Case study: MATERNAL COMPLICATIONS IN PREGNANCY, CAESAREAN SECTION AND ASSOCIATION WITH WHEEZING AND ASTHMA

Presented by: NINFEA cohort study, Italy

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With participation of: Charité Universitätsmedizin Berlin, and the CHICOS cohorts

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1. Background

**Early life factors and wheezing/asthma**

There is accumulating evidence of a relationship between early life environmental factors and a wide range of chronic diseases in children and adults, including obstructive lung diseases. With regard to asthma, the greater influence of maternal compared with paternal asthma and atopy on the development of asthma in offspring suggests a role of the pre- and perinatal environment. In previous studies we demonstrated that taking into account specific phenotypes, based on time of appearance and duration of wheezing (transient early wheezing: wheezing confined to the first 2-3 years of life; persistent wheezing: wheezing persistent up to school age; late-onset wheezing: wheezing only at school age) is crucial to evaluate the role of pre-peri- and post-natal determinants (Rusconi, Galassi et al., Am J Respir Crit Care Med. 1999).

1.1 Maternal complications in pregnancy

Epidemiologic studies investigating whether maternal complications in pregnancy are associated to respiratory problems in the offspring, in particular wheezing and asthma, are comparatively scarce and conflicting.

In a large cross sectional study we found a relationship between hypertension/pre-eclampsia and both transient early wheezing, persistent wheezing and late-onset wheezing (Rusconi, Galassi et al., Am J Respir Crit Care Med, 2007). An association between hypertensive disorders in pregnancy and asthma/wheeze in the first years of life has been found in two other recent studies (Reichman, Matern Child Health, 2008; Prabhu, presented at ERS 2010) while it has been denied in other studies (Nafstad P, Eur J Epidemiol 2003; Annesi-Maesano I, Allergy 2001). We also found results showing an association between diabetes in pregnancy and early and persistent wheezing (Rusconi, Galassi et al., Am J Respir Crit Care Med, 2007); in addition an association between maternal diabetes and asthma at 6 years of life has been found in a recent study (Risnes KR, Am J Epidemiol 2011). Some patophysiological mechanisms could explain these associations. Hypertension in pregnancy may result in intrauterine growth restriction (IUGR) and hence decreased airway function, or in abnormalities in the fetal placental circulation and in a direct fetal airways damage, independent of IUGR.

Abnormalities in the fetal placental circulation have been described also in diabetic pregnancies; in these pregnancies a delay in the production of phospatidyl glycerol, and hence a surfactant deficiency, could also account for an excess of risk of respiratory problems, at least in the neonatal period.

Two recent prospective cohort studies found an association between pre-pregnancy obesity and asthma in the first 3 years of life (Reichman, Matern Child Health, 2008) and wheezing at 6-18 months of age (Haberg, Pediatr Perinat Epidemiol 2009) in the offspring. We have found an association between weight gain in pregnancy > 15 kg and early and persistent wheezing. Haberg and Coll (2009) speculated that elevated levels of inflammatory substances (leptin, a hormone secreted by adipocites) in obese mothers during pregnancy could influence the utero environment.
and the foetal development either via inflammatory mediators or through impaired placental function.

The main problems in studies on maternal complication in pregnancy and wheezing/asthma in the offspring are the time of ascertain of both risk factors and outcomes (recall bias, inaccuracy in retrospective reports and misclassification) and the complex linkage between maternal prenatal characteristics and child outcomes (e.g. Pregnant women with chronic hypertension have a higher risk of gestational diabetes, low birth weight newborns and preterm delivery; maternal obesity might be associated with a different pattern of nutrition and growth in the child).

1.2 Caesarean section

An association between caesarean delivery and asthma has been found in many but not all studies. Two recent meta-analyses (Thavagnanam, 2007; Bager, 2008) found a small increase in risk, but the authors discuss the problem of causality vs. confounding.

Several biological mechanisms have been reported in order to explain the association:

- method of delivery influences immune system ontogeny (neonatal immune responses) by either a direct effect on immune regulatory cells or by reducing exposure to microbes which are acquired when infants swallow vaginal fluid containing microorganisms from the mother’s gastrointestinal tract (hygiene hypothesis).
- elective caesarean section near term (37-39 weeks gestational age) has been linked with increased risk of neonatal respiratory morbidity (lack of physiological changes due to labour: cathecolamine secretion, reasorption of fetal lung liquid, production of surfactant) and later asthma
- caesarean section is associated with a decreased rate of initiation or duration of breastfeeding, which in turn has been associated in many but not all studies to an increase risk of wheezing/asthma.
- Caesarean section is associated with macrosomia which in turn has been associated to asthma (but macrosomia is also associated to diabetes and this to caesarean)

In addition there are a number of possible confounding factors:
- several maternal complications in pregnancy and/or at birth (including obesity)
- maternal asthma (especially in pregnancy)
- maternal antibiotics at delivery (administered prophylactically in cesarean)

Conclusions

The associations between maternal complications in pregnancy and mode of delivery and wheezing/asthma in childhood remain controversial, possibly due to methodological issues and variations in indications for caesarean section and delivery practices in different countries. The associations observed need to be replicated in birth cohort studies and in large population samples
Ref. no. 2011-35

2. Objective

The objective of this case-study is to analyze the associations between maternal complications in pregnancy (hypertension, diabetes, obesity) and caesarean section, and wheezing/asthma in childhood in the context of the birth-cohorts participating in the CHICOS project.

Pooling data from several cohorts would provide adequate power to study more severe and rare conditions, such as pre-eclampsia/eclampsia and diabetes and to control for several confounders. Since rates of (and indications for) caesarean section greatly vary among EU countries, international comparisons will be important to confirm the association with wheezing/asthma and, if any, to elucidate mechanisms involved. All these issues are relevant for policy making.

We are planning to prepare two scientific papers, one for each of the above mentioned risk factors (maternal complications in pregnancy and caesarean section).

As a further objective, for cohorts who already participated in ENRIECO case studies, we are planning to use as far as possible variables in the database from on-going case studies; this experience will be useful also in the light of future cooperation studies among cohorts.

3. Methods

3.1. Selection criteria for cohorts inclusion

1) Cohorts that started the enrolment after 1990.

2) Cohorts enrolling either during pregnancy or at birth, or cohorts enrolling during the first 2 months of life

3) Cohorts having recorded complications (hypertension, diabetes, pre-pregnancy body mass index, BMI) at any time during pregnancy and/or at birth or soon after birth.

4) Cohorts having recorded asthma/wheezing in the first 2-3 years of life.

Table 1 shows ENRIECO birth cohorts that, according to the ENRIECO DATABASE, have collected information on asthma/wheezing and maternal complications in pregnancy. Other cohorts not included in this list are encouraged to participate.

3.2. Exposure variables

- Maternal hypertension: either chronic hypertension before pregnancy or hypertension/pre-eclampsia/eclampsia in pregnancy
- Maternal diabetes: either chronic diabetes before pregnancy or diabetes in pregnancy
- Maternal pre-pregnancy BMI (height and weight)
• Mode of delivery

3.3. Outcomes variables

• Wheezing in the first 2-3 years of life *
• Diagnosis of asthma recorded in a questionnaire administered at school age (6-12/13 years) + wheezing recorded at school age.

*This variable is potentially available from Enrieco case studies

Cohorts having recorded both mode of delivery and asthma/wheezing at school age will participate also in the case study on caesarean section.

3.4. Possible confounding variables

Note: not all the listed variables are requested in order to participate

• Maternal/paternal education *
• Maternal age*
• Maternal/paternal asthma*
• Maternal/paternal hay fever*
• Maternal asthma in pregnancy
• Smoking in pregnancy*
• Maternal previous deliveries/parity before the index pregnancy
• Number of siblings at birth *
• Twin pregnancy
• Sex*
• Gestational age*
• Birth weight*
• Breastfeeding: yes/no; < 6 months and >= 6 months
• Apgar score < 7 at 5 minutes
• Intrapartum antibiotic prophylaxis

*these variables are potentially available from Enrieco case studies

3.5. Data collection and analysis

Each cohort will prepare the variables dataset and send it to the Unit of Cancer Epidemiology of Turin (Daniela Zugna), where relevant variables will be harmonized. We are planning to use, as far as possible, the already existing databases from on-going ENRIECO case-studies; therefore, cohorts
listed in Table 1 that are already participating in the ENRIECO case-studies will be given the option to deliver only relevant key variables that are not included in the ENRIECO case-studies database.

The proposed step of analyses will be:

- bivariate (“univariate”) analyses, pooled and separately for each cohort (descriptive analyses)
- multiple logistic regression analyses, pooled and separately for each cohort
- stratified analyses (e.g. by parental allergy status)
- sensitivity analyses: with/without cohorts that (i) do not have all confounding variables; (ii) used different recruitment procedures, etc. In the analysis for mode of delivery, in order to make the group as homogeneous as possible and to avoid confounding: exclusion of children with birth weight < 2500 g and GA < 37 weeks, and (if available) Apgar score < 7 at 5 minutes (Werner et al. 2006)
- meta-analyses (if pooling is not reasonable e.g. number of confounding variables differs among cohorts).
- mediation analyses when appropriate (e.g. for hypertension in pregnancy, caesarean section, and asthma)

A detailed analysis plan will be prepared and agreed by all cohorts as soon as first descriptive analyses for each cohort will be completed.

3.6. Organisation, time distribution and publications

3.6.1. Organization

Daniela Zugna will coordinate data collection, prepare analyses datasets with the cohorts, and conduct statistical analyses (in collaboration with the biostat group at the Unit of Cancer Epidemiology) according to the plan discussed with all participating cohorts. Franca Rusconi, Claudia Galassi and Lorenzo Richiardi will supervise the work. ENRIECO cohorts that agree to participate in the present CHICOS case study will be given the chance to release already prepared variables from the ENRIECO databases. For this purpose the cohorts and the ENRIECO WP5 coordinators (Charité Universitätsmedizin Berlin, Thomas Keil, Cynthia Hohmann) have to sign an agreement form listing each variable which is allowed to be sent to the CHICOS case studies database. Each cohort team will extract and format the set of key variables according to the uniform protocol. Each cohort team will actively participate in the analysis protocol, interpretation of data and results, and drafting of scientific papers. All working group members will co-author the CHICOS report and scientific papers.
3.6.2. Time table

August 2011  Contact cohorts – send protocol, discuss participation with each cohort.
September 2011  Answers from cohorts, data transfer agreement, final list of participating cohorts
September 2011  Protocol to be sent to CHICOS Project Executive committee.
October 2011- February 2012  Definition of key variables of interest (including exact wording from cohorts); extraction of key variables from ENRIECO database; extraction of further key variables in each cohort.
May 2012  Preliminary analyses and agreement on the analysis protocol
May 2012-October 2012  Final analyses and interpretation of findings
October 2012  Final report for CHICOS
Up to June 2013  Papers writing

3.6.3. Publications
Publications planned:
- Maternal complications in pregnancy and early wheezing in childhood
- Is caesarean section associated to asthma and wheezing in preschool and school children in birth cohorts from different European countries? (only for cohorts with available data on mode of delivery AND asthma at school age)

3.6.4 Permissions and ethical issues
The principal investigators obtain the necessary permissions to perform data analyses at the international level. Permissions to use the existing and already prepared data from ENRIECO case-studies database will be obtained from each ENRIECO cohort. The principal investigators keep all personal identifiers according to national guidelines. Data analyses and presentation of papers should adhere to good epidemiological practice and the STROBE guidelines. Aggregated data sets with individual anonymous observations, if any, are to be deleted, when the data analysis is finished. As soon as we receive response from cohorts we will send the proposal to the ethical committee of the Anna Meyer Children University Hospital, Florence.

If cohort accepts to participate in the case study:
1) Reply by September 5 to Daniela Zugna (daniela.zugna@unito.it) and Franca Rusconi (f.rusconi@meyer.it) indicating whether the cohort is interested in joining the study, and which steps (if any) are needed to formalize participation.
4. References

Annesi-Maesano I, Moreau D, Strachan D. In utero and perinatal complications preceding asthma. Allergy 2001; 56: 491-497.


Reichman NE and Nepomnyasky N. Maternal pre-pregnancy obesity and diagnosis of asthma in offspring at age 3 years. Matern Child Health 2008; 12: 725-33


5. Table I -

Cohorts of potential interest for the case study (i.e., with available information on asthma/wheezeing and complications in pregnancy) according to the Enrieco Database.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Country</th>
<th>Calendar period of enrolment</th>
<th>Enrolment</th>
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<th>Participating in Enrieco studies</th>
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<td>C. Faroes V</td>
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<td>2007-2009</td>
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<td>Co.N.ER</td>
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<td>7500</td>
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<td>RHEA</td>
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<td>1500</td>
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<td>Lifeways Cross generation Study</td>
<td>Ireland (not in ENRIECO database)</td>
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