-up time of three years was used, and the most recent years, 2011 and 2012, were excluded from the analysis of this specific outcome.

In accordance with the World Health Organisation (WHO), neonatal death was defined as death within 28 days after birth.[14]

Shoulder dystocia and nerve injury were only assessed in vaginal deliveries.

Potential confounders

To describe the timing of potential confounders, we gathered information on maternal age, parity, plurality, smoking, and body mass index. The definitions are presented in the appendix (Table 3S).

Calculations

To calculate the crude and adjusted hazard ratios (HRs), Cox regression analyses were performed with gestational age as the underlying time scale. The period from 2000-02 was used as the reference period. Adjustments were made for maternal age, parity, plurality, and smoking. Because body mass index was not registered until 2004, we assessed the influence of body mass index in a sub-analysis that was restricted to the years 2004-12. Because the results changed by less than 5%, body mass index was not included in the main analyses.

Incidence rates in the total population and within the three delivery cohorts were calculated. A chi-square test was used to analyse differences in incidence rates, with a p-value of less than 0.05 considered significant.

Results

During the 13-year study period, a total of 832,935 children were born in Denmark. Of these, 770,926 children (92.6%) were born after 37 gestational weeks, constituting the study group. Within the group, 104,107 (13.5%) children were born after labour induction, 602,219 (78.1%) were born after planned vaginal delivery, and 64,600 (8.4%) were born after elective Caesarean section (Table 1).

The use of medical induction of labour within our study group (>37 weeks) increased from 9.1% in 2000 to 26.0% in 2012 (p<0.001) (Figure 1). A steep increase was observed, especially in 2010-11. Correspondingly, the percentage of pregnancies that continued beyond 42 gestational weeks decreased from 8.0% in 2000 to 1.5% in 2012 (p<0.001) (Figure 1).

The percentage of women with planned spontaneous vaginal delivery decreased linearly from 84.5% in 2000-02 to 67.7% in 2011-12 (p<0.001), whereas the elective Caesarean section rate increased from 5.9% to 9.8% (p<0.001) (Table 1).

Asphyxia indicators

The adjusted risk of umbilical cord pH <7.0 decreased by 23% (HR 0.77, 95% confidence interval (CI) 0.67-0.89) when comparing 2003-04 with 2011-12 (Table 1 and Figure 2).

Subdivision into the three delivery cohorts revealed that the frequency of low pH decreased significantly in all cohorts and was similar in the induced and spontaneous vaginal delivery cohorts in 2011-12 at 4.9‰ (Table 2).

Except from the changes in the crude incidence rate of Apgar scores <7 at five minutes (<7/5) within the total population, all other results indicated that the rate of Apgar scores <7 was stable over time and across all study groups (Table 1, Figure 2, and Table 2).

Potential manifestations of asphyxia

Throughout the study period, the adjusted risk of admission to a neonatal intensive care unit increased by 56% (HR 1.56, 95% CI 1.47-1.66) (Table 1, and Figure 2). In the three cohorts, admission rates were stable in the induced labour cohort, whereas the incidence rates of children born after planned vaginal delivery and elective Caesarean section increased significantly (Table 2).

The adjusted risk of neonatal death was almost halved (HR 0.56, 95% CI 0.45-0.70) (Table 1 and Figure 2). Although significant decreases were observed in all three cohorts, the steepest decrease in risk was observed among children born after elective Caesarean section, from 2.7‰ in 2000-02 to 1.0‰ in 2011-12 (p<0.001) (Table 2).

The adjusted risk of cerebral palsy decreased by 26% (HR 0.74, 95% CI 0.60-0-90) from 2000-02 to 2009-10 (Table 1 and Figure 2). Only the planned vaginal delivery group experienced a significant reduction in incidence rate from 1.6‰ in 2000-02 to 1.1‰ in 2009-10 (p=0.003) (Table 2).

Prevention of macrosomia

Throughout the study period, the adjusted risk of birth weight ≥4500 grams decreased by one-third (HR 0.68, 95% CI 0.65-0.71), from 4.2% in 2000-02 to 2.8% in 2011-12 (p<0.001) (Table 1, Table 2 and Figure 3).

Despite the presence of fewer children with macrosomia, the risk of shoulder dystocia increased by 32% (HR 1.32, 95 % CI 1.21-1.44) during the same period (Table 1 and Figure

3). In contrast, the adjusted risk of peripheral nerve injury decreased by 43% overall (HR 0.57, 95% CI 0.45-0.73), and decreases were observed in both vaginal delivery cohorts (Table 1 and Figure 3).

Time trends in potential confounders

Mean maternal age increased linearly from 30.1 years in 2000-02 to 30.9 years in 2010-11 (Appendix, Table 4S) but has stagnated since then. The prevalence of pregnant women >40 years of age increased considerably from 2.0% in 2000-02 to 3.5% in 2011-12 (p<0.001) (Appendix, Table 4S).

The prevalence of smokers in the study population was almost halved from 21.1% to 11.6% (p<0.001) (Appendix, Table 4S). However, Cox regression analyses with and without adjustments for smoking demonstrated, that this factor did not explain the reported decreases in perinatal outcomes.

Body mass index was relatively constant, with a mean of 24.3 kg/m^2 (Appendix, Table 4S). However, the prevalence of severely obese pregnant women (body mass index >35 kg/m^2) increased from 3.6% in 2003-05 to 4.4% in 2011-12 (p<0.001) (Appendix, Table 4S).

Although statistically significant, the incidence rate of multiple pregnancies changed only minimally, ranging from 2.4% to 2.6% (p<0.001) (Appendix, Table 4S). The proportion of nulliparous women increased slightly from 43.0% in 2000-03 to 44.5% in 2011-12 (p<0.001) (Appendix, Table 4S).

Discussion

Main findings

More than one quarter of Danish women who are pregnant beyond 37 weeks now experience induced labour, and our recent study demonstrated a simultaneous reduction in stillbirths.[5]

The results of the present study demonstrate that the reduction in the number of stillborn infants was not at the expense of increased perinatal morbidity or neonatal mortality. On the contrary, we detected significant reductions in newborn asphyxia, neonatal mortality, newborn macrosomia, and peripheral nerve injuries. The incidence rate of admission to neonatal intensive care units increased, but only in neonates born after planned vaginal delivery or elective Caesarean section and not in neonates born after labour induction.

Consistent with the decrease in asphyxia, the incidence rate of cerebral palsy decreased, although this reduction was only statistically significant in the planned vaginal delivery cohort.

Strengths and limitations

The unique personal identity number that every individual in the Nordic countries carries is the cornerstone of the Nordic medical registers. The Nordic registry's tradition of gathering data for decades offers unique possibilities for research that are difficult to find anywhere else in the world. [13] These data enable researchers to include a broad and unselected sample of individuals, to achieve high external validity, which is one of the strengths of this study. However, one of the limitations of register-based studies such as ours is their observational and retrospective design, which makes it difficult to effectively account for all confounders. Moreover, it is difficult to ensure that the data reporting is constant throughout the study period.

Interpretation

Before interpreting the results, it is important to remember that the reason for labour induction often involves some type of pregnancy complication and is not necessarily limited to post-term pregnancy. Secondly, it is essential to keep in mind that, due to more proactive induction practices, the induced group has become gradually less burdened by pathological pregnancies, as more women are now induced with prolonged pregnancy as the only reason for labour induction. The size of the planned vaginal delivery group has consequently been reduced, and includes less overborne and fewer high-risk deliveries. To summarise, overborne pregnant women are generally transferred from the planned vaginal delivery group, where they constitute a high-risk group, to the labour induction group, where they constitute a low-risk group compared to the rest of the women in the induction group. Hypothetically, if the decrease in adverse perinatal outcomes in the planned vaginal delivery group were associated with an increase in adverse outcomes in the induced delivery group, then an earlier induction practice would be questionable. However, simultaneous reductions in adverse perinatal outcomes in both the labour induction group and the vaginal delivery group would support a more proactive induction practice.

The stable risk of Apgar scores <7 at 5 minutes corresponds well with the findings of earlier studies,[4, 15, 16] including a thorough Cochrane review from 2012, which suggested no increase in newborn asphyxia with an earlier birth induction practice.[8] Although the decrease in asphyxia may have been reflected in fewer Apgar scores <7 at 5 minutes, this outcome was also influenced by a range of other factors, such as drug use, trauma, congenital abnormalities, infections, and hypervolemia, problems that have not been resolved by an earlier labour induction policy.[17] Because umbilical cord pH is more objective than Apgar score assessments,[18] cord pH is our preferred indicator of asphyxia in newborns.[19]

The increased risk of admission to neonatal intensive care units among children born after planned vaginal delivery is worrisome. A lowered threshold for transfer to such units most likely explains this increase, as a similar increase was observed in the elective Caesarean section group. Furthermore, the increase in referrals to neonatal units was associated with a substantial reduction in the risk of neonatal deaths. Earlier studies have encountered difficulties achieving sufficient statistical power to demonstrate any difference between children born after labour induction and those born according to expectant management,[4, 8] but recent studies suggest that labour induction significantly reduces perinatal mortality, which agrees with our results.[7, 20] However, the reduction in neonatal deaths was undoubtedly also influenced by improved neonatal care throughout the study period.[21, 22]

The reduction in cerebral palsy corroborates with the decrease in asphyxia. Through the last decade, our capacity to more precisely diagnose neurological pathologies has improved, especially with the increased use of magnetic resonance imaging.[23] In addition, the treatment regimen has also improved, resulting in enhanced neuroprotection.[24, 25] For example, since 2006, Danish neonatal units have initiated moderate hypothermia in cases of severe asphyxia,[26] which has improved the rate of survival without cerebral palsy or other disabilities by 40%.[24, 27]

The proportion of newborns ≥4500 grams has increased over the last several decades in Denmark.[28, 29] The proactive induction practice reversed this development. While this improvement was not the primary aim of the post-term labour induction guideline, it constitutes an additional positive side effect.

In theory, the reduction in vaginal deliveries of macrosomic children should reduce the risk of shoulder dystocia.[30-33] However, we detected increases in shoulder dystocia in both vaginal delivery cohorts. The total incidence rate of shoulder dystocia of 0.8% in 2006-08 is still low compared to a 2006 American study, which reported an incidence rate of shoulder dystocia of 1.6% in 2006.[34] Thus, shoulder dystocia may previously have been underreported, an explanation that is further supported by the reduction in peripheral nerve injuries. Recently, many obstetrical units in Denmark have focused on the management of shoulder dystocia, resulting in more thorough diagnosis and training of medical staff. This increased attention could explain why more cases of shoulder dystocia are being diagnosed, even though fewer children suffer from nerve injuries.

Children born after labour induction demonstrated the highest incidence rates of the majority of the adverse outcomes. If this effect were a consequence of the intervention itself, one would expect more complications following the increased use of labour induction. However, most adverse outcomes actually decreased in frequency with the increased induction rate. This disparity suggests that the higher incidence rates in the labour induction cohort are a consequence of selection bias, with high-risk pregnant women being induced more often than women awaiting spontaneous delivery.

However, the improved perinatal outcomes might also be influenced by other factors not related to labour induction. Awareness of the dangers related to smoking has grown,[35] explaining the significant reduction in pregnant smokers; this reduction contributed significantly to the decrease in stillbirths but only marginally contributed to reductions in the perinatal outcomes described in this study.

The increased maternal age, greater nulliparity, and higher body mass index indicated that more women were at risk according to time in our study population, which suggests that the crude results reported have underestimated the positive effect of labour induction.[36] However, adjusting for these factors only minimally changed the results (Table 1).

Conclusion

This study assessed the changes in different perinatal outcomes over a decade during which the management of post-term pregnancies changed considerably. The results suggest an overall improvement in perinatal outcomes in children born from 37 weeks' gestation. Although smoking, maternal age and parity changed significantly over our study period, adjusting for these factors did not change the estimates substantially.

Our results are in accordance with earlier studies, but reporting on the effects of an earlier post-term labour induction policy on a national level is unique; such effects have not been previously reported. Labour induction is a simple and inexpensive intervention that can be implemented in countries throughout the world, to improve perinatal outcomes.

Acknowledgements

Contribution to authorship

M.H, M.H and Ø.L planned the study. C.W.S and L.S.M retrieved data from The Danish National Health Register and The Medical Birth Register. L.S.M, C.W.S, M.H, M.H, and Ø.L analysed the data. M.H, M.H, and Ø.L. wrote the manuscript. All authors revised the manuscript and accepted the final version. Morten Hedegaard is the guarantor.

Funding

The study was supported by a scholar grant from Rigshospitalet. Other expenses were covered by Department of Gynaecology, Rigshospitalet, University of Copenhagen.

Disclosure of interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that Ø.L. within the last three years received honoraria for speeches in pharmacoepidemiological issues. M.H, M.H, C.W.S and L.S.M did not declare any conflicts.

References

1. American Congress of Obstetricians and Gynaecologists (ACOG). Clinical management guidelines for obstetrician-gynecologists: Induction of labour. Practice bulletin (107). http://amoripat.com/_assets/acog--practice_bulletin_107_2009.pdf. Published August, 2009. Accessed March 18, 2014.

2. National Institute for Health and Care Excellence (NICE). Induction of labour. Secondary Induction of labour. http://publications.nice.org.uk/induction-of-labour-cg70. Published in 2001. Updated July, 2008. Accessed March 18, 2014.

3. Danish Society for Obstetricians and Gynaecologists (DSOG). Guideline on prolonged pregnancy. http://www.dsog.dk/files/Graviditas%20prolongata2011_endelig.pdf Published in 2009. Updated in 2011. Accessed March 18, 2014.

4. Caughey AB, Sundaram V, Kaimal AJ, et al. Agency for Healthcare and Research Quality (AHRQ). Maternal and neonatal outcomes of elective induction of labour: Evidence report number 176. http://www.ahrq.gov/research/findings/evidence-based-reports/eil-evidence-report.pdf Published in 2009. Accessed April 2, 2014.

5. Hedegaard M, Lidegaard OE, Skovlund CW, Mørch LS, Hedegaard M. Reduction in stillbirths at term after new birth induction paradigm. Results of a national intervention. *BMJ open* submitted, May 2014.

6. Liu S, Joseph KS, Hutcheon JA, et al. Gestational age-specific severe maternal morbidity associated with labour induction. *Am J Obstet Gynecol* 2013;**209**:209 e1-8 doi: 10.1016/j.ajog.2013.05.033

7. Grunewald C, Hakansson S, Saltvedt S, et al. Significant effects on neonatal morbidity and mortality after regional change in management of post-term pregnancy. *Acta Obstet Gynecol Scand* 2011;**90**:26-32 doi: 10.1111/j.1600-0412.2010.01019.x

8. Gulmezoglu AM, Crowther CA, Middleton P, et al. Induction of labour for improving birth outcomes for women at or beyond term. *Cochrane Database Syst Rev* 2012;**6**:CD004945 doi: 10.1002/14651858.CD004945.pub3

9. Caughey AB. Perinatal outcomes related to induction of labour: A call for randomized trials. *Am J Obstet Gynecol* 2013;**209**:168-9 doi: 10.1016/j.ajog.2013.07.011

10. Wennerholm UB, Hagberg H, Brorsson B, et al. Induction of labour versus expectant management for post-date pregnancy: Is there sufficient evidence for a change in clinical practice? *Acta Obstet Gynecol Scand* 2009;**88**:6-17 doi: 10.1080/00016340802555948

11. Blenstrup LT, Knudsen LB. Danish registers on aspects of reproduction. *Scand J Public Health* 2011;**39**:79-82 doi: 10.1177/1403494811399957

12. Smith GC, Pell JP, Dobbie R. Birth order, gestational age, and risk of delivery related perinatal death in twins: Retrospective cohort study. *BMJ* 2002;**325**:1004

13. Langhoff-Roos J, Krebs L, Klungsoyr K, et al. The Nordic medical birth registers - a potential goldmine for clinical research. *Acta Obstet Gynecol Scand* 2013; doi: 10.1111/aogs.12302

14. WHO. Neonatal and perinatal mortality: Country, regional and global estimates. http://whqlibdoc.who.int/publications/2006/9241563206_eng.pdf Published 2006. Accessed March 18, 2014.

