The Dutch perinatal and neonatal registers : applications in perinatal epidemiology

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La réalité d'aujourd'hui est
l'utopie d'hier

(Le Corbusier, 1887-1965, Notes et Carnets)

Voor Jari, Luc & Thom

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Chapter 1

Introduction

Introduction

Each year, over 200,000 children are born in the Netherlands. The “miracles of life” of pregnancy and birth have a huge impact – and not only on individual parents. At national and international level, information on births and their outcomes is often used to describe the health status of an entire country. Thus we see that perinatal and neonatal mortality – to take but one example – are widely used as indicators of quality of obstetric and neonatal care.

Though mortality rates are sometimes used for international comparisons, there is debate on whether or not it is justified to compare mortality parameters between countries. [1;2] The use of such statistics as indicators of quality of care is made difficult by differences between registration practices and between the distributions of risk factors for perinatal mortality, such as birthweight and gestational age. [3-7] When mortality figures are compared, it is therefore a prerequisite to know precisely what information has been collected and how it was registered.

Over recent decades, perinatal and neonatal mortality in Western countries have decreased substantially. As a result, morbidity in the first weeks of life has become more important as a measure of perinatal and neonatal care. For this reason, the registration of perinatal and neonatal morbidity is becoming essential.

Continuous registration is needed to evaluate the effects of medical developments such as assisted reproductive techniques and the treatment of premature infants on the health status of children. Perinatal outcomes in the Netherlands are also influenced by demographic changes such as the rising maternal age of first-time mothers or the increasing proportion of women from ethnic minorities. These developments further emphasize the need for the continuous registration of perinatal information.

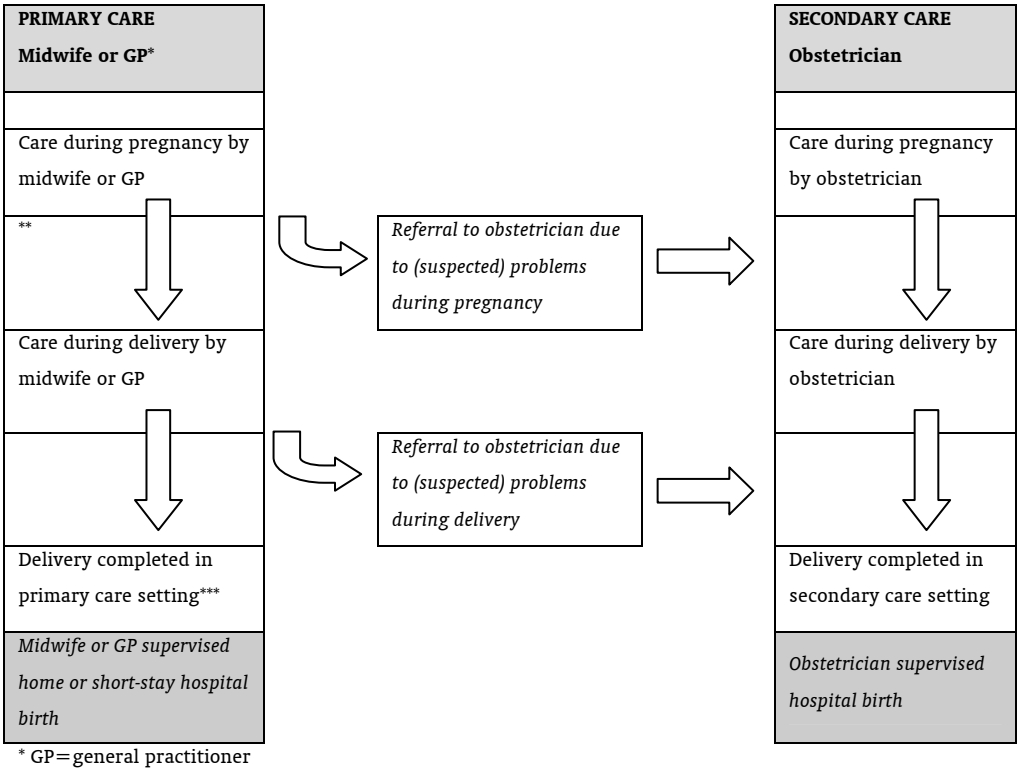
Such examples underline the importance of registering perinatal and neonatal information at a national level. These statistics are essential to monitoring the health of

newborns, detecting potential risk factors of morbidity and mortality in the perinatal period, and to evaluating perinatal care.

The Dutch maternity system

In most Western countries, births take place in a hospital under the supervision of an obstetrician. An notable exception to this rule is the Netherlands, where planned home births, usually under the supervision of a midwife, currently represent around 30% of births. [8,9] Figure 1 shows the different types of obstetric care by caregiver and place of birth for the Dutch situation.

Figure 1: Obstetric care by type of caregiver and place of birth in the Netherlands



* GP=general practitioner

** An obstetrician may be consulted without resulting in referral to secondary care

*** Referral to secondary care may take place after delivery, for example due to excessive blood loss

Within the Dutch maternity system, most women start their pregnancy care with an independent midwife or general practitioner – in other words, both in primary care. Referral to an obstetrician (i.e. secondary care) occurs only when complications arise or are suspected during pregnancy, labour or puerperium. Only a small percentage of women start their pregnancy care with an obstetrician, for example when they have a history of obstetric problems, such as a previous caesarean section, or otherwise of medical problems such as epilepsy. The majority of births in primary care take place under the supervision of an independent midwife. In 2000, no more than 7% of births were estimated to have take place under the care of a GP. [8] Even if the birth takes place in the care of an obstetrician, medical check ups during puerperium are mostly provided at home by a midwife. Postpartum care of the mother and child is provided at home by a *kraamverzorgster*, i.e. a maternity home care assistant.

The key principle of the Dutch maternity care system is the performed risk-selection procedure by midwives. Women with a low-risk pregnancy remain under the responsibility of a midwife up to and including delivery, whereas women with a high-risk pregnancy are always referred for secondary obstetric care. Compared to other countries in Western Europe, where women may deliver only in a clinical setting, the Dutch maternity system is unique. The need to continuously monitor this maternity care system also makes it essential to register information on perinatal care and neonatal outcomes on an ongoing basis.

Registration of perinatal and neonatal information in the Netherlands

As stated above, the registration of perinatal and neonatal information is fundamental to monitoring a newborn's health, detecting potential perinatal risk factors and evaluating perinatal and neonatal care. At present, however, the Netherlands has no single national-level registration for recording full perinatal and neonatal information on all births. Instead, information is collected separately in a number of registers.

One central organisation, Statistics Netherlands (CBS, *Centraal Bureau voor de Statistiek*), collects concise population statistics, including certain perinatal statistics, on the basis of the automated municipal population registers (GBA, *Gemeentelijke Basis Administratie*

persoonsgegevens) which store demographic information on all inhabitants at municipal level. [10] On the basis of the municipal registers, demographic data on a range of factors such as the number of births, live births, fetal deaths, multiple births and maternal age and ethnicity are compiled yearly. Other information such as place of birth and use of oral contraceptives are generated only periodically via surveys in a random population sample (the so-called *Gezondheidsenquête*). However, the perinatal information gathered by Statistics Netherlands is very limited with regard not only to the number of items, but also to the level of detail. The limitations with regard to national perinatal data are illustrated in the following two examples.

First, the last year in which annual information was collected on the place of delivery and the corresponding obstetric assistance was 1993. Since then, this information has been gathered via periodic survey in a randomly selected population sample. As a consequence, no continuous data are available to monitor Dutch trends in planned home births – a rather odd situation for a country with such a unique maternity care system.

Second, Statistics Netherlands data does not make it possible to calculate perinatal mortality rates according to the World Health Organisation (WHO) definitions, [11] which require data on birthweight or gestational age – information which the municipal registers do not record for all births. These registers record birthweight only for early neonatal deaths, and gestational age only for stillbirths and early neonatal deaths.

To a certain extent, the limited perinatal data available from Statistics Netherlands is supplemented by perinatal information contained in a number of other national or regional registers. Table 1 gives an overview of these registers. The following registers have national coverage: Statistics Netherlands, NSCK, NVSCA, LMR, PALGA, LVR-1, LVR-2 and LNR. The coverage of EUROCAT is regional. Four registers (EUROCAT, NVSCA, PALGA, NSCK) contain detailed information only on specific perinatal topics, whereas others, such as Statistics Netherlands, register more perinatal topics, but not in detail.

The most obvious national registers usable to create detailed Dutch national perinatal and neonatal information are the national perinatal and neonatal registers, LVR-1, LVR-2 and LNR, which are used respectively by midwives, obstetricians and paediatricians to record a large amount of detailed information on pregnancy, delivery, puerperium, and also on newborns admitted to a paediatric ward. These registers contain some overlaps (due to frequent referrals between the different disciplines) and have so far been separate. Together, they represent a unique source for generating national perinatal statistics.

Combining the existing perinatal (LVR-1 and LVR-2) and neonatal (LNR) registers

The current absence of a single national register containing perinatal information for the Netherlands makes it is worth investigating the option of linking the separate perinatal registers, LVR-1 and LVR-2, and the neonatal register LNR. If this proves realistic, a single national perinatal database could be created, providing a basis for epidemiological research and for the generation of various types of national perinatal statistics. For example, over longer periods, trends in birth outcomes or known perinatal risk factors could be monitored and related to changes in demographic factors or changes in medical care. The care received during pregnancy and delivery could be mapped and directly related to perinatal outcomes, even if referral had taken place from a midwife to an obstetrician. Similarly, care during pregnancy and delivery could be related to neonatal outcomes registered by the paediatrician. The database could also play a role in the quality monitoring of Dutch maternity care.

In general, this linked perinatal database could play an important role in the performance of extensive epidemiological research, in quality assurance activities within the obstetric profession, and in supporting policy-making and evaluation in this field.

Table 1: Overview of Dutch registers containing perinatal information (in random order)

Name of the register or organisation	First year of registration	Coverage of the data	Data supplier	Content of registration	Collected perinatal data
Statistics Netherlands (CBS, *Centraal Bureau voor de Statistiek*) [10]	1994 (*GBA*)	National	*Municipal population registers (*GBA*) *Periodic survey in random population sample (*Gezondheids-enquete*)	Various population statistics	Limited number of perinatal items such as number of e.g. births, live births, fetal deaths, neonatal deaths, multiple births; distribution of e.g. maternal ethnicity, maternal age, place of birth, oral contraceptive use
European Registration Of Congenital Anomalies and Twins (EUROCAT), [12;13] part of the worldwide International Clearinghouse for Birth Defects.	1981	Regional (Groningen, Friesland and Drenthe)	*Physicians and midwives (after parental informed consent) *Parents of affected child (detailed questionnaire)	Congenital malformations	Detailed data on e.g. pregnancy, medication use, occurrence of congenital malformation in the family, exposure to teratogenic factors
Dutch Paediatric Surveillance System (NSCK, *Nederlands SignaleringsCentrum Kindergeneeskunde*) [14;15] under responsibility of the Paediatric Association of the Netherlands (NVK, *Nederlandse Vereniging Kindergeneeskunde*)	1992	National	*Paediatricians (monthly notification)	Rare paediatric diseases	Data on occurrence and possible risk factors of the diseases. Included diseases are e.g. neural tube defects (until 2002) and Down syndrome (since 2003)

Dutch national register for schisis and craniofacial malformations of the Dutch Society for schisis and craniofacial malformations (NVSCA, *Nederlandse Vereniging voor Schisis en Craniofaciale Afwijkingen*) [16]	1997	National	*Caregivers working in one of the 15 Dutch schisis teams treating all affected patients	Detailed registration of the exact diagnosis	Apart from the registration of schisis or craniofacial malformation, also other co-existing malformations are registered. Some demographic data such as gender and ethnicity of mother and father and data on birthweight and gestational age are collected
Dutch national register for histopathology and cytopathology (PALGA, *Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief*) [17]	1971	National	*All Dutch pathology departments	Abstracts of all pathology reports	Lethal congenital malformations
National Medical Database (LMR, *Landelijke Medische Registratie*) [18]	1986	National	*All Dutch hospitals	All clinical hospital admissions (e.g. diagnoses, durations of hospitalisation, treatments)	Information on hospital births (excluding short-stay hospital births under responsibility of the midwife), data on e.g. caesarean sections percentage
National Perinatal Register for primary care (LVR-1, *Landelijke Verloskunde Registratie, 1ste lijn*)	1985	National	*Independent midwives	All pregnancies of at least 16 weeks under responsibility of midwives	Information about pregnancy, delivery and puerperium
National Perinatal Register for secondary care (LVR-2, *Landelijke Verloskunde Registratie, 2de lijn*)	1982	National	*Obstetricians	All pregnancies of at least 16 weeks under responsibility of obstetricians	Information about pregnancy, delivery and puerperium
National Neonatology Register (LNR, *Landelijke Neonatologie Registratie*)	1991	National	*Paediatricians	All admissions of newborns to neonatal departments within the first 28 days of life or re-admissions	Information on e.g. diagnosis and treatments. Concise information on pregnancy and delivery

Objectives of this thesis

Within the scope of what has been outlined above, this thesis has the following objectives:

- to investigate the possibility of creating a single national perinatal and neonatal database based on the professional LVR-1 and LVR-2 perinatal registers and the LNR neonatal register;
- to describe the methods used to create one national perinatal and neonatal database representative of all Dutch births;
- to examine the reliability of this perinatal and neonatal database;
- to demonstrate various possible applications of such a database for epidemiological research, in order to generate information and knowledge for professionals and policymakers.

Outline of the thesis

Chapter 2 describes the methods used to combine the three separate perinatal and neonatal registers and thereby to create one database covering all Dutch pregnancies, deliveries and newborns. Chapter 3 discusses the reliability of the perinatal and neonatal database thus created. Mortality rates calculated on the basis of this database are compared with mortality rates published by Statistics Netherlands (*CBS*). Chapters 4 to 8 illustrate epidemiological research based on this perinatal and neonatal database, with Chapter 4 describing the trend in planned home births in the Netherlands over 1995-2000, and Chapter 5 examining the maternal demographic factors related to the probability of a planned home birth. Chapter 6 relates maternal ethnicity to the risk of having a child with congenital malformations. Chapter 7 compares the risk of congenital malformations between naturally conceived children and children conceived after In Vitro Fertilisation. Chapter 8 provides insight into the changes over time (1983 versus 1995) in perinatal care and survival of Dutch preterm infants. After a discussion of the results of the previous chapters, conclusions are drawn in Chapter 9.

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Chapter 2

Theoretical background to the methods used to prepare the Dutch perinatal and neonatal registers for epidemiological research purposes

To create one perinatal database representative of all Dutch births, methods were developed to link the three separate professional registers and to extrapolate the linked database for missing data due to non-participating caregivers. The outline of this chapter describing these methods is as follows:

- Description of the Dutch perinatal and neonatal registers
- Linkage of the separate registers
- Extrapolation of the linked database for non-participation
- Defining variables in the linked database

Description of the Dutch perinatal and neonatal registers

As stated in the introduction, Dutch perinatal and neonatal care in the Netherlands are registered separately in three registers: 1. the National Perinatal Database for primary care by independent midwives (LVR-1, *Landelijke Verloskunde Registratie 1e lijn*); 2. the National Perinatal Database for secondary care by obstetricians (LVR-2, *Landelijke Verloskunde Registratie 2e lijn*); and 3. the National Neonatology Database of paediatricians (LNR, *Landelijke Neonatologie Registratie*). As the database for primary obstetrical care by general practitioners has not yet been implemented well enough, it cannot be used.

Per calendar year midwives, obstetricians and paediatricians voluntarily register in these databases the care they have provided during pregnancy, delivery and puerperium. This information is recorded per child, meaning that in a multiple pregnancy each child is represented by his or her own birth record. The child's date of birth determines the year in which the data are registered.

According to the year of registration and the type of caregiver, registration has been made either on a paper form or in a computer system. LVR-2 has been totally computerised in all obstetric departments since 1984, and LNR since 1996. Since 2004, all midwifery practices have been using a computerised version of LVR-1.

Table 1: The Dutch perinatal and neonatal registers, 1995-2000 (registration years included in this thesis)

	National Perinatal Register for primary care (LVR-1)	**National Perinatal Register for secondary care (LVR-2)**	**National Neonatology Register (LNR)**
First year of registration	1985	1982	1991
Participant	Independent midwives*	Obstetricians	Paediatricians
Participation	Voluntary	Voluntary	Compulsory for NICUs** Voluntary for general paediatric departments
Participation rate			
1995	89%	-university hospital (level III): 100% -teaching hospital (level II): 100% -general hospital (level I): 84%	-NICU: 100% -general paediatric department: 50%
2000	92%	-university hospital (level III): 100% -teaching hospital (level II): 100% -general hospital (level I): 96%	-NICU: 100% -general paediatric department: 50%
Objectives	-to stimulate a consistent form of quality control for individual care providers and professional groups involved in obstetric care. -to stimulate peer review between colleague care providers in primary and secondary care. -to collect and make available obstetric information for policy-making and evaluation, scientific research and education. [1]	Same as LVR-1	-to stimulate a consistent form of quality control for individual care providers and professional groups involved in neonatal care. -to stimulate a continuous form of peer review between colleague care providers. -to make available regional and national neonatal information for policy evaluation and policy-making. -to make information available for scientific research and education. [2]
Registration criteria	All pregnancies of at least 16 weeks gestation	All pregnancies of at least 16 weeks gestation	All admissions of newborns to neonatal departments within the first 28 days of life and re-admissions for perinatal problems
Data on the following subjects	Mother; pregnancy and pregnancy outcome; delivery; puerperium; child; special focus on e.g. type of care (midwife or referred to obstetrician)	Mother; pregnancy and pregnancy outcome; delivery; child; special focus on e.g. mode of delivery	Mother; pregnancy and delivery (all concise); child; diagnoses; type and duration of neonatal care; discharge and referrals
Detailed list of all registered variables	See appendix I	See appendix II	See appendix III

* GP's did not systematically register the obstetric care given in the period 1995-2000
** NICU = Neonatal Intensive Care Unit
[1] and [2]: see references

Checks for obvious errors or impossible values in variables are performed directly when the data is entered into the computer system, and also when they are sent to PRISMANT, the holder of the databases. PRISMANT gives feedback to the participants on records containing variables that do not fit within the range of accepted values. This provides opportunities to correct erroneous data.

Caregivers use the data to generate discharge letters for other healthcare providers and to create personal overviews. Each year, PRISMANT supplies all the participants with per-practice or per-department overviews, together with national data and data on previous years. It is generally thought that this additional output benefits the quality of the data, and also that it stimulates participation. Since the registries were founded, participation has gradually increased. [1] By 2004, almost all obstetric caregivers were registering details of their care in LVR-1 or LVR-2. Participation in LNR is not yet near 100%. Table 1 summarizes some of the features of the three registers.

Linkage of the separate registers

Within the Dutch maternity system, most women start their pregnancy care with a midwife or general practitioner (i.e. both in primary care). Referral of the pregnant woman to an obstetrician (secondary care) occurs when complications arise or are suspected during pregnancy, labour or puerperium. Care postpartum and medical check ups during puerperium are mostly provided by a midwife at home, even if the birth took place under the care of an obstetrician. Due to these frequent referrals between midwives and obstetricians, women and their children are often registered both by the midwife in LVR-1 and by the obstetrician in LVR-2. It would be misleading to merely combine the LVR-1 and LVR-2 registers, as this would artificially increase the number of registered women and children by counting them twice. For example, in 2000, Statistics Netherlands (*CBS*) published a birth count of 207,872 newborns. [3] Simply adding the LVR-1 records (n=154,742) and the LVR-2 records (n=124,716) would result in a total number of births of 279,458. To prevent double counting, the first step in linking the separate perinatal registers is therefore to identify all records on the same child contained in LVR-1 and LVR-2.

Formally, registration in a LVR record is closed seven days after birth. In practice, however, information on newborns is rarely included after the first hours post partum. [4] To complete perinatal outcomes such as mortality and morbidity and to include any neonatal care that may have been received, it is possible to add information on all newborns admitted to a neonatal or paediatric department by linking the records in the LNR register to the corresponding birth records in the LVR registers. A newborn can be recorded in the LNR register also more than once, for example whenever a newborn is transferred to an intensive care unit or is re-admitted after discharge. As a result, it is also necessary to prevent double counting by identifying the same child within the LNR register. Failure to make such an internal linkage within LNR would create a bias, as the chance of double counting due to referral or re-admission is especially high in the case of very preterm or severely ill newborns.

Scandinavian birth registers, such as that in Norway, use a unique child or mother identification number. [5] In the Netherlands, such a unique number is not yet available. The perinatal registers are anonymous and include no names or addresses. To identify identical child records, other identification variables or combinations of variables should therefore be used.

Linkage by identification of duplicate records

Because the three registers contain many variables (see appendix I, II and III), we studied the variables that might be useful for identifying identical child records in LVR-1, LVR-2 and LNR. In this respect, it was only possible to use variables that were sufficiently capable of distinguishing between two records on the same child and two records on different children who looked similar. To decide which variables were the most informative and useful in searching for duplicate records, we consulted obstetric caregivers involved in daily practice. Their clinical insights were essential to our choice of the best variables. Another important issue in this regard was a thorough knowledge of the registers – for example, of the way variables are registered in practice, and whether or not clear definitions of them exist. The use of a variable was limited by a high percentage of discrepancies or missing values. Variables such as ethnicity and

parity of the mother were found to be too inconsistent to be used. In others, such as birthweight (in grams), we had to allow small differences so as to take account of existing digit preference and any rounding up or down of the birthweight this may have led to. Due to the possible differences in gestational age that were calculated on the basis of the first day of the last menstruation or of an ultrasound, some variation also had to be allowed for gestational age (in days).

This search for a first step towards identifying duplicate records led to the following combination of variables: mother's postal code; mother's date of birth; child's place of birth (home or hospital code); child's date of birth; gender of the child; and singleton, or, in the case of multiples, order of birth. The search for identical records by matching on these variables was computerised. While this computerised method was being developed, extensive manual checks were performed to determine whether the automated runs correctly marked records as identical or non-identical. The first matching step was based on all the variables listed above.

