Data collection on risk factors in pregnancy
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Section 1
General Introduction
Many pregnancies are carefully planned nowadays and generally, when a woman gets pregnant, she will do anything possible to protect the health of her yet unborn child. Not all negative birth outcomes can be prevented, but due to extensive research, more and more is known about risk factors and subsequent preventive actions in pregnancy. Yet in spite of this increasing knowledge many risks are still unclear and a lot is to be uncovered about the effects of certain health and lifestyle factors before and during pregnancy.

Epidemiologic research provides a substantial contribution to healthy pregnancies. The two main types of observational analytical epidemiological studies are the cohort study and the case-control study. Generally, a cohort study measures the occurrence of disease or outcome in two groups of individuals followed over a period of time (the cohorts), one exposed and one unexposed, allowing for direct measurement of incidence of outcome in both groups and examining multiple effects of a single exposure. In a case-control study participants are grouped based on the expression of the disease studied. The proportions exposed in both groups are compared. The advantage of a case-control design is its suitability for investigating relatively rare outcomes or outcomes with long latent periods, since participants have already developed the outcome, but it can only be performed retrospectively [1]. Both study-types have its variants, like the retrospective cohort study, the case-crossover study and the case-population design.

To be able to appoint negative or protective effects of health and lifestyle factors around pregnancy on the future health of the child, epidemiologic researchers ideally need complete and valid information about the widest possible range of pregnancy characteristics and detailed information on the outcome under investigation. These data can be obtained in various ways. Health care providers or medical records can be consulted retrospectively. This information was originally collected for medical reasons and data important for epidemiological research might be missing. Another approach is to form a pregnancy cohort. Women planning a pregnancy or being pregnant are asked to join the cohort and provide information about their pregnancy, lifestyle choices, health and medication use. This information prospectively provided by the women themselves can be complemented with data from health care providers, medical records or tissue samples.

Prospective data collection directly from pregnant women has several advantages. Since the pregnancy has not ended yet, women will remember their health and lifestyle choices and recall bias is avoided. Yet for a rare exposure to be associated with a rare outcome, large numbers of participants will be needed. There are several methods to collect direct prospective data from pregnant women. Traditionally pen-and-paper surveys are handed out or send to potential participants by mail. Another approach is to conduct an interview either face-to-face or by telephone.
The cost-effectiveness of these traditional modes has been a point of discussion. Distributing and collecting questionnaires or performing interviews is time consuming and expensive and recruitment rates are declining over the years.

Ever since the Internet is emerging, researchers have been investigating its possibilities as a tool for data collection. A Web-based survey is convenient for participants, data collection is efficient, direct entry of the data in the database assures data quality and many potentially eligible subjects are to be reached [2,3]. Internet access is still increasing and although literature shows that respondents attending a web-based survey are comparable to the ones participating in traditional survey methods and information acquired is at least as reliable, researchers are still debating the validity of the data collected and the selectivity of the sample acquired [2,4-6].

To explore the possibilities of collecting information on medication use and other potential risk factors directly from pregnant women via the Internet, the PROTECT pregnancy study has been set up. Pregnant women were recruited in four participating countries: The United Kingdom (UK), Denmark, The Netherlands and Poland. After enrolment women were to complete a baseline questionnaire to provide demographic information, information about their health and lifestyle, their pregnancy and medication use just before and during this pregnancy. On a periodic basis participants were asked to give an update of this information, and when the pregnancy had ended women were asked to fill in a short questionnaire about the pregnancy outcome. The design of the study is shown in Appendix 1.

This thesis aims to investigate the different methods of data collection of risk factors in pregnancy. In addition several observational epidemiologic study designs were used to assess associations with negative birth outcomes. The benefits and drawbacks of the use of the Internet for data collection were elaborated, along with those of more traditional methods and direct data collection from the pregnant women themselves is compared to indirect data collection from existing databases. The databases used for the studies in this thesis are the IADB.nl pregnancy database and EUROCAT NNL.

EUROCAT NNL is a population-based birth defect registry in the northern part of the Netherlands, covering approximately 10% of all births in the country. All livebirths, stillbirths and terminations of pregnancy affected with a major malformation of which the mother lived in the EUROCAT region at the time of birth can be recorded in the database. Regional obstetricians and physicians are asked to report birth defects and in addition eligible cases are actively traced in hospital reports. Information about the malformations present and about possible risk factors is collected from the parents, hospital records and pharmacies.

The IADB.nl is a population-based pharmacy prescription database containing data on prescriptions filled at 55 pharmacies in the Northern Netherlands, covering a population of approximately 500,000 individuals.
Because of the high level of commitment of patients to their pharmacies, the IADB.nl contains an almost-complete medication history for each individual registered, except for medications prescribed during hospitalization or bought over-the-counter. The IADB.nl has established a pregnancy database by connecting every child registered in the database with a female, 15–50 years old, with the same address code, providing there is only one. Using this method, the pregnancy period can be identified for the mother by subtracting 273 days (3 trimesters of 91 days) from the child’s date of birth.

One of the area’s in which there is still a lack of information about possible effects on the fetus is the use of medications during pregnancy. Many pregnant women use medications during pregnancy. Drug use during pregnancy cannot always be avoided, especially for women with chronic conditions. And since the first weeks of pregnancy are the most critical for the developing embryo, possible negative effects have already taken place when a pregnancy is identified and actions are taken. A literature review reported estimates of overall prescription drug use in pregnancy in developed countries of 27-93% (excl. vitamins and minerals) [7]. For many drugs on the market, the effects on the unborn child still have to be established. Since results from animal studies do not always predict teratogenicity in humans and pregnant women are excluded from pre-marketing trials for ethical reasons, post-marketing surveillance is necessary. Therefore, one of the focal points of this thesis is the collection of data on medication use during pregnancy and the investigation of relations between the use of particular medications during pregnancy and several negative effects for the child.

Another focal point is the use of folic acid supplements before and during pregnancy. The use of folic acid before and during pregnancy to prevent neural tube defects (NTDs) are known for quite a while now [8,9] and ever since other benefits have been discovered [10,11]. Yet, the use of folic acid in Europe can still be improved. Unlike USA, Canada and other countries, most European countries did not yet introduce mandatory fortification of food with folic acid and periconceptional supplementation of folic acid in several European countries showed to vary from 7-51% [12,13]. On the other hand, there has always been discussion about the safe upper limit of folic acid supplementation. Folic acid use has been linked to the development of cancer although findings were contradictory, and there have been concerns about the long term health effects for the offspring [14-18].

Besides evaluating folic acid as a supplement to promote the health of the baby we will also focus on asthma and the use of asthma medication during pregnancy as potential risk factors for the baby’s health. Asthma prevalence has increased worldwide, with estimates up to 12% of pregnant women having asthma [19,20]. While negative effects of asthma medication on the unborn child have shown to be minimal [21], uncontrolled asthma during pregnancy is associated with significant risks for the mother as well as the baby [22,23].
Therefore, current international guidelines on the treatment of asthma recommend optimal asthma control during pregnancy [24,25]. In this thesis we will use different methods to investigate the use of asthma medication before and during pregnancy.

**Contents of this thesis**

The next section of this thesis will cover direct data collection via pen-and-paper questionnaires. **Chapter 2.1** describes a survey conducted in 2009 among pregnant women in the Northern Netherlands at their knowledge and use of folic acid. **Chapter 2.2** shows the results of a follow-up survey conducted five years later. **Chapter 2.3** describes a comparison study evaluating the representativeness of a Dutch non-malformed control group to see if it is useful as a control-group for EUROCAT NNL.

Section three of the thesis is about indirect data collection and the studies outlined in this section all use the IADB.nl or EUROCAT NNL database. **Chapter 3.1** shows the results of a drug-utilization study, describing the use of asthma medication around pregnancy using the IADB.nl pregnancy database. In **Chapter 3.2** the IADB.nl pregnancy database is used in a cohort study to investigate the association of high dose folic acid use in pregnancy with the use of asthma medication in the offspring. **Chapter 3.3** consists of a case-control study using EUROCAT NNL data to assess the association of folic acid antagonists with folic acid sensitive birth defects. Section three ends with a case-population study investigating whether a comparison of drug use rates in case pregnancies from EUROCAT NNL with population based prescription rates from the IADB.nl, could be used to detect signals of teratogenic risk of drugs (**Chapter 3.4**).

Section four describes data collection in pregnancy using web-based questionnaires and starts with an introductory chapter (**Chapter 4.1**) showing the results of a review investigating the use of web-based surveys examining a pregnancy-related topic. Benefits and drawbacks are evaluated, along with the topics covered, and validity and completeness of the web-based surveys compared to traditional methods. The study shown in **Chapter 4.2** compares data about lifestyle factors and birth outcomes entered by the women participating in the PROTECT pregnancy study with figures of pregnant women in the general population of the participating countries to explore representativeness of the sample and validity and completeness of the data collected. **Chapter 4.3** describes a survey with pregnant women having asthma asking about their medication use, the course of their condition during pregnancy and their perceptions about the risks of their asthma and asthma medications for their baby.

Finally the thesis concludes with a general discussion of our findings, practical implications and recommendations for further research.
References

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