15. Nielsen PE, Howard BC, Hill CC, et al. Comparison of elective induction of labour with favorable bishop scores versus expectant management: A randomized clinical trial. *J Matern Fetal Neonatal Med* 2005;**18**:59-64 doi: 10.1080/14767050500139604

16. Heimstad R, Skogvoll E, Mattsson LA, et al. Induction of labour or serial antenatal fetal monitoring in postterm pregnancy: A randomized controlled trial. *Obstet Gynecol* 2007;**109**:609-17 doi: 10.1097/01.aog.0000255665.77009.94

17. Li F, Wu T, Lei X, et al. The Apgar score and infant mortality. *PLoS One* 2013;**8**:e69072 doi: 10.1371/journal.pone.0069072

18. Bharti B, Bharti S. A review of the Apgar score indicated that contextualization was required within the contemporary perinatal and neonatal care framework in different settings. *J Clin Epidemiol* 2005;**58**:121-9 doi: 10.1016/j.jclinepi.2004.04.012

19. Casey BM, McIntire DD, Leveno KJ. The continuing value of the Apgar score for the assessment of newborn infants. *N Engl J Med* 2001;**344**:467-71 doi: 10.1056/nejm200102153440701

20. Stock SJ, Ferguson E, Duffy A, et al. Outcomes of elective induction of labour compared with expectant management: Population based study. *BMJ* 2012;**344**:e2838

21. Singh BS, Clark RH, Powers RJ, et al. Meconium aspiration syndrome remains a significant problem in the nicu: Outcomes and treatment patterns in term neonates admitted for intensive care during a ten-year period. *J Perinatol* 2009;**29**:497-503 doi: 10.1038/jp.2008.241

22. Amin HJ, Aziz K, Halamek LP, et al. Simulation-based learning combined with debriefing: Trainers satisfaction with a new approach to training the trainers to teach neonatal resuscitation. *BMC Res Notes* 2013;**6**:251 doi: 10.1186/1756-0500-6-251

23. Ostergaard JR, Christensen T, Schoitz PO. [Magnetic resonance imaging in neuropediatrics]. *Ugeskr Laeger* 2005;**167**:382-5

24. Johnston MV, Fatemi A, Wilson MA, et al. Treatment advances in neonatal neuroprotection and neurointensive care. *Lancet Neurol* 2011;**10**:372-82 doi: 10.1016/s1474-4422(11)70016-3

25. Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: Multicentre randomised trial. *Lancet* 2005;**365**:663-70 doi: 10.1016/s0140-6736(05)17946-x

26. Lando A, Jonsbo F, Hansen BM, et al. [Induced hypothermia in infants born with hypoxic-ischaemic encephalopathy]. *Ugeskr Laeger* 2010;**172**:1433-7

27. Shankaran S. Outcomes of hypoxic-ischemic encephalopathy in neonates treated with hypothermia. *Clin Perinatol* 2014;**41**:149-59 doi: 10.1016/j.clp.2013.10.008

28. Meeuwisse G, Olausson PO. [increased birth weights in the nordic countries. A growing proportion of neonates weigh more than four kilos]. *Lakartidningen* 1998;**95**:5488-92

29. Orskou J, Kesmodel U, Henriksen TB, et al. An increasing proportion of infants weigh more than 4000 grams at birth. *Acta Obstet Gynecol Scand* 2001;**80**:931-6

30. Cheng YK, Lao TT, Sahota DS, et al. Use of birth weight threshold for macrosomia to identify fetuses at risk of shoulder dystocia among Chinese populations. *Int J Gynaecol Obstet* 2013;**120**:249-53 doi: 10.1016/j.ijgo.2012.10.019

31. Cheng YW, Sparks TN, Laros RK, Jr., et al. Impending macrosomia: Will induction of labour modify the risk of Caesarean delivery? *BJOG* 2012;**119**:402-9 doi: 10.1111/j.1471-0528.2011.03248.x

32. Mollberg M, Hagberg H, Bager B, et al. High birthweight and shoulder dystocia: The strongest risk factors for obstetrical brachial plexus palsy in a Swedish population-based study. *Acta Obstet Gynecol Scand* 2005;**84**:654-9 doi: 10.1111/j.0001-6349.2005.00632.x

33. Overland EA, Spydslaug A, Nielsen CS, et al. Risk of shoulder dystocia in second delivery: Does a history of shoulder dystocia matter? *Am J Obstet Gynecol* 2009;**200**:506 e1-6 doi: 10.1016/j.ajog.2008.12.038

34. Darney BG, Snowden JM, Cheng YW, et al. Elective induction of labour at term compared with expectant management: maternal and neonatal outcomes. *Obstet Gynecol 2013*;122:761-9

35. Wisborg K, Henriksen TB. [Pregnancy and tobacco. A status article focusing on Danish conditions]. *Ugeskr Laeger* 2003;**165**:4537-40

434 36. Timofeev J, Reddy UM, Huang CC, et al. Obstetric complications, neonatal morbidity, and indications for cesarean delivery by maternal age. *Obstet Gynecol* 2013;**122**:1184-95 doi: 10.1097/aog.0000000000000017

440 **Table 1**

441 *Absolute number of individuals in the three delivery cohorts and changes in overall hazard*
442 *ratios for adverse perinatal outcomes in children born from 37 weeks' gestation in Denmark*
443 *from 2000 to 2012.*

444 *Ratios adjusted for maternal age, smoking, parity and plurality.*

	2000-2002	2003-2005	2006-2008	2009-2010	2011-2012
Number of deliveries					
Induced delivery	17,673	20,060	23,066	18,788	24,520
Planned vaginal	15,4681	145,118	140,747	87,829	73,844
Elective Caesarean	10,741	14,790	17,039	11,336	10,694
Total	183,095	179,968	180,852	117,953	109,058
Umbilical cord pH <7.0					
Hazard ratio, crude	-	1.00	0.88	0.71*	0.76*
Hazard ratio, adjusted	-	1.00	0.89	0.72*	0.77*
Confidence intervals, adjusted	-	*Reference*	*0.77-1.02*	*0.62-0.84*	*0.67-0.89*
Apgar scores <7/5 min					
Hazard ratio, crude	1.00	0.97	0.95	0.95	1.09
Hazard ratio, adjusted	1.00	0.97	0.93	0.93	1.07
Confidence intervals, adjusted	*Reference*	*0.89-1.05*	*0.86-1.02*	*0.84-1.02*	*0.97-1.18*
Admission to neonatal intensive care units					
Hazard ratio, crude	1.00	1.10*	1.12*	1.47*	1.60*
Hazard ratio, adjusted	1.00	1.08*	1.11*	1.45*	1.56*
Confidence intervals, adjusted	*Reference*	*1.02-1.14*	*1.04-1.17*	*1.37-1.54*	*1.47-1.66*
Neonatal death					
Hazard ratio, crude	1.00	0.81*	0.71*	0.52*	0.54*
Hazard ratio, adjusted	1.00	0.82*	0.69*	0.52*	0.56*
Confidence intervals, adjusted	*Reference*	*0.70-0.96*	*0.59-0.82*	*0.42-0.64*	*0.45-0.70*
Cerebral palsy					
Hazard ratio, crude	1.00	0.81*	0.79*	0.74*	-
Hazard ratio, adjusted	1.00	0.81*	0.79*	0.74*	-
Confidence intervals, adjusted	*Reference*	*0.68-0.95*	*0.66-0-93*	*0.60-0.90*	-
Birth weight ≥4500g					
Hazard ratio, crude	1.00	0.95*	0.81*	0.75*	0.65*
Hazard ratio, adjusted	1.00	0.99	0.85*	0.76*	0.68*
Confidence intervals, adjusted	*Reference*	*0.96-1.03*	*0.82-0.88*	*0.73-0.80*	*0.65-0.71*
Shoulder dystocia					
Hazard ratio, crude	1.00	0.97	1.13*	1.34*	1.30*
Hazard ratio, adjusted	1.00	0.99	1.15*	1.36*	1.32*
Confidence intervals, adjusted	*Reference*	*0.91-1.07*	*1.07-1.25*	*1.25-1.48*	*1.21-1.44*
Nerve injury					
Hazard ratio, crude	1.00	0.77*	0.73*	0.83	0.59*
Hazard ratio, adjusted	1.00	0.77*	0.71*	0.80*	0.57*
Confidence intervals, adjusted	*Reference*	*0.64-0.93*	*0.58-0.86*	*0.65-0.99*	*0.45-0.73*

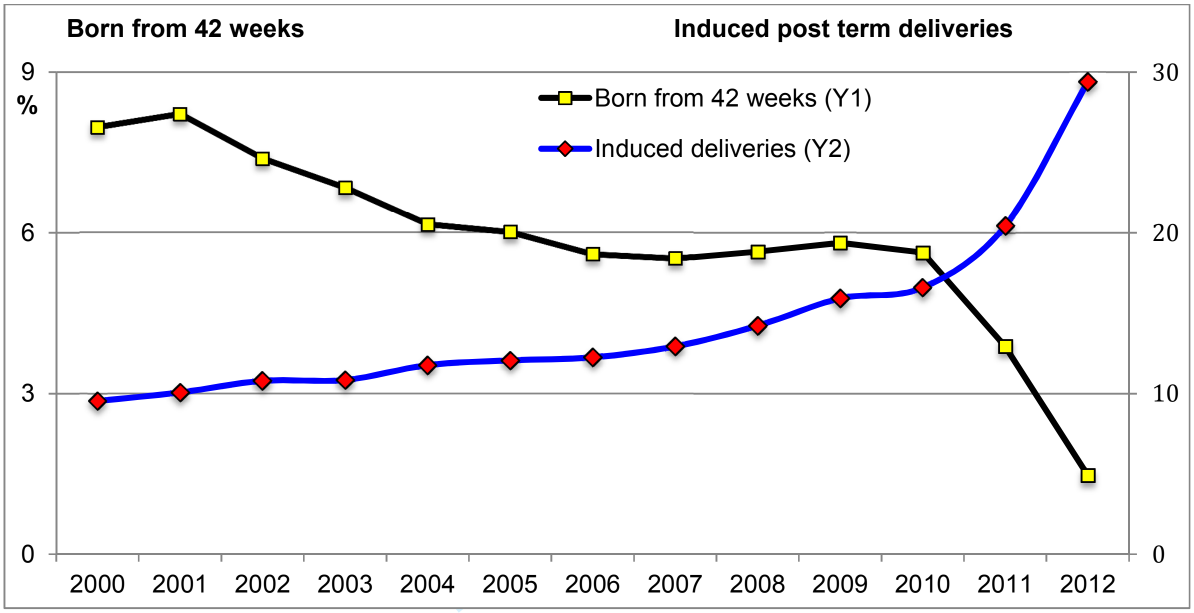
445

446

447

448 **Figure 1**

449 *Percentages of deliveries induced after 37 weeks and of children born after 42 weeks in*
450 *Denmark from 2000-2012.*

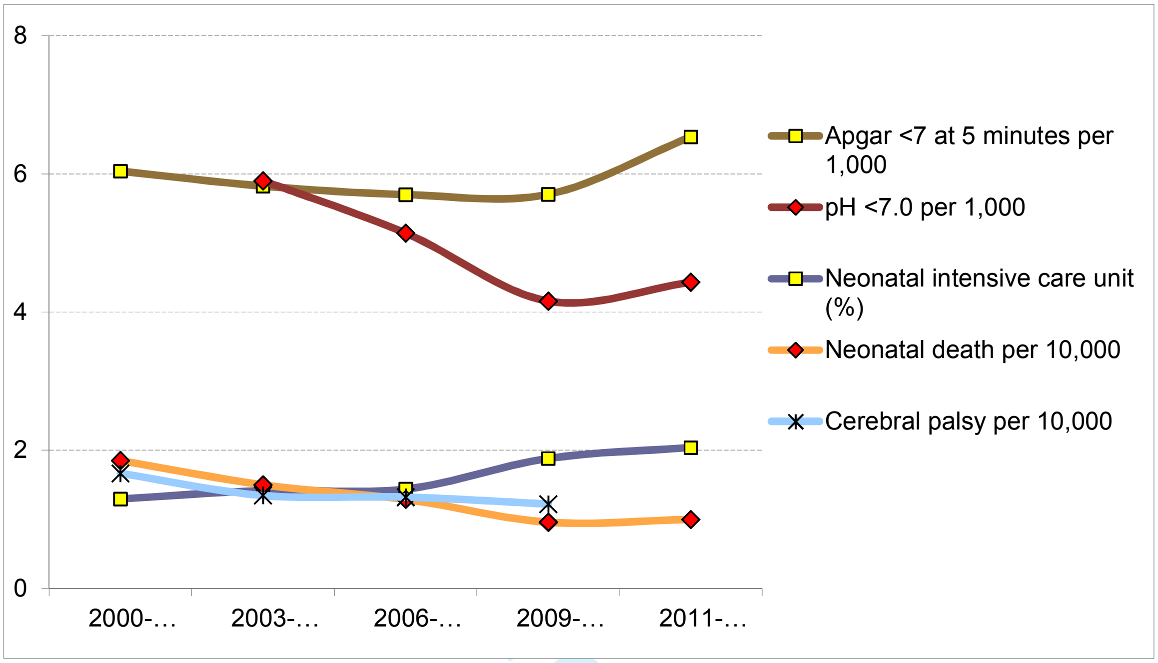


451
452
453
454
455
456
457
458
459
460
461
462
463
464
465

Figure 2

Incidence rates of asphyxia indicators and their potential manifestations from 37 weeks' gestation in Denmark from 2000 to 2012.

Incidence rates are expressed per 1,000 newborns, unless otherwise specified.*



**) All results are significant. However, the significance for Apgar scores <7/5 disappears after adjusting for potential confounders.*

Table 2

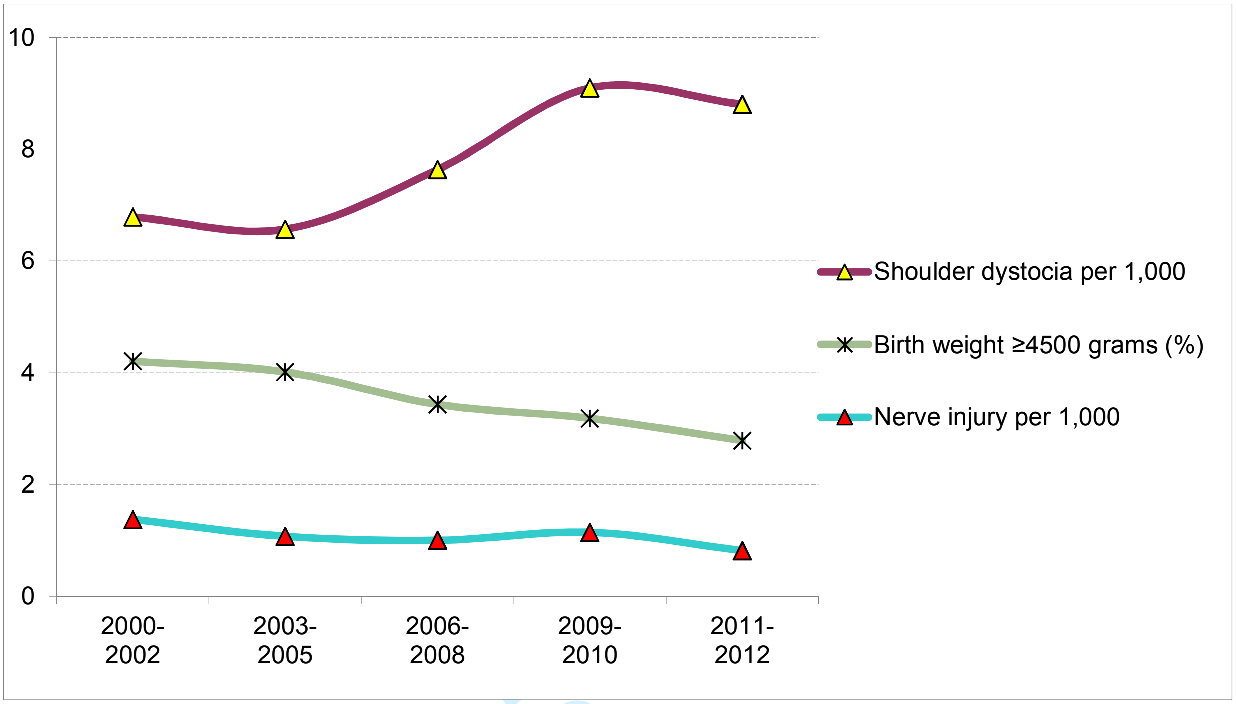
Incidence rates of morbidity indicators among children born after a) induced delivery, b) planned spontaneous vaginal delivery, and c) elective Caesarean section from 37 weeks' gestation in Denmark from 2000 to 2012.