To find duplicate records even if one of the matching variables was missing or discrepant between records, the search for double child records was repeated several times, allowing one matching variable to be discrepant or missing in each run. Per additional search, we either defined extra criteria so as to prevent erroneous matching, or included other variables to facilitate the matching. This is illustrated by the following two examples. As extra criteria, we included the variables birthweight and gestational age. Birthweight either had to be similar in the two records, or the difference in birthweight had to be less than 100 grams at the same time as having a difference in gestational age of seven days or less. In the search without the child's date of birth, other variables had to be used. A missing date of birth usually occurred together with missings in other child variables such as gender, birthweight and gestational age. Such variables could not, therefore, be used to search duplicate records for records containing a missing child's date of birth. Instead of these variables we therefore used the expected date of delivery in this additional search. Once again, precise knowledge of the registration practices and information provided by obstetrical caregivers played an

important role in defining the specific criteria for each additional search. Table 2 shows the number of duplicate records identified in each search.

Table 2: Duplicate records identified in the consecutive automated searches of the method used to link the LVR-1 and LVR-2 registers. Results for the year 2000.

	Used variables	Number of duplicate records identified
Search 1	mother's postal code mother's date of birth place of birth (home or hospital code) child's date of birth gender of the child singleton or birth order for multiple births	N = 68,915
Search 2	As search 1 minus mother's postal code*	N = 2,126
Search 3	As search 1 minus mother's date of birth*	N = 1,533
Search 4	As search 1 minus place of birth (home or hospital code)*	N = 2,206
Search 5	As search 1 minus child's date of birth*	N = 3,695**
Search 6	As search 1 minus gender of the child*	
Search 7	As search 1 minus birth order*	N = 115
Total number of identified double records		N = 78,590

* Including additional criteria on items such as gestational age and birthweight to control for erroneous matching

** Records with a missing child's date of birth usually also lack the variable gender. The results of these searches, expressed in the number of identified duplicate records, are therefore taken together.

The choice of variables and the specific criteria included in the additional searches are both essential choices, and determine the result of the linkage. The same unique number was given to records identified as double by the method described above. Using this unique number, the LVR-1 and LVR-2 databases could be linked by aggregation, reducing duplicate records on a child to a single record. Per registration year, the resulting linked

professional database therefore contained one record per newborn. In the event of a multiple birth, each child was represented by his or her own birth record.

In the registration year 2000, the initial number of LVR-1 and LVR-2 records was 279,458. A total number of 78,590 records in these registers were identified as double records. After aggregation on the unique number, the resulting number of records in the linked LVR-1/LVR-2 database was 200,868. In other words, 39% of the children in the original databases had been recorded more than once. As shown in Table 2, most of the duplicate records (88%) were identified directly in the first automated search using the complete set of variables. The research in this thesis is based on the 1995-2000 registration years. The average percentage of children with duplicate records in these years was 36%, ranging from 32% in 1995 to 39% in 2000. This increase can be explained by the increase (referred to above) in the participation rate of caregivers in the LVR-1 and LVR-2 registers, which resulted in a higher chance of double registration. This increase may also be explained by the increasing referral rates between the midwife and the obstetrician; these recur later in this thesis in Chapter 4.

Approximately 7% of the LVR-1 records lacked all the newborn variables (date of birth, gender, birthweight, gestational age etc.). Although these records often coded referral to an obstetrician, linkage was made impossible by the absence of too much data. To avoid double counting, it was decided that because these records did not contain information on the birth itself, they should not be included in the final linked database. The final database of 2000 therefore consisted of 186,801 registered births.

By using a method similar to the one described above, records of newborns registered in the LNR after paediatric admission were linked to the corresponding birth records in the already matched LVR-1 and LVR-2 registers. However, before matching the LNR records to the LVR register, different records on the same newborn within the LNR, as occurred after referral to another level of care or after re-admission, had to be identified and marked. Because postal code was released only partially and because the mother's year of birth was often missing, this matching procedure used a number of extra criteria

based on gestational age and birthweight, the hospital code of the referring hospital, and the date of referral. For the years 1995-2000, it was possible to match on average 91% of the LNR records to their corresponding LVR birth records (range: 89% - 92%). Non-matching occurred mainly when births had been assisted by midwives or obstetricians not yet participating in the LVR-1 or LVR-2. To avoid double counting, non-matched LNR records were excluded in research based on a linked LVR/LNR database that was corrected for non-participating caregivers.

Extrapolation of the linked database for non-participation

As stated above, some births are not included in the LVR registers because a small percentage of obstetrical caregivers do not yet participate in these registers. For every registration year, we therefore determined the degree of participation in LVR-1 and LVR-2. With regard to LVR-1 participation, the database holder PRISMANT annually reports the number of midwifery practices registering in LVR-1. Each year, the Netherlands Institute for Health Services Research (NIVEL, *Nederlands Instituut voor onderzoek van de gezondheidszorg*) publishes the total number of midwifery practices in the Netherlands. The degree of participation in LVR-2 was calculated by comparing the hospitals coded in LVR-2 with all the Dutch obstetric departments published by level of care in the yearbook of the Dutch Society for Obstetrics and Gynaecology (NVOG, *Nederlandse Vereniging voor Obstetrie en Gynaecologie*). The participation rate increased between 1995 and 2000: 89% of all midwifery practices participated in LVR-1 in 1995, and 92% in 2000. In the same period, participation by general (level I) hospitals increased from 84% to 96%. Throughout the same period, there was full participation by all university hospitals (level III) and teaching hospitals (level II).

Since non-participation is limited to low-risk pregnancies and uncomplicated births in primary care (i.e. by midwives and GPs) and in level I hospitals, a database that did not take this into account would obviously overrate perinatal problems. To generate proper absolute national numbers and prevalences, an extrapolation which took account of the level of care was therefore necessary. By applying weighting factors depending on the participation rate of the level of care recorded during delivery, the database was thus

extrapolated to 100% participation (Table 3). However, this extrapolation was not performed when relationships between variables were investigated.

Table 3: Distribution of level of care and number of births in the linked professional database, before and after extrapolation for non-participation (1995)

	before extrapolation	participation	after extrapolation
	N newborns	rate	N newborns
Linked professional LVR/LNR database			
Primary care (LVR-1)	61,286	89%	68,861
Secondary care (LVR-2), level I	16,061	84%	19,120
Secondary care (LVR-2), level II/III	18,048	100%	18,048
Combination of care			
LVR-1 + LVR-2 level I, linked	25,898	84%	30,831
LVR-1 + LVR-2 level II/III, linked	16,922	100%	16,922
LVR-2 level I, LVR-1 not linked	14,349	84%	17,082
LVR-2 level II/III, LVR-1 not linked	8,405	100%	8,405
Total (including all stillbirths)	160,969		179,269
Total (stillbirths <24 weeks of gestation excluded)	160,104		178,328
Number of births attributed to GPs*			13,472
Total LVR/LNR (stillbirths <24 weeks of gestation excluded)			191,800

* Calculation= (number of liveborns registered by Statistics Netherlands – liveborns in extrapolated LVR/LNR) + same percentage of stillbirths as for midwifery care (0.04%)

In the 1995-2000 period, the database for primary obstetrical care by general practitioners (GPs) had not yet been implemented. As a result, births that took place under the care of GPs were not present in the linked LVR/LNR database. The number of births thus absent was determined by subtracting the extrapolated numbers of liveborns in the linked professional database from the number of liveborns reported in the national statistics of Statistics Netherlands (*CBS*). To determine the additional number of stillbirths in GP care, we used death rates for births under the care of a midwife, basing

this on the assumption that births assisted by GPs are most comparable to those assisted by midwives, as all are low-risk births. We thus added four perinatal deaths for GPs in the 1995 registration year. The correction for the missing births under the care of GPs was subsequently incorporated within the weighting factor of the LVR-1 records.

Participation in the LNR register was also incomplete during the 1995-2000 study period. In 1995, 50% of the general paediatric departments (level I/II) and all Neonatal Intensive Care Units (NICU, level III) participated in the LNR. In the following years this participation rate did not substantially change. Because there is a concentration of severe neonatal problems in NICUs, such problems will be overrepresented in the LNR if no correction is made for the existing difference in participation rate. At the LNR level, an extrapolation was therefore applied that took account of the registered level of care. This extrapolation was restricted to information which was available only via an entry in the LNR and not already available via registration in LVR-1 or LVR-2. As described above, data registered both in the LVR-1 or LVR-2 and in the LNR had already been extrapolated via the LVR extrapolation at birth level. Because the non-participation rate of these departments was 50%, this additional LNR extrapolation was applied by adding a weighing factor of two to records originating from general paediatric departments.

Defining variables in the linked database

Certain variables are registered in more than one register: for example, LVR-1, LVR-2 and LNR all include birthweight and gestational age. After linkage of the separate registers, it had to be decided how these individual variables from the separate registers could be combined within one overall variable in the linked database. For gestational age and birthweight, after the exclusion of improbable values, the average of all LVR-1, LVR-2 and LNR values was calculated to avoid systematic bias. In general, the method for combining separate variables differed per variable, depending on the specific research question and on the content of the variable. Some variables were averaged, others were built up by taking the lowest or highest value. A variable with missing information in one register could be completed with the information on the same variable in one of the

other registers. A more general coding in one variable could be completed by a more specific coding in one of the other registers. Two examples are provided below.

To build the overall mortality variable, the general assumption was made that if a death was coded by one of the caregivers, this overruled the possible presence of a coding of 'no death' in the other registers. An exception to this assumption was made when a child's LVR-1 or LVR-2 record coded a fetal death while the child also had a paediatric admission entry in a LNR record coding 'no death' and several days of paediatric admission. There were also discrepancies in the time of death between the registers. In general, the latest time of death coded was used in the combined mortality variable.

Congenital malformations are coded differently in the three registers. The most detailed coding options are available in LNR; the codes in LVR-1 and LVR-2 are less specific. To build an overall variable, coding for a certain congenital malformation in the linked database, a more specific diagnosis always overruled a more general coding. As an example, LVR-1 and LVR-2 register a *Tetralogy of Fallot* as 'other congenital malformations of the heart and circulatory system' because no specific code is available for this malformation in these registers. In LNR, however, a *Tetralogy of Fallot* can be coded as such and will therefore replace the general coding of LVR-1 or LVR-2 when the congenital malformation variables are combined. For every new variable created on the basis of the variables in the separate registers, definitions had to be made on the basis of certain assumptions and choices.

A new LVR/LNR database containing detailed perinatal and neonatal information on all births in the Netherlands was constructed in three methodological steps: linkage of the separate registers, a weighed extrapolation, and the combining and recoding of similar variables. The epidemiological research described in the following chapters is based on the linked databases thus produced for the 1995-2000 registration years.

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Appendix I: Detailed list of all variables registered in the perinatal register for primary care by independent midwives (LVR-1)

Registratie
Identificatie
Praktijknummer
Actiecode
Administratienummer
Meerling 1
Meerling 2
Onze zorg betrof
Onze zorg betrof
Nummer verloskundige of huisarts
Datum eerste onderzoek
Hoe kwam contact tot stand
Geboortedatum van de moeder
Woonplaats
Type vrouw
Aantal graviditeiten
Aantal abortussen, EUG en/of Mola
A terme datum
Zekerheid
Medium risk/overlegsituatie
Reden medium risk/overlegsituatie
Onderzoeken/verrichtingen 1
Onderzoeken/verrichtingen 2
Onderzoeken/verrichtingen 3
Kind aangepakt door
Onder verantwoordelijkheid van
Wanneer braken de vliezen, datum
Wanneer braken de vliezen, uur
Amniotomie
Kleur vruchtwater
Duur ontsluitingsperiode
Begin actief meepersen
Ligging
Perineum/vulva 1
Perineum/vulva 2
Perineum/vulva 3
Medicatie na geboorte kind
Bloedverlies
Geslacht
Geboortedatum kind
Geboortetijdstip kind
Apgarscore na 5 minuten
Geboortegewicht
Weegmethode
Kraamzorg
Voeding op de 7e dag
Reden zorg 2e lijn 1
Reden zorg 2e lijn 2
Kind overleden in 1e lijn
Kind overleden in 2e lijn
Afgesproken plaats baring
Werkelijke plaats baring
Ziekenhuis baring
Laatste consult bij gynaecoloog
Reden consult bij gynaecoloog 1
Reden consult bij gynaecoloog 2
Reden consult bij gynaecoloog 3
Overdracht aan gynaecoloog
Ziekenhuis overdracht
Datum overdracht of beëindiging
Reden overdracht 1
Reden overdracht 2
Reden overdracht 3
Consult bij pediater
Reden consult bij pediater
Overdracht aan pediater

Appendix I continued

Reden overdracht aan pediater
Ziekenhuisnummer overdracht
Overige problematiek kind 1
Overige problematiek kind 2
Overige problematiek kind 3
Lijst bijzonderheden 1
Lijst bijzonderheden 2
Lijst bijzonderheden 3
Overige problematiek moeder 1
Overige problematiek moeder 2
Overige problematiek moeder 3
Individuele codering 1
Individuele codering 2
Individuele codering 3
Partusnummer

Appendix II: Detailed list of all variables registered in the perinatal register for secondary care by obstetricians (LVR-2)

Praktijknummer
Actiecode
Partusnummer
Meerlingnummer
Meerling
Geboortedatum moeder
Woonplaats (4 cijfers postcode)
Type vrouw
Aantal graviditeiten
Waarvan abortus/EUG/Mola-grav
Datum vorige bevalling/partus immaturus
Zhs vorige bevalling/partus immaturus
Overname
Overname praktijk/ziekenhuis
Begeleiding door u
Datum 1e controle
Intra-uteriene vruchtdood
Hoogste diastol. tensie
A terme datum
Zekerheid a terme datum
Kind aangepakt door
Kind aangep. – gyn.nr.
Supervisie
Supervisie – gyn.nr.
Begin baring 1
Begin baring 2
Indicatie inleiding/primaire sectio
Datum breken vliezen
Tijdstip breken vliezen
Total fetal loss
Begin actief meepersen
Ligging bij de geboorte
Hulp bij baring 1
Hulp bij baring 2
Indicatie hulp/secundaire sectio
Perineum (Ruptuur)
Perineum (Epi)
Nageboortetijdperk 1
Nageboortetijdperk 2
Geslacht
Geboortedatum kind
Geboortetijdstip
Geboortegewicht
Apgarscore
Kind overleden
Congenitale afwijkingen 1
Congenitale afwijkingen 2
Congenitale afwijkingen 3
Pediatrische betrokkenheid
Kind mee naar huis

Appendix III: Detailed list of all variables registered in the neonatology register of paediatricians (LNR)

Registratie-identificatie	LVR1	Diagnose 11
Actiecode	Praktijknummer LVR2	Diagnose 12
Praktijkcode	Partusnummer LVR2	Diagnose 13
Praktijk patiëntnummer	IVF-nummer	Diagnose 14
Ziekenhuis	Bijzonderheid partus 1	Diagnose 15
patiëntnummer	Bijzonderheid partus 2	Diagnose 16
Postcode	Bijzonderheid partus 3	Diagnose 17
Geboortedatum kind	Bijzonderheid partus 4	Diagnose 18
Geslacht	Apgarscore na 1 min.	Diagnose 19
Zwangerschap in weken	Apgarscore na 5 min.	Diagnose 20
Zwangerschap in dagen	Reanimatie 1	Diagnose 21
Geboortegewicht	Reanimatie 2	Diagnose 22
Meerlingnummer	Reanimatie 3	Diagnose 23
Meerlingcode	Opname volgnummer	Diagnose 24
Geboortedatum moeder	Opname nummer	Diagnose 25
Bijzonderheid moeder 1	Opnamedatum	Diagnose 26
Bijzonderheid moeder 2	Herkomst	Diagnose 27
Bijzonderheid moeder 3	Ziekenhuisnummer	Diagnose 28
Bijzonderheid moeder 4	herkomst	Diagnose 29
Bijzonderheid moeder 5	Gespecialiseerd transport	Diagnose 30
Bijzonderheid moeder 6	bij opname	Opname indicatie 1
Bijzonderheid moeder 7	Diagnose 1	Opname indicatie 2
Bijzonderheid moeder 8	Diagnose 2	Opname indicatie 3
Bijzonderheid moeder 9	Diagnose 3	Congenitale afwijking 1
Bijzonderheid moeder 10	Diagnose 4	Congenitale afwijking 2
Plaats geboorte	Diagnose 5	Congenitale afwijking 3
Zorg tijdens	Diagnose 6	Congenitale afwijking 4
zwangerschap, baring of	Diagnose 7	Congenitale afwijking 5
kraambed verleend door	Diagnose 8	Congenitale afwijking 6
Praktijknummer LVR1	Diagnose 9	Congenitale afwijking 7
Administratienummer	Diagnose 10	Congenitale afwijking 8

Appendix III continued

Congenitale afwijking 9
Congenitale afwijking 10
Congenitale afwijking 11
Congenitale afwijking 12
Congenitale afwijking 13
Congenitale afwijking 14
Congenitale afwijking 15
Congenitale afwijking 16
Congenitale afwijking 17
Congenitale afwijking 18
Congenitale afwijking 19
Congenitale afwijking 20
Behandeling 1
Behandeling 2
Behandeling 3
Behandeling 4
Behandeling 5
Behandeling 6
Behandeling 7
Behandeling 8
Behandeling 9
Behandeling 10
Behandeling 11
Behandeling 12
Behandeling 13
Behandeling 14
Behandeling 15
Behandeling 16
Behandeling 17
Behandeling 18
Behandeling 19
Behandeling 20
Behandeling 21
Behandeling 22
Behandeling 23
Behandeling 24
Behandeling 25
Behandeling 26
Behandeling 27
Behandeling 28
Behandeling 29
Behandeling 30
Restverschijnsel 1
Restverschijnsel 2
Restverschijnsel 3
Restverschijnsel 4
Restverschijnsel 5
Restverschijnsel 6
Datum 1000 gram
IC dagen
Primaire HC dagen
Behandeldagen CPAP
Behandeldagen IPPV
Behandeldagen parent. voeding
Behandeldagen O2
Behandeldagen couveuse
Behandeldagen monitor
Behandeldagen infuus
Behandeldagen fototherapie
Ontslagdatum
Wijze ontslag
Ziekenhuisnummer van overdracht
Reden van overdracht
Kind overleden
Obductie
Post IC-HC dagen
Patient ID
Prismant-keurmerk
Totale lengte

Chapter 3

The reliability of perinatal and neonatal mortality rates: differential under-reporting in linked professional registers versus Dutch civil registers

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Summary

Official Dutch perinatal mortality rates are based on birth and death certificates. These civil registration data are not detailed enough for international comparisons or extensive epidemiological research. In this study we linked and extrapolated three national, incomplete, professional registers from midwives, obstetricians and paediatricians, containing detailed perinatal information. This linkage and extrapolation resulted in one detailed professional database which is representative of all Dutch births and from which gestational age-specific perinatal mortality rates could be calculated. The reliability of these calculated mortality rates was established by comparing them with the rates derived from the national civil registers. The professional database reported more perinatal deaths and fewer late neonatal deaths than the civil registers. The under-reporting in the civil registers amounted to 1.2 fewer perinatal deaths per 1000 births and was most apparent in immature newborns. We concluded that under-reporting of perinatal and neonatal deaths depends on the data source used. Mortality rates for the purpose of national and international comparison should therefore be defined with caution. This study also demonstrated that combining different incomplete professional registers can result in a more reliable database containing detailed perinatal information. Such databases can be used as the basis for extensive perinatal epidemiological research.

Introduction

Perinatal and neonatal mortality rates have been widely used as indicators of the quality of obstetric and neonatal care. They are also used to compare quality of care and health status in different countries. The mortality rates used in these international comparisons, however, often lack comparability. [1-5] Different definitions are used to determine stillbirths and neonatal deaths, the statutory lower limit for the registration of perinatal deaths varies between countries and there is a large diversity in sources of mortality information. Moreover, information is often lacking as to the completeness and validity of these sources. [6]

In developed countries, the rate of perinatal and neonatal deaths is also determined by factors other than quality of care. The proportion of low or very-low-birthweight and of preterm infants, the frequency of congenital malformations (taking into account the frequency of antenatal screening and induced abortions) and the distribution of socio-economic conditions are all factors that influence the frequency of perinatal mortality. [1,7-10] Therefore, to ensure a fair comparison of national and international perinatal mortality rates, detailed information about such risk factors should be available. Comparisons of mortality rates can then be stratified or standardised for such risk factors, for example by using birthweight or gestational age-specific mortality rates. The Dutch national perinatal statistics derived from the civil registers do not contain such detailed information on risk factors for perinatal mortality.

It is mandatory for Dutch citizens to report all births to the local authorities. The notification of deaths is directly related to the permission needed for the obligatory burial or cremation. For each death physicians have to complete a death certificate that is send to the local authorities. For stillbirths <24 weeks of gestation burial or cremation is not obligatory and, therefore, no death certificates are completed. The civil birth and deaths registers of the local authorities together with the death certificates of the physicians form the basis for the annual vital statistics reported by Statistics Netherlands (CBS). Statistics Netherlands reports on all the births and deaths of

stillborns of more than 24 weeks of gestation and all liveborns. These reported statistics are the primary source for the Dutch perinatal and neonatal mortality rates. These national birth and death statistics, however, do not contain detailed perinatal information on, for example, risk factors for mortality. Hence, it is impossible to calculate birthweight-standardised mortality rates or perinatal mortality rates according to the World Health Organisation (WHO) definitions using the data from the civil registers. [11] The WHO definitions use either birthweight or gestational age to define the lower limit for registration of all births. The civil data managed by Statistics Netherlands contain gestational age only for stillbirths and early neonatal deaths and birthweight only for early neonatal deaths. For late neonatal deaths and newborns who stay alive, used in the denominators of these rates, this information is not available. The usefulness of the data derived from the civil registers for perinatal epidemiological research is, therefore, limited. These data must be supplemented by alternative sources of perinatal information.

In the Netherlands, independent midwives, obstetricians and paediatricians register the care they provide in three separate professional databases. Not all professional care providers participate in the registers yet, and therefore, the databases are not complete. These databases contain more detailed information than the civil registers of Statistics Netherlands and can, therefore, constitute the basis for more extensive perinatal epidemiological research.

In the present study, we developed a method for linking and extrapolating these databases in order to create one perinatal database representative of all Dutch births and containing detailed information about pregnancy, birth, puerperium and the newborns. To determine the reliability, we compared the mortality rates calculated using this linked professional database with the mortality rates derived from the civil registers of Statistics Netherlands. Reasons for observed discrepancies and implications for future research using these databases are discussed.

Data and method

Data

We used the 1995 data from three Dutch professional registers: the National Perinatal Database for primary care by independent midwives (Landelijke Verloskunde Registratie 1e lijn, LVR-1), the National Perinatal Database for secondary care by obstetricians (Landelijke Verloskunde Registratie 2e lijn, LVR-2) and the National Neonatology Database of paediatricians (Landelijke Neonatologie Registratie, LNR). The database for primary obstetric care by general practitioners (GPs) is still being developed and could not yet be used.

Midwives, obstetricians and paediatricians record information about the perinatal period and information on newborns admitted to a paediatric ward. The National Perinatal Databases (LVR-1 and LVR-2) contain anonymous records of all pregnancies with a gestational age of at least 16 weeks. The National Neonatology Database (LNR) contains anonymous records on all admissions of newborns to paediatric neonatal departments within the first 28 days of life and re-admissions for perinatal problems.

Method

To calculate perinatal mortality (stillbirths and early neonatal deaths within the first week of life) and neonatal mortality (neonatal deaths within the first month of life), all births registered in the LVR-1 and LVR-2 were combined. In the LVR-1 and LVR-2 deaths are registered up to 7 days after birth. The LNR was added to assess early and late neonatal mortality within 1 month after birth for newborns referred to a paediatric department.

The creation of one linked, perinatal database representative of all births in the Netherlands consisted of two different steps: linkage and extrapolation. The first step was to identify identical child records in the different databases to prevent double counts of births and deaths. Births and deaths could be recorded more than once because of frequently occurring referral between the different levels of care, mostly from

primary to secondary care in case of complications during pregnancy, labour or puerperium. These pregnancies are often registered both in the LVR-1 and LVR-2. If the newborn is referred to the paediatrician after birth, he or she is also registered in the LNR. Newborns can also be registered more than once in the LNR if neonatal transfer to an intensive care unit or re-admission takes place.

In the second step, the linked professional database was extrapolated to correct for the non-participation of several midwifery practices, non-teaching (level I) hospitals and the GPs. Because non-participation only occurred in pregnancies with low risk of mortality, correction is essential to obtain a representative database of all births and deaths in the Netherlands.

Linkage by identification of duplicate records

The computerised method used to identify duplicate records and link the three databases is described in brief below. First, the LVR-1 and LVR-2 records were linked by matching based on mother's postal code, mother's date of birth, place of birth (at home or by individual hospital code), child's date of birth, sex of the child and birth order for multiple births. To find duplicate records even if one of these variables was missing or discrepant between records, the search for identical child records was repeated several times, allowing one variable to be discrepant or missing at each run, while including an extra check on birthweight and gestational age. While developing the computerised method for identification of duplicate records, extensive manual checks were performed to determine whether the automated runs correctly marked records as identical or non-identical.

After the identification of duplicate records within the LVR-1 and LVR-2, the newborns in the LNR database were matched with their corresponding LVR record using a method similar to the one described above. Before matching the LNR records with the LVR, different records for the same newborn within the LNR were identified and marked.

Once all duplicate records within the LVR-1, LVR-2 and LNR had been marked, the duplicate records were reduced to single records by aggregating them. The resulting linked professional LVR/LNR database, therefore, contained one record for each newborn.

Adjustment for non-participation by extrapolation

In 1995, 89% of all midwifery practices participated in the LVR-1. All university (level III, $n=12$) and teaching hospitals (level II, $n=22$) participated and 84% of the non-teaching hospitals (level I, $n=69$) participated in the LVR-2. To obtain a database representative of the entire population of births in the Netherlands both in number and in risk profile, the database was extrapolated to 100% participation by applying a weighting factor to the records. The applied weighting depended on the participation rate of the level of care recorded during delivery.

The missing number of births in the care of GPs was determined by subtracting the extrapolated numbers of liveborns in the linked professional database from the number of liveborns reported in the civil registers from Statistics Netherlands. To determine the additional number of stillbirths and the number of neonatal deaths in GP care, death rates for births under midwifery care were used. Births assisted by GPs are similar to those assisted by midwives as all are low-risk births.

Neonatal deaths are expected to be under-reported in the LVR-1 and LVR-2 databases as they may occur after referral of the newborn to a paediatric ward. In 1995, 50% of the general paediatric departments (level I/II) and all Neonatal Intensive Care Units (NICU, level III) participated in the LNR. Neonatal deaths reported in the LNR and not in the LVR were also extrapolated to 100% participation by weighting the records depending on the level of recorded care.

Comparison of mortality rates

The calculated perinatal and neonatal mortality rates for 1995 were compared to the rates derived from the civil registers of Statistics Netherlands. [12] As stillbirths <24 weeks of gestation are not reported by Statistics Netherlands and are, therefore, not

included in the calculated rates, the same selection was applied when calculating the mortality rates from the professional LVR/LNR database. For livebirths, no lower limit was needed.

Results

In 1995, the LVR-1 database for independent midwives contained 130570 records and the LVR-2 database for obstetricians contained 100887 records, resulting in a combined total of 231457 records. Linkage of these two databases showed that approximately 32% of all the newborns were registered in the database of both primary (LVR-1) and secondary (LVR-2) obstetric care providers. After excluding the double records by aggregation and excluding records including no actual births (records with only pregnancy or puerperium information), each record in the linked professional LVR database represented one birth ($n = 160969$).

The LNR was matched to the LVR to add the early and late neonatal deaths registered in the LNR but not in the LVR. The LNR of 1995 consisted of 21818 records. Of these records, 20083 are first admissions of newborns to a paediatric department. This number, therefore, corresponds to the number of newborns registered in the LNR of 1995. Of these LNR records, 89% could be matched to their corresponding LVR record. The main reason for non-linkage of the remaining LNR records was non-participation of a number of obstetrics departments, midwifery practices and GPs.

Linkage of the LNR database to the LVR database added 35 early neonatal deaths and 75 late neonatal deaths registered in the LNR database but not in the LVR database. Apart from six neonatal deaths in a general hospital, all others occurred in one of the NICU's with a complete register.

The number of births by level of care in the linked professional LVR/LNR database before and after extrapolation for non-participating midwifery practices and non-teaching level I hospitals is shown in Table 1.

Table 1: Distribution of level of care and number of births in the linked professional database, before and after extrapolation for non-participation (1995)

	before extrapolation	participation	after extrapolation
	N of newborns	rate	N of newborns
Linked professional LVR/LNR database			
Primary care (LVR-1)	61286	89%	68861
Secondary care (LVR-2), level I	16061	84%	19120
Secondary care (LVR-2), level II/III	18048	100%	18048
Combination of care			
LVR-1 + LVR-2 level I, linked	25898	84%	30831
LVR-1 + LVR-2 level II/III, linked	16922	100%	16922
LVR-2 level I, LVR-1 not linked	14349	84%	17082
LVR-2 level II/III, LVR-1 not linked	8405	100%	8405
Total (including all stillbirths)	160969		179269
Total (stillbirths <24 weeks of gestation excluded)	160104		178328
Number of births ascribed to GPs[a]			13472
Total LVR/LNR (stillbirths <24 weeks of gestation excluded)			191800

[a] Calculation = (number of liveborns registered by Statistics Netherlands – liveborns in extrapolated LVR/LNR) + same percentage of stillbirths as for midwifery care (0.04%).

After extrapolation, the linked professional database consisted of 179269 births. For comparison with the civil register statistics, stillbirths <24 weeks of gestation were excluded. This resulted in 178328 birth records. The calculated number of births assisted by GPs was 13472 (the number of liveborns reported by Statistics Netherlands minus the number of liveborns in the linked and extrapolated professional database plus the same percentage of stillbirths [0.04%] as reported for the primary care of midwives).

Table 2: Number of deaths and calculated mortality rates from linked and extrapolated professional LVR/LNR database compared with Statistics Netherlands data (1995)

	LVR/LNR + GPs	Statistics Netherlands
Total births (*n*)		
stillbirths <24 weeks gestation excluded	191800	191735
stillbirths <28 weeks gestation excluded	191499	191474
Stillbirths (*n*)		
≥24 weeks gestation	1287	1222
≥28 weeks gestation	986	961
Live births (*n*)		
Total	190513	190513
Early neonatal deaths (1st week)	762	588
Late neonatal deaths (2nd-4th week)	84	144
Alive after 4 weeks	189667	189781
Stillbirths per 1000 births		
≥24 weeks gestation	6.71	6.37
≥28 weeks gestation	5.15	5.02
Neonatal mortality per 1000 live births	4.44	3.84
Early neonatal mortality	4.00	3.09
Late neonatal mortality	0.44	0.76
Perinatal mortality per 1000 births		
Stillbirths <24 weeks gestation excluded	10.68	9.44
Stillbirths <28 weeks gestation excluded	9.13	8.09

Table 2 shows the number of stillbirths, early neonatal deaths and late neonatal deaths as well as the perinatal and neonatal mortality rates calculated from both the linked professional database and the civil registers of Statistics Netherlands. The number of stillbirths and early neonatal deaths and, therefore, the calculated mortality rates were higher in the professional LVR/LNR database than in the civil registers, at limits of both 24 and 28 weeks of gestation for stillbirths. For perinatal mortality, the professional database reported 1.2 more deaths per 1000 births than the civil statistics of Statistics

Netherlands. The opposite was observed for the late neonatal deaths where the professional LVR/LNR database reported fewer cases than the civil registers (84 vs. 144).

To find a possible explanation for the observed discrepancies between the number of deaths in the professional database and the civil registers, we compared the gestational age distribution of all the deaths (Table 3). The number of stillbirths in the professional LVR/LNR database was similar to the civil statistics reported by Statistics Netherlands for infants with a gestational age between 28 and 36 weeks. However, the number of reported stillbirths for immature newborns (24-27 weeks of gestation) as well as for full-term newborns was higher in the professional database. Likewise, a higher number of early neonatal deaths, both registered and after extrapolation, was found in the professional LVR/LNR database. Although the civil registers contain a large number of omissions for the gestational age distribution of early neonatal deaths and are therefore incomplete, this observed difference in early neonatal deaths could be ascribed mainly to the under-registration of immature newborns. There were fewer late neonatal deaths registered in the professional LVR/LNR database than in the civil registers. A distribution by gestational age is not available for these deaths reported by Statistics Netherlands because this information is not registered for these cases. This also applies to the largest category: the newborns who stay alive.

Table 3: Number of deaths by gestational age for the linked and extrapolated professional LVR/LNR database and the national statistics of Statistics Netherlands (1995)

	Stillbirths			**Early neonatal deaths**			**Late neonatal deaths**		**Alive after 4 weeks**	
gestational age (weeks)	LVR/LNR	Statistics Netherlands	Difference	LVR/LNR	Statistics Netherlands	Difference	LVR/LNR	Statistics Netherlands [b]	LVR/LNR	Statistics Netherlands [b]
<24	(941)	- [a]		208	43	165	0	-	2	-
24–27	301	260	41	170	132	38	19	-	225	-
28–31	239	241	-2	79	63	16	21	-	1273	-
32–36	306	309	-3	108	85	23	23	-	11380	-
>36	442	398	44	197	154	43	21	-	176774	-
Missing	0	14	-14	0	111	-111	0	-	13	-
Total	1287	1222	65	762	588	174	84	144	189667	189781

[a] Stillbirths <24 weeks are not registered by Statistics Netherlands.

[b] Gestational age not registered by Statistics Netherlands.

Discussion

To compare perinatal mortality between countries or between regions, official national birth and death statistics are often used. Birthweight and gestational age distribution, frequency of congenital malformations and related induced abortions, ethnicity and socio-economic conditions are all factors that influence the perinatal mortality rates of a country or region. In the Dutch civil registration statistics, as in statistics of many other countries, information on these risk factors is either not available at all or not available for all births. In the Netherlands, alternative sources of information have to be used to supplement the national civil registers because these statistics are currently not complete enough to calculate meaningful estimates of, for example, perinatal mortality.

In the Netherlands, detailed perinatal information can be obtained from three separate professional databases in which independent midwives, obstetricians and paediatricians register their care. There are two problems with these databases. First of all, newborns can be registered in more than one database because of referrals between the different care providers. Second, these separate databases do not cover all births in the Netherlands because, as yet, not all providers of obstetric care enter records in the databases. In this study, we developed a method for linking these three professional databases using a linkage key for the detection of duplicate records for the same newborn. In addition, an extrapolation was performed on the linked database for the non-participating care providers. In this extrapolation, the level of the obstetric care provided was taken into account because of the specific under-representation of providers of care for low-risk pregnancies.

Approximately 32% of the newborns registered in the linked professional database were registered in both primary and secondary care. After linkage and extrapolation for the non-participation of certain midwifery practices and obstetric hospitals, the total number of births in the professional perinatal database was 7% lower than the total number registered in the civil registers and reported by Statistics Netherlands. As the births assisted by the GPs were not yet registered in the professional database, these 7%

of births were ascribed to the GPs. Estimates of the percentage of births assisted by GPs of 10%, 9% and 7.8% were reported in 1991, 1993, and 1998. [13-15] Percentages reported previously reveal a decrease in the number of births assisted by GPs over the years. Our estimate of 7% confirms this trend. The concurrence of our derived percentage with previously published percentages provides an important check for our linkage and extrapolation methodology.

Two assumptions were made. First, it was assumed that the linkage key used was informative enough to detect most of the duplicate records of newborns. On the other hand, it was also assumed that the key was specific enough to prevent linkage of records belonging to different newborns. Undetected duplicate records could affect the resulting total number of births after extrapolation and thereby the derived percentage of births ascribed to the GPs. Another assumption made in our extrapolation was that non-participating midwives, hospitals and GPs annually assist approximately the same number of births and deaths as participating midwives and hospitals at the same level of obstetric care. For the non-teaching hospitals a check could be performed on the number of births. It was concluded that the distribution of the number of births in the non-participating hospitals was similar to those in the participating non-teaching hospitals. Concerning the deaths, there is no reason to assume that the risk profile of women delivering in participating hospitals or midwifery practices is different from the one in non-participating hospitals or practices.

For privacy reasons, the three linked professional databases (LVR-1, LVR-2 and LNR) contain only anonymous records. The development of the linkage procedure was, therefore, complicated and time-consuming. Algorithms had to be defined to decide when records were similar enough to belong to the same child. The linkage of these databases would be much easier and less time-consuming if every child were to receive a unique identification number at birth. This number could then be used to identify the child on every (computerised) form that is filled out by the different care providers during the perinatal period and also later in life. This would have clear benefits in terms of facilitating epidemiological research. In some of the Nordic countries such

identification numbers are available but in most countries linkage of different registers is performed using similar methods as in this study.

To determine the reliability of the linked professional database, the deaths registered in the professional perinatal database were compared with the deaths reported in the civil registers of Statistics Netherlands. More stillbirths and more early neonatal deaths were reported in the professional database. The calculated perinatal mortality rate was 1.2 deaths per 1000 births higher in the linked professional database, indicating an under-registration of 11.7% in the civil registers.

For both the stillbirths and early neonatal deaths, under-registration was mainly concentrated in the gestational age categories <28 weeks. This is close to the lower legal limit for stillbirth registration and at the lower limit of viability. The discrepancies between the linked professional database and the civil registers observed in the other gestational age categories are smaller. Slight differences in the determination and registration of gestational age and time of death between the two data sources can explain part of the differences. Moreover, for the early neonatal deaths, the differences can mostly be explained by missing gestational age data in the civil registers. Gestational age is missing for 20% of the registered early neonatal deaths in the civil data of Statistics Netherlands. If these deaths are proportionally divided over the defined gestational age categories, the differences between the number of registered deaths disappears for all the gestational age categories except for the lowest gestational age category. The observed over-reporting of full-term stillbirths may to some extend, be caused by duplicate records which have not been linked. This gestational age category contains the largest number of records, making it more difficult to link all the records correctly, especially as, for the stillbirths, some of the linkage information is often missing.

The discrepancies between the numbers of stillbirths and early neonatal deaths in the lower gestational age groups of the civil registers and the professional database are caused by the confusing rules of birth and death notification around the limit of

viability. In the Netherlands, stillbirths with a gestational age <24 weeks are not registered and the obligation to register stillbirths with a gestational age of 24 - 28 weeks is relatively recent (1991). Although birth registration of all liveborns is mandatory, liveborn newborns around the limit of viability that die before birth notification are often not registered in the civil registers. Since 1991 permission of the local authorities is no longer needed for burial or cremation of newborns with a gestational age <24 weeks of gestation and, therefore, not all births and deaths of these newborns will be notified. As a result, the vital statistics reported by Statistics Netherlands miss certain deaths as was revealed in this study.

When health care providers want to spare parents the additional burden and costs resulting from obligatory notification, they may be inclined, when gestational age is close to the registration limit, to redefine the gestational age so that registration is no longer obligatory. They may also declare a child to be stillborn under the registration limit instead of liveborn, in case the child was born at the lower limit of viability and died shortly after birth. The reporting of an early neonatal death or stillbirth is, therefore, partly determined by the compliance of the doctors with the legal definitions and partly by the wish of the parents to notify and bury or cremate the child. Thus, registration of a child close to the limit for legal registration depends on emotional, financial, cultural and religious factors. From the literature there is ample evidence that these factors play a major role in the way statutory regulations for the registration of births and deaths are being observed.[16,17]

A trend in under-reporting of perinatal deaths in national statistics, especially of immature newborns, has been reported before. In the Netherlands, two comparisons of local registers with the civil registers of Statistics Netherlands reported an under-registration of perinatal mortality of 14.3%, and at least 8.1%.[18,19] This supports our finding of almost 12% under-reporting. Other countries also report under-registration of perinatal deaths. [20-25] Scott *et al.* [20] described an under-reporting of 10% of perinatal deaths in Ireland. In Belgium, perinatal deaths were under-reported by 14% in national statistics. [25] In the United States, under-reporting of fetal deaths ranging from 7% to almost 50% was found, depending on the state registry used.[21,22] It was shown that the

lower the gestational age at death, the smaller the chance of being registered. The Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI) set up since 1992 in England, Wales and Northern Ireland reports on average 4.6% fewer deaths than the vital statistics derived from the national birth and death registration system. [26] The completeness of different kinds of perinatal death registration systems depends on existing incentives, laws and perceptions of viability all resulting in a certain registration practice.[27,28]

Late neonatal deaths (occurring more than 1 week after birth) were under-reported in the linked professional database compared with the civil register statistics. Late neonatal deaths in the professional LVR/LNR database all originate from the neonatal LNR database as the obstetric LVR databases only register care during the first 7 days after birth. In the LNR database, only late neonatal deaths occurring in paediatric departments are registered. Late neonatal deaths occurring at home or in other hospital departments, for example, in the surgical departments, are therefore not registered in the LNR and will not be present in the linked professional LVR/LNR database. This hypothesis was tested and confirmed by studying the underlying cause of the late neonatal deaths in the civil registers. On the basis of the cause of death, the deaths were divided into categories with different probabilities of being registered in the neonatal LNR database. If the death categories with no or little probability of registration in the LNR database were not left out of consideration in the civil statistics, the number of late neonatal deaths in the professional database was similar to that in the civil registers.

The comparison made between deaths registered in the linked professional perinatal database and deaths reported in the civil registers revealed differential under-reporting of perinatal and neonatal deaths in the two data sources. The fact that there was an explanation for most of the observed differences confirms that the linkage and extrapolation of the three separate professional perinatal databases resulted in one reliable database representative of the total number of births in the Netherlands. If its limitations are respected, this linked database can be used for a broad field of perinatal

epidemiological research because it contains detailed information for all births about pregnancy, delivery, puerperium and the newborn.

In conclusion, the present study has shown that it is possible to create a representative national perinatal database based on three incomplete professional databases. This perinatal database was derived directly from available data without further data collection. The method of record linkage and the applied extrapolation by level of care to correct for the incompleteness of the database resulting from non-participation, provided a representative perinatal database with more detailed perinatal information than available at present from the national civil registers. The linked professional perinatal database can provide denominator data for estimates of all kinds of rates for all births. Moreover, it can be used for surveillance, monitoring of trends or detailed national and international comparisons of different obstetric outcomes, taking into account important risk factors. Other countries should also search for and use alternative sources of perinatal information to supplement the existing limited national statistics. Only then will they be able to meet the current increasing requirements for good epidemiological and public health research.

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Chapter 4

The trend in home births in the Netherlands: 1995-2000

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Introduction

The present Dutch system

While giving birth in the hospital has become the virtual standard elsewhere in the Western world, in the Netherlands home birth remains an important feature of the national obstetrical system. The most characteristic feature of Netherlands' unique maternity service is that midwives play a dominant role in care of normal pregnancy and birth. Public and private insurance systems pay for prenatal, intrapartum and postpartum care. This care is delivered by midwives except in a relatively small percentage of low risk pregnancies and births where it is being provided by general practitioners. Care by an obstetrician is always in hospital and funded only in problem pregnancies and births. Dutch midwives are being trained to be independent professionals. A four year midwifery training program, without prior nursing training, is offered in three midwifery schools. The emphasis in the training is on the education and assisting of women through their low risk pregnancy and birth and on screening for pathology. Generally, referral to the obstetrician is the midwife's decision. Referrals can take place very early in pregnancy, during the course of the pregnancy, in case of problems during the birth, or in the postpartum period. If they take place early in pregnancy, referrals are often based on prior pregnancy/birth pathology.

A low risk woman can choose to have a midwife attend her birth at home or in the hospital. In the latter situation the hospital stay after delivery is short, ranging from a few to a maximum of 24 hours and the postpartum period is spent at home. A maternity home care assistant assists the midwife during the delivery. She further provides postnatal care during the direct postpartum hours and the first week after birth, helping the mother and father with care of the baby and with house hold tasks.

Historical developments

Until 1993, the Dutch Central Bureau of Statistics (CBS) monitored the trend in home births in the Netherlands. The registry data show that since the introduction of the system of short stay hospital birth with a midwife in low risk pregnancies, the home

birth rate has been declining steadily (Figure 1). In 1965 around 68% of all children in the Netherlands were born at home while in 1993 this percentage had decreased to around 31%. [1] After that year detailed birth information has ceased to become available through the Civil Registry Authorities to the Ministry of Health and the Central Bureau of Statistics (CBS).

Figure 1: Percentage of home births in the Netherlands from 1965 to 1993

Recent developments

Around the mid 1990's a deterioration occurred in midwives' work circumstances. Many felt their working hours were too long and the pay was inadequate. A substantial percentage of midwives every year left active practice before they had reached retirement age. Even though hard evidence was lacking the impression existed, also among policy makers and government officials, that the percentage of home births kept declining. In 1997 the Minister of Health decided to fund a program aimed at stimulating home birth, decreasing work pressure among midwives and developing professional guidelines as well as a quality control system. The Royal Dutch Midwifery Organisation (KNOV) was subsequently put in charge of carrying out the program, named 'PROVER' that was to last through 2001. During the course of the program a number of partly unexpected developments caused a further deterioration of the Dutch

midwives' work situation. A substantial number of GP's who traditionally carried out a large percentage of the home births stopped this practice. [2] Postpartum home care became a scarcer commodity which in turn increased midwives' workload in taking care of mother and baby directly after a home birth. A number of hospitals had a shortage of personnel and were unable to offer facilities for short stay hospital births. Further, the proportion of ethnic minority pregnant women is increasing steadily. These women are less likely to opt for a home birth, compared to Dutch women. Last, the number of births per year in the Netherlands kept increasing. All these factors increased midwives' workload and thereby negatively influenced a woman's chance of being able of having a home birth.

Method

Monitoring the trend in home births

At the start of the *PROVER program* it was decided that it was pivotal to monitor the prevalence of home births and to study the trend in home births. However, as mentioned above, no routinely collected data on home births had been in existence since 1993. It was therefore decided to use data from the National Perinatal Database of obstetrical care delivered by midwives (LVR-1) and the National Perinatal Database of obstetrical care delivered by obstetricians (LVR-2). Midwives and obstetricians register information about pregnancy, delivery and puerperium of pregnancies with a gestational age of at least 16 completed weeks. In case women are referred during pregnancy or birth from a midwife to an obstetrician, often both the midwife and the obstetrician register their care in corresponding databases. When simply joining the two databases, pregnancies can thus occur twice. Records in the databases do not have a unique number that can be used to identify the double records. A method was devised to avoid the problem of double counting of a single case. [3] For each year from 1995 through 2000, an aggregated perinatal data file was created. In order to identify each anonymous pregnancy as a single record, for each record double records were identified. A number of identifying variables were used to search for these double

records such as mother's postal code, mother's and child's date of birth and sex of the child. Next, the aggregated data file had to be extrapolated for a number of non-participants. For each registration year, data existed on the total number of hospitals and midwifery practices in the Netherlands. Those data could be compared to the number of practices that had registered their birth data in the LVR. In 1995 for instance, 89% of all midwives, all obstetricians in academic and training hospitals and 84% of obstetricians in non-training hospitals participated in the LVR. Since births by midwives are different from births by obstetricians, a weighing factor was assigned for each registration year by subgroup of caregiver in order to extrapolate to 100% participation. While weighing the existing records to simulate a participation of 100%, the assumption was made that participating practices do not differ from non-participating practices in their characteristics. Non-participating practices are known to the authors. No obvious selection bias appears to exist. The GP's participation in the registration was very limited during the time period 1995-2000. The number of births carried out by GP's was subsequently estimated for each year to be the difference between the number of births in the Netherlands for that year as registered by the CBS minus the number of births supervised by midwives or obstetricians in that year as calculated after extrapolation.

After that, the database had to be subdivided into the different possible types of caregivers during birth and the different places of birth. Figure 2 provides an overview of potential places of birth and types of caregiver during delivery. The home birth prevalence is dependent on a number of different determining factors in the referral pathway. If in a given year, for instance, more women start their care with an obstetrician than in previous years because of pathology in a previous pregnancy, a smaller group will start their care with a midwife and will be 'eligible' early in pregnancy for a home birth. Conversely, if midwives refer fewer women at any time during the pregnancy, more women will deliver at home, even if the percentage of referrals during birth remains stable.

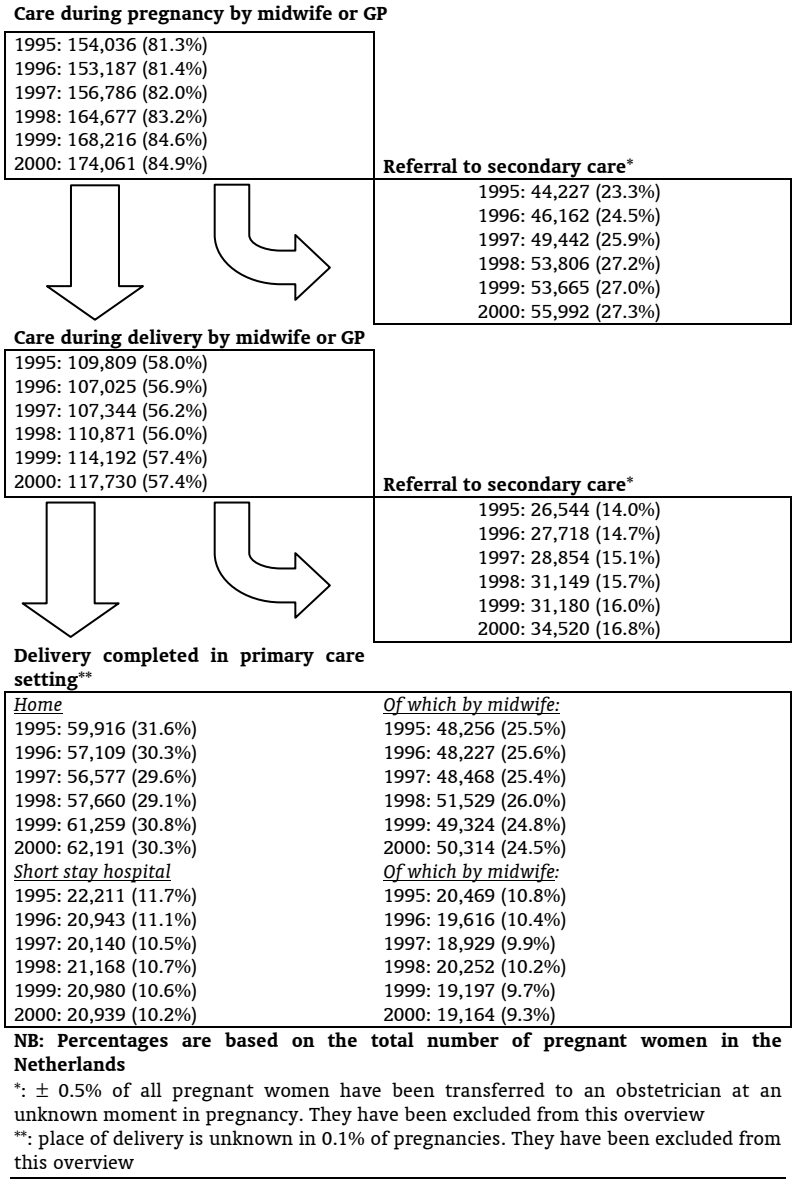
Figure 2: Overview of the possible combinations of place of delivery and type of caregiver.

A: Midwife supervised home birth	B: Midwife supervised (short stay) hospital birth
C: Delivery started at home, referral to obstetrician during delivery	D: Delivery in hospital, short stay/midwife supervised. Referral to obstetrician during delivery
E: Care started with midwife, referral to obstetrician during pregnancy. Delivery by obstetrician	
F: Care by obstetrician started early in pregnancy. Delivery by obstetrician	

Results

Figure 3 provides an overview of deliveries by place and type of caregiver during the years 1995 through 2000. Of all pregnancies, 81.3% started out as being under the care of a midwife or GP in 1995. In 2000, that percentage had increased to 84.9%. A steady increase occurred in referrals during pregnancy, from 23.3% in 1995 to 27.3% in 2000, and during delivery from 14.0% in 1995 to 16.8% in 2000.

Figure 3: Flowchart of type of caregiver and place of birth for all pregnancies starting under care of a midwife or GP in the period 1995-2000.



NB: Percentages are based on the total number of pregnant women in the Netherlands

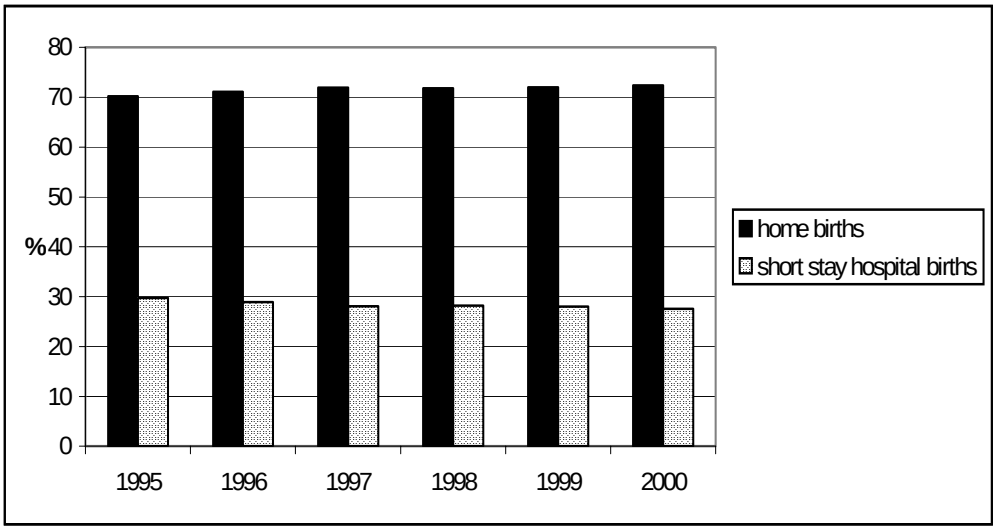
*: ± 0.5% of all pregnant women have been transferred to an obstetrician at an unknown moment in pregnancy. They have been excluded from this overview

**: place of delivery is unknown in 0.1% of pregnancies. They have been excluded from this overview

This resulted in a higher number of deliveries by an obstetrician after referral from a midwife or GP during pregnancy or delivery. In the same period, the percentage of home births (either by midwife or GP) declined from 31.6% in 1995 to 30.3% in 2000. The percentage of short stay hospital births also decreased in this period.

Figure 4 shows that within the group of births completed under care of a midwife, an increase has occurred between 1995 and 2000 in favour of births at home instead of in the hospital. In 1995, 70.2% of these births were home births and 29.8% were hospital births where as in 2000 these percentages were 72.4% and 27.6%.

Figure 4: Home births and short stay hospital births completed under care of a midwife



Discussion

In 1995, the percentage of home births in the Netherlands was 31.6%. Six years later, in 2000, it was 30.3%. It appears that the home birth rate has more or less stabilized after the initial dramatic decline in the sixties and seventies. However, a slight but noticeable decrease can be seen in our data. It appears from the data that the increase in referrals

is the largest single threat to the chance of a woman to deliver at home. In 1995, the chance for a woman to be transferred from the midwife or GP to the obstetrician either during pregnancy or during labour, was 37.3%. In 2000, that chance had increased to 44.1%. When a woman is being transferred to secondary care, she will by definition be unable to have a home birth, even if she initially wishes to have one. The reason that this increase in referrals has during our study period not caused a more obvious decline in home births, seems to be the fact that during the same period an increase occurred in number of women who started their pregnancy care with a midwife. It is unclear what may have caused that phenomenon. Obviously, if the referral rate continues to increase without concomitant further increase in percentage of women being under care of a midwife from early in pregnancy, the home birth rate will start to decline again.

Midwives, GP's and obstetricians have together agreed in a written document on conditions under which midwives take care of pregnant or labouring women and conditions under which referrals from the midwife or GP to the obstetrician should take place. [4] Women with a poor obstetric history or a chronic medical problem may start their care with an obstetrician, others may develop problems later during pregnancy or during delivery and will be referred when the pregnancy has further progressed. Referrals during pregnancy may take place for pre-eclampsia or growth restriction, for instance. During delivery, insufficient progress of labour is a commonly occurring reason for referral. This distinction between 'physiology' and 'pathology' is considered by midwives and obstetricians to be a pivotal part of the Dutch system. The document with agreed-upon reasons for referral has been in place since 1973. [5] Since then several revisions took place and the latest version is from 2003. [4] During our study period, however, the reasons for referral have remained the same. In spite of this, the referral rate increased quite markedly. We can only speculate about the underlying mechanism. It is unlikely that the risk profile of Dutch women has increased during the study period to such extent that it can explain the extra referrals. One hypothesis is that midwives practice increasingly 'defensively' and more and more err on the side of caution. Referring a woman unnecessarily may then appear less problematic than not referring her while in retrospect she may have benefited from obstetrical intervention. Many of the agreed reasons for referral such as insufficient progress of labour are subjective

enough that a midwife's clinical perception of the situation rather than an objectively measured end point, will be the most important determinant of the decision to refer or not. The push towards increasing referral may be more felt during times when the work load is high and the individual midwives' case load is too large, as has increasingly been the case during our study period. From our data it cannot be concluded whether the increase in referrals will influence the health of the mother and/or the baby, either positively or negatively.

From our data it appears that the slight decrease in percentage of home births does not reflect a decrease in women's interest in giving birth at home. Within the group of women delivering under care of a midwife, a slight shift occurred towards home births instead of short stay hospital births. Women under care of a midwife during the entire pregnancy have an explicit choice to give birth either at home with the midwife or in the hospital with the midwife. The only exceptions are so-called medium risk situations which are rare and for instance occur when a women has a history of heavy blood loss after a previous delivery. In such cases, the woman can remain under the care of a midwife, but the delivery should take place in the hospital. This occurred in only 1% of all births under care of a midwife in 2000. If home birth was becoming a less attractive option to women, this would have been shown by a shift towards short stay hospital births, particularly in the group remaining in the care of a midwife. Instead, the reverse seems to be the case.

The Dutch have a unique situation compared to other Western countries. Home birth is a viable, frequently chosen and much appreciated option for labouring women. Midwives determine the risk status of women and decide whether to refer during pregnancy or delivery or to provide care during the entire pregnancy and delivery. In spite of the relative stability of the home birth rate, the system may be under threat. The rising referral rate to obstetrical care may make it increasingly difficult for women to opt for a home birth. More research is needed into the mechanisms underlying this increase. Monitoring of the home birth rate will continue over the years to come to

determine whether a decrease will indeed take place and if so, whether policy measures can be implemented to reverse that trend.

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Chapter 5

Maternal factors and the probability of a planned home birth

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Abstract

Objectives: In the Netherlands, approximately one-third of births are planned home births, mostly supervised by a midwife. The relationship between maternal demographic factors and home births supervised by midwives was examined.

Design: Cross-sectional study.

Setting: Dutch national perinatal registries of the year 2000.

Population: All women starting their pregnancy care under the supervision of a midwife, because these women have the possibility of having a planned home birth.

Methods: The possible groups of birth were as follows: planned home birth or short stay hospital birth, both under the supervision of a midwife, or hospital birth under the supervision of an obstetrician after referral from the midwife during pregnancy or birth. The studied demographic factors were maternal age, parity, ethnicity and degree of urbanisation. Probabilities of having a planned home birth were calculated for women with different demographic profiles.

Main outcome measures: Place of birth.

Results: In all age groups, the planned home birth percentage in primiparous women was lower than in multiparous women (23.5% vs 42.8%). A low home birth percentage was observed in women younger than 25 years. Dutch and non-Dutch women showed almost similar percentages of obstetrician-supervised hospital births but large differences in percentage of planned home births (36.5% vs 17.3%). Fewer home births were observed in large cities (30.5%) compared with small cities (35.7%) and rural areas (35.8%).

Conclusions: This study demonstrates a clear relationship between maternal demographic factors and the place of birth and type of caregiver and therefore the probability of a planned home birth.

Introduction

In contrast to most other Western countries, planned home births are relatively common in the Netherlands. In the year 2000, 30.3% (n=62,000) of all Dutch births took place at home. [1] The majority of planned home births take place under the care of midwives. In rural regions where no midwives practise, these births take place under the care of a general practitioner (GP). Since 1965, the percentage of home births, then 69%, [2] decreased, mostly due to the introduction of the short stay hospital birth under the care of a midwife. Over the years 1995-2000, the home birth rate stabilised again around one-third of all Dutch births. [1]

In the Dutch maternity care system, midwives provide independent care for women with uncomplicated pregnancies. Women with low risk pregnancies can choose to either have a home birth or a hospital birth under the responsibility and care of their midwife. In the latter situation, the women and their babies are generally discharged within a few hours after birth for postpartum home care. Women with high risk pregnancies *a priori* receive care from an obstetrician in the hospital. As soon as the midwife suspects or diagnoses a complication during pregnancy or birth, a woman is referred to an obstetrician. As a result of this risk selection procedure, three combinations of birth place and caregiver are possible: midwife-supervised planned home birth, midwife-supervised short stay hospital birth and obstetrician-supervised hospital birth (either due to an *a priori* high risk pregnancy or after referral from the midwife).

So far, most studies into home births focus on outcomes such as mortality and morbidity [3-9] or on attitudes towards home births. [10-12] Little is known about demographic factors of women such as age, parity, ethnicity and degree of urbanisation and a woman's probability of having a planned home birth. In the present study, the relationship between these maternal demographic factors and home births was examined. The probability of having a home birth was calculated for each demographic profile of the women. Home births may be promoted by using this knowledge of the effect of different maternal factors on the home birth rate.

Methods

This study was part of a programme called 'PROVER', funded by the National Health Care Insurance Council (CvZ) and was carried out by the Royal Dutch Midwifery Organisation (KNOV). One of the aims of the programme was to monitor the prevalence of home births in the Netherlands during the period 1995-2000. [13] Routinely collected data on Dutch home births are not available since 1993, the last year in which Statistics Netherlands (CBS) published these statistics. To monitor the prevalence of home births, a new system had to be developed. Within this new monitoring system, it is also possible to study the relationship between maternal demographic factors and home births.

The monitoring system is based on two professional registers: the National Perinatal Database for Primary Care, a register of midwife-assisted births, and the National Perinatal Database for Secondary Care, a register of obstetrician-assisted births. In these databases, midwives and obstetricians register in anonymous records, detailed information on pregnancy, delivery and puerperium and brief maternal demographic factors. In case of referrals of complicated pregnancies from midwives to obstetricians, both the midwife and the obstetrician separately register information on the same pregnancy. Since 1995, these databases are annually linked and aggregated using a matching procedure based on maternal and child variables to form one Dutch birth cohort per registration year. [14] After linkage, an extrapolation is performed to correct for a small number of non-participants in both registers. Because the percentage of non-participants differs between midwives and obstetricians, this extrapolation is based on assigning different weighing factors to the midwife and obstetrician records, depending on their participation rate in that specific year. In the present study, we analysed the linked database for 2000. In that year, 92% of all midwives, all obstetricians in academic and training hospitals and 96% of obstetricians in non-training hospitals participated in the registers.

The maternal demographic factors that are registered in the linked perinatal database are age, parity and ethnicity of the mother and the degree of urbanisation of the maternal place of residence. In the present study, these variables were defined as

follows: parity was categorised as primiparous (no prior birth) and multiparous (one or more prior birth). The age of the mother was calculated using the birth date of mother and child and categorised as under 25 years; 25 - 29 years, 30 - 34 years and above 34 years. In the National Perinatal Database, ethnicity is categorised as 'Dutch', 'Mediterranean', 'other European', 'Black', 'Hindu', 'Asian' and 'Other'. For this study, the ethnicity of the mother was divided into the dichotomous variable 'Dutch' *versus* 'non-Dutch'. The degree of urbanisation was defined using the definition of Statistics Netherlands. [15] This definition uses five categories based on the number of households per km^2. For this study we reduced these categories to three categories: large city (at least 1500 households per km^2); small city (1000-1499 households per km^2) and rural area (less than 1000 households per km^2).

GPs supervise around 5-6% of all births in the Netherlands. [13] Due to the fact that GPs do not yet register in the perinatal database, these births were not included in this study. This study focuses on all births under the care of a midwife or obstetrician. First, an overview is given of births in the different categories: midwife-supervised home births; midwife-supervised short stay hospital births, obstetrician-supervised hospital births after referral from the midwife during pregnancy or birth and obstetrician-supervised hospital births of women with an *a priori* high risk pregnancy and therefore starting pregnancy care directly with the obstetrician. For all further analysis, the latter group of women starting their pregnancy care directly in hospital with an obstetrician due to an *a priori high* risk pregnancy was excluded because these women did not have any possibility of having a planned home birth. Next, the relationship between the maternal demographic factors and the combination of place of birth and caregiver, with a special focus to planned home births, was explored in univariate analyses. Finally, within the same subgroup of women the probability of a planned home birth was determined for the different combinations of demographic factors. By this stratification into the different demographic profiles possible confounding between the different demographic factors was taken into account.
All statistical analyses were performed in SPSS, version 11.

Results

The number of births under the care of midwives and obstetricians was 191,471 in the year 2000. Table 1 shows the distribution of these births by place of birth and type of caregiver. More than a quarter of these births (n=50,314) were home births under the supervision of a midwife and 10% (n= 19,164) were hospital births supervised by a midwife. Another 47.5% (n= 90,851) of the births took place under the supervision of the obstetrician after referral from the midwife.

Table 1: Distribution of births under the care of midwives and obstetricians by place of birth and type of caregiver in the year 2000.

	n	%
Midwife-supervised home birth	50,314	26.3
Midwife-supervised short stay hospital birth	19,164	10.0
Obstetrician-supervised hospital birth - after referral from midwife	90,851	47.5
Obstetrician-supervised hospital birth - a priori high risk pregnancy	31,062	16.2
Total births under care of midwives or obstetricians*	191,391	100.0

* Of 80 midwife-supervised births, the place of birth (home or hospital) was unknown. These births were therefore not included in this table and further analyses.

The distribution of the maternal demographic factors for the subgroup of women starting their pregnancy care with the midwife and therefore initially having the option of a planned home birth is shown in Table 2.

Almost 50% of the women starting their pregnancy care with a midwife are primiparous. The age group of 25 - 29 years includes the largest group of primiparous women (39.6%), whereas the age group of 30 - 34 years is the largest age group for the multiparous women (46.7%). Almost 85% of the women starting pregnancy care with a midwife are of Dutch origin. Most of the women starting pregnancy care with a midwife live in a large city (44.1%) followed by the group of women living in rural areas (34.6%).

Table 2: Distribution of maternal demographic factors for the subgroup of women starting their pregnancy care with the midwife in the year 2000.

	n	%
Number of women starting pregnancy care with midwife	160,329	100
Parity*		
Primiparous	71,837	48.0
Multiparous	77,928	52.0
Maternal age of primiparous women*		
<25 yrs	13,514	18.8
25-29 yrs	28,435	39.6
30-34 yrs	24,182	33.7
>34 yrs	5,682	7.9
Maternal age of multiparous women*		
<25 yrs	4,702	6.0
25-29 yrs	19,610	25.2
30-34 yrs	36,375	46.7
>34 yrs	17,203	22.1
Ethnicity*		
Dutch	127,020	84.8
Non-Dutch	22,836	15.2
Degree of urbanisation*		
Large city	65,921	44.1
Small city	31,927	21.4
Rural area	51,685	34.6

* The total number of women per factor differs from the overall number of women starting pregnancy care with a midwife due to a varying number of missing values depending on the factor under study

Figure 1: Distribution of place of birth and type of caregiver per parity and age group of the woman for the subgroup of women starting pregnancy care with a midwife

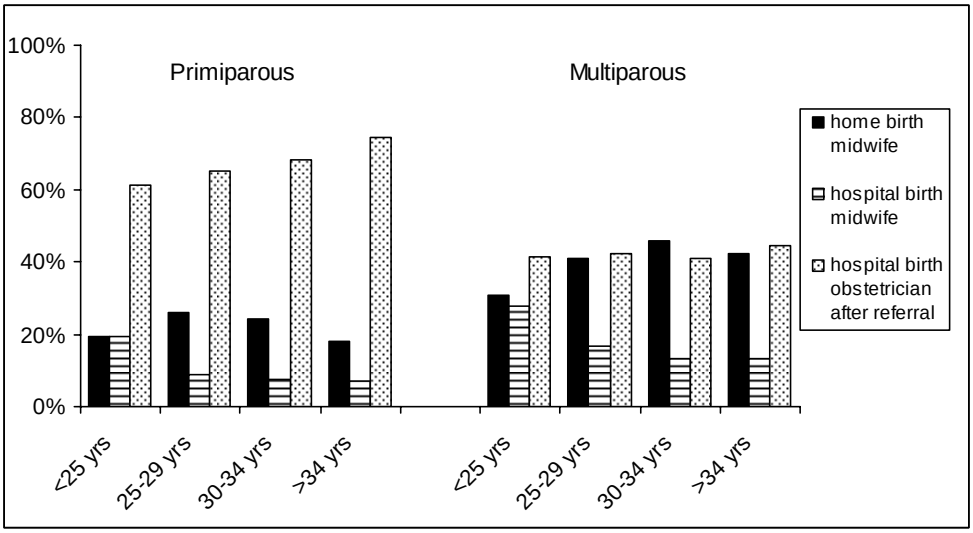
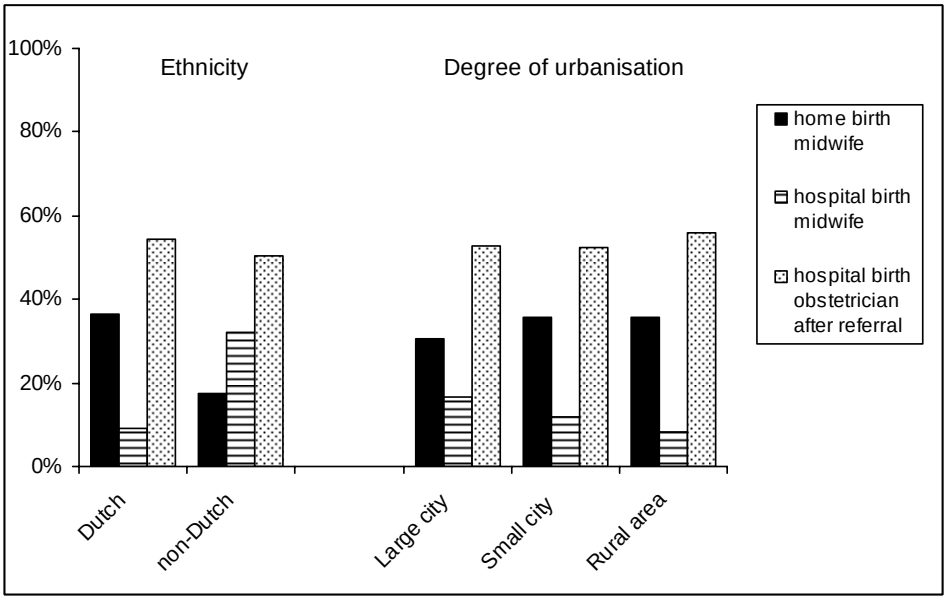


Figure 1 shows the distribution of place of birth and type of caregiver for primiparous and multiparous women by age distribution. In all age groups, the home birth rate for primiparous women is lower than that for multiparous women. A similar trend is observed in all age groups for the proportion of short stay hospital births with a midwife. Overall, 23.5% of the primiparous women delivered at home, 10.3% delivered in hospital under the supervision of the midwife and 66.1% delivered in hospital with an obstetrician after referral. For the multiparous women, these figures are 42.8%, 15.0% and 42.1%, respectively.

A low home birth rate is observed in the youngest age group both in the primiparous women and multiparous women. This is not caused by more referrals for obstetrician-supervised hospital births but by the high percentage of midwife-supervised short stay hospital births in this age group. In primiparous women, the 25 - 29 years age group shows the highest home birth rate (25.9%); whereas in multiparous women, the highest home birth rate is seen in the 30 - 34 years age group (45.7%).

A small difference exists between Dutch and non-Dutch women in proportion of obstetrician-supervised hospital births after referral (54.2% and 50.4%, respectively). A large difference exists in percentage of home and hospital births with the midwife. In the Dutch group, 36.5% are home births and 9.3% short stay hospital births; whereas in the non-Dutch group, 17.3% are home births and 32.3% short stay hospital births (Figure 2).

Figure 2: Distribution of place of birth and type of caregiver per ethnicity of the woman and degree of urbanisation of the place of residence for the subgroup of women starting pregnancy care with a midwife



In rural areas, referral from the midwife to the obstetrician occurs slightly more often than in large and small cities (56.0% instead of 52.8% and 52.3%). Fewer home births are observed in large cities (30.5%) compared with small cities (35.7%) and rural areas (35.8%). In large cities, more short stay hospital births, supervised by a midwife, take place.

Within the subgroup of women starting their pregnancy care with a midwife, the probability of having a planned home birth was determined for women with different demographic profiles (Table 3). Overall, multiparous women and Dutch women are more likely to have a home birth than primiparous women and non-Dutch women. The probability that a Dutch primiparous woman within the age group of 25 - 29 years living in a rural area has a planned home birth is 31%, whereas the probability that a multiparous woman with the same ethnicity, age and urbanisation characteristics has a home birth is 55%. A Dutch multiparous woman aged between 30 and 34 years and living in a large city is at least two times more likely to have a home birth than a woman with the same characteristics who is of non-Dutch origin (52% vs 23%).

Table 3: Probability (in %) of having a home birth for women with different profiles of demographic factors, calculated within the subgroup of women starting their pregnancy care with a midwife in the year 2000.

	Dutch				**Non-Dutch**			
	<25 yrs*	25–29 yrs	30–34 yrs	≥35 yrs	<25 yrs	25-29 yrs	30-34 yrs	≥35 yrs
Primiparous								
Large city	22	28	26	20	11	12	15	15
Small city	27	29	26	19	12	15	18	13
Rural area	33	31	28	22	14	16	22	10
Multiparous								
Large city	39	49	52	51	21	22	23	22
Small city	47	52	53	49	25	24	24	23
Rural area	52	55	56	53	23	25	29	25

*Years of age

Discussion

The Dutch maternity care system is based on a risk selection procedure under the responsibility of midwives, who make a distinction between women at elevated risks of obstetric complications and requiring referral to the obstetrician, and women with a low risk and remaining under their care. Whether a woman with a low obstetric risk chooses a home birth or a short stay hospital birth, both under the supervision of a midwife is a matter of personal preference.

The aim of this study was to examine the relationship between place of birth and type of caregiver and demographic characteristics of women starting pregnancy care with a midwife, with a special focus on home births. Multiparous women under the care of a midwife deliver at home almost twice as frequently as primiparous women (42.8% vs 23.5%). This difference is largely explained by the *a priori* risk selection of multiparous women with obstetric problems in previous pregnancies. Multiparous women with obstetric problems in a previous pregnancy will be brought directly under the care of the obstetrician in a next pregnancy. Therefore, multiparous women starting pregnancy care with a midwife are selected women with low risks of complications during pregnancy or birth. A similar selection obviously cannot be made in the group of primiparous women. In this study, referral from the midwife to the obstetrician was observed in 66.1% of the primiparous women and in 42.1% of the multiparous women. The observed difference in home birth percentage is largely explained by this difference.

Low home births percentages are seen in the youngest age group under 25 years. This is not explained by a higher referral rate to the obstetrician but by more short stay hospital births under the supervision of the midwife. It is not clear why younger women more often choose a short stay hospital birth. Their living conditions might be less conducive to a home birth, for example, if they are living in an apartment building without an elevator. Social economic characteristics such as level of education may also explain this difference. Perhaps additional patient information and better instructions by the midwife might increase the proportions of home births in this group of young pregnant women.

Dutch and non-Dutch women starting their pregnancy care with the midwife show similar percentages of referrals to the obstetrician. Dutch and non-Dutch women giving birth with a midwife, however, make different choices concerning their place of birth. Twice as many Dutch than non-Dutch women choose a home birth (36.5% vs 17.3%). This difference in choice may possibly be explained by the existing attitude towards birth in most other countries than the Netherlands, where childbirth is more medicalised and hospital centred. Additional patient information and better instruction by the midwife may possibly increase the number of non-Dutch women choosing a home birth.

Referral from the midwife to the obstetrician occurs slightly more often in rural areas than in cities. Midwives may anticipate earlier to problems in rural regions where the distance to the nearest hospital is larger than in cities. Women in large cities more often choose a short stay, midwife-supervised hospital birth than women in small cities and rural areas. This may be related to the fact that the more urbanised an area is, the more hospital facilities are available within a short distance.

One of the limitations of this study is that births under the supervision of the GP, representing around 5% of all Dutch births, could not be included as these births are not yet registered in the National Perinatal Databases. These births take place especially in rural areas where no midwife is practising. The results from this study are not directly applicable to births under the care of GPs because the distribution of the maternal demographic factors, such as degree of urbanisation, of women giving birth with a GP will be different from both births with a midwife and births with an obstetrician.

This study is based on routinely collected data. Misclassification within the used categories of demographic factors is possible. For example, no clear instructions for the registration of ethnicity exist. One caregiver may classify a second generation immigrant as ‘Dutch’, whereas another caregiver may register the same woman as ‘non-Dutch’. It is, however, assumed that this misclassification is random and not dependent on the place of birth or type of caregiver. Therefore it, cannot explain the observed relationships between demographic factors and place of birth and type of caregiver. It

remains possible that these relationships are weakened due to the potential misclassification.

When comparing the results of this study with international studies, one should bear in mind that maternity care systems are totally different in different countries and therefore difficult to compare. Australian data confirm the observed higher referral rate for primiparous women. [16] A study in the United States into home births concluded that mothers who gave birth at home were more likely to be of higher parity. [17] In the same study, a maternal age of 30 years and over was associated with more home births. This was also confirmed in another Dutch study where women choosing a home birth were older on average than women choosing a short stay hospital birth. [18] As in our study, Statistics Netherlands showed in the year 1990 that within the group of primiparous women, the age group of 25 - 29 was most likely to have a home birth; whereas for all women, the age group of 30 - 34 had the highest home birth rate. [2] In that year also, more than twice as many Dutch women chose a home birth than non-Dutch women. This relationship was also confirmed in a prospective Dutch cohort of 1836 women, showing more short stay hospital births than home births for women belonging to an ethnic minority. [19] In the United States also, it has been described that white women more often choose a home birth. [17] Differences in home birth rates depending on the degree of urbanisation have already been described for the Dutch situation. Statistics Netherlands showed that the home birth rate decreased the more inhabitants lived in a municipality. [2] Hingstman and Boon concluded that 'the supply of hospital beds and population density in a region (which are intercorrelated to a certain extent) have a negative effect on the proportion of home confinements'. [20] In another Dutch study examining the determinants of the choice for home or hospital birth, urbanisation was not found to be a predictor of choice. [12]

This study demonstrates clear relationships between maternal demographic factors and the place of birth and type of caregiver and the probability of a home birth. The place of birth is partly determined by the risk of referral from the midwife to the obstetrician during pregnancy or birth. This risk is, for example, higher for primiparous than for multiparous women. Apart from this medical risk, women giving birth with a midwife

can choose between a home birth and a short stay hospital birth. This choice is dependent on the preference of the woman. Non-Dutch women, for example, prefer a short stay hospital birth above a home birth. If home births are to be promoted, special attention should be focussed on non-Dutch women, a growing number in the Netherlands, young pregnant women and women in large cities. The choice of place of birth is often made early in pregnancy or even before pregnancy [21] and often is influenced by 'significant others' such as family and friends. [12] Apart from information via the midwife, alternative ways of informing young and non-Dutch women and their 'significant others' about the Dutch maternity system with its possible places of birth should be explored.

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Chapter 6

Ethnic differences in congenital malformations in the Netherlands
Analyses of a 5-year birth cohort

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Summary

Congenital malformations are among the major causes of perinatal mortality and morbidity at present. Research into the ethnic diversity of congenital malformations can form a basis both for aetiological studies and for health care advice and planning. This study compared the overall prevalence of congenital malformations, the prevalence in different organ systems and of several specific malformations between different maternal ethnic groups in the Netherlands using a 5-year national birth cohort (1996-2000) containing 881,800 births. Maternal ethnic groups considered were Dutch; Mediterranean (Moroccan/Turkish); other European; Black; Hindu and Asian. Mediterranean women had a 20% higher risk of having a child with a congenital malformation than Dutch women (age-adjusted OR=1.21 [95% CI 1.16,1.27]). They showed an increased risk of malformations in several organ systems such as the central nervous system and sensory organs, the urogenital system and skin and abdominal wall. Further, they had an increased risk of the group of chromosomal malformations/multiple malformations/syndromes. For the specific group of multiple malformations the maternal age adjusted OR was 1.80 [95% CI 1.47,2.20]. The Black group showed a significantly increased risk of skeletal and muscular malformations (age adjusted OR=1.76 [95% CI 1.53,2.02]) with a six fold increased risk of polydactyly compared with the Dutch group. For Mediterranean women, the largest and fastest growing group of immigrants in the Netherlands, this study demonstrated an increased risk of congenital malformations.

Introduction

Perinatal mortality and morbidity resulting from perinatal infections and birth trauma have significantly decreased over the last decades. As a result, the impact of congenital malformations on perinatal mortality and morbidity has increased.[1-3] Nowadays, congenital malformations are among the major causes of perinatal mortality and morbidity.

Several studies have reported ethnic differences in perinatal mortality and morbidity, at least partly ascribed to ethnic differences in the prevalence of congenital malformations.[2-5] Differences in the prevalence of congenital malformations may be due to variations in genetic predisposition and to variations in environmental factors such as lifestyle factors.[1] Higher incidences of consanguineous marriages in specific ethnic groups and possible differences in health care consumption may play a role. Research into the ethnic diversity in congenital malformations can form a basis for aetiological studies and may be valuable for health care advice and planning.

Since the prevalence of most congenital malformations is low, large numbers of births in each ethnic group are required to detect possible differences in the prevalence of certain congenital malformations. Therefore, we used a 5-year national birth cohort from the Dutch National Perinatal and Neonatal Registers. This enabled us to study the relationship between maternal ethnicity and the overall prevalence of congenital malformations, the prevalence in different organ systems and some specific congenital malformations in a population of 881,800 births.

Methods

In the Netherlands, routine perinatal and neonatal data are registered in three national professional registers: the National Perinatal Database for Primary Care, a register of midwife-assisted births; the National Perinatal Database for Secondary Care, a register of

obstetrician-assisted births; and the National Neonatology Database, carried out by paediatricians. The National Perinatal Databases contain anonymous records of pregnancies with a gestational age of at least 16 weeks. Midwives and obstetricians register concise maternal demographic information, detailed information on the pregnancy and delivery, and concise information on the newborn including congenital malformations detected at birth or within the first week after birth. The National Neonatology Database contains anonymous records of admissions of newborns to paediatric neonatal departments within the first 28 days of life, and of re-admissions for neonatal problems. The paediatricians register brief perinatal information and detailed information about the physical condition of the newborns, including congenital malformations diagnosed within the first month of life.

Since 1995, these databases have been linked annually using a statistical matching procedure based on maternal and child variables to form one Dutch birth cohort per year containing perinatal and neonatal information.[6] In the present study we combined the years 1996 - 2000 to create a 5-year birth cohort. In this birth cohort 881,800 births were registered, which is approximately 90% of all Dutch births in this 5-year period.[7]

In the combined national perinatal and neonatal database the variable “ethnicity” is divided into seven categories: Dutch; Mediterranean (Moroccan or Turkish); other European (all other European countries besides the Netherlands and from the USA and Canada); Black (African or Black from Surinam and Antilles); Hindu (Pakistani, Indian and Hindu from Surinam); Asian (Chinese, Japanese, Indonesian, Moluccan and Vietnamese); Other (South-American and other non-specified groups).

After linking the three databases, for some women more than one record was available, for example after referral from the midwife to the obstetrician. In these records the coding of the ethnic category was not always consistent. If one record coded “Dutch” whereas the other coded another origin, we chose to recode the record to the other origin. Combinations of two specified, non-Dutch, categories were recoded as “ethnicity unclear”. In the analyses the categories “other” and “ethnicity unclear” were combined into the category “unknown” since for both categories the exact ethnicity is unknown.

Statistical methods

In the database congenital malformations are classified through a standard coding system by organ system into specific categories or into non-specific categories if no details are known. Eight different organ systems are distinguished for which there are 51 specified and 20 unspecified categories of congenital malformations. Logistic regression models were used to study the relationship between maternal ethnicity and congenital malformations. The overall relationship between ethnic group and the total prevalence of congenital malformations, the total prevalence within the eight organ systems and the prevalence of some specific congenital malformations was determined with the Likelihood Ratio Test (LRT). If this test was significant it showed the existence of an overall relationship between ethnicity and congenital malformations. Thereafter, the individual significance of the calculated odds ratios (ORs) expressing the observed risk differences in prevalence between the different ethnic groups and the Dutch group, used as reference group, was studied. Because maternal age is related to the ethnic group and to the occurrence of certain congenital malformations, we calculated the ORs both unadjusted and adjusted for the age of the mother.

Because the prevalence of some malformations was low, even in this 5-year birth cohort, not all could be tested. We decided that the predicted number of malformations had to be at least 5 in each ethnic group to perform a worthwhile and clinically significant test. Therefore, from the 51 specific malformations registered in the linked national database only the following 15 were analysed for possible differences between ethnic groups: neural tube defects (NTD); congenital malformations of the ears; ventricular septal defect; single umbilical artery; cleft lip with/without cleft palate; cleft palate without cleft lip; intestinal/anorectal atresia; hypospadias and/or epispadias; undescended testes; polydactyly; syndactyly; deformities of the foot without NTD; Down's syndrome; other chromosomal malformations; and multiple malformations.

Many comparisons were performed to test for a possible ethnic difference in prevalence of any congenital malformations. To avoid chance findings resulting from to multiple testing we applied a Bonferroni correction in which the usual critical value of 0.05 is adapted to a lower one depending on the number of tests performed. For example, to

determine in which of the ethnic groups a possible difference in overall prevalence of malformations exists, the critical value used was 0.05/6=0.008. To test whether there is any significant relationship between ethnicity and one of the eight organ systems the critical value used for the LRT's was 0.05/8=0.006. Significant organ systems were selected for further examination to determine which ethnic group differed significantly from the Dutch reference group using a critical value of 0.05/8*6=0.001. For the analyses of the specific malformations similar adaptations of the critical value were performed depending on the number of malformations tested within each organ system. This article will only focus on the significant observations where the calculated P-values are below the Bonferroni corrected critical values. The Bonferroni correction is conservative. Therefore, the overall risk of stating a possible relationship of any malformation with ethnicity, while in reality it does not exist, is kept at least below 5%.
All statistical analyses were performed in SPSS, version 11.

Results

The number of women and the mean maternal age as observed for every ethnic group in the 5-year birth cohort of 1996-2000 is shown in Table 1. The Dutch women form the largest and oldest group whereas the Mediterranean women are the second largest and youngest group, with a 3-year difference in mean maternal age compared with the Dutch group.

Table 1: Number of women and mean maternal age per ethnic group in the 5-year birth cohort of 1996-2000 from the Dutch linked national perinatal database.

Ethnic group	**Number**	**%**	**Mean maternal age (years)**
Dutch	725,137	82.3	30.9
Mediterranean	66,846	7.6	27.9
Other European	18,368	2.1	30.0
Black	21,448	2.4	28.8
Hindu	10,865	1.2	28.7
Asian	15,924	1.8	29.9
Unknown	22,269	2.5	29.2
Total	880,857	100	30.5

Note: Total number is different from total number of women in the 5-year birth cohort (n=881,800) due to missing ethnicity codes

Table 2 shows the overall prevalence of all congenital malformations and the calculated LRT and ORs for the different ethnic groups. The Mediterranean group has 20% more risk of having a child with a congenital malformation than the Dutch group (age-adjusted OR=1.21 [95% CI 1.16,1.27]). The group with unknown ethnicity also shows a significant increase in risk of having a child with a congenital malformation (OR= 1.18, [95% CI 1.09,1.27]). The Black group tends to a somewhat higher risk and the other European and Asian group both tend to a somewhat lower risk than the Dutch groups. The calculated P-values, however, were not below the Bonferroni defined critical value correcting for multiple testing.

Table 2: Overall prevalence of congenital malformations for the different ethnic groups and calculated Likelihood Ratio Test and Odds Ratio unadjusted and adjusted for maternal age. Data from the Dutch linked National Perinatal Database of 1996-2000.

	Prevalence		Unadjusted		Adjusted for maternal age	
All congenital malformations	per 10,000	LRT[a]	OR[b]	95% C.I.[c]	OR	95% C.I.
		p<0.0001				
Dutch	279.1		1.00		1.00	
Mediterranean	330.2		1.19**	[1.14 , 1.24]	1.21**	[1.16 , 1.27]
Other European	253.7		0.91	[0.83 , 1.00]	0.91	[0.83 , 1.00]
Black	302.6		1.09	[1.00 , 1.18]	1.10	[1.02 , 1.19]
Hindu	297.3		1.06	[0.95 , 1.19]	1.08	[0.97 , 1.21]
Asian	246.8		0.88	[0.80 , 0.98]	0.89	[0.80 , 0.98]
Unknown	322.9		1.16**	[1.08 , 1.25]	1.18**	[1.09 , 1.27]

[a]: LRT = Likelihood Ratio Test to test whether there is an overall relation between the ethnic groups and the risk of congenital malformations

[b]: OR = odds ratio

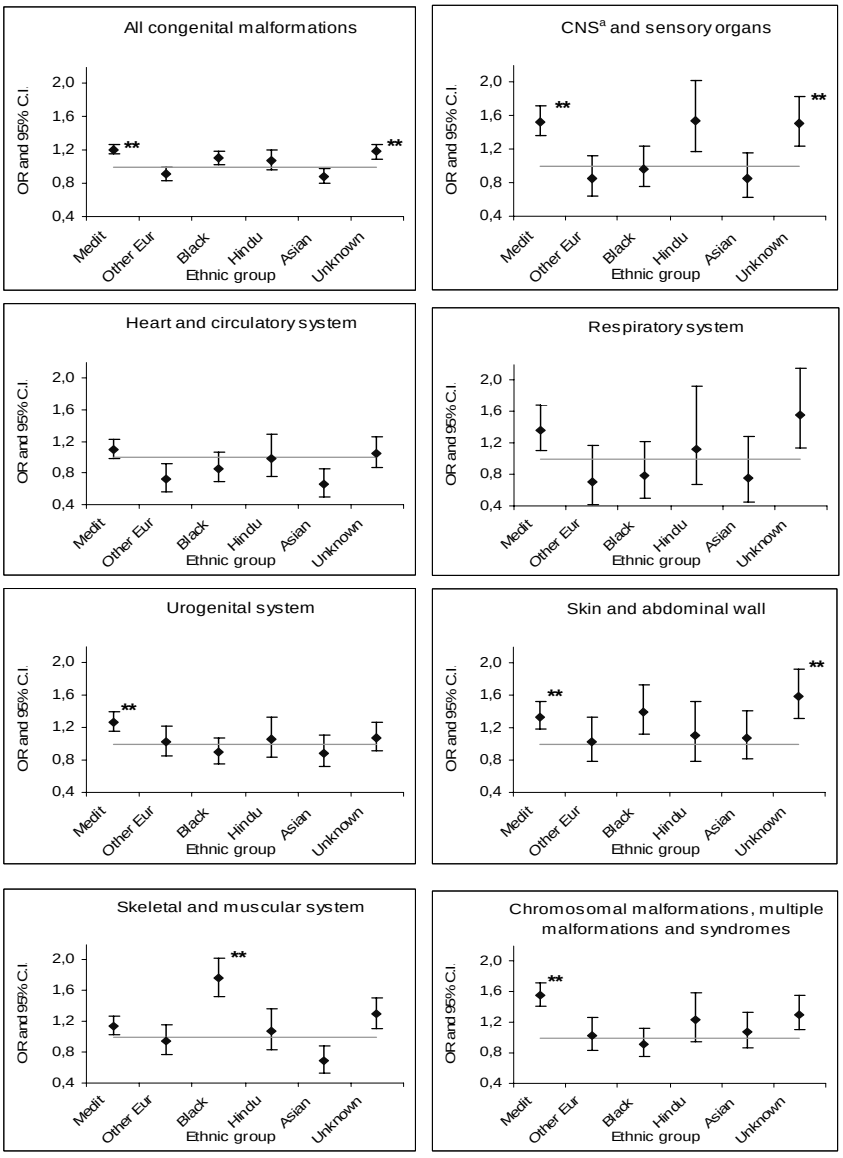
[c]: 95% C.I. = 95% confidence interval

**: Significance below critical P-value defined by the Bonferroni method taking into account multiple testing (see Methods section)

The calculated ORs for the different organ systems show similar trends for the different ethnic groups (Figure 1 and Appendix 1). Only for the digestive system is there no relationship found between ethnicity of the woman and risk of congenital malformations.

The Mediterranean group shows significantly increased risks for the following organ systems: central nervous system and sensory organs (OR=1.53 [95% CI 1.36,1.72]), urogenital system (OR=1.27 [95% CI 1.16,1.39]), skin and abdominal wall (OR=1.34 [95% CI 1.18,1.52]), chromosomal malformations/multiple malformations/syndromes (OR=1.56 [95% CI 1.41,1.72]).

Figure 1: Overall Odds Ratio and Odds Ratio per organ system (adjusted for maternal age) for the different ethnic groups compared with the Dutch reference group



Horizontal line indicates Odds Ratio=1 for the Dutch reference group
[a]: CNS = Central Nervous System
Digestive system is not shown because no relation was found between ethnic group and congenital malformations of the digestive system using the likelihood ratio test
**: Significance below critical P-value defined by the Bonferroni method taking into account multiple testing (see Methods section)

For the respiratory system (OR=1.36 [95% CI 1.11,1.68]) and skeletal and muscular system (OR=1.14 [95% CI 1.03,1.26]) the corresponding P-values were not below the Bonferroni defined critical value correcting for multiple testing. The group with unknown ethnicity shows significantly increased risks in the central nervous system and sensory organs (OR=1.51 [95% CI 1.24,1.83]) and the malformations of skin and abdominal wall (OR=1.59 [95% CI 1.31,1.93]). For the Black group a large significant increase in malformations of the skeletal and muscular system is observed (OR=1.76 [95% CI 1.53,2.02]).

As stated in the method section 15 specific congenital malformations occurred frequently enough to test whether they were statistically related to ethnic origin. A significant relationship (i.e. LRT) was observed for the following five specific malformations: congenital malformations of the ears, single umbilical artery, cleft lip with/without cleft palate, polydactyly and multiple malformations (Appendix 2). For both single umbilical artery and cleft lip with/without cleft palate the calculated ORs were below one for all the ethnic groups, pointing to lower risks compared with the Dutch group. However, none of the P-values corresponding to these ORs were below the Bonferroni defined critical value and therefore we will refrain from a positive statement about these associations. The risk of polydactyly was significantly increased for the Black group, the Hindu group and the group with unknown ethnicity (OR, respectively, 6.46 [95% CI 5.31,7.86], 2.27 [95% CI 1.48,3.48] and 2.43 [95% CI 1.81,3.27]). The group with unknown ethnicity also showed a twofold higher risk of congenital malformations of the ears (OR=2.14 [95% CI 1.46,3.14]). In the Mediterranean group a significant OR of 1.80 [95% CI 1.47,2.20] was observed for the group of multiple malformations.

Discussion

Comparisons in a 5-year birth cohort from the National Perinatal and Neonatal Registries of 1996-2000 show that Mediterranean women (Turkish and Moroccan) have a 20% higher risk of giving birth to a child with a congenital malformation than Dutch women. This is caused by similar increased risks in practically all organ systems. Specifically

notable is an 80% increased risk of multiple malformations. Women of unknown ethnic origin show similar increased risks. However, this group is difficult to interpret because it contains a large mix of ethnicities. A notable observation within the Black group is the almost 80% increased risk in the skeletal and muscular organ system. This increased risk is largely explained by the sixfold higher risk of having a child with polydactyly in this group compared with the Dutch reference group. The Hindu group also shows a more than twofold higher risk of polydactyly.

Even though the cohort included 881,800 births, the prevalence of certain malformations was still too low to study possible ethnic differences. It is possible that even within the congenital malformations studied, the numbers were not always sufficient to demonstrate an existing difference or to prove statistical significance after Bonferroni correction.

Under-reporting of congenital malformations in the routine perinatal and neonatal databases used in this study is possible. Due to the fact that the perinatal database is completed shortly after birth, it will not include malformations diagnosed later. Moreover, one caregiver may fill in the registry with more care and detail than another. However, we assume that the possible under-reporting of congenital malformations in these registries is similar for all ethnic groups. Therefore, the observed differences in risks cannot be explained by a difference in reporting practice between the ethnic groups.

Misclassification of ethnicity may have occurred especially since the instructions on how to fill in this item in the registries are not sufficiently clear and detailed. One caregiver may register ethnicity based on the appearance of a woman whereas another caregiver may ask about her country of origin. This misclassification cannot explain the observed ethnic differences in risk of congenital malformations. It is possible, however, that due to this misclassification risks are weakened or even masked.

Comparing this study with the existing literature is difficult because of differences in the definitions of congenital malformations and ethnicity used. Ethnicity may be based on

the race of the woman, the country of origin or the country of birth of the child. Often, as in this study, the ethnicity of the father and the time elapsed since immigration or the generation status is not available.

An ethnic variation in prevalence of neural tube defects has been reported in the literature.[8,9] A survey in Turkey reported that the prevalence of neural tube defects in Turkey was much higher than expected based on prevalences in the EUROCAT registries.[10] As an explanation, the low social class and the low intake of folic acid related to a low social class were given. Chitty and Winter [4] reported that Pakistani women had a more than twofold higher risk of perinatal death due to neural tube defects than European women (OR=2.7, [95 CI 1.2,6.3]). In our study it was notable that the prevalence of central nervous system defects was strongly increased in the Mediterranean group but no significant increase in neural tube defects could be shown. Whether there is really no existing difference in prevalence of neural tube defects within the Mediterranean group of women living in the Netherlands or whether these women possibly have a better intake of folic acid than women in their country of origin is not possible to say on the basis of this study.

Ethnic differences in chromosomal malformations and syndromes may be related to different use of prenatal diagnostics. Khoshnood et al.[11] reported that the impact of increasing maternal age on the prevalence of Down's syndrome in the United States was higher in African American women than in non-Hispanic white women. This may be explained by differences in access to or use of prenatal diagnostic services. This has also been reported in other populations.[12] This could also explain, apart from consanguinity, the increased risk of chromosomal/multiple malformations/syndromes observed for the Mediterranean group in our study. A study in Jerusalem reported an almost twofold higher risk of having a child with Down's syndrome for women from North-Africa than in women from Europe and the United States.[13] No relation was found between Down's syndrome and ethnic group in our study.

The possible lower risks of cleft lip with or without cleft palate for all the ethnic groups compared with our Dutch reference group has already been described before. Croen et

al.[14] reported a lower risk in the black population of the United States than in the white population (OR=0.56, [95% CI 0.45,0.69]). Another study in the United States reported an OR of 0.40 for black children compared with white, non-Hispanic children.[15] In Great Britain, Leck and Lancashire [16] reported lower risks for cleft lip with or without cleft palate for Caribbeans than for Europeans (OR=0.52; 0.001<P<0.01).

The largest observed difference in our study was the sixfold higher risk of having a child with polydactyly in the Black group than in the Dutch group. This finding is in accordance with Leck [16] who reported an almost 10-fold higher risk for polydactyly in Caribbeans in Great Britain compared with Europeans.

Our study demonstrated an increased risk of congenital malformations for a large number of organ systems for the Mediterranean group living in the Netherlands. This is an important finding because the Mediterranean group nowadays is the largest group of immigrants in the Netherlands. It is also the fastest growing group of immigrants. Schulpen et al.[17] also described an increased perinatal mortality and morbidity, including congenital malformations, in Turkish and Moroccan children. He reported that the excess mortality risk in the first year after birth observed in the Turkish and Moroccan children is mainly the result of congenital malformations. In the age group 0-15 years the mortality as a result of an inherited (metabolic) malformation was twice as high as in the Dutch children.

A genetic difference may explain the increased risk of congenital malformations in the Mediterranean group. An alternative explanation may be cultural differences in, for example, lifestyle factors. Mediterranean women in the Netherlands more often than Dutch women are from a lower socio-economic background. Low socio-economic class is known to be related to higher prevalences of congenital malformations,[18-20] possibly resulting in poor nutrition and poor use of prenatal care. Since socio-economic class is not registered in the perinatal databases used in this study this factor could not be analysed.

Another important explanatory factor for this observation may be the higher occurrence of consanguinity in the Mediterranean group. Around 50% of the marriages in the Turkish and Moroccan community in the Netherlands are with a partner who moves from the home country for the marriage.[17] It is estimated that around half of these partners are cousins of whom approximately half are first cousins. Many studies describe the large impact of consanguinity on the prevalence of congenital malformations.[21-24] Bundey and Alam [25] demonstrated that 60% of the mortality and severe morbidity, largely caused by congenital malformations, of children born from consanguine parents may be prevented. Stoltenberg et al.[26] showed a twofold higher risk of congenital malformations among children whose parents were first cousins in Norway.

In the present study the Mediterranean group, the largest group of Dutch immigrants, showed an increased risk of congenital malformations. Research is needed to determine the aetiological factors explaining the observed ethnic differences in prevalence of congenital malformations. Thereafter, it might be possible to narrow the existing gap in congenital malformation risk using primary and secondary prevention, by paying more attention to subjects such as lifestyle factors, intake of folic acid, risks of consanguinity and the use of prenatal care.

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***Appendix 1**: Prevalence of congenital malformations per organ system for the different ethnic groups and calculated Likelihood Ratio Test and Odds Ratio unadjusted and adjusted for the maternal age. Data from the Dutch linked national perinatal database of 1996-2000.*

	Prevalence		Unadjusted		Adjusted for maternal age	
	per 10,000	LRT[a]	OR[b]	95% C.I.[c]	OR	95% C.I.
CNS[d] and sensory organs		p<0.0001**				
Dutch	30.6					
Mediterranean	48.0		1.57**	[1.39 , 1.76]	1.53**	[1.36 , 1.72]
Other European	26.1		0.85	[0.64 , 1.14]	0.85	[0.64 , 1.13]
Black	29.8		0.97	[0.75 , 1.25]	0.96	[0.75 , 1.23]
Hindu	47.9		1.56	[1.19 , 2.06]	1.54	[1.17 , 2.03]
Asian	26.4		0.86	[0.63 , 1.17]	0.85	[0.63 , 1.16]
Unknown	46.7		1.53**	[1.25 , 1.86]	1.51**	[1.24 , 1.83]
Heart and circulatory system		p=0.0006**				
Dutch	52.0					
Mediterranean	54.8		1.05	[0.95 , 1.17]	1.09	[0.98 , 1.22]
Other European	37.0		0.71	[0.56 , 0.91]	0.72	[0.57 , 0.92]
Black	43.8		0.84	[0.69 , 1.03]	0.86	[0.70 , 1.06]
Hindu	49.7		0.96	[0.73 , 1.25]	0.98	[0.75 , 1.29]
Asian	33.9		0.65	[0.50 , 0.85]	0.66	[0.50 , 0.86]
Unknown	53.4		1.03	[0.86 , 1.24]	1.05	[0.87 , 1.26]
Digestive system		p=0.29				
Dutch	35.5					
Mediterranean	33.5					
Other European	32.7					
Black	26.1					
Hindu	32.2					
Asian	32.7					
Unknown	32.3					
Respiratory system		p=0.0086				
Dutch	11.9					
Mediterranean	15.3		1.28	[1.04 , 1.57]	1.36	[1.11 , 1.68]
Other European	8.2		0.69	[0.41 , 1.15]	0.70	[0.42 , 1.17]
Black	8.9		0.75	[0.47 , 1.17]	0.78	[0.49 , 1.22]
Hindu	12.9		1.08	[0.64 , 1.84]	1.13	[0.67 , 1.92]

	Prevalence per 10,000	LRT[a]	Unadjusted OR[b]	95% C.I.[c]	Adjusted for maternal age OR	95% C.I.
Asian	8.8		0.74	[0.44 , 1.25]	0.75	[0.45 , 1.28]
Unknown	18.0		1.51	[1.10 , 2.07]	1.56	[1.14 , 2.15]
Urogenital system		p<0.0001**				
Dutch	63.9					
Mediterranean	82.0		1.27**	[1.18 , 1.41]	1.27**	[1.16 , 1.39]
Other European	65.3		1.02	[0.85 , 1.23]	1.02	[0.85 , 1.22]
Black	58.3		0.91	[0.76 , 1.09]	0.90	[0.76 , 1.08]
Hindu	68.1		1.07	[0.85 , 1.34]	1.06	[0.84 , 1.33]
Asian	57.1		0.89	[0.73 , 1.10]	0.89	[0.72 , 1.10]
Unknown	69.2		1.08	[0.92 , 1.27]	1.08	[0.92 , 1.26]
Skin and abdominal wall		p<0.0001**				
Dutch	29.8					
Mediterranean	40.4		1.36**	[1.20 , 1.54]	1.34**	[1.18 , 1.52]
Other European	30.5		1.03	[0.79 , 1.34]	1.02	[0.78 , 1.33]
Black	42.0		1.41	[1.14 , 1.74]	1.40	[1.13 , 1.73]
Hindu	33.1		1.11	[0.80 , 1.55]	1.10	[0.79 , 1.53]
Asian	32.0		1.08	[0.82 , 1.42]	1.07	[0.81 , 1.41]
Unknown	47.6		1.60**	[1.32 , 1.95]	1.59**	[1.31 , 1.93]
Skeletal and muscular system		p<0.0001**				
Dutch	55.9					
Mediterranean	66.7		1.19**	[1.08 , 1.32]	1.14	[1.03 , 1.26]
Other European	53.4		0.96	[0.78 , 1.17]	0.94	[0.77 , 1.15]
Black	100.7		1.81**	[1.58 , 2.08]	1.76**	[1.53 , 2.02]
Hindu	62.6		1.10	[0.87 , 1.41]	1.07	[0.84 , 1.37]
Asian	38.9		0.70	[0.54 , 0.89]	0.69	[0.53 , 0.88]
Unknown	74.1		1.33**	[1.14 , 1.55]	1.30	[1.11 , 1.51]
Chromosomal malformations, multiple malformations and syndromes		p<0.0001**				
Dutch	51.6					
Mediterranean	68.1		1.32**	[1.20 , 1.46]	1.56**	[1.41 , 1.72]
Other European	51.2		0.99	[0.81 , 1.22]	1.03	[0.84 , 1.27]
Black	42.9		0.83	[0.68 , 1.02]	0.92	[0.75 , 1.13]

	Prevalence per 10,000	LRT[a]	Unadjusted OR[b]	Unadjusted 95% C.I.[c]	Adjusted for maternal age OR	Adjusted for maternal age 95% C.I.
Hindu	56.1		1.09	[0.85 , 1.40]	1.23	[0.95 , 1.59]
Asian	53.4		1.04	[0.83 , 1.28]	1.08	[0.87 , 1.34]
Unknown	61.5		1.19	[1.01 , 1.42]	1.30	[1.10 , 1.55]

[a]: LRT = Likelihood Ratio Test to test whether there is an overall relation between the ethnic groups and the risk of congenital malformations

[b]: OR = odds ratio

[c]: 95% C.I. = 95% confidence interval

[d]: CNS = Central Nervous System

**: Significance below critical p-value defined by the Bonferroni method taking into account multiple testing (see methods section)

***Appendix 2**: Specific malformations showing a significant relationship with the ethnicity of the women, even after Bonferroni correction for multiple testing. Prevalence, calculated Likelihood Ratio Test and Odds Ratio unadjusted and adjusted for the maternal age are given. Data from the Dutch linked national perinatal database of 1996-2000.*

	Prevalence		Unadjusted		Adjusted for maternal age	
	per 10,000	LRT[a]	OR[b]	95% C.I.[c]	OR	95% C.I.
Congenital malformations of the ears		p=0.0014**				
Dutch	6.0					
Mediterranean	7.2		1.20	[0.89 , 1.62]	1.23	[0.91 , 1.67]
Other	2.2		0.37	[0.14 , 0.98]	0.37	[0.14 , 0.99]
Black	6.1		1.02	[0.58 , 1.76]	1.03	[0.59 , 1.80]
Hindu	10.1		1.70	[0.93 , 3.09]	1.73	[0.95 , 3.15]
Asian	5.7		0.95	[0.49 , 1.83]	0.95	[0.49 , 1.85]
Unknown	12.6		2.11	[1.44 , 3.09]	2.14**	[1.46 , 3.14]
Single umbilical artery		p<0.0001**				
Dutch	18.1					
Mediterranean	16.2		0.90	[0.74 , 1.09]	0.91	[0.75 , 1.11]
Other	14.2		0.79	[0.53 , 1.16]	0.79	[0.54 , 1.16]
Black	7.5		0.42	[0.25 , 0.68]	0.42	[0.26 , 0.69]
Hindu	17.5		0.97	[0.62 , 1.53]	0.98	[0.62 , 1.55]
Asian	8.2		0.45	[0.26 , 0.78]	0.46	[0.26 , 0.79]
Unknown	14.4		0.80	[0.56 , 1.13]	0.80	[0.57 , 1.14]
Cleft lip with/without cleft palate		p<0.0001**				
Dutch	12.1					
Mediterranean	7.6		0.63	[0.48 , 0.84]	0.62	[0.47 , 0.83]
Other	9.3		0.77	[0.48 , 1.24]	0.77	[0.47 , 1.24]
Black	3.7		0.31	[0.16 , 0.62]	0.31	[0.15 , 0.62]
Hindu	7.4		0.61	[0.31 , 1.23]	0.60	[0.30 , 1.21]
Asian	11.9		0.99	[0.63 , 1.56]	0.99	[0.63 , 1.55]
Unknown	8.1		0.67	[0.42 , 1.07]	0.67	[0.98 , 1.01]
Polydactyly		p<0.0001**				
Dutch	8.6					
Mediterranean	12.4		1.44	[1.14 , 1.81]	1.38	[1.09 , 1.74]
Other	5.4		0.63	[0.34 , 1.18]	0.62	[0.33 , 1.16]

	Prevalence per 10,000	LRT[a]	Unadjusted OR[b]	Unadjusted 95% C.I.[c]	Adjusted for maternal age OR	Adjusted for maternal age 95% C.I.
Black	57.3		6.67	[5.50 , 8.10]	6.46**	[5.31 , 7.86]
Hindu	21.2		2.35	[1.53 , 3.59]	2.27**	[1.48 , 3.48]
Asian	8.2		0.95	[0.55 , 1.64]	0.93	[0.54 , 1.61]
Unknown	21.6		2.50	[1.86 , 3.35]	2.43**	[1.81 , 3.27]
Multiple congenital malformations		p<0.0001**				
Dutch	10.1					
Mediterranean	17.1		1.69	[1.39 , 2.06]	1.80**	[1.47 , 2.20]
Other	11.4		1.14	[0.74 , 1.75]	1.16	[0.75 , 1.78]
Black	7.9		0.79	[0.49 , 1.27]	0.82	[0.51 , 1.33]
Hindu	12.9		1.28	[0.75 , 2.17]	1.34	[0.79 , 2.27]
Asian	8.2		0.81	[0.47 , 1.40]	0.83	[0.48 , 1.43]
Unknown	16.6		1.65	[1.19 , 2.30]	1.71	[1.23 , 2.38]

Note: No significant relationship (after correction for multiple testing) between the ethnic groups and the following specific malformations were found: neural tube defect, ventricular septal defect; cleft palate without cleft lip; intestinal/anorectal atresia; hypospadia and/or epispadia; undescended testes; syndactyly; deformities of the foot without NTD; Down's syndrome and other chromosomal malformations.

[a]: LRT = Likelihood Ratio Test to test whether there is an overall relation between the ethnic groups and the risk of congenital malformations

[b]: OR = odds ratio

[c]: 95% C.I. = 95% confidence interval

**: Significance below critical p-value defined by the Bonferroni method taking into account multiple testing (see methods section)

Chapter 7

Congenital malformations in 4224 children conceived after IVF

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Abstract

Background: The percentage of children born after IVF will continue to increase due to demographic changes such as increasing maternal age and new developments in assisted reproduction techniques. IVF conceptions may carry an increased risk of congenital malformations.

Methods: We compared overall and specific congenital malformation rates calculated for IVF children (n=4224) and naturally conceived children (n=314 605), using records from the same Dutch national database for the years 1995 and 1996 and controlling for confounding maternal factors.

Results: The overall crude odds ratio (OR) for the risk of any malformation for IVF children compared with naturally conceived children was 1.20 [95% confidence interval (CI): 1.01-1.43]. After correction for differences in maternal age, parity and ethnicity between the IVF and control population the OR was 1.03 (95% CI: 0.86-1.23). The crude OR for IVF children appeared higher for the cardiovascular organ system and for several specific minor congenital malformations. However, these could be chance findings due to comparison of many malformation categories or may result from remaining differences in ascertaining malformations between IVF and naturally conceived children.

Conclusions: The small increase in overall congenital malformations observed in the IVF children appears to be attributable to differences in maternal characteristics and not to any aspect of the IVF procedure.

Keywords: Congenital malformations / IVF children / national registry / Netherlands

Introduction

At present 1.5% of all babies in the Netherlands are born after IVF or ICSI. In the coming years this percentage is likely to increase further as a result of demographic changes such as increasing maternal age and due to new developments in assisted reproduction techniques.

Many studies have concluded that IVF pregnancies carry an increased risk for multiplicity, perinatal mortality, preterm birth and low birth weight in comparison with pregnancies after spontaneous conception. (Beral and Doyle, 1990; Rufat et al., 1994; Koudstaal et al., 2000) It has also been hypothesized that IVF conceptions may carry an increased risk of congenital malformations. Theoretically, an increase in congenital malformations after IVF may be caused by an increase in chromosomal aberrations due to the relatively advanced age of the infertile couples and an increased rate of fertilization by abnormal sperm. Moreover, the IVF procedure may induce point mutations by the actions of physical and chemical teratogens, thereby enhancing the risk of congenital malformations. (Biggers, 1981)

Several studies have investigated the incidence of congenital malformations in IVF conceptions. Some report a possible increase in the incidence of central nervous system (CNS) defects, specifically neural tube defects. (Lancaster, 1987; Beral and Doyle, 1990; Rizk et al., 1991; FIVNAT, 1995; Bergh et al., 1999; Ericson and Källen, 2001) Others indicate possible higher risks of chromosomal abnormalities, alimentary tract atresia, urogenital abnormalities and limb malformations. (Rizk et al., 1991; Westergaard et al., 1999; Ericson and Källen, 2001; Hansen et al., 2002) However, other studies have concluded that there is no evidence of an increase in the occurrence of malformations. (Wennerholm et al., 1991; Rufat et al., 1994; Saunders et al., 1996; D'Souza et al., 1997; Dhont et al., 1997; Olivennes et al., 1997)

Because most of these reports only concern small numbers of IVF pregnancies, without proper control groups, no firm conclusions can be drawn. Most of the studies use general population statistics as reference rates for congenital malformations, which is

not appropriate as IVF mothers differ in age, parity and obstetric history from the general population of women. Other methodological problems involve the difference in procedures by which malformations are diagnosed and registered in the compared groups. The malformation rates in the general population are mostly derived from routine registers, whereas the rates within the IVF population often result from detailed examination and follow-up.

In this study we investigated whether a difference existed in overall and specific congenital malformation rates between children born after IVF (n=4224) and naturally conceived children, (n=314 605) controlling for several confounding maternal factors. Records of the National Database of Obstetrics and Neonatology were used both for the IVF children and for the controls.

By comparing the number of congenital malformations registered for the IVF children in the national database with the number registered in specific questionnaires collected from the same group of children as part of a large survey of IVF pregnancies, the difference in registration practice of congenital malformations between these two data sources was determined.

Materials and methods

Routine data on congenital malformations in IVF children and naturally conceived children were obtained from three national professional perinatal and neonatal registers: the National Perinatal Database for Primary Care, a register of midwife-assisted births; the National Perinatal Database for Secondary Care, a register of obstetrician-assisted births; and the National Neonatology Database, carried out by paediatricians. The National Perinatal Databases contain anonymous records on pregnancies with a gestational age of at least 16 weeks. Midwives and obstetricians register concise maternal demographic information, detailed information on the pregnancy and delivery, including conception method if not natural, and information on the newborn, including congenital malformations detected in the first week after birth.

The National Neonatology Database contains anonymous records on all admissions of newborns to paediatric neonatal departments within the first 28 days of life, and on re-admissions for neonatal problems. Paediatricians register brief perinatal information and detailed information about the physical condition of the newborns, including congenital malformations diagnosed within the first month of life. Since 1995, these databases have been linked annually. (Anthony et al., 2001) The years 1995 and 1996 were used for this study. In this period, complete information from 85% of all Dutch births was registered in this linked perinatal database and partial information from an additional 7% of all births on either the pregnancy or the post-natal period was registered.

In this perinatal database, all birth records of children conceived after spontaneous pregnancies were selected to constitute a control population (n=314 605) by excluding all pregnancies where the use of any assisted reproduction method such as hormonal ovulation induction, intrauterine insemination or IVF was coded.

The IVF study population consisted partially of a cohort of 1925 IVF children (including 9% ICSI) born in 1995 and 1996. This IVF cohort is part of a larger survey including > 50% of all IVF births in The Netherlands from 1994-1996. (Buitendijk, 2000) Detailed information on the kind of congenital malformations was collected by questionnaires addressed to both the mothers of the IVF children and the obstetricians involved in the pregnancy and delivery care. These questionnaires were completed within 2 months after birth.

Comparing information resulting from specific questionnaires for this IVF cohort with information recorded on a routine basis for the controls may introduce a large bias. To avoid this ascertainment bias we traced the birth records of the children in the IVF cohort in the National Perinatal Database. Because no unique identification is currently available in the Netherlands, a statistical matching procedure had to be applied using the following maternal and infant variables: birth date (day, month, year) of the child and the mother, gender of the child and birth order for multiple births. Additional checks on birthweight and gestational age were also performed. Using this matching

procedure we were able to find the birth records of 89% of the children of this IVF cohort (n=1716). In 79% of these traced records the conception method was correctly coded as 'IVF'. Furthermore, all other birth records in this National Perinatal Database coding 'IVF' as conception method (n=2508) were added to the IVF study population. The IVF study population therefore included a total of 4224 IVF children. A small proportion of these were ICSI children. In these birth records, however, no distinction can be made between IVF and ICSI because no separate coding exists for ICSI. The congenital malformations recorded in the birth records of these IVF children were compared with the congenital malformations recorded in the birth records of the control population selected from the same database.

Possible differences in registration practice of congenital malformations were investigated in the children of the IVF cohort for whom information on congenital malformations was available both from the traced standard birth records in the National Perinatal Database and from the specific questionnaires completed by the IVF mothers and obstetricians (n=1716).

In the National Perinatal Database congenital malformations are classified through a standard coding system. Congenital malformations are coded by organ system in specific categories or in non-specific categories if no details are known. Eight different organ systems are distinguished with 51 specified and 20 unspecified categories of congenital malformations. This classification was also used to code the malformations reported in the specific questionnaires of the IVF cohort. All specific malformations, the total number of malformations per organ system and the overall incidence of all malformations were compared for the IVF study population and the control population. In this study a distinction was also made between major and minor congenital malformations based on the severity of the malformation. The calculated differences in malformation rates were expressed using OR and 95% confidence intervals (CI). The chi-square test was used to test for any significant difference in malformation rate ($P < 0.05$). The Fischer Exact test was used when the numbers were very small. A logistic regression model was used to correct the estimated OR for the overall number of malformations for the distribution of the maternal characteristics 'age of the mother',

'parity' and 'ethnicity' by introducing them into the model as covariates. The statistical analyses were performed in SPSS, version 10.

Results

Characteristics of both the IVF mothers and children and the control mothers and children are presented in Table I. The IVF group differs significantly from the control group on a number of these characteristics.

Table I: Characteristics of the IVF study population (n=4224) and the naturally conceived control population (n=314605)

	IVF population	Control population	p value
Characteristics of the mother			
Mean age (years)	33.3	29.7	< 0.001[a]
Parity (%)			
Primiparae	69.2	44.2	< 0.001[b]
Multiparae	30.8	55.8	
Ethnicity (%)			
Dutch	78.2	78.6	NS[b]
Non-Dutch	21.8	21.4	
Characteristics of the children			
Multiplicity (%)			
Singleton	56.5	97.1	< 0.001[b]
Multiple	43.5	2.9	
Gestational age (%)			
< 37 weeks	33.4	8.2	< 0.001[b]
≧ 37 weeks	66.6	91.8	

[a] t-test

[b] Pearson Chi-Square test

NS = not significant

Table II shows the overall number of children with congenital malformations and the number of children with minor, major and unspecified congenital malformations in both the IVF study population (n=4224) and the naturally conceived control population (n=314 605).

Table II: Number of children with one or more congenital malformation in the IVF study population and the naturally conceived control population, with corresponding odds ratios (OR)

	IVF population n=4224	Control population n=314605	Crude OR (95% CI)	Corrected OR[a] (95% CI)
No. of children with one or more congenital malformation	137	8526	1.20 (1.01-1.43)	1.03 (0.86-1.23)
No. of children with one or more *minor* congenital malformation	54	3445	1.17 (0.90-1.54)	[b]
No. of children with one or more *major* congenital malformation	28	1700	1.23 (0.85-1.79)	[b]
No. of children with one or more *unspecified* congenital malformation[c]	55	3381	1.22 (0.93-1.59)	[b]

[a] A logistic regression model was used to correct the crude OR for the maternal confounders 'maternal age', 'parity' and 'ethnicity'.

[b] Correction for maternal confounders was not performed since the crude OR was not significant and the numbers of congenital malformations in the different categories were small.

[c] These congenital malformations could not be divided into major or minor malformations because they were coded as general non-specific categories of malformations e.g. 'other congenital malformations of CNS'.

CI = confidence interval.

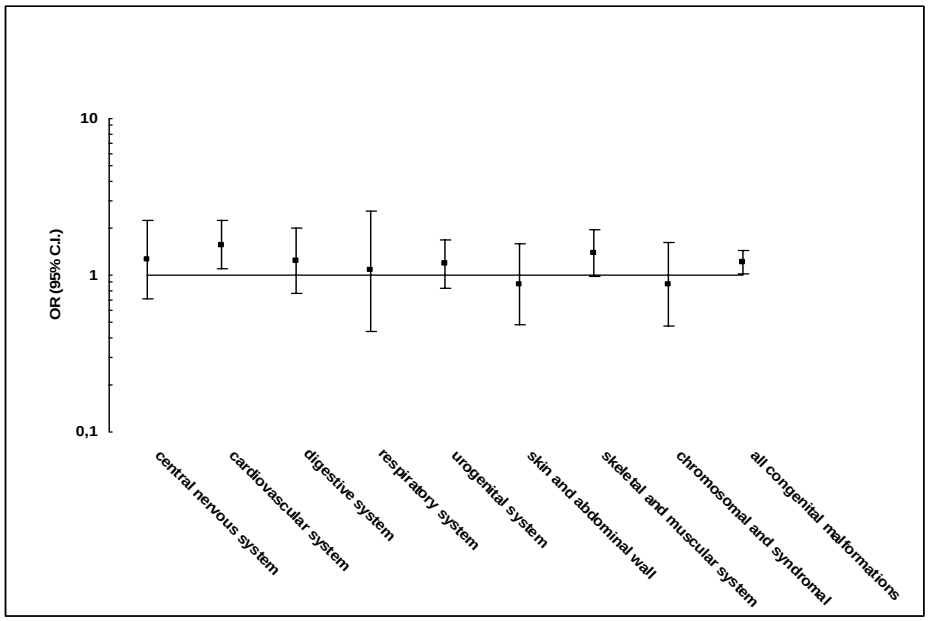
Congenital malformations were observed in 137 IVF children (3.2%) and in 8526 of the control children (2.7%). The complete list of all specific congenital malformations is provided in Appendix I. The overall OR for the risk of any malformation for IVF children compared with naturally conceived control children was 1.20 (95% CI: 1.01-1.43). Similar ORs were found for children with major, minor and unspecified congenital

malformations. These ORs were, however, no longer significant due to the smaller number of congenital malformations in these different subcategories.

After taking into account differences in maternal characteristics between the IVF and control population by correcting for the confounding factors, 'maternal age', 'parity' and 'ethnicity', the OR was 1.03 (95% CI: 0.86-1.23, Table II).

Further investigation of congenital malformations occurring in the different organ systems was performed (Figure 1).

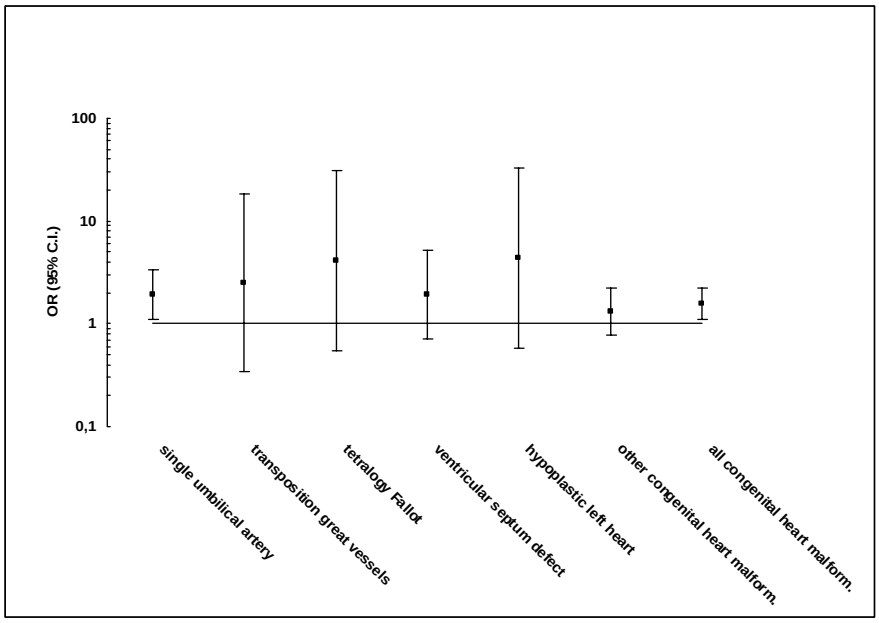
Figure 1: Calculated odds ratios (OR) for different organ systems, for the IVF study population versus the naturally conceived control population



Except for the category 'skin and abdominal wall malformations' and 'chromosomal and syndromal malformations', the OR for IVF children appeared slightly higher for every specific organ system. The difference only reached statistical significance for cardiovascular malformations (OR=1.56, 95% CI: 1.10-2.22).

Further exploration of the cardiovascular system abnormalities showed that all specific cardiovascular malformations were more frequently reported in IVF children, the ORs ranging from 1.32 to 4.38 (Figure 2). However, only the difference in occurrence of 'single umbilical artery', reached statistical significance (OR=1.93, 95% CI: 1.11-3.35).

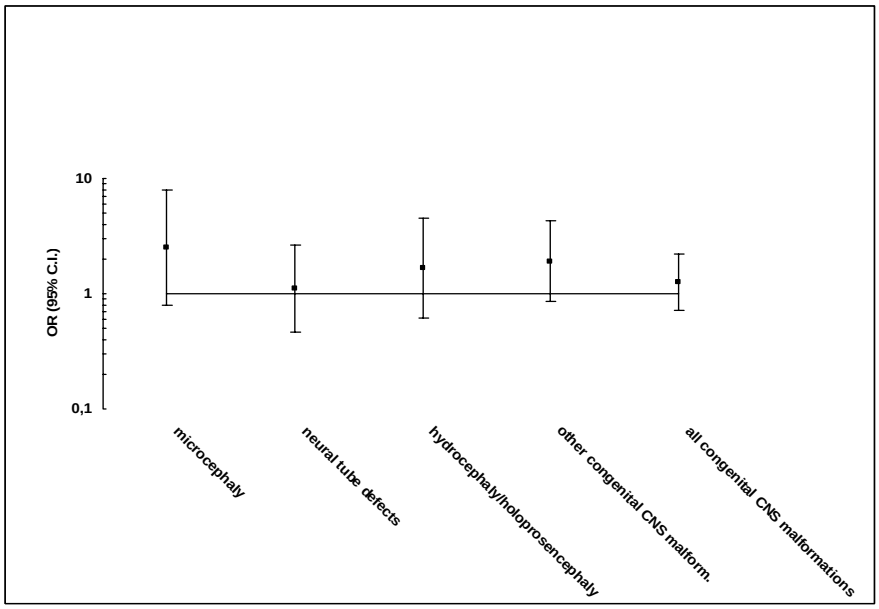
Figure 2: Calculated odds ratios (OR) for cardiovascular malformations, for the IVF study population versus the naturally conceived control population.



Note: 'Coarctation aortae' and 'tricuspid atresia/stenosis' are not shown because these malformations were not reported in the IVF study population.

Neural tube defects did not occur more frequently in the IVF group. Although the ORs of all specific CNS malformations ranged between 1.10 and 5.73, none of the differences reached statistical significance (Figure 3).

Figure 3: Calculated odds ratios (OR) for central nervous system malformations, for the IVF study population versus the naturally conceived control population.



Note: No 'encephalocoele' was reported in the IVF study group and the category 'neuromuscular disease' is not depicted because the 95% confidence interval (CI) is large (OR=5.73 (0.75-43.81)).

When comparing all specific malformations that can be coded in the national database, the results were variable, some malformations being more frequent in IVF children and others less frequent. The only malformations that occurred significantly more frequently in IVF children were the relatively minor malformations, 'single umbilical artery', 'inguinal hernia', 'club foot' and 'other unspecified skeletal and muscular malformations'. These findings could, however, be chance findings due to the many categories of congenital malformations compared between the IVF study population and the control population.

The congenital malformation prevalence was compared for the 1716 children of our IVF survey for whom both routinely completed national birth records and specific questionnaire information was available to determine the difference in registration practice between these two data sources.

In these 1716 children a total of 95 congenital malformations were coded. The prevalence of congenital malformations recorded in the specific questionnaires appeared almost twice as high as the prevalence based on the birth records of the same children (5.0% versus 2.7% respectively). Of the non-registered cases, 67% concerned congenital malformations not visible at birth and therefore not recorded within the time period between birth and the completion of the birth record or concerned minor malformations that may not have been considered worth recording such as 'single umbilical artery', 'hypospadia' or 'skin tags'. However, for 16 of the 95 congenital malformations, non-recording in the birth records could not be explained, resulting in a true under-registration of congenital malformations in birth records of the national perinatal database of 17%. The list of 16 non-registered malformations is given in Table III.

Table III: List of the 16 malformations not registered in the perinatal database and for whom there was no obvious reason for this non-registration, for example, because the diagnosis is often made later than the time span of the perinatal database

Malformations	*n*
Polydactyly	3
Syndactyly	2
Anomaly of the ear	1
Clubfoot	3
Spina bifida	1
Multiple malformations	6
Total	16

Discussion

Hypothetically, the number of birth defects may be increased when ovulation, fertilization and early embryonic development occur under influence of medicine and in an artificial environment. In our study we found a slightly increased risk of malformations for IVF children (OR=1.20, 95% CI 1.01-1.43). However, after taking into

account differences in maternal characteristics between the IVF and control mothers by controlling for the fact that IVF mothers were older and of lower parity the increased risk disappeared (OR=1.03, 95% CI 0.86-1.23). No further corrections for child factors were performed since the increased risk was completely attributable to maternal factors. It was concluded that the small increase in malformations observed in the IVF children resulted from differences in maternal characteristics and not from any aspect of the IVF procedure.

The strength of our study in comparison with earlier studies is that we were able to use the same data source of congenital malformations for both the IVF and the naturally conceived children. Moreover, our sample size was sufficiently large to test for differences into overall rate of malformations as well as to correct for confounding maternal characteristics. A large number of previous studies are difficult to interpret due to small sample size, different data sources used to ascertain malformations for the IVF and the control group and the fact that no adequate control population was available and controlling for confounding factors was not possible. (Morin et al., 1989; Ron-El et al., 1994; Rufat et al., 1994; Petersen et al., 1995; Sutcliffe et al., 1995; Verlaenen et al., 1995; Olivennes et al., 1997)

A limitation of our study is that we were not able to distinguish the small number of ICSI children included in our IVF study population because no separate coding exists for ICSI in the National Perinatal Database. However, other studies showed that ICSI children do not differ from IVF children in the risk of congenital malformations or in the number of neonatal complications. (Govaerts et al., 1998; Bonduelle et al., 2002) Furthermore, the estimated percentage of ICSI children is only 9%.

A small proportion of IVF birth records in the perinatal database is not included in the IVF study population because the conception method is not correctly filled in. Due to this misclassification these records are either wrongly excluded if another artificial conception method is coded or these records are wrongly added to the naturally conceived control group. However, the proportion of IVF birth records wrongly added to

the control group is so small compared with the large control group (n=314 605) that the effect will be negligible.

Our study is based on > 85% of all Dutch births in 1995 and 1996. Non-participation in the perinatal database is caused by logistic aspects such as the availability of staff and registration software. It is not influenced by whether or not pregnancies have been conceived through assisted reproductive techniques. Therefore, selection bias cannot be an issue in this study.

We determined that the standard birth records in the National Perinatal Database used for the comparison of malformation rates tend to under-report 17% of the congenital malformations visible at birth. This under-reporting is probably similar for the IVF group and the naturally conceived control group or slightly higher in the control group because IVF children are possibly examined more thoroughly at birth. This would not, however, influence the drawn conclusion of no difference in congenital malformations between IVF and naturally conceived children. The under-registration of congenital malformations in routinely completed birth records is a well-known phenomenon. A longer and more detailed follow-up often results in more accurate registration of congenital malformations. (Marazita et al., 2002)

A small excess risk of malformations in IVF children was shown for all organ systems except for the categories ‘skin and abdominal wall malformations’ and ‘chromosomal and syndromal malformations’. Only the prevalence of the cardiovascular organ system defects reached statistical significance. The specific malformations within the different organ systems often occurred slightly more frequently in the IVF children and sometimes less frequently. Of all the specific malformations, only the increases in the IVF children of the relatively minor malformations, ‘single umbilical artery’, ‘inguinal hernia’, ‘club foot’ and ‘other unspecified skeletal and muscular malformations’ reached statistical significance. Many comparisons were made for all the specific malformations between the IVF and the control group. Therefore, these increases could be chance findings due to multiple testing. Due to relatively small numbers in each specific congenital malformation group, we were not able to correct for possible confounding

factors. It is likely that, as was observed for the overall incidence of malformations, maternal factors such as age and parity, rather than the IVF procedure itself, may have an influence on the occurrence of specific malformations. Therefore, the interpretation of the small increases in congenital malformations observed in almost all organ systems is difficult. The increases could indicate a real increase in malformations that becomes more pronounced when using a larger study size. On the other hand we would expect that, if there was a harmful effect of the IVF procedure, malformations of only some specific organ systems or malformations originating from one common cause would be increased. Instead, we observed small increases in malformations of various organ systems. Therefore it is, more likely that special surveillance of children conceived by IVF, such as antenatal surveillance or more thorough paediatric examination after birth, could have resulted in some defects being diagnosed and recorded in the IVF birth records that would not have been noted and recorded for naturally conceived children, despite the use of the same data source. This is particularly likely for minor malformations since minor defects do not always have firm diagnostic criteria.

Ericson and Källen studied the Medical Birth Registry of 1982-1997 and reported an excess of congenital malformations for IVF children (OR=1.47). (Ericson and Källen, 2001) In accordance with the present study, the excess risk disappeared when confounders were taken into account. In the study of Dhont the increase in overall risk of congenital malformations was also no longer significant after correcting for maternal age. (Dhont, 1999) Westergaard also concluded that the characteristics of the patients rather than the assisted reproductive technology determine the higher risks of malformations in IVF pregnancies. (Westergaard et al., 1999)

Our study did not reveal any increased risk of neural tube defects or other defects of the CNS for IVF children, contrary to other studies. (Lancaster, 1987; Beral and Doyle, 1990; Rizk et al., 1991; FIVNAT, 1995; Bergh et al., 1999; Ericson and Källen, 2001) Neither did our study confirm the higher than expected numbers of chromosomal malformations in IVF children reported by others. (Rizk et al., 1991; Macas et al., 2001; Hansen et al., 2002) Likewise, our study did not reveal the excess risk for alimentary atresia reported by Ericson et al. (Ericson and Källen, 2001) In the present study an increase in the number

of club foot and other skeletal and muscular malformations was found. Rizk et al. also showed a higher than expected number of limb malformations and Hansen et al. reported more musculoskeletal defects. (Rizk et al., 1991; Hansen et al., 2002) Animal studies also reported more limb malformations in calves born after in-vitro production. (Wagtendonk-de Leeuw van et al., 2000)

Several studies reported an increase in hypospadias for boys born after IVF and especially after ICSI, relating the occurrence of hypospadia to the paternal subfertility. (Silver et al 1999; Wennerholm et al., 2000; Ericson and Källen, 2001) Using the standard birth records, we found no overall increase in hypospadias in our IVF children. However we were, unable to distinguish between IVF and ICSI children within the birth records of the National Perinatal Database since no separate coding for ICSI is being used. In the subgroup of IVF children for whom detailed questionnaire information was available, a distinction could be made between IVF and ICSI conception. When comparing the number of diagnosed hypospadias within these two groups a significantly higher number of hypospadias was reported for the ICSI children (OR=5.48, 95% CI 1.70-17.65) than for the IVF children. This increase in hypospadias should be further investigated by comparing children conceived through ICSI with naturally conceived children, controlling for confounding factors.

In conclusion, in our study the overall risk of congenital malformations was slightly increased for IVF children compared with to naturally conceived children. This increase could, however, be totally ascribed to differences in maternal characteristics between the IVF mothers and the mothers conceiving naturally. To make statistically meaningful comparisons of specific malformations with sufficient power, data pooling of malformations reported in several comparable studies and continued follow-up is necessary to achieve large enough numbers of specific malformations.

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Appendix I

List of all the specific congenital malformations registered in the national perinatal database (1995-1996) for the IVF study population (n=4,224) and the naturally conceived control group (n=314,605) and the total number of children with one or more congenital malformations in the different organ systems

	IVF study population	Naturally conceived control group
	n	n
Congenital malformations of the central nervous system of the CNS		
Not specified[a]	-	20
Anencephaly	1	128
Microcephaly	3	88
Spina bifida+meningo(myelo)coele	4	212
Encephalocoele[b]	-	26
Neural tube defects (NTD)	5	338
Hydrocephaly /holoprosencephaly	4	178
Hydrocephaly /holoprosencephaly without NTD	2	104
Neuromuscular disease[a]	1	13
Other	6	234
Microphthalmia[a]	-	5
Congenital malformations of the eye[b]	-	53
Congenital malformations of the ears[b]	3	175
Congenital malformations of heart and circulatory system		
Not specified[a]	8	328
Single umbilical artery	13	502
Transposition great vessels[a]	1	30
Tetralogy Fallot[a]	1	18
Ventricular septum defect[a]	4	153
Hypoplastic left heart[a]	1	17
Coarctation aortae[a]	-	14
Tricuspid atresia/stenosis[a]	-	5
Complex heart malformation[a] (> 1 heart malformation)	-	79
Other	6	461
Congenital malformations of the digestive system		
Not specified[a]	-	26
Cleft lip +/- cleft palate	4	341
Cleft palate without cleft lip	2	162
Oesophageal atresia/stenose/fistula[b]	-	66
Intestinal/anorectal atresia	4	139

	IVF study population	Naturally conceived control group
	n	n
Hirschsprung's disease[a]	-	13
Malrotation/volvulus[a]	1	9
Other	7	340
Congenital malformations of the respiratory system		
Not specified[a]	1	36
Choanal atresia[b]	-	19
Congenital malformation of the trachea[a]	-	11
Hypoplasia of the lung[a]	1	37
Congenital lobular emphysema[a]	-	3
Hydro/chylo thorax[a]	-	5
Hernia diaphragmatica	3	63
Relaxation of the diaphragm[a]	-	4
Other	-	181
Congenital malformations of the urogenital system		
Not specified[a]	1	32
Hypospadias and/or epispadias	10	653
Undescended testes[c]	2	307
Exstrophy of the bladder[a]	-	2
Renal agenesis[c]	1	73
Congenital cystic kidney[a]	1	28
Obstructive uropathy[a]	-	44
Other	15	847
Congenital malformations of the skin and abdominal wall		
Not specified[c]	3	392
Haemangioma	-	165
Naevus pigmentosus[e]	2	123
Other congenital malformations of the skin[b]	3	191
Gastroschisis[a]	-	3
Omphalocele[a]	-	16
Hernia umbilicalis[a]	-	28
Hernia inguinalis[a]	4	51
Other[a]	-	12
Congenital malformations of the skeletal and muscular system		
Not specified[a]	1	41
Polydactyly	1	320
Syndactyly	3	240

	IVF study population	Naturally conceived control group
	n	n
Reduction defects of the upper limbs or lower limbs[b]	-	18
Congenital hip dislocation	3	115
Deformities of the foot without NTD	12	443
Other	20	819
Chromosomal and syndromal congenital malformations		
Not specified[a]	1	45
Down syndrome (trisomy 21)	2	362
Other chromosomal malformations[b]	6	222
Situs inversus[b]	1	12
Multiple congenital malformations (not listed before)	3	322
Congenital hypothyreoidy[b]	-	32
Other, not specified	6	588
Total number of children with one or more congenital malformations in the different organ systems:		
Central nervous system	15	934
Heart and circulatory system	32	1531
Digestive system	17	1029
Respiratory system	5	349
Urogenital system	30	1904
Skin and abdominal wall	11	934
Skeletal and muscular system	34	1836
Chromosomal, syndromal and other malformations	16	1471
Total number of children with one or more congenital malformations	137	8526

[a]: only registered in the National Neonatology Database
[b]: only registered in the National Neonatology Database and the National Perinatal Database for Secondary Care
[c]: only registered in the National Neonatology Database and the National Perinatal Database for Primary Care
[d]: only registered in the National Perinatal Database for Secondary Care
[e]: only registered in the National Perinatal Database for Primary Care and Secondary Care

Chapter 8

Changes in perinatal care and survival in very preterm and extremely preterm infants in The Netherlands between 1983 and 1995

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Abstract

Objective:

To evaluate changes in obstetrical and neonatal care for very preterm and extremely preterm infants between 1983 and 1995 in The Netherlands and to evaluate the effect of those changes.

Study design:

Data on all very preterm or VLBW infants from the linked national obstetrical and neonatal databases of 1995 (N=2066) were compared to data on similar infants from a nation-wide study of very preterm infants born in 1983 (N=1338).

Results:

Obstetrical and neonatal management changed over time, with an increased number of deliveries in tertiary centres (35.7 - 60.7%), an increase in C-sections (43.7 - 56.8%) and prolonged artificial ventilation (3.4 - 9.5%). Survival until discharge increased from 75 to 90% and neonatal morbidity decreased in relative terms.

Conclusions:

The short-term outcome for these very preterm and extremely preterm infants has improved. Long-term follow-up through to school age and adulthood of preterm infants is needed to investigate the changes in the sequelae of intensive obstetrical and neonatal care.

Keywords: Obstetrical and neonatal management, survival, implications

Introduction

Advances in perinatal care in recent decades have improved the survival chances of low-birthweight and short-gestational age infants. In particular, the increase in the survival rate for extremely preterm infants has been spectacular, and now ranges from 0% at 20 weeks to 85% at 25 weeks gestation [1]. This increase changed beliefs about viability and therefore changed obstetrical care. Extremely preterm infants are considered to be eligible for birth at an increasingly early stage of pregnancy. In some countries, infants born at 23 weeks of gestation or even less are considered viable and receive maximum intensive-care treatment since they apparently have the potential for independent life. Differences in policies and in exclusion criteria mean that survival rates vary widely, ranging from 35 to 85% at 25 weeks of gestation [2-4].

There is concern that the ongoing trend in intensive obstetrical and neonatal care does not result in a decrease in late morbidity because the neurodevelopmental handicap rate in early childhood has not changed in very preterm infants (28-31 weeks). Moreover, there is growing evidence that mild developmental problems detected at school age occur more frequently in this group of infants and may hamper independent functioning in adolescence and later life [1,5]. As a review of the world literature shows that major neonatal morbidity increases with decreasing gestational age and birthweight, the higher survival rates may even lead to more frequent and more severe morbidity in these surviving infants. This is shown by a recent follow-up study of all extremely preterm survivors in England, Scotland and Wales that shows a high rate of severe mental and physical handicaps [6].

This concern has led to a tendency for care for extremely preterm newborns in The Netherlands to be conservative [7,8]. Obstetric care focuses on the prolongation of pregnancy and not the delivery of a liveborn infant. A recent guideline from the Dutch Association of Obstetrics and Gynaecology and the Dutch Association of Paediatrics advises against active treatment for infants of less than 24 weeks gestation, the referral of pregnant women to a level-three perinatal centre for further diagnostics and counselling if delivery is expected between 24 and 26 weeks. If delivery is expected

between 26 and 32 weeks, intensive treatment is recommended [9]. However, the intensity of obstetrical and neonatal care in general has also apparently increased in The Netherlands in recent years.

The objective of the present study is to establish a better picture of the changes in obstetrical and neonatal care in The Netherlands during the study period. To evaluate these changes, we studied all infants with a gestational age of less than 32 weeks or a birthweight of less than 1500 g born in 1995 and registered in the national obstetrical and neonatal databases. We compared the data of this group to the data of a comparable group of very preterm infants born in 1983 and included in a nation-wide survey Project on Preterm and Small for gestational age infants (POPS).

Materials and methods

The 1995 data were obtained by linking the data from the National Obstetrical Database on primary care, the National Obstetrical Database on secondary care and the National Neonatal Database. These databases contain records for all infants born in level-two and level-three hospitals and 84% of children born in level-one hospitals [10]. Given the referral pattern for very preterm infants, we expect all infants between 26 and 30 weeks to be included in these databases. Below 26 and after 30 weeks, the records for some infants born in level-one hospitals might be missing. For the purposes of the comparison, this study included only liveborn infants with a gestational age of less than 32 weeks or a birthweight of less than 1500 g (N = 2066). After extrapolation for non-registered infants, the total number of admitted very preterm or VLBW infants in 1995 in The Netherlands was estimated at 2151 [11].

The 1983 data were derived from the Project on Preterm and Small for gestational age infants, a nation-wide collaborative study of liveborn infants weighing less than 1500 grams or with a gestational age of less than 32 weeks born in The Netherlands in the period between 1 January and 31 December 1983 (N=1338) [12]. This cohort included

94% of all 1423 liveborn infants born in that year who fulfilled the inclusion criteria. Non-enrolment was mainly caused by the non-participation of some hospitals and by infants dying in the delivery room before they could be admitted to a neonatal ward.

To quantify the changing characteristics of the study population between 1983 and 1995, we used the age of the mother, ethnicity (Dutch or non-Dutch), parity (primiparity or multiparity), multiple pregnancy rate, birthweight and sex of the infant. For obstetrical changes, we used hypertension (diastole > 90 mmHg) during pregnancy and chorioamnionitis. To measure increased intensiveness in obstetrical care, we used ante-partum referral, duration of pregnancy, percentage of small for date (small for gestational age (SGA, < 10th centile of the Dutch growth chart) and very small for gestational age (VSGA, < 2.3rd centile of the Dutch growth chart), and percentage of Caesarean sections. The prevalence and duration of mechanical ventilation were used as estimates for the intensity of neonatal care. Neonatal morbidity and mortality were chosen as outcome measures for the care given. Neonatal morbidity included low Apgar scores (<7 at 5 min after birth), respiratory disorders (respiratory distress syndrome with the need of ventilatory support), neurological disorders (intraventricular haemorrhage grade I - IV according to Papile or periventricular leukomalacia) and infections (neonatal sepsis or meningitis). Apart from a low Apgar score, the other neonatal morbidity parameters were estimated in only 4 out of 10 existing health regions (45% of all preterm infants) because only these units had full records of neonatal morbidity. Data about mechanical ventilation were available in 9 of the 10 health regions in the 1995 cohort. Since perinatal characteristics, early neonatal mortality and survival were similar in NICUs with and without registered data on neonatal morbidity and mechanical ventilation, we considered this selection to be representative for the whole cohort. Consequently, and with the sole purpose of estimating the absolute incidence of the various morbidity and ventilation measures, we applied a straightforward extrapolation based on the observations with fully registered data (which yield the appropriate risk estimates) and the absolute number of patients in both the registering and non-registering NICUs and general hospitals using the formula:

absolute number in total population = α x total number in NICU + β x total number in general hospital

where α is the percent neonatal morbidity in four tertiary centres (or percent mechanical ventilation in nine tertiary centres) and β the percent neonatal morbidity in general hospitals (or percent mechanical ventilation in general hospitals).

All other measures (such as relative risks etc.) are based on the analysis of the available data and do not use any extrapolation at all.

Neonatal mortality, available for all infants, included early neonatal mortality (< 1 week), late neonatal mortality (< 28 days) and in-hospital mortality. Data on extremely preterm infants with a gestation between 22 and 28 weeks gestation were also analysed separately.

Statistical method

To analyse the changes between 1983 and 1995, a variable to distinguish these two cohorts was introduced. This variable is referred to as the time period effect. It is dealt with as a factor, or fixed covariate, in the analyses.

To describe the relation between individual risk factors and the time period for any given outcome, a Mantel-Haenszel approach was used in which the time period is a stratification factor and the risk factor under study is crossed with the outcome measure. This approach yielded the relative risk for each risk factor for the outcome separately for 1983 and 1995. The usual test for a common odds ratio provided an answer to the question of whether the relative risk had changed between 1983 and 1995. Conversely, by using the risk factor as the stratification factor and crossing the time period with the outcome, we obtained the time period effects separately in the absence and presence of the risk factor. Here, the test for the common odds ratio provided an answer to the question of whether the time period effect was statistically different for low- and high-risk patients.

This Mantel-Haenszel approach is adequate for three-way analyses. It can be generalized both for more than three variables and for continuous risk factors by fitting logistic-regression models predicting the probability of a certain outcome as a function of the various risk factors involved.

One should note that both Mantel-Haenszel approaches above are contained in one and the same logistic-regression model, where the significance of the interaction term time period risk factor corresponds to both questions: “Does the period effect depend on the risk status?” and “Does the relative risk of the factor depend on the year it was evaluated?”. Both questions are answered by one and the same estimate.

Whenever a model simplification was required, we used backward elimination of non-significant factors. To test for interaction, we started from a full model that also includes all interactions of the type risk factor x time period and removed those that were insignificant at the 10% level. From there, the main factors were removed at the 5% level if they did not occur in any interaction term.

As the outcome variable for the models, we used “mortality”, “birth in or referral to a tertiary centre”, “birth by Caesarean section”, “Apgar score”, “RDS”, “intracranial haemorrhage” and “sepsis”. The main risk factor under study was the time period indicator (1995 versus 1983) and we adjusted for the effect of relevant confounding factors. We did not however adjust for gestational age except in Table 5 where we added the results of such an adjustement: the goal is to assess whether any changes in the period 1983-1995 have occurred which can not be traced back to a simple change in the incidence of the various risk factors. Gestational age is itself correlated with many of the risk factors under study. By allowing gestational age to enter the models as a confounder, we would remove automatically and unwarrantedly that part of the effect of the time period which is in any way correlated to gestational age through those intermediate risk factors. It is our (modest) purpose only to show what changes have taken place over time and whether these changes depend in particular on the presence of certain risk factors (like hypertension in Table 5). By adjusting for a general risk factor as “gestational age” we would artificially make such observation impossible

(since hypertension is correlated with gestational age). However, there is a clinical interpretation of a gestational-age-adjusted relative-risk: it measures that part of the change in risk in the time period associated with a certain risk factor that is not attributable to an associated change in gestational age (or birthweight). Hence, for this purpose only, we added the gestational-age adjusted estimates to Table 5.

SPSS version 10 was used for both the cross-tabulations and the fitting of the logistic regression models (likelihood ratio).

Results

In the 1995 national databases, 2204 liveborn infants fulfilled the inclusion criteria. Of those infants, 138 (6.2%) died in the delivery room before admission to a paediatric ward. To enable comparison with the POPS cohort that included infants enrolled by the paediatrician, these 138 infants were excluded. The data on 1833 mothers and 2066 infants admitted to a paediatric or neonatal ward in 1995 could therefore be compared to similar data on 1214 mothers and 1338 infants in 1983.

Table 1 shows the demographic and obstetrical characteristics of the mothers. Maternal age increased by more than 2.5 years and the percentage of mothers over 30 years of age therefore rose from less than 30% in 1983 to more than 50% in 1995. In the same period, the percentage of primiparity increased. The percentage of multiple pregnancies increased from 16 to 18%. Obstetrical data show that hypertension during pregnancy increased and chorioamnionitis decreased. Obstetrical management changed over time, with an increase in, respectively, prenatal transfers, births in tertiary centