PROTOCOL

Risk factors for cause-specific stillbirth and neonatal death
-a study within the Danish Birth Cohort

Ellen Aagaard Nøhr, Jørn Olsen, Bodil Hammer Beck, Anne-Marie Nybo Andersen, Anette Werner & Sanne Lausen Wolff

Introduction
Globally, the incidence of stillbirth and neonatal mortality differs considerably (1) and high rates are believed to be attributable to poor baseline maternal health, poor prevention and treatment of maternal and fetal conditions during pregnancy, and inappropriate management of complications during childbirth. The national perinatal mortality rates are considered to be a relevant marker to assess the standard of living within a population (2), and thus with increasing wealth, the rates have been reduced immensely within high-income nations through the 20th century (3). In Denmark, the incidence has been steady at 0.07% through the past years (4). This rate is among the world’s lowest, however in comparison, Norway, Sweden, Finland and Iceland have achieved even lower rates (<0.05%) (2). Given this, a potential of reducing the more than 400 yearly perinatal losses in Denmark possibly remains.

Insight in the causes and risk factors for stillbirth and neonatal death is necessary to be able to identify which areas of effort can improve clinical practice and obviate future losses. In addition, such knowledge is important in the dialogue with parents who have lost and who need to know what went wrong and what the prospects are in future pregnancies (5).

The large size of the Danish National Birth Cohort (DNBC) including more than 100,000 pregnancies (6) and approximately 600 peri- and neonatal deaths (7,8) and containing uniquely detailed information on potential risk factors (9) makes this cohort a significant contribution to the evidence on this important issue.

Objective
The aim of this study is to:
1) classify cases of stillbirth and neonatal deaths according to the main cause of death and
2) examine selected risk factors.

Hypotheses
We hypothesize that:
1) The cause of stillbirth and neonatal mortality varies according to maternal risk factors.
2) Causes of stillbirth and neonatal death vary according to gestational age at birth.

Methods and materials
Design
Prospective cohort study based upon data from DNBC.

Data
Exposure variables are obtained from the first and second telephone interviews.

Information about pregnancy outcome is based on data from the Medical Birth Registry in Denmark and the National Discharge Registry, which have been linked to DNBC by personal identification numbers (12).

All medical records including autopsy results have already been collected – for stillbirths by Ellen Aagaard Nøhr and Bodil Hammer Bech – for neonatal deaths by Anette Werner. All stillbirths were prior to this study blindly categorized by Bodil Hammer Bech and Ellen Aagaard Nøhr independently (14) according to a modified version of the classification system of Andersen et al. (13). Neonatal deaths will be classified according to the same system by Sanne Wolff. In case of doubt, another investigator will be consulted.

Study population
The study population consists of pregnant women who completed the first telephone interview, and who gave birth after a minimum of 28 weeks of pregnancy. Women with missing information on gestational age will be excluded.

Exposures
Subfecundity:
Time to pregnancy
Infertility treatment

Reproductive history:
A history of spontaneous abortion
A history of stillbirth or neonatal death
A history of SGA or preterm birth

Environmental characteristics (GIS data)
Geographical residence during pregnancy

Infection during pregnancy
Self-reported infections (hyperthermia, urinary tract infections, vaginal infections, diarrhea, cough, herpes labialis, genital herpes, venereal warts)
Paracetamol use in pregnancy
Life style and nutrition
Smoking and nicotine replacement therapy
Alcohol consumption
Weight gain in first trimester of pregnancy
Physical activity
Preconceptional intake of folic acid
Intake of caffeine (coffee, tea and cola)
Eating disorders
Socio-economic position

Other
Maternal and paternal age
Thyroid function

Outcome
Cause-specific stillbirth or neonatal death at ≥28 weeks of gestation categorized according to classification system by Andersen et al. In some analyses, late miscarriages (after 22 weeks of gestation will be included) to cover the entire range of stillbirth according to the Danish definition after 2004.
This system is a combination of two British classification systems, which focuses on fetal, obstetric and neonatal factors (13). Because we want to study stillbirth and neonatal death related to placental causes, Andersen’s category “feto-placental dysfunction,” was modified a priori. Thus the cause “umbilical cord complications” was placed in a separate category, whereas “fetal growth restriction” (FGR), “infarction of the placenta without FGR,” and “abruptio placenta” are combined into a single category, placental dysfunction (11).

Statistics
STATA12 will be used for all statistical analyses.
Descriptives will include frequencies of demographic and clinical characteristics across live births and peri- or neonatal death. Furthermore, the incidence of different causes of death will be displayed according to gestational age at birth.
To examine potential variations in cause of death according to chosen exposure variables, all categories of cause specific death will be analyzed by comparing incidences in the exposure groups with incidences in the control group (RR with 95% CI). The results of the univariate analyses will be adjusted for potential confounders chosen a priori, using logistic regressions or Cox regression analyses. Interactions between the main exposure and confounding factors will be assessed.

Collaborators
Ellen Aagaard Nøhr (Institute of Clinical Research, University of Southern Denmark), Jørn Olsen and Bodil Hammer Bech (Department of Public Health, Section for Epidemiology,
Time schedule

The project has been approved by the Danish Data Protection Agency, and the classification of neonatal deaths will start immediately after the permission from the DNBC has been granted. Analytic work and draft preparation will begin in January 2014. We expect all analyses to be published ultimo 2018.

Three articles are planned as part of the Master’s thesis of stud.scient.san., Sanne Lausen Wolff:

- Peri- and neonatal mortality classified by cause of death.
- Subfecundity and cause-specific peri- and neonatal death.
- Reproductive history and cause-specific peri- and neonatal death.

Other articles will be based on the listed risk factors.
References