Incidence rates are expressed per 1,000 newborns unless otherwise specified

	2000-2002	2003-2005	2006-2008	2009-2010	2011-2012	*P-value**	Total
Umbilical cord pH <7.0							
Induced delivery	-	8.0	7.9	5.7	4.9	*<0.001*	6.3
Planned vaginal	-	6.0	5.1	4.3	4.9	*0.002*	5.0
Elective Caesarean	-	2.2	1.5	0.4	0.5	*0.002*	1.0
Total	-	5.9	5.1	4.2	4.4	*<0.001*	4.8
Apgar scores <7/5 min							
Induced delivery	9.7	7.9	9.3	8.5	8.2	*0.259*	8.7
Planned vaginal	5.7	5.8	5.4	5.5	6.3	*0.153*	5.7
Elective Caesarean	4.7	3.4	2.9	3.0	4.5	*0.051*	3.6
Total	6.0	5.8	5.7	5.7	6.5	*0.037*	5.9
Admission to neonatal intensive care units (%)							
Induced delivery	2.5	2.6	2.5	2.7	2.6	*0.738*	2.6
Planned vaginal	1.1	1.2	1.2	1.6	1.7	*<0.001*	1.3
Elective Caesarean	2.2	1.9	1.7	2.4	2.7	*<0.001*	2.1
Total	1.3	1.4	1.4	1.9	2.0	*<0.001*	1.6
Neonatal death							
Induced delivery	2.4	1.5	1.8	1.3	1.0	*0.005*	1.6
Planned vaginal	1.7	1.5	1.3	0.9	1.0	*<0.001*	1.4
Elective Caesarean	2.7	1.8	0.7	0.5	1.0	*<0.001*	1.3
Total	1.9	1.5	1.3	1.0	1.0	*<0.001*	1.4
Cerebral palsy							
Induced delivery	2.2	1.6	1.3	1.7	-	*0.178*	1.7
Planned vaginal	1.6	1.2	1.3	1.1	-	*0.003*	1.4
Elective Caesarean	1.9	2.0	1.6	1.7	-	*0.804*	2.0
Total	1.7	1.3	1.3	1.2	-	*0.005*	1.5
Birth weight ≥4500g (%)							
Induced delivery	6.2	5.6	4.6	4.2	3.7	*<0.001*	4.8
Planned vaginal	4.0	3.8	3.3	3.0	2.5	*<0.001*	3.5
Elective Caesarean	3.7	3.7	2.9	3.1	2.6	*<0.001*	3.2
Total	4.2	4.0	3.4	3.2	2.8	*<0.001*	3.6
Shoulder dystocia							
Induced delivery	8.4	8.8	9.4	11.8	12.1	*<0.001*	10.2
Planned vaginal	7.1	6.9	8.3	9.7	9.0	*<0.001*	7.9
Total	6.8	6.6	7.6	9.1	8.8	*<0.001*	7.6
Nerve injury							
Induced delivery	2.3	1.6	1.5	1.9	1.2	*0.076*	1.7
Planned vaginal	1.3	1.1	1.0	1.1	0.8	*0.003*	1.1
Total	1.4	1.1	1.0	1.1	0.8	*<0.001*	1.1

Figure 3

Incidence rates of macrosomia from 37 weeks in Denmark from 2000 to 2012. Incidence rates are expressed per 1,000 newborns, unless otherwise specified.*



**) All results are significant.*

Appendix

Table 1S

Diagnosis codes defining groups of women who had a) induced delivery, b) planned spontaneous vaginal delivery, and c) elective Caesarean section in Demark from 2000 to 2012.

Medically induced delivery (group A)	
Diagnosis-codes	
DO499	Duration of pregnancy as main indication for induction of labour.
DO838A	Assisted single delivery after induction of labour.
DO848A	Assisted multiple deliveries after induction of labour.
Procedure-codes	
BKHD2	Labour induced by medications.
BKHD20	Labour induced by prostaglandins.
BKHD20A	Labour induced by Misoprostol.
BKHD21	Labour induced by Oxytocin.
Planned vaginal delivery (Group C)	
Defined as all deliveries minus group A and B.	
Elective Caesarean Section (Group B)	
Diagnosis-codes	
DO820	Delivery by elective Caesarean Section.
DO842	Multiple deliveries, all by Caesarean Section.
Operational-codes	
KMCA11	Elective Caesarean Section in uterine isthmus (from 2000-01)
KMCA10B	Elective Caesarean Section in uterine isthmus (from 2001-12)

Table 2S

Diagnosis codes and other criteria defining eight adverse perinatal outcomes.

Asphyxia indicators	
Umbilical cord pH > 7.0	
	Arterial, venous or unspecified pH.
Apgar scores >7/5	
	Apgar score less than 7 after five minutes.
Potential manifestations of asphyxia	
Neonatal intensive care unit	
	Admission to neonatal intensive care unit within 28 days after birth.
Neonatal death	
	Death of neonate within 28 days after birth.
Cerebral palsy	
DG800	Spastic quadriplegic cerebral palsy.
DG801	Spastic diplegic cerebral palsy.
DG802	Spastic hemiplegic cerebral palsy.
DG803	Dyskinetic cerebral palsy.
DG803A	Athetoid cerebral palsy.
DG803B	Dystonic cerebral palsy.
DG804	Ataxic cerebral palsy.
DG808	Other cerebral palsy.
DG808A	Mixed cerebral palsy syndromes.
DG809	Cerebral palsy, unspecified.
Prevention of macrosomia	
Fetal weight ≥4500 grams	
	Fetal weight ≥4500 grams.
Shoulder dystocia	
DO660	Delivery complicated by shoulder dystocia.
Nerve injury	
DP140	Erb paralysis due to birth injury.
DP141	Klumpke paralysis due to birth injury.
DP143	Other brachial plexus injuries.

Table 3S

Diagnosis codes and other criteria defining possible confounders.

Maternal age	
	Using personal registration number and day of delivery
Parity	
	Number of prior pregnancies
Plurality	
	Single or multiple gestation
Smoker	
	Smoker or non-smoker, registered at first contact with doctor
Body mass index	
	Using maternal height and weight.

Table 4S

Maternal age, parity, plurality, smoking, and body mass index among pregnant women from 37 weeks' gestation in Denmark from 2000 to 2012.

Possible confounders	2000-2002	2003-2005	2006-2008	2009-2010	2011-2012	*P-value**	Total
Maternal age							
Mean maternal age, years	30.1	30.6	30.8	30.9	30.9		30.7
Numbers of mothers>40 years	3,584	4,366	5,436	3,740	3,777		20,903
Incidence rate	2.0	2.4	3.0	3.2	3.5	*<0.001*	2.7
Parity							
Number of nulliparous women	78,718	77,231	77,685	51,675	48,584		333,893
Incidence rate	43.0	42.9	43.0	43.8	44.5	*<0.001*	43.3
Plurality (‰)							
Number of multigravidas	4,353	4,617	4,727	3,116	2,747		19,560
Incidence rate	2.4	2.6	2.6	2.6	2.5	*<0.001*	2.5
Smoker							
Number of smokers	37,540	30,782	25,656	14,891	12,527		121,396
Incidence rate	21.1	17.5	14.5	12.9	11.6	*<0.001*	16.1
Body mass index							
Mean body mass index	-	24.1	24.2	24.4	24.4		24.3
Number of women with BMI >35	-	4,032	6,813	4,880	4,689		20,414
Incidence rate	-	3.6	4.1	4.4	4.4	*<0.001*	4.1

Reduction in stillbirths at term after new birth induction paradigm.
Results of a national intervention

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005785.R1
Article Type:	Research
Date Submitted by the Author:	19-Jul-2014
Complete List of Authors:	Hedegaard, Mette; Rigshospitalet, Dept. of Gynaecology Lidegaard, Øjvind; Rigshospitalet, University of Copenhagen, DK-2100 Copenhagen, Denmark, Gynecological Clinic 4232, DK-2100 Skovlung, Charlotte; Rigshospitalet, University of Copenhagen, DK-2100 Copenhagen, Denmark, Gynecological Clinic 4232, DK-2100 Mørch, Lina; Rigshospitalet, University of Copenhagen, DK-2100 Copenhagen, Denmark, Gynecological Clinic 4232, DK-2100 Hedegaard, Morten; Rigshospitalet, University of Copenhagen, Dept. of Obstetrics
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Epidemiology, Evidence based practice, Public health
Keywords:	EPIDEMIOLOGY, Fetal medicine < OBSTETRICS, OBSTETRICS

July 11, 2014

Reduction in stillbirths at term after new birth induction paradigm. Results of a national intervention

Mette Hedegaard[1], scholar researcher

Øjvind Lidegaard[1], professor in Obstetrics and Gynaecology,

Charlotte Wessel Skovlund[1], data manager

Lina Steinrud Mørch, epidemiologist, and

Morten Hedegaard[2], head of dept, of obstetrics,

Word counts: *Title: 15 words, 102 characters including space*

Abstract: 300 words

Text: 3,054 words (excl, abstract, references, tables and figures)

Tables: 2

Figures: 4

Supplementary online appendix: One with one table

1) Department of Gynecology, Rigshospitalet, Faculty of Health Science, University of Copenhagen

2) Department of Obstetrics, Rigshospitalet, Faculty of Health Science, University of Copenhagen

Correspondence: Oejvind.Lidegaard@regionh.dk

Abstract

Objective. The risk of fetal death increases steeply after 42 gestational weeks. Since 2009, a more proactive policy including prevention of prolonged pregnancy, and early intervention of women with diabetes, preecampsia, high body mass index, and high age. The aim of this study was to describe the development in fetal deaths with this more proactive birth induction practice, and to identify and quantify contributing factors for this development.

Design. National cohort study.

Setting. Denmark

Participants. Delivering women in Denmark, January 1, 2000 to December 31, 2012.

Outcome measures. Stillbirths per 1,000 women at risk (prospective risk of stillbirth) and per 1,000 new-born from 37 and 40 gestational weeks, respectively, through the study period.

Results. During the study period, 829,165 children were live-born and 3,770 (0.45%) stillborn. Induction of labour increased from 12.4 % in year 2000 to 25.1 % in 2012 (p<0.001), and the per cent of children born at or after 42 weeks decreased from 8.0 % to 1.5 % (p<0.001).

Through the same period, the prospective risk of stillbirth after 37 weeks fell from 0.70 to 0.41 per 1,000 ongoing pregnancies (p<0.001), and from 2.4 to 1.4 per 1,000 new-born (p<0.001).

The regression analysis confirmed the inverse association between year of birth and risk of stillbirth. The lowest risk was observed in the years 2011-2012 as compared to years 2000-2002 with a fully adjusted hazard ratio of 0.69 (95% CI 0.57-0.83). The general earlier induction, the focused earlier induction of women with body mass index >30, twins, and of women above 40 years, and a halving of smoking pregnant women were all independent contributing factors for the decrease.

Conclusion. A gradually more proactive and a differential earlier labour induction practice are likely to have the main responsibility for the substantial reduction in stillbirths in Denmark.

Key words: Birth induction, fetal death, stillbirth, misoprostol

Abbreviations: None.

Strengths and limitations

Strengths

- Complete national data through a 13-year long study period
- Data analysed for all births after 37 weeks and after 40 weeks, respectively
- Access to important confounders
- Complete follow-up on all children born during the study period
- Advanced regression analysis
- A clear clinical message

Limitations

- Several clinical improvements have been undertaken during the study period
-

Introduction

Fetal death is still a dreaded complication of pregnancy, not least when occurring at term. The worldwide number of stillborn infants is estimated to 2.6 million per year, and the causes of a substantial part of these deaths are still unknown.[1] Identified risk factors include high maternal age, adiposity, fetal asphyxia, infections, and different maternal medical diseases.[2-5] Randomised studies have suggested a potential for prevention of fetal deaths by earlier induction of deliveries.[6]

Over the last two decades, the discussion of induction of labour versus expectant management has been prevalent among obstetricians.[7] A national Danish guideline in 2009 recommended induction of pregnant women ensuring delivery before 42 weeks.[8] Generally, pregnant women have since been offered labour induction at 41+3-5, while women at risk (body mass index >30 or age >40 years) have been offered induction at 41 weeks. Lastly, women at a high risk such as women with multiple pregnancies, preeclampsia or intrauterine growth restriction are often recommended induction before term.

The aim of this study was to describe birth induction practice in Denmark since year 2000, the corresponding development in post-term deliveries, and the stillbirth rates from 37 and 40 weeks of gestation (prospective stillbirth rate) and per 1,000 new-born. Secondly, to adjust these trends in rates of stillbirth for important risk factors of stillbirth.

Methods

Design and setting

In a historical cohort design data were collected from the Danish Birth Register, covering the period January 2000 through December 2012. The Registry is considered complete through this period. In order to reduce random variation, the 13-year study period was subdivided into five sub-periods of three, three, three, two, and two years length, respectively.

Participants

All live births and stillbirths during the study period were included. For each gestational day after 37 weeks, the number and distribution of all new-born and stillbirths were assessed. The gestational ages were generally assessed from first trimester ultrasound examinations. For few women not attending this routine offer to all pregnant women in Denmark, the last menstrual period was used.

Outcome measures

Rates of stillbirth per 1,000 ongoing pregnancies, also called the prospective risk of stillbirth, were calculated with a daily update from 37 weeks of gestation, accounting for the rapidly declining denominator especially after term. [9] The proportion of deliveries and of stillbirths after 37, 40, 41,

and 42 weeks per 1,000 new-born were calculated annually from year 2000 through 2012, and in different sub-periods within this study period.

The gestational age was recorded in 99.4 % of all new-born during the study period. Of 146 missing gestational ages among stillborn infants, we sought in medical charts and local registers and achieved this information in 42 women, all of whom had ended their pregnancy before 37 weeks. Therefore, all with a missing gestational age were allocated to the premature group. Gestational ages were however achieved for all stillbirths in 2011 and 2012.

From 2004 a birth has in Denmark been defined as any pregnancy that ends after 22 weeks of gestation, and live-born before 22 weeks. Before 2004 only live-births between 22 and 28 weeks were considered as births, while delivery of dead fetuses before 28 weeks and live-born before 22 weeks were considered as abortions. This technicality explains a minor increase in stillbirths before 37 weeks of gestation from 2003 to 2004.

Deaths within the first week after delivery was assessed for all included live-born, and rates of death were calculated in each study year.

In the analytical assessment, analyses of the cumulative risk of stillbirth with increasing gestational age per 1,000 ongoing pregnancies was estimated using Nielson Aalen estimator with gestational age (in days) as the time scale.[10] By cox regression analyses, the hazard ratios of stillbirth by year of birth were estimated using year 2000-2002 as the reference group. Gestational age was underlying time scale in these analyses. The following potential confounders were included in the model: Plurality, parity, maternal age, year, smoking, and body mass index. The regression model aimed to quantify the contribution from each of the potential confounders for the association between calendar year and rates of stillbirth.[10] Hazard ratios with 95% confidence limits were calculated, and p-values below 0.05 were considered significant. Logistic regression was used to generate crude odds ratios.

The main analysis was done on all deliveries from 37 weeks of gestation. As body mass index was not routinely recorded in the birth registry until 2004, additional sensitivity analyses were done for the sub-period 2004-2012, in order to quantify specifically the influence of body mass index on the decreasing stillborn rate. Finally, sensitivity analyses were conducted restricted to singletons.

Results

During the study period, 832,935 children were born. Of these were 3,770 (0.45 %) stillbirths and 829,165 (99.55 %) live-born. The distribution of new-born and stillborn infants in different pregnancy weeks, the crude rate of stillborn per 1,000 ongoing pregnancies and per 1,000 new-born in different gestational weeks, from different gestational ages and in different periods are shown in Table 1.

The frequency of birth induction increased from 12.4 % in year 2000 to 25.1 % in 2012, with a steep increase after 2010 (**Figure 1**). The earlier birth induction reduced the per cent of children born from 42 weeks of gestation from 8.0 % in year 2000 to 1.5 % in 2012 (**Figure 1**). The increasing induction rate and fall in deliveries from 42 weeks was, however, already observable from 2001.

Stillbirths with increasing gestational age.

The background for the new induction paradigm in Denmark is illustrated for the period 2000-2008 in **Figure 2**. With increasing gestational age the risk of fetal death rises, peaking after 43 weeks of gestation with more than 14 deaths per 1,000 ongoing pregnancies, a risk more than ten times higher than in the weeks before term.

During the period 2009-2012, the stillborn rates were reduced 21-39%, and from 41+3 stillbirths were eliminated (**Figure 2**).

The crude rates of fetal deaths with increasing gestational age were reduced by 30-66% when adjusting for age, year, parity, plurality, and smoking (**Figure 3**). Adjustment for body mass index did not change the estimates significantly.

Stillbirths by time.

The rate of stillborn infants from 37 weeks of gestation decreased from 0.70 (95% confidence interval 0.64-0.77) per 1,000 ongoing pregnancies (prospective stillbirth rate) during the period 2000-2002 to 0.41 (0.35-0.48) during the period 2011-2012 (**Figure 4**). The corresponding rate of stillborn infants from 40 weeks fell from 1.8 (1.6-2.1) during the period 2000-2002 to 0.74 (0.56-0.98) during 2011-2012, a reduction of 60 % (p<0.001). The fall was steepest from 2009-10 to 2011-12.

The rate of stillborn infants per 1,000 new-born after 37 weeks demonstrated a similar decrease from 2.4 (2.2-2.6) during the period 2000-2002 to 1.4 (1.2-1.6) during 2011-2012, a fall of 43% (**Figure 4**). Among children born from 40 weeks, the corresponding stillborn rates fell from 2.1 (1.9-2.4) per 1,000 new-born to 0.77 (0.58-1.0) or by 63% (p<0.001) (**Figure 4**).

Regression analysis

Several conditions, which may have influenced the risk of fetal death, changed during the study period (**Table 2**), The mean age of delivering women after 37 weeks of gestation increased from 30.1 years in 2000-2002 to 30.9 years in 2011-12, and the proportion of delivering women ≥40 years increased from 2.0 % to 3.5 % ($p<0.001$).

The mean body mass index increased from 24.1 kg/m^2 in 2003-2005 to 24.4 kg/m^2 during 2011-2012, and delivering women with a body mass index above 25 kg/m^2 increased from 32.0 % to 34.4 % through the same period ($p<0.001$).

While these changes are expected to increase the risk of fetal death, the proportion of pregnant smokers decreased from 20.5 % in 2000-2002 to 11.5 % in 2011-2012, almost a halving ($p<0.001$).

The proportion of primiparous increased slightly from 43.0 % to 44.5 % through the study period, while the proportion of multiple pregnancies after 37 weeks was almost stable; 2.4 % in 2000-2002, 2.6 % in 2006-2008, and 2.5 % in 2011-12 (**Table 2**). The proportion of multiple deliveries after 40 weeks of gestation from already low 0.12 % decreased to 0.04 %. Thereby, post term multiple deliveries almost disappeared through the study period.

In the fully adjusted model the following hazard ratios of fetal death were demonstrated: Smoking 1.4 (1.2-1.6), body mass index >25 kg/m^2; 1.5 (1.3-1.7), decreasing from 1.7 (1.4-2.0) during the period 2004-2008 to 1.3 (1.0-1.6) in 2009-2012. Primiparous had a relative risk of stillbirth of 1.2 (1.1-1.3), and multiple pregnancy of 51.5 (44.4-59.6).

With adjustment for gestational age at delivery, the decline in stillbirths was reduced from -41.5 % to -35.5 % suggesting that the general earlier induction in it self accounted for about 15 % of the reduction. Further adjustment for smoking, age at delivery, and parity increased the fall from -35.5 % to -37.6 %, because the decrease in smoking counterbalanced the influence of the slightly increasing age and proportion of primiparous by time. By additional adjustment for plurality, the relative risk of stillbirth by time was reduced from -37.6 % to -31.4 %, suggesting that the changes in the management of twin pregnancies accounted for approximately 16 % of the decrease.

In the sub-analysis covering the period 2004-2012, during which information about body mass index was available, the decreasing risk of stillbirth among women with high body mass index by time implied a further non significant four per cent reduction in overall stillbirth rates by time.

The rest of the reduction in stillbirths is thus apparently due to the differential induction practice, where women with high-risk pregnancies are induced more proactively (earlier) than low-risk pregnancies,

The risk of fetal death in the week after term was reduced by 33-38 % ($p<0.01$), in the week after 41 weeks by 30-33 % ($p<0.01$), and after 42 weeks by 30-33 % ($p<0.05$)(**Figure 2**). Thus, the new

induction paradigm firstly moved deliveries from late weeks with a high risk of stillbirth to earlier weeks with a lower risk. Secondly, in particular moved high-risk pregnancies to earlier induction, but thirdly, also reduced the risk of fetal death in each post term week.

The decrease in the rate of stillbirth corresponds to a reduction in absolute numbers of stillborn infants after 37 weeks from 136 stillbirths per year to now about 75 per year, a reduction of approximately 60 per year (p<0.001), corresponding to one saved stillborn infant per 1,000 new-born.

During gestational weeks 37 to 40, the annual number of stillbirths fell from around 80 per year during the period 2000-2008 to 50 per year during 2009-2012. This reduction coincided with an increase in second trimester induced abortions on fetal indication from annually 292 during the period 2000-2008 to 410 per year during the period 2009-2012, an increase of 118 induced abortions per year.[11]

The risk of dying during the first week of life was reduced among children born after 37 weeks from 1.7 (1.4-2.0) per 1,000 new-born in 2000 to 0.8 (0.6-1.0) per 1,000 live-born in 2012.[12]

The Caesarean section rate in Denmark has after a steady increase over more than 40 years been stable throughout the last ten years at about 20 % of all deliveries, even with a slight reduction from 20.4 % in 2009 to 19.8 % in 2012 (p<0.01).[12]

The sensitivity analysis excluding women with unknown gestational age did not change anything after 37 weeks, but decreased slightly the risk of fetal deaths before 37 weeks (data not shown).

Sensitivity analyses restricted to singletons enhanced the fall in stillbirth rates by time. For all deliveries, the adjusted fall by time was -31% and for singletons -43%,

Discussion

We report a decrease in risk of fetal death after 37 weeks to 0.14 % on a national level, which is the lowest risk ever reported in Denmark. Nor have any similar rate to our knowledge been published elsewhere.

Ever since the 1990´s, there has been an ongoing discussion of induction of labour versus expectant management of women after term.[7] Through the last ten years, a gradually more proactive induction practice has gained ground over expectant management in several countries, including Denmark. The decision to make a Danish guideline in 2009 was stimulated by the NICE-guideline on induction of labour published in 2008 and the ACOG practice bulletin from 2009.[13, 14]

Before 2009, many women were still not offered induction until after they passed 42 weeks of gestation. From 2009, the recommended induction regimen prevented many pregnancies from reaching post term gestational weeks of a high risk of fetal death. This change reduced the number of fetal deaths after term, but should in principle not influence the rate of deaths per 1,000 ongoing pregnancies in a certain post term week. The gestational age specific stillbirth rate after 41 weeks was, however, also reduced. This reduction could not be explained by the general earlier induction practice, but is according to our analyses a result of an even more proactive induction practice in women at an increased risk of stillbirth, such as women with body mass index >30, and women over 40 years. An increased fetal monitoring after term by time may also have influenced the decrease.

Through the last ten years, the majority of Danish units have used misoprostol for induction of labour, either applied vaginally or orally. It has been questioned, if induction by misoprostol could increase the risk of uterine hyperstimulation, asphyxia, and ultimately of neonatal death. In theory, an initiative to reduce the risk of fetal death could lead to neonatal complications and neonatal death. It is therefore important that the reduction in stillbirths was not associated with an increase in early neonatal deaths. On the contrary, the early neonatal deaths were halved during the study period, a circumstance, which undoubtedly was also influenced by an improved neonatal care through the study period.

It has been discussed, if induction of labour causes more Caesarean sections.[15] Some have argued that expectant management of labour increases the Caesarean section rate due to the risks associated with prolonged pregnancy.[16] The slight reduction in Caesarean sections with the new induction paradigm demonstrates that a proactive induction practice not necessarily increases the frequency of surgical interventions.

The offer of first trimester combined screening (double test and nuchal translucency scan), has in Denmark been widened to all pregnant women from year 2005-2006.[17] Before then, only women at 35 years or older were routinely offered first trimester screening. With the new routine, a majority of chromosomal abnormalities are detected and pregnancy most often terminated, accounting for the increase of approximately 118 annual second trimester induced abortions. Before the general screening was fully implemented, some fetuses with undetected abnormalities died later in pregnancy. From 20 weeks of gestation until term, 13 % of trisomy 21, 75 % of trisomy 18, and 35 % of trisomy 13 experience fetal death [18], a majority of these before 37 gestational weeks. This circumstance may explain a reduction of about 15 fetal deaths per year, but only about seven after 37 weeks corresponding to 12 % (7/60) of the observed reduction in stillborn infants.

During the study period, the quality of screening for structural abnormalities (offered in general throughout the period) and Doppler ultrasound both improved the monitoring of fetuses in utero,

making it easier to detect threatened fetuses and to intervene to avoid further complications including fetal death. However, these circumstances are probably of minor importance for the decrease in stillbirths, as other countries with the same technical improvement have not observed a similar decrease in stillbirths. In Sweden, the proportion of deliveries after 42 weeks was 7.5 % in year 2000 and 6.5 % in 2011. During the same period, the stillbirth rate after 37 gestational weeks was stable between 1.6 and 1.9 per 1,000 new-born.[19] In Norway, 4.8 % of deliveries occurred at 42 weeks or later, and the stillbirth rate after 37 weeks was 1.47 per 1,000 new-born [20], figures close to Danish figures in 2010.

The earlier induction of multiple pregnancies explained about 15 % of the reduction in stillbirths. The selective early induction of high-risk pregnancies such as pregnancies in women with high body mass index, women above 40 years, and women with multiple pregnancies explains, why the impact of these risk factors decreased by time. Worldwide, maternal age at delivery has increased over the last five decades, and Denmark is no exception.[21] As high maternal age is associated with stillbirth, this increase should have increased the stillbirth rates slightly by time.[5, 22, 23]

Determining the optimal time to deliver necessarily involves balancing induction risks and benefits. According to earlier studies, the risks of post-term deliveries include an increased perinatal mortality, meconium aspiration, macrosomnia, low umbilical cord artery pH, and low Apgar score at five minutes.[24] Inducing labour too early, on the other hand, may cause iatrogenic prematurity and respiratory complications.[25, 26]

When considering the overall risk of either fetal or infant death, previous studies have suggested the risk of expectant management to be lower than the risk of delivery until about 38 weeks. Passing 38 weeks, the risk of expectant management was found to be higher than the risk of delivery, and the risk difference increases substantially after 40 and 41 weeks of gestation, favouring delivery over expectant management.[27]

A Scottish historical cohort study by Stock et al. demonstrated similarly a substantial lower perinatal mortality in women induced at 41 weeks as compared with expectant management; OR 0.30 (95% CI 0.20.0.46).[28]

Among the strengths of this study are the almost complete coverage of deliveries [29], and access to data making an evaluation of circumstances, which might have influenced the stillbirth rates possible. The main limitation is the observational design, and the difficulty to account effectively for all potential confounders. The significant reduction in fetal deaths seen in Denmark has not been observed in Sweden, where the handling of post term pregnancies has undergone less change.[19]

In conclusion, the striking decrease in risk of late fetal deaths through recent years is likely primarily to be due to the earlier and increased induction rate. The additional health costs to save these lives were low, and the reduction was obtained without an increase in surgical interventions.

An important issue, which needs further studies, is the morbidity in new-born through the same study period, to confirm that the reduced mortality is not at the expense of an increased morbidity in new-born.

Denmark already had a low stillbirth rate a decade ago.[1] With the further reduction in stillbirths, we may now have achieved the lowest stillbirth rate ever reported. We see no reason why a similar more proactive induction paradigm could not be implemented in other countries, with a succeeding further reduction in late stillbirths worldwide.

Acknowledgements

The study was approved by the Danish Data Protection Agency (J.no: 2013-41-2063) and the National Board of Health (J.no, FSEID 00000579). Ethical approval is not requested for registry based studies in Denmark

Contributions

Hedegaard, Hedegaard and Lidegaard planned the study, Skovlund retrieved data from the National Birth Registry and National Health Registry. Mørch, Lidegaard, and Skovlund analysed the data. Hedegaard and Lidegaard wrote the manuscript. All authors revised the manuscript and accepted the final version. Morten Hedegaard is the guarantor.

Funding

The study was supported by a scholar grant from Rigshospitalet. Other expenses were covered by Department of Gynaecology, Rigshospitalet, University of Copenhagen.

Conflict of interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that Lidegaard within the last three years received honoraria for speeches in pharmacoepidemiological issues. Hedegaard, Hedegaard, Mørch and Skovlund did not declare any conflicts.

derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above."

Data sharing

No additional data available.

References

1. Cousens S, Blencowe H, Stanton C, et al. National, regional, and worldwide estimates of stillbirth rates in 2009 with trends since 1995: a systematic analysis. *Lancet* 2011; **377**: 1319-30. doi: 10.1016/S0140-6736(10)62310-0
2. The Stillbirth Collaborative Research Network Writing Group. Causes of death among stillbirths. *JAMA*. 2011; **306**:2459-68
3. Page JM, Snowden JM, Cheng YW, et al. The risk of stillbirth and infant death by each additional week of expectant management stratified by maternal age. *Am J Obstet Gynecol* 2013; **209**: xx-xx. http://dx.doi.org/10.1016/j.ajog.2013.05.045.
4. Flenady V, Koopmans L, Middleton P, et al. Major risk factors for stillbirth in high-income countries: A systematic review and meta-analysis. Lancet 2011; 377: 1331-40.
5. Flenady V, Middleton P, Smith GC, et al. Stillbirths: The way forward in high-income countries. Lancet 2011; 377: 1703-17.
6. Gülmezoglu AM, Crowther CA, Middelton P, et al. Induction of labour for improving birth outcomes at or beyond term (Review). *Cochrane Database* of Systematic Reviews 2012, Issue 6.
7. Hannah ME, Hannah WJ, Hellmann J, et al. Induction of labor as compared with serial antenatal monitoring in post-term pregnancy. A randomized controlled trial. *N Engl J Med* 1992; **326**: 1587-92.
8. Sandbjerg guidelines[internet]. Graviditas prolongata [Danish]. Available from: http://clin.au.dk/fileadmin/www.ki.au.dk/forskning/forskningsenheder/gyn_kologisk-obstetrisk_afd__y/logistics/sandbjerg_m__der/sandbjerg_2011/Graviditas_prolongata2011_1.pdf Visited March 13, 2014.
9. Yudkin PL, Wood L, Redman CW. Risk of unexplained stillbirth at different gestational ages. *Lancet* 1987; **1**: 1192-1194.
10. Smith GCS. Estimating risks of perinatal death. Am J Obstet Gynecol 2005; 192: 17-22.
11. Lidegaard Ø. Early pregnancy and abortions. Annual report for year 2012 [Danish]. National Quality Database for Early Pregnancy and Abortions. 2013. Online www.tigrab.dk. Visited March 13, 2014.
12. Danish birth registry online. http://www.ssi.dk/Sundhedsdataogit/Dataformidling/Sundhedsdata/Fodsler/Fodte%201973.aspx. Visited August 7, 2013.
13. Induction of Labour. NICE Guideline (CG70), July 2008. http://guidance.nice.org.uk/CG70. Visited March 13, 2014.
14. Clinical management guidelines for obstetrician-gynecologists. Induction of labor. ACOG Practice bulletin (107), August 2009. http://www.pqcnc.org/documents/sivbdoc/sivbeb/2ACOG2009PracticeBulletin107InductionofLabor.pdf Visited March 13, 2014.

15. Heffner LJ, Elkin E, Fretts RC. Impact of labor induction, gestational age, and maternal age on caesarean delivery rates. *Obstet Gynecol* 2003; **102**: 287-93.

16. Caughey AB. Perinatal outcomes related to induction of labor: a call for randomized trials. *Am J Obstet Gynecol* 2013; http://dx.doi.org/10.1016/j.ajog.2013.07.011. Visited February 24, 2014

17. Ekelund CK, Jørgensen FS, Petersen OB, et al. Impact of new national screening policy for Down's syndrome in Denmark: population based cohort study. BMJ 2008; 337: a2547.

18. Nicolaides KH. Nuchal translucency and other first-trimester sonographic markers of chromosomal abnormalities. Am J Obstet Gynecol 2004; 191: 45-67.

19. Socialstyrelsen. Pregnancies, deliveries and newborn. Medical Birth Registry 1973-2011. Assisted reproduction 1991-2010. [Swedish]. National Board of Health [Hälso- och Sjukvård] 2013. http://www.socialstyrelsen.se/publikationer2013/2013-2-7. Visited March 13, 2014.

20. Ebbing M, Klungsøyr K. Deliveries in Norway 2011. [Norweigian]. Folkehelseinstituttet 2013. http://www.fhi.no/dokumenter/2a92108f4f.pdf. Visited January 24, 2014.

21. Statistics of Denmark. http://www.statistikbanken.dk/statbank5a/default.asp?w=1024. Visited March 13, 2014.

22. Fretts RC, Schmittdiel J, McLean FH, et al. Increased maternal age and the risk of fetal death. *N Engl J Med* 1995; **333**: 953-7.

23. Reddy UM, Ko CW, Willinger M. Maternal age and the risk of stillbirth throughout pregnancy in the United States. *Am J Obstet Gynecol* 2006;**195**:764-70.

24. Kaimal AJ, Little SE, Odibo AO et al. Cost-effectiveness of elective induction of labor at 41 weeks in nulliparous women. *Am J Obstet Gynecol* 2011; **204**: 137. e1-9.

25. Clark SL, Frye DR, Meyers JA, et al. Reduction in elective delivery at <39 weeks of gestation: comparative effectiveness of 3 approaches to change and the impact on neonatal intensive care admission and stillbirth. Am J Obstet Gynecol 2003:449.e1-6. doi: 10.1016/j.ajog.2010.05.036. Epub 2010 Jul 8.

26. Agency for Healthcare Research and Quality [internet]. Evidence report number 176: Maternal and Neonatal Outcomes of Elective Induction of Labor. Available from: http://www.ahrq.gov/research/findings/evidence-based-reports/eil-evidence-report.pdf Visited March 13, 2014.

27. Rosenstein MG, Cheng YW, Snowden JM, et al. Risk of Stillbirth and Infant Death Stratified by Gestational Age. *Obstet Gynecol* 2012; **120**: 76-82. doi: 10.1097/AOG.0b013e31825bd286

28. Stock SJ, Ferguson E, Duffy A, et al. Ourcomes of elective induction of labour compared with expectant management: population based study. BMJ 2012; 344:e2838 doi: 10.1136/bmj.e2838

29. Blenstrup LT, Knudsen LB. Danish registers on aspects of reproduction. *Scand J Public Health*. 2011; 39: Suppl 7: 79-82.

Table 1

Rates of born and stillborn in and from different gestational weeks and periods in Denmark 2000-2012.*

	2000-02	2003-05	2006-08	2009-10	2011-12	2000-08	2009-12	2000-12
Number of born and stillborn infants								
Born (n)	197,222	194,774	196,023	127,165	117,751	588,019	244,916	832,935
Stillborn (n)	835	915	992	539	489	2,742	1,028	3,770
Stillbirths per 1,000 ongoing pregnancy weeks (prospective risk of stillbirth)								
<37	0.22	0.20	0.21	0.17	0.17	0.21	0.17	0.20
37+0-6	0.39	0.46	0.39	0.27	0.23	0.41	0.25	0.37
38+0-6	0.36	0.51	0.46	0.41	0.34	0.44	0.38	0.42
39+0-6	0.56	0.54	0.63	0.44	0.46	0.57	0.45	0.54
40+0-6	1.20	0.95	0.97	0.93	0.76	1.04	0.85	0.98
41+0-6	2.29	2.40	1.73	1.35	0.54	2.15	0.98	1.82
42+	15.55	6.09	11.16	6.60	7.83	11.60	6.96	10.86
Total	0.35	0.29	0.28	0.23	0.21	0.30	0.22	0.27
From 37 w	0.70	0.67	0.63	0.50	0.41	0.67	0.46	0.61
From 40 w	1.84	1.43	1.30	1.10	0.74	1.54	0.93	1.36
From 41 w	3.12	2.46	2.09	1.51	0.69	2.60	1.14	2.21
Stillborn per 1.000 new-born								
From 37 w	2.39	2.21	2.07	1.68	1.36	2.23	1.52	2.02
From 40 w	2.11	1.59	1.41	1.20	0.77	1.71	0.99	1.50
From 41 w	2.43	1.82	1.46	1.04	0.41	1.93	0.73	1.57
From 42 w	3.16	1.05	1.55	0.82	0.95	2.04	0.86	1.79

**) Absolute numbers given in supplementary appendix Table 1S.*

Table 2

Characteristics of women giving birth at term and relative risk of stillbirth by time.

	2000-02	2003-05	2006-08	2009-10	2011-12
Mean age	30.1	30.6	30.8	30.9	30.9
Mother ≥40 yrs	3,584	4,366	5,436	3,740	3,777
% ≥40 years	2.0	2.4	3.0	3.2	3.5
BMI recorded (n)	na	112,635	167,962	111,972	106,201
Mean BMI	na	24.1	24.2	24.3	24.4
BMI >25	na	36,076	54,903	37,616	36,528
% BMI >25	na	32.0	32.7	33.6	34.4
BMI >30	na	12,480	19,683	13,946	13,720
% BMI >30	na	11.1	11.7	12.5	12.9
BMI >35	na	4,032	6,813	4,880	4,689
% BMI >35	na	3.6	4.1	4.4	4.4
Smoker	37,540	30,782	25,656	14,891	12,527
% smokers	20.5	17.1	14.2	12.6	11.5
Multiple pregnancies	4,353	4,617	4,727	3,116	2,747
% multiples	2.4	2.6	2.6	2.6	2.5
Stillborn multiples	51	111	61	40	29
% stillborn multiples	1.2	2.4	1.3	1.3	1.1
Para 0	78,718	77,231	77,685	51,675	48,584
% Para 0	43.0	42.9	43.0	43.8	44.5

Regression analysis	Hazard ratio[§] of stillborn (2000-2002 reference)				
Crude[#]	1	0.95	0.89	0.72	0.59
Adjusted for GA[¤]	1	1.02	0.98	0.78	0.65
95% confidence intervals		0.89-1.17	0.85-1.12	0.66-0.92	0.53-0.78
Adjusted excpt, Plurality*[¤]	1	1.03	0.89	0.73	0.62
95% confidence intervals		0.90-1.18	0.78-1.03	0.61-0.86	0.52-0.75
Fully Adjusted[¤]**	1	1.07	0.96	0.78	0.69
95% confidence intervals		0.93-1.23	0.83-1.11	0.65-0.92	0.57-0.83

*) Adjusted only for age, smoking, and parity **) Additionally adjusted for plurality

§) Hazard ratios by cox regression. The crude estimates were calculated by logistic regression, and the risk estimates were odds ratios

Legends for tables and figures

Table 1

Rates of born and stillborn in and from different gestational weeks and periods in Denmark 2000-2012.

Table 2

Characteristics of women giving birth at term and relative risk of stillbirth by time.

Figure 1

Proportion (%) of induced deliveries and of children born from 41 weeks and 42 weeks, respectively, in Denmark from 2000 through 2012, Number of children born: 832,935.

Figure 2

Fetal deaths per 1,000 ongoing pregnancies according to gestational age during the periods 2000-2008 and 2009-2012. Number of weeks: 3,406,615. Number of fetal deaths: 3,770. Lower part the same in a semi-logarithmic plot

Figure 3

Crude fetal deaths per 1,000 ongoing pregnancies according to gestational age during the period 2000-2012 and after adjustment for different confounders. Lower part the same in a semi-logarithmic plot.*

Figure 4

Fetal deaths per 1,000 ongoing pregnancies (upper), and per 1,000 new-born (lower) after 37 and 40 gestational weeks, respectively, in different sub-periods from year 2000 through 2012. 95% confidence limits indicated,

Supplementary online appendix (optional)

Table 1S

Number of born and stillborn in and from different gestational weeks and periods in Denmark 2000-2012.

July 11, 2014

Reduction in stillbirths at term after new birth induction paradigm. Results of a national intervention

Mette Hedegaard[1], scholar researcher

Øjvind Lidegaard[1], professor in Obstetrics and Gynaecology,

Charlotte Wessel Skovlund[1], data manager

Lina Steinrud Mørch, epidemiologist, and

Morten Hedegaard[2], head of dept, of obstetrics,

Word counts:	*Title: 15 words, 102 characters including space*
	Abstract: 300 words
	Text: 3,054 words (excl, abstract, references, tables and figures)
	Tables: 2
	Figures: 4
	Supplementary online appendix: One with one table

1) *Department of Gynecology, Rigshospitalet, Faculty of Health Science, University of Copenhagen*

2) *Department of Obstetrics, Rigshospitalet, Faculty of Health Science, University of Copenhagen*

Correspondence: Oejvind.Lidegaard@regionh.dk

Abstract

Objective. ~~Fetal deaths are still a key challenge for obstetricians worldwide.~~ The risk of fetal death increases steeply after 42 gestational weeks. ~~From~~Since 2009, ~~Danish national guidelines recommended~~ a more proactive policy including prevention of prolonged pregnancy, and early intervention of women with diabetes, preecampsia, high body mass index, and high age.~~pregnant women to be offered induction to ensure delivery before 42 weeks.~~ The aim of this study was to describe the development in fetal deaths with this more proactive birth induction practice, and to identify and quantify contributing factors for this development.

Design. National cohort study.

Setting. Denmark

Participants. Delivering women in Denmark, January 1, 2000 to December 31, 2012.

Outcome measures. Stillbirths per 1,000 women at risk (prospective risk of stillbirth) and per 1,000 new-born from 37 and 40 gestational weeks, respectively, through the study period.

Results. During the study period, 829,165 children were live-born and 3,770 (0.45%) stillborn. Induction of labour increased from 12.4 % in year 2000 to 25.1 % in 2012 ($p<0.001$), and the per cent of children born at or after 42 weeks decreased from 8.0 % to 1.5 % ($p<0.001$).

Through the same period, the prospective risk of stillbirth after 37 weeks fell from 0.70 to 0.41 per 1,000 ongoing pregnancies ($p<0.001$), and from 2.4 to 1.4 per 1,000 new-born ($p<0.001$).

The regression analysis confirmed the inverse association between year of birth and risk of stillbirth. The lowest risk was observed in the years 2011-2012 as compared to years 2000-2002 with a fully adjusted hazard ratio of 0.69 (95% CI 0.57-0.83). The general earlier induction, the focused earlier induction of women with body mass index >30, twins, and of women above 40 years, and a halving of smoking pregnant women were all independent contributing factors for the decrease.

Conclusion. A gradually more proactive and a differential earlier labour induction practice are likely to have the main responsibility for the substantial reduction in stillbirths in Denmark.

Key words: Birth induction, fetal death, stillbirth, misoprostol

Abbreviations: None.

Strengths and limitations

Strengths

- Complete national data through a 13-year long study period
- Data analysed for all births after 37 weeks and after 40 weeks, respectively
- Access to important confounders
- Complete follow-up on all children born during the study period
- Advanced regression analysis
- A clear clinical message

Limitations

- Several clinical improvements have been undertaken during the study period
-

Introduction

Fetal death is still a dreaded complication of pregnancy, not least when occurring at term. The worldwide number of stillborn infants is estimated to 2.6 million per year, and the causes of a substantial part of these deaths are still unknown.[1] Identified risk factors include high maternal age, adiposity, fetal asphyxia, infections, and different maternal medical diseases.[2-5] Randomised studies have suggested a potential for prevention of fetal deaths by earlier induction of deliveries.[6]

Over the last two decades, the discussion of induction of labour versus expectant management has been prevalent among obstetricians.[7] A national Danish guideline in 2009 recommended induction of pregnant women ensuring delivery before 42 weeks.[8] Generally, pregnant women have since been offered labour induction at 41+3-5, while women at risk (body mass index >30 or age >40 years) have been offered induction at 41 weeks. Lastly, women at a high risk such as women with multiple pregnancies, preeclampsia or intrauterine growth restriction are often recommended induction before term.

The aim of this study was to describe birth induction practice in Denmark since year 2000, the corresponding development in post-term deliveries, and the stillbirth rates from 37 and 40 weeks of gestation (prospective stillbirth rate) and per 1,000 new-born. Secondly, to adjust these trends in rates of stillbirth for important risk factors of stillbirth.

Methods

Design and setting

In a historical cohort design data were collected from the Danish Birth Register, covering the period January 2000 through December 2012. The Registry is considered complete through this period. In order to reduce random variation, the 13-year study period was subdivided into five sub-periods of three, three, three, two, and two years length, respectively.

Participants

All live births and stillbirths during the study period were included. For each gestational day after 37 weeks, the number and distribution of all new-born and stillbirths were assessed. The gestational ages were generally assessed from first trimester ultrasound examinations. For few women not attending this routine offer to all pregnant women in Denmark, the last menstrual period was used.

Outcome measures

Rates of stillbirth per 1,000 ongoing pregnancies, also called the prospective risk of stillbirth, were calculated with a daily update from 37 weeks of gestation, accounting for the rapidly declining denominator especially after term. [9] The proportion of deliveries and of stillbirths after 37, 40, 41,

and 42 weeks per 1,000 new-born were calculated annually from year 2000 through 2012, and in different sub-periods within this study period.

The gestational age was recorded in 99.4 % of all new-born during the study period. Of 146 missing gestational ages among stillborn infants, we sought in medical charts and local registers and achieved this information in 42 women, all of whom had ended their pregnancy before 37 weeks. Therefore, all with a missing gestational age were allocated to the premature group. Gestational ages were however achieved for all stillbirths in 2011 and 2012.

From 2004 a birth has in Denmark been defined as any pregnancy that ends after 22 weeks of gestation, and live-born before 22 weeks. Before 2004 only live-births between 22 and 28 weeks were considered as births, while delivery of dead fetuses before 28 weeks and live-born before 22 weeks were considered as abortions. This technicality explains a minor increase in stillbirths before 37 weeks of gestation from 2003 to 2004.

Deaths within the first week after delivery was assessed for all included live-born, and rates of death were calculated in each study year.

In the analytical assessment, analyses of the cumulative risk of stillbirth with increasing gestational age per 1,000 ongoing pregnancies was estimated using Nielson Aalen estimator with gestational age (in days) as the time scale.[10] By cox regression analyses, the hazard ratios of stillbirth by year of birth were estimated using year 2000-2002 as the reference group. Gestational age was underlying time scale in these analyses. The following potential confounders were included in the model: Plurality, parity, maternal age, year, smoking, and body mass index. The regression model aimed to quantify the contribution from each of the potential confounders for the association between calendar year and rates of stillbirth.[10] Hazard ratios with 95% confidence limits were calculated, and p-values below 0.05 were considered significant. Logistic regression was used to generate crude odds ratios.

The main analysis was done on all deliveries from 37 weeks of gestation. As body mass index was not routinely recorded in the birth registry until 2004, additional sensitivity analyses were done for the sub-period 2004-2012, in order to quantify specifically the influence of body mass index on the decreasing stillborn rate. Finally, sensitivity analyses were conducted restricted to singletons.

Results

During the study period, 832,935 children were born. Of these were 3,770 (0.45 %) stillbirths and 829,165 (99.55 %) live-born. The distribution of new-born and stillborn infants in different pregnancy weeks, the crude rate of stillborn per 1,000 ongoing pregnancies and per 1,000 new-born in different gestational weeks, from different gestational ages and in different periods are shown in Table 1.

The frequency of birth induction increased from 12.4 % in year 2000 to 25.1 % in 2012, with a steep increase after 2010 (**Figure 1**). The earlier birth induction reduced the per cent of children born from 42 weeks of gestation from 8.0 % in year 2000 to 1.5 % in 2012 (**Figure 1**). The increasing induction rate and fall in deliveries from 42 weeks was, however, already observable from 2001.

Stillbirths with increasing gestational age.

The background for the new induction paradigm in Denmark is illustrated for the period 2000-2008 in **Figure 2**. With increasing gestational age the risk of fetal death rises, peaking after 43 weeks of gestation with more than 14 deaths per 1,000 ongoing pregnancies, a risk more than ten times higher than in the weeks before term.

During the period 2009-2012, the stillborn rates were reduced 21-39%, and from 41+3 stillbirths were eliminated (**Figure 2**).

The crude rates of fetal deaths with increasing gestational age were reduced by 30-66% when adjusting for age, year, parity, plurality, and smoking (**Figure 3**). Adjustment for body mass index did not change the estimates significantly.

Stillbirths by time.

The rate of stillborn infants from 37 weeks of gestation decreased from 0.70 (95% confidence interval 0.64-0.77) per 1,000 ongoing pregnancies (prospective stillbirth rate) during the period 2000-2002 to 0.41 (0.35-0.48) during the period 2011-2012 (**Figure 4**). The corresponding rate of stillborn infants from 40 weeks fell from 1.8 (1.6-2.1) during the period 2000-2002 to 0.74 (0.56-0.98) during 2011-2012, a reduction of 60 % ($p<0.001$). The fall was steepest from 2009-10 to 2011-12.

The rate of stillborn infants per 1,000 new-born after 37 weeks demonstrated a similar decrease from 2.4 (2.2-2.6) during the period 2000-2002 to 1.4 (1.2-1.6) during 2011-2012, a fall of 43% (**Figure 4**). Among children born from 40 weeks, the corresponding stillborn rates fell from 2.1 (1.9-2.4) per 1,000 new-born to 0.77 (0.58-1.0) or by 63% ($p<0.001$) (**Figure 4**).

Regression analysis

Several conditions, which may have influenced the risk of fetal death, changed during the study period (**Table 2**), The mean age of delivering women after 37 weeks of gestation increased from 30.1 years in 2000-2002 to 30.9 years in 2011-12, and the proportion of delivering women ≥40 years increased from 2.0 % to 3.5 % ($p<0.001$).

The mean body mass index increased from 24.1 kg/m^2 in 2003-2005 to 24.4 kg/m^2 during 2011-2012, and delivering women with a body mass index above 25 kg/m^2 increased from 32.0 % to 34.4 % through the same period ($p<0.001$).

While these changes are expected to increase the risk of fetal death, the proportion of pregnant smokers decreased from 20.5 % in 2000-2002 to 11.5 % in 2011-2012, almost a halving ($p<0.001$).

The proportion of primiparous increased slightly from 43.0 % to 44.5 % through the study period, while the proportion of multiple pregnancies after 37 weeks was almost stable; 2.4 % in 2000-2002, 2.6 % in 2006-2008, and 2.5 % in 2011-12 (**Table 2**). The proportion of multiple deliveries after 40 weeks of gestation from already low 0.12 % decreased to 0.04 %. Thereby, post term multiple deliveries almost disappeared through the study period.

In the fully adjusted model the following hazard ratios of fetal death were demonstrated: Smoking 1.4 (1.2-1.6), body mass index >25 kg/m^2; 1.5 (1.3-1.7), decreasing from 1.7 (1.4-2.0) during the period 2004-2008 to 1.3 (1.0-1.6) in 2009-2012. Primiparous had a relative risk of stillbirth of 1.2 (1.1-1.3), and multiple pregnancy of 51.5 (44.4-59.6).

With adjustment for gestational age at delivery, the decline in stillbirths was reduced from -41.5 % to -35.5 % suggesting that the general earlier induction in it self accounted for about 15 % of the reduction. Further adjustment for smoking, age at delivery, and parity increased the fall from -35.5 % to -37.6 %, because the decrease in smoking counterbalanced the influence of the slightly increasing age and proportion of primiparous by time. By additional adjustment for plurality, the relative risk of stillbirth by time was reduced from -37.6 % to -31.4 %, suggesting that the changes in the management of twin pregnancies accounted for approximately 16 % of the decrease.

In the sub-analysis covering the period 2004-2012, during which information about body mass index was available, the decreasing risk of stillbirth among women with high body mass index by time implied a further non significant four per cent reduction in overall stillbirth rates by time.

The rest of the reduction in stillbirths is thus apparently due to the differential induction practice, where women with high-risk pregnancies are induced more proactively (earlier) than low-risk pregnancies,

The risk of fetal death in the week after term was reduced by 33-38 % ($p<0.01$), in the week after 41 weeks by 30-33 % ($p<0.01$), and after 42 weeks by 30-33 % ($p<0.05$)(**Figure 2**). Thus, the new

induction paradigm firstly moved deliveries from late weeks with a high risk of stillbirth to earlier weeks with a lower risk. Secondly, in particular moved high-risk pregnancies to earlier induction, but thirdly, also reduced the risk of fetal death in each post term week.

The decrease in the rate of stillbirth corresponds to a reduction in absolute numbers of stillborn infants after 37 weeks from 136 stillbirths per year to now about 75 per year, a reduction of approximately 60 per year (p<0.001), corresponding to one saved stillborn infant per 1,000 new-born.

During gestational weeks 37 to 40, the annual number of stillbirths fell from around 80 per year during the period 2000-2008 to 50 per year during 2009-2012. This reduction coincided with an increase in second trimester induced abortions on fetal indication from annually 292 during the period 2000-2008 to 410 per year during the period 2009-2012, an increase of 118 induced abortions per year.[11]

The risk of dying during the first week of life was reduced among children born after 37 weeks from 1.7 (1.4-2.0) per 1,000 new-born in 2000 to 0.8 (0.6-1.0) per 1,000 live-born in 2012.[12]

The Caesarean section rate in Denmark has after a steady increase over more than 40 years been stable throughout the last ten years at about 20 % of all deliveries, even with a slight reduction from 20.4 % in 2009 to 19.8 % in 2012 (p<0.01).[12]

The sensitivity analysis excluding women with unknown gestational age did not change anything after 37 weeks, but decreased slightly the risk of fetal deaths before 37 weeks (data not shown).

Sensitivity analyses restricted to singletons enhanced the fall in stillbirth rates by time. For all deliveries, the adjusted fall by time was -31% and for singletons -43%,

Discussion

We report a decrease in risk of fetal death after 37 weeks to 0.14 % on a national level, which is the lowest risk ever reported in Denmark. Nor have any similar rate to our knowledge been published elsewhere.

Ever since the 1990´s, there has been an ongoing discussion of induction of labour versus expectant management of women after term.[7] Through the last ten years, a gradually more proactive induction practice has gained ground over expectant management in several countries, including Denmark. The decision to make a Danish guideline in 2009 was stimulated by the NICE-guideline on induction of labour published in 2008 and the ACOG practice bulletin from 2009.[13, 14]

Before 2009, many women were still not offered induction until after they passed 42 weeks of gestation. From 2009, the recommended induction regimen prevented many pregnancies from reaching post term gestational weeks of a high risk of fetal death. This change reduced the number of fetal deaths after term, but should in principle not influence the rate of deaths per 1,000 ongoing pregnancies in a certain post term week. The gestational age specific stillbirth rate after 41 weeks was, however, also reduced. This reduction could not be explained by the general earlier induction practice, but is according to our analyses a result of an even more proactive induction practice in women at an increased risk of stillbirth, such as women with body mass index >30, and women over 40 years. An increased fetal monitoring after term by time may also have influenced the decrease.

Through the last ten years, the majority of Danish units have used misoprostol for induction of labour, either applied vaginally or orally. It has been questioned, if induction by misoprostol could increase the risk of uterine hyperstimulation, asphyxia, and ultimately of neonatal death. In theory, an initiative to reduce the risk of fetal death could lead to neonatal complications and neonatal death. It is therefore important that the reduction in stillbirths was not associated with an increase in early neonatal deaths. On the contrary, the early neonatal deaths were halved during the study period, a circumstance, which undoubtedly was also influenced by an improved neonatal care through the study period.

It has been discussed, if induction of labour causes more Caesarean sections.[15] Some have argued that expectant management of labour increases the Caesarean section rate due to the risks associated with prolonged pregnancy.[16] The slight reduction in Caesarean sections with the new induction paradigm demonstrates that a proactive induction practice not necessarily increases the frequency of surgical interventions.

The offer of first trimester combined screening (double test and nuchal translucency scan), has in Denmark been widened to all pregnant women from year 2005-2006.[17] Before then, only women at 35 years or older were routinely offered first trimester screening. With the new routine, a majority of chromosomal abnormalities are detected and pregnancy most often terminated, accounting for the increase of approximately 118 annual second trimester induced abortions. Before the general screening was fully implemented, some fetuses with undetected abnormalities died later in pregnancy. From 20 weeks of gestation until term, 13 % of trisomy 21, 75 % of trisomy 18, and 35 % of trisomy 13 experience fetal death [18], a majority of these before 37 gestational weeks. This circumstance may explain a reduction of about 15 fetal deaths per year, but only about seven after 37 weeks corresponding to 12 % (7/60) of the observed reduction in stillborn infants.

During the study period, the quality of screening for structural abnormalities (offered in general throughout the period) and Doppler ultrasound both improved the monitoring of fetuses in utero,

making it easier to detect threatened fetuses and to intervene to avoid further complications including fetal death. However, these circumstances are probably of minor importance for the decrease in stillbirths, as other countries with the same technical improvement have not observed a similar decrease in stillbirths. In Sweden, the proportion of deliveries after 42 weeks was 7.5 % in year 2000 and 6.5 % in 2011. During the same period, the stillbirth rate after 37 gestational weeks was stable between 1.6 and 1.9 per 1,000 new-born.[19] In Norway, 4.8 % of deliveries occurred at 42 weeks or later, and the stillbirth rate after 37 weeks was 1.47 per 1,000 new-born [20], figures close to Danish figures in 2010.

The earlier induction of multiple pregnancies explained about 15 % of the reduction in stillbirths. The selective early induction of high-risk pregnancies such as pregnancies in women with high body mass index, women above 40 years, and women with multiple pregnancies explains, why the impact of these risk factors decreased by time. Worldwide, maternal age at delivery has increased over the last five decades, and Denmark is no exception.[21] As high maternal age is associated with stillbirth, this increase should have increased the stillbirth rates slightly by time.[5, 22, 23]

Determining the optimal time to deliver necessarily involves balancing induction risks and benefits. According to earlier studies, the risks of post-term deliveries include an increased perinatal mortality, meconium aspiration, macrosomnia, low umbilical cord artery pH, and low Apgar score at five minutes.[24] Inducing labour too early, on the other hand, may cause iatrogenic prematurity and respiratory complications.[25, 26]

When considering the overall risk of either fetal or infant death, previous studies have suggested the risk of expectant management to be lower than the risk of delivery until about 38 weeks. Passing 38 weeks, the risk of expectant management was found to be higher than the risk of delivery, and the risk difference increases substantially after 40 and 41 weeks of gestation, favouring delivery over expectant management.[27]

A Scottish historical cohort study by Stock et al. demonstrated similarly a substantial lower perinatal mortality in women induced at 41 weeks as compared with expectant management; OR 0.30 (95% CI 0.20.0.46).[28]

Among the strengths of this study are the almost complete coverage of deliveries [2~~9~~8], and access to data making an evaluation of circumstances, which might have influenced the stillbirth rates possible. The main limitation is the observational design, and the difficulty to account effectively for all potential confounders. The significant reduction in fetal deaths seen in Denmark has not been observed in Sweden, where the handling of post term pregnancies has undergone less change.[19]

In conclusion, the striking decrease in risk of late fetal deaths through recent years is likely primarily to be due to the earlier and increased induction rate. The additional health costs to save these lives were low, and the reduction was obtained without an increase in surgical interventions.

An important issue, which needs further studies, is the morbidity in new-born through the same study period, to confirm that the reduced mortality is not at the expense of an increased morbidity in new-born.

Denmark already had a low stillbirth rate a decade ago.[1] With the further reduction in stillbirths, we may now have achieved the lowest stillbirth rate ever reported. We see no reason why a similar more proactive induction paradigm could not be implemented in other countries, with a succeeding further reduction in late stillbirths worldwide.

Acknowledgements

The study was approved by the Danish Data Protection Agency (J.no: 2013-41-2063) and the National Board of Health (J.no, FSEID 00000579). Ethical approval is not requested for registry based studies in Denmark

Contributions

Hedegaard, Hedegaard and Lidegaard planned the study, Skovlund retrieved data from the National Birth Registry and National Health Registry. Mørch, Lidegaard, and Skovlund analysed the data. Hedegaard and Lidegaard wrote the manuscript. All authors revised the manuscript and accepted the final version. Morten Hedegaard is the guarantor.

Funding

The study was supported by a scholar grant from Rigshospitalet. Other expenses were covered by Department of Gynaecology, Rigshospitalet, University of Copenhagen.

Conflict of interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that Lidegaard within the last three years received honoraria for speeches in pharmacoepidemiological issues. Hedegaard, Hedegaard, Mørch and Skovlund did not declare any conflicts.

Field Code Changed

derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above."

References

1. Cousens S, Blencowe H, Stanton C, et al. National, regional, and worldwide estimates of stillbirth rates in 2009 with trends since 1995: a systematic analysis. *Lancet* 2011; **377**: 1319-30. doi: 10.1016/S0140-6736(10)62310-0

2. The Stillbirth Collaborative Research Network Writing Group. Causes of death among stillbirths. *JAMA*. 2011; **306**:2459-68

3. Page JM, Snowden JM, Cheng YW, Doss AE, Rosenstein MG, Caughey AB. The risk of stillbirth and infant death by each additional week of expectant management stratified by maternal age. *Am J Obstet Gynecol* 2013; **209**: xx-xx. http://dx.doi.org/10.1016/j.ajog.2013.05.045.

4. Flenady V, Koopmans L, Middleton P, et al. Major risk factors for stillbirth in high-income countries: A systematic review and meta-analysis. Lancet 2011; 377: 1331-40.

5. Flenady V, Middleton P, Smith GC, et al. Stillbirths: The way forward in high-income countries. Lancet 2011; 377: 1703-17.

6. Gülmezoglu AM, Crowther CA, Middelton P, Heatley E. Induction of labour for improving birth outcomes at or beyond term (Review). *Cochrane Database* of Systematic Reviews 2012, Issue 6.

7. Hannah ME, Hannah WJ, Hellmann J, et al. Induction of labor as compared with serial antenatal monitoring in post-term pregnancy. A randomized controlled trial. *N Engl J Med* 1992; **326**: 1587-92.

8. Sandbjerg guidelines[internet]. Graviditas prolongata [Danish]. Available from: http://clin.au.dk/fileadmin/www.ki.au.dk/forskning/forskningsenheder/gyn_kologisk-obstetrisk_afd__y/logistics/sandbjerg_m__der/sandbjerg_2011/Graviditas_prolongata2011_1.pdf Visited March 13, 2014.

9. Yudkin PL, Wood L, Redman CW. Risk of unexplained stillbirth at different gestational ages. *Lancet* 1987; **1**: 1192-1194.

10. Smith GCS. Estimating risks of perinatal death. Am J Obstet Gynecol 2005; 192: 17-22.

11. Lidegaard Ø. Early pregnancy and abortions. Annual report for year 2012 [Danish]. National Quality Database for Early Pregnancy and Abortions. 2013. Online www.tigrab.dk. Visited March 13, 2014.

12. Danish birth registry online. http://www.ssi.dk/Sundhedsdataogit/Dataformidling/Sundhedsdata/Fodsler/Fodte%201973.aspx. Visited August 7, 2013.

13. Induction of Labour. NICE Guideline (CG70), July 2008. http://guidance.nice.org.uk/CG70. Visited March 13, 2014.

14. Clinical management guidelines for obstetrician-gynecologists. Induction of labor. ACOG Practice bulletin (107), August 2009. http://www.pqcnc.org/documents/sivbdoc/sivbeb/2ACOG2009PracticeBulletin107InductionofLabor.pdf Visited March 13, 2014.

Field Code Changed

Field Code Changed

Field Code Changed

Field Code Changed

Field Code Changed

15. Heffner LJ, Elkin E, Fretts RC. Impact of labor induction, gestational age, and maternal age on caesarean delivery rates. *Obstet Gynecol* 2003; **102**: 287-93.

16. Caughey AB. Perinatal outcomes related to induction of labor: a call for randomized trials. *Am J Obstet Gynecol* 2013; http://dx.doi.org/10.1016/j.ajog.2013.07.011. Visited February 24, 2014

17. Ekelund CK, Jørgensen FS, Petersen OB, Sundberg K, Tabor A. Impact of new national screening policy for Down's syndrome in Denmark: population based cohort study. BMJ 2008; 337: a2547.

18. Nicolaides KH. Nuchal translucency and other first-trimester sonographic markers of chromosomal abnormalities. Am J Obstet Gynecol 2004; 191: 45-67.

19. Socialstyrelsen. Pregnancies, deliveries and newborn. Medical Birth Registry 1973-2011. Assisted reproduction 1991-2010. [Swedish]. National Board of Health [Hälso- och Sjukvård] 2013. http://www.socialstyrelsen.se/publikationer2013/2013-2-7. Visited March 13, 2014.

20. Ebbing M, Klungsøyr K. Deliveries in Norway 2011. [Norweigian]. Folkehelseinstituttet 2013. http://www.fhi.no/dokumenter/2a92108f4f.pdf. Visited January 24, 2014.

21. Statistics of Denmark. http://www.statistikbanken.dk/statbank5a/default.asp?w=1024. Visited March 13, 2014.

22. Fretts RC, Schmittdiel J, McLean FH, Usher RH, Goldman MB. Increased maternal age and the risk of fetal death. *N Engl J Med* 1995; **333**: 953-7.

23. Reddy UM, Ko CW, Willinger M. Maternal age and the risk of stillbirth throughout pregnancy in the United States. *Am J Obstet Gynecol* 2006;**195**:764-70.

24. Kaimal AJ, Little SE, Odibo AO et al. Cost-effectiveness of elective induction of labor at 41 weeks in nulliparous women. *Am J Obstet Gynecol* 2011; **204**: 137. e1-9.

25. Clark SL, Frye DR, Meyers JA, Belfort MA, Dildy GA, Kofford S, et al. Reduction in elective delivery at <39 weeks of gestation: comparative effectiveness of 3 approaches to change and the impact on neonatal intensive care admission and stillbirth. Am J Obstet Gynecol 2003:449.e1-6. doi: 10.1016/j.ajog.2010.05.036. Epub 2010 Jul 8.

26. Agency for Healthcare Research and Quality [internet]. Evidence report number 176: Maternal and Neonatal Outcomes of Elective Induction of Labor. Available from: http://www.ahrq.gov/research/findings/evidence-based-reports/eil-evidence-report.pdf Visited March 13, 2014.

27. Rosenstein MG, Cheng YW, Snowden JM, Nicholson JM, Caughey AB. Risk of Stillbirth and Infant Death Stratified by Gestational Age. *Obstet Gynecol* 2012; **120**: 76-82. doi: 10.1097/AOG.0b013e31825bd286

28. Stock SJ, Ferguson E, Duffy A, Ford I, Chalmers J, Norman JE. Outcomes of elective induction of labour compared with expectant management: population based study. BMJ 2012; 344:e2838 doi: 10.1136/bmj.e2838

Field Code Changed

Field Code Changed

Field Code Changed

Field Code Changed

Formatted: Font: (Default) Arial, 10 pt

29. Blenstrup LT, Knudsen LB. Danish registers on aspects of reproduction. *Scand J Public Health*. 2011; 39: Suppl 7: 79-82.

Field Code Changed

Legends for tables and figures

Table 1

Rates of born and stillborn in and from different gestational weeks and periods in Denmark 2000-2012.

Table 2

Characteristics of women giving birth at term and relative risk of stillbirth by time.

Figure 1

Proportion (%) of induced deliveries and of children born from 41 weeks and 42 weeks, respectively, in Denmark from 2000 through 2012, Number of children born: 832,935.

Figure 2

Fetal deaths per 1,000 ongoing pregnancies according to gestational age during the periods 2000-2008 and 2009-2012. Number of weeks: 3,406,615. Number of fetal deaths: 3,770. Lower part the same in a semi-logarithmic plot

Figure 3

Crude fetal deaths per 1,000 ongoing pregnancies according to gestational age during the period 2000-2012 and after adjustment for different confounders. Lower part the same in a semi-logarithmic plot.*

Figure 4

Fetal deaths per 1,000 ongoing pregnancies (upper), and per 1,000 new-born (lower) after 37 and 40 gestational weeks, respectively, in different sub-periods from year 2000 through 2012. 95% confidence limits indicated,

Supplementary online appendix (optional)

Table 1S

Number of born and stillborn in and from different gestational weeks and periods in Denmark 2000-2012.

Table 1

Rates of born and stillborn in and from different gestational weeks and periods in Denmark 2000-2012.*

	2000-02	2003-05	2006-08	2009-10	2011-12	2000-08	2009-12	2000-12
Number of born and stillborn infants								
Born (n)	197,222	194,774	196,023	127,165	117,751	588,019	244,916	832,935
Stillborn (n)	835	915	992	539	489	2,742	1,028	3,770
Stillbirths per 1,000 ongoing pregnancy weeks (prospective risk of stillbirth)								
<37	0.22	0.20	0.21	0.17	0.17	0.21	0.17	0.20
37+0-6	0.39	0.46	0.39	0.27	0.23	0.41	0.25	0.37
38+0-6	0.36	0.51	0.46	0.41	0.34	0.44	0.38	0.42
39+0-6	0.56	0.54	0.63	0.44	0.46	0.57	0.45	0.54
40+0-6	1.20	0.95	0.97	0.93	0.76	1.04	0.85	0.98
41+0-6	2.29	2.40	1.73	1.35	0.54	2.15	0.98	1.82
42+	15.55	6.09	11.16	6.60	7.83	11.60	6.96	10.86
Total	0.35	0.29	0.28	0.23	0.21	0.30	0.22	0.27
From 37 w	0.70	0.67	0.63	0.50	0.41	0.67	0.46	0.61
From 40 w	1.84	1.43	1.30	1.10	0.74	1.54	0.93	1.36
From 41 w	3.12	2.46	2.09	1.51	0.69	2.60	1.14	2.21
Stillborn per 1.000 new-born								
From 37 w	2.39	2.21	2.07	1.68	1.36	2.23	1.52	2.02
From 40 w	2.11	1.59	1.41	1.20	0.77	1.71	0.99	1.50
From 41 w	2.43	1.82	1.46	1.04	0.41	1.93	0.73	1.57
From 42 w	3.16	1.05	1.55	0.82	0.95	2.04	0.86	1.79

**) Absolute numbers given in supplementary appendix Table 1S.*

Table 2

Characteristics of women giving birth at term and relative risk of stillbirth by time.

	2000-02	2003-05	2006-08	2009-10	2011-12
Mean age	30.1	30.6	30.8	30.9	30.9
Mother ≥40 yrs	3,584	4,366	5,436	3,740	3,777
% ≥40 years	2.0	2.4	3.0	3.2	3.5
BMI recorded (n)	na	112,635	167,962	111,972	106,201
Mean BMI	na	24.1	24.2	24.3	24.4
BMI >25	na	36,076	54,903	37,616	36,528
% BMI >25	na	32.0	32.7	33.6	34.4
BMI >30	na	12,480	19,683	13,946	13,720
% BMI >30	na	11.1	11.7	12.5	12.9
BMI >35	na	4,032	6,813	4,880	4,689
% BMI >35	na	3.6	4.1	4.4	4.4
Smoker	37,540	30,782	25,656	14,891	12,527
% smokers	20.5	17.1	14.2	12.6	11.5
Multiple pregnancies	4,353	4,617	4,727	3,116	2,747
% multiples	2.4	2.6	2.6	2.6	2.5
Stillborn multiples	51	111	61	40	29
% stillborn multiples	1.2	2.4	1.3	1.3	1.1
Para 0	78,718	77,231	77,685	51,675	48,584
% Para 0	43.0	42.9	43.0	43.8	44.5

Regression analysis	**Hazard ratio§ of stillborn (2000-2002 reference)**				
Crude#	1	0.95	0.89	0.72	0.59
Adjusted for GA¤	1	1.02	0.98	0.78	0.65
95% confidence intervals		0.89-1.17	0.85-1.12	0.66-0.92	0.53-0.78
Adjusted excpt, Plurality*¤	1	1.03	0.89	0.73	0.62
95% confidence intervals		0.90-1.18	0.78-1.03	0.61-0.86	0.52-0.75
Fully Adjusted¤**	1	1.07	0.96	0.78	0.69
95% confidence intervals		0.93-1.23	0.83-1.11	0.65-0.92	0.57-0.83

*) Adjusted only for age, smoking, and parity **) Additionally adjusted for plurality
§) Hazard ratios by cox regression. The crude estimates were calculated by logistic regression, and the risk estimates were odds ratios

Figure 1

Proportion (%) of induced deliveries and of children born from 41 weeks and 42 weeks, respectively, in Denmark from 2000 through 2012, Number of children born: 832,935.

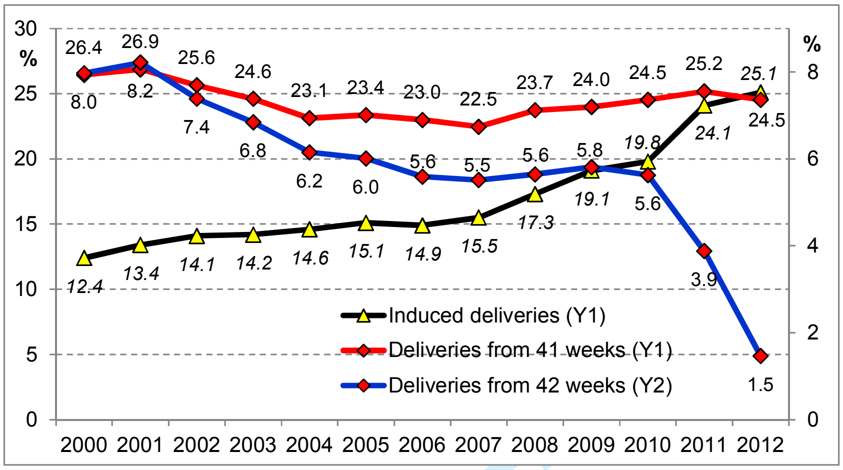


Figure 2

Fetal deaths per 1,000 ongoing pregnancies according to gestational age during the periods 2000-2008 and 2009-2012.

Number of weeks: 3,406,615, Number of fetal deaths: 3,770.

Lower part the same in a semi-logarithmic plot.

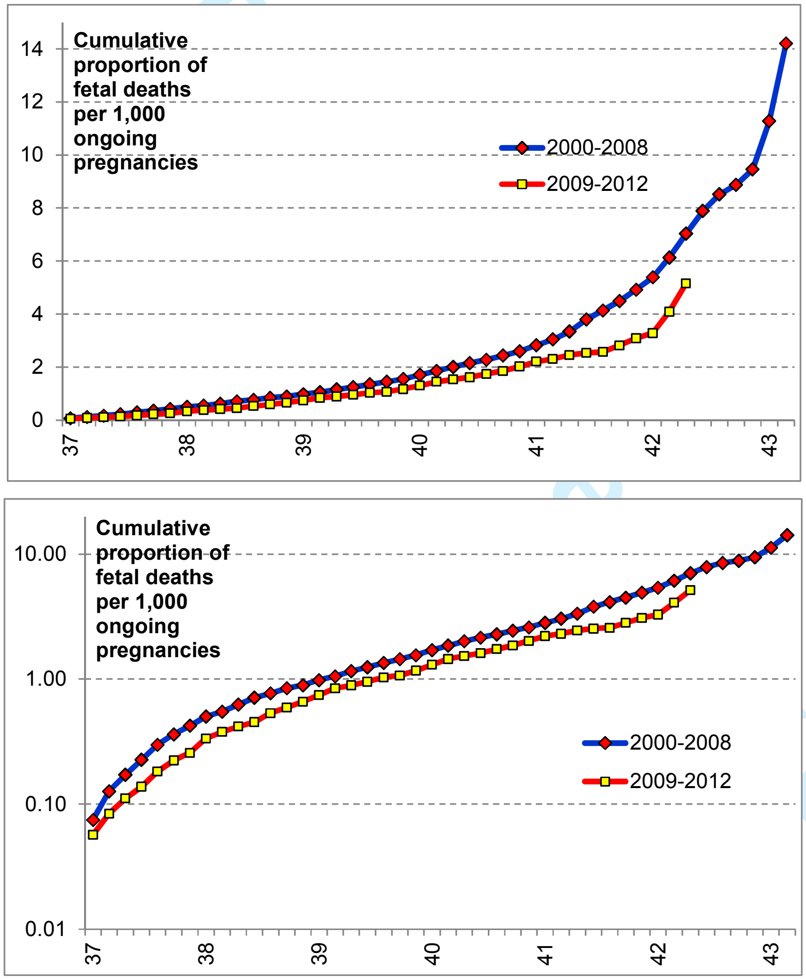
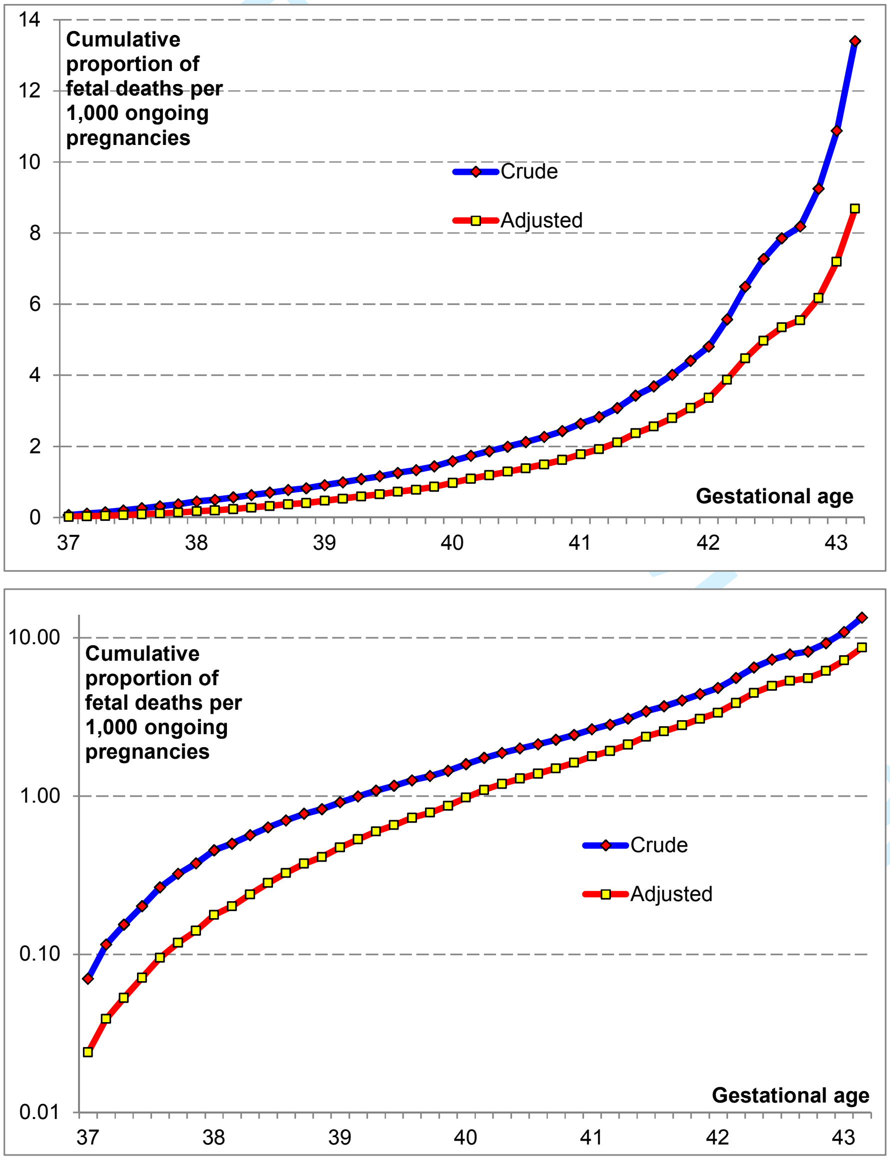


Figure 3

Crude fetal deaths per 1,000 ongoing pregnancies according to gestational age during the period 2000-2012 and after adjustment for different confounders.*

Number of weeks: 3,406,615. Number of fetal deaths: 3,770.

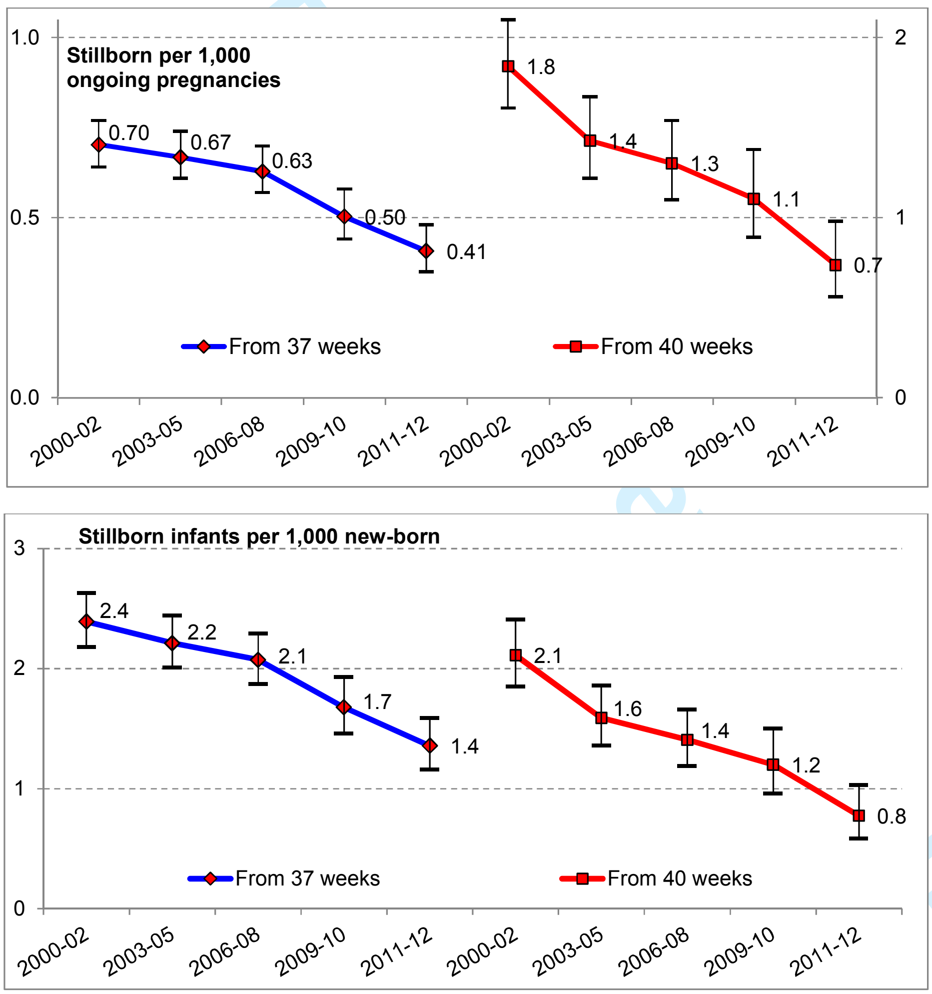
Lower part the same in a semi-logarithmic plot



*) Adjusted for age, calendar year, parity, plurality, and smoking

Figure 4

Fetal deaths per 1,000 ongoing pregnancies (upper), and per 1,000 new born (lower) after 37 and 40 gestational weeks, respectively, in different sub-periods from year 2000 through 2012. 95% confidence limits indicated.

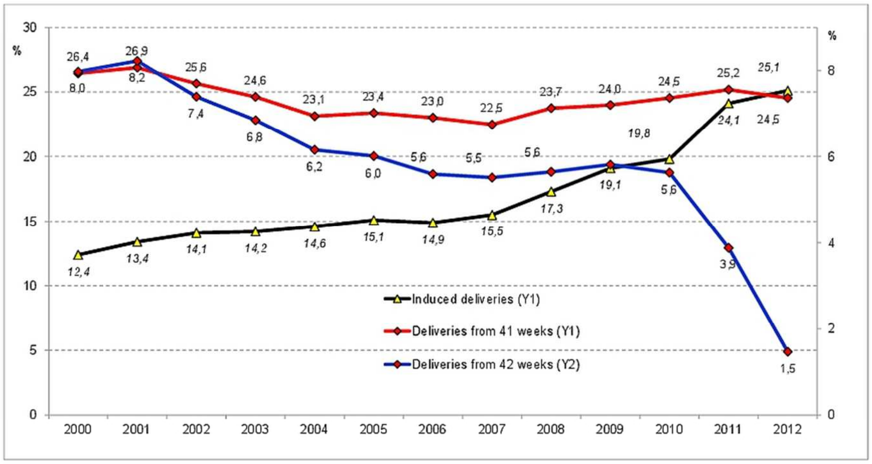


Online supplement

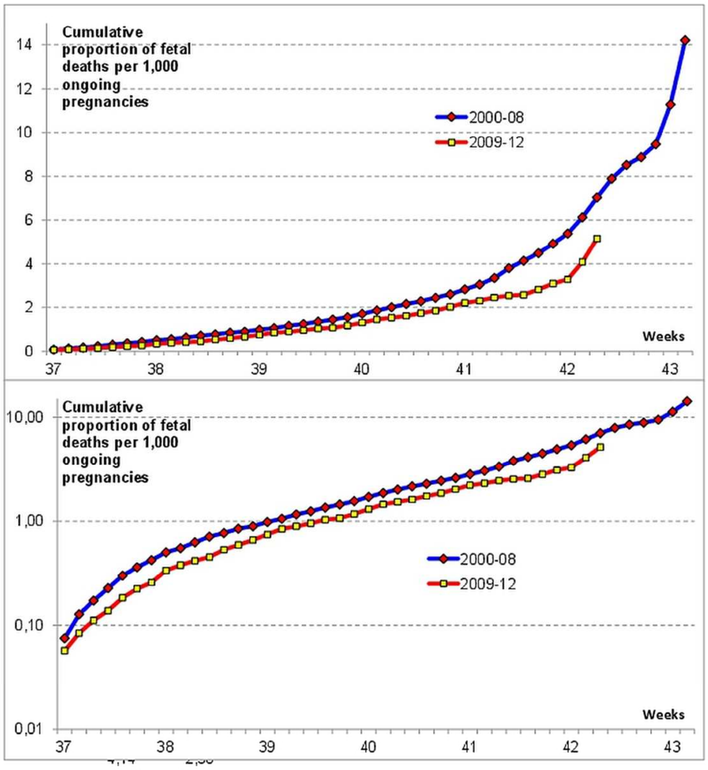
Table 1S

Number of born and stillborn in and from different gestational weeks and periods in Denmark 2000-2012.

	2000-02	2003-05	2006-08	2009-10	2011-12	2000-08	2009-12	2000-12
New-born								
<37	14,127	14,806	15,171	9,212	8,693	44,104	17,905	62,009
37+0-6	10,964	12,129	11,533	7,066	6,369	34,626	13,435	48,061
38+0-6	24,807	27,976	28,521	17,757	16,121	81,304	33,878	115,182
39+0-6	42,212	42,303	42,711	27,282	24,523	127,226	51,805	179,031
40+0-6	53,193	51,410	52,874	35,005	32,777	157,477	67,782	225,259
41+0-6	36,415	33,813	34,267	23,570	26,106	104,495	49,676	154,171
42+	15,504	12,337	10,946	7,273	3,162	38,787	10,435	49,222
Total	197,222	194,774	196,023	127,165	117,751	588,019	244,916	832,935
37+	183,095	179,968	180,852	117,953	109,058	543,915	227,011	770,926
40+	105,112	97,560	98,087	65,848	62,045	300,759	127,893	428,652
41+	51,919	46,150	45,213	30,843	29,268	143,282	60,111	203,393
Number of stillborn infants								
<37	397	517	617	341	341	1,531	682	2,213
37+0-6	72	83	70	32	25	225	57	282
38+0-6	62	85	78	46	35	225	81	306
39+0-6	82	75	89	41	40	246	81	327
40+0-6	96	71	72	47	36	239	83	322
41+0-6	77	71	49	26	9	197	35	232
42+	49	13	17	6	3	79	9	88
Total	835	915	992	539	489	2,742	1,028	3,770
37+	438	398	375	198	148	1211	346	1557
40+	222	155	138	79	48	515	127	642
41+	126	84	66	32	12	276	44	320

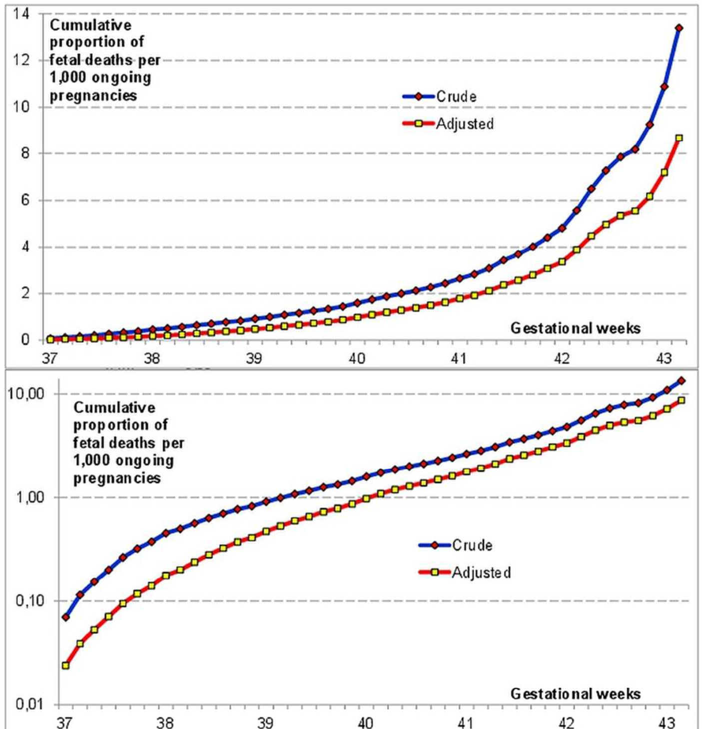


90x69mm (300 x 300 DPI)



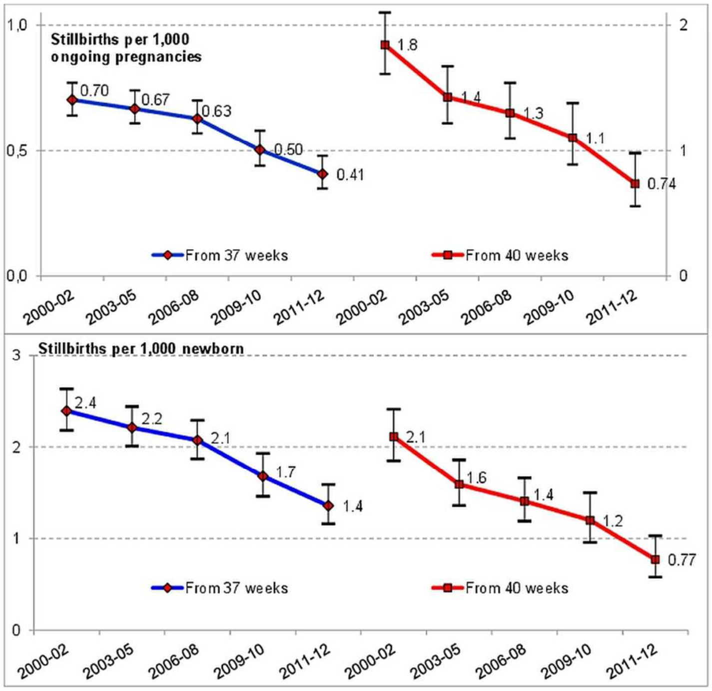
	4,49	2,82
	4,92	3,09
42	5,39	3,28
	6,13	4,09
	7,04	5,16
	7,89	
	8,52	
	8,88	
	9,46	
43	11,29	
	14,21	

90x116mm (300 x 300 DPI)



	3,7	2,6
	4,0	2,8
	4,4	3,1
42	4,8	3,4
	5,6	3,9
	6,5	4,5
	7,3	5,0
	7,9	5,4
	8,2	5,6
	9,3	6,2
43	10,9	7,2
	13,4	8,7

90x116mm (300 x 300 DPI)



90x116mm (300 x 300 DPI)

Online supplement

Table 1S

Number of born and stillborn in and from different gestational weeks and periods in Denmark 2000-2012.

	2000-02	2003-05	2006-08	2009-10	2011-12	2000-08	2009-12	2000-12
				New-born				
<37	14,127	14,806	15,171	9,212	8,693	44,104	17,905	62,009
37+0-6	10,964	12,129	11,533	7,066	6,369	34,626	13,435	48,061
38+0-6	24,807	27,976	28,521	17,757	16,121	81,304	33,878	115,182
39+0-6	42,212	42,303	42,711	27,282	24,523	127,226	51,805	179,031
40+0-6	53,193	51,410	52,874	35,005	32,777	157,477	67,782	225,259
41+0-6	36,415	33,813	34,267	23,570	26,106	104,495	49,676	154,171
42+	15,504	12,337	10,946	7,273	3,162	38,787	10,435	49,222
Total	197,222	194,774	196,023	127,165	117,751	588,019	244,916	832,935
37+	183,095	179,968	180,852	117,953	109,058	543,915	227,011	770,926
40+	105,112	97,560	98,087	65,848	62,045	300,759	127,893	428,652
41+	51,919	46,150	45,213	30,843	29,268	143,282	60,111	203,393
				Number of stillborn infants				
<37	397	517	617	341	341	1,531	682	2,213
37+0-6	72	83	70	32	25	225	57	282
38+0-6	62	85	78	46	35	225	81	306
39+0-6	82	75	89	41	40	246	81	327
40+0-6	96	71	72	47	36	239	83	322
41+0-6	77	71	49	26	9	197	35	232
42+	49	13	17	6	3	79	9	88
Total	835	915	992	539	489	2,742	1,028	3,770
37+	438	398	375	198	148	1211	346	1557
40+	222	155	138	79	48	515	127	642
41+	126	84	66	32	12	276	44	320

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract: *Line 35*
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found: *Line 38-43*
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported: *Line 66-76*
Objectives	3	State specific objectives, including any prespecified hypotheses: *Line 73-76*
Methods		
Study design	4	Present key elements of study design early in the paper: *Page 3 line 79*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection: *Line 79-80*
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up: *Line 81-86*
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed: *This study was not matched*
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable: *Line 88-93*
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group: *Line 79-87*
Bias	9	Describe any efforts to address potential sources of bias: *Line 106-119*
Study size	10	Explain how the study size was arrived at: *Line 84*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why: *Line 88-119*
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding: *Line 106-119*
		(*b*) Describe any methods used to examine subgroups and interactions 116-119
		(*c*) Explain how missing data were addressed: *Line 94-98*
		(*d*) If applicable, explain how loss to follow-up was addressed: *Line 94-98*
		(*e*) Describe any sensitivity analyses: *Line 119*
Results		
Participants	13*	(a) Report numbers of individuals included in the study, completing follow-up, and analysed: *Line 94-98, 123-127*
		(b) Give reasons for non-participation at each stage: *Not relevant*
		(c) Consider use of a flow diagram: *Not relevant in this case*
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders: *Table 1*
		(b) Indicate number of participants with missing data for each variable of interest: *Line 94-98*
		(c) Summarise follow-up time (eg, average and total amount): *Not relevant*
Outcome data	15*	Report numbers of outcome events or summary measures over time: *Table 1, Table 2 and Table 1S, Line 133-152*

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included: *Fig. 2 and Fig. 3*
		(*b*) Report category boundaries when continuous variables were categorized: *Line Table 1*
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period: *Line 144-152, 191-193*
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses: *Line 206-207*
Discussion		
Key results	18	Summarise key results with reference to study objectives: *Line 211-2123*
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. *Line 280-283*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. *Line 252-261*
Generalisability	21	Discuss the generalisability (external validity) of the study results: *Line 239-242*
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based: *Line 299-306*

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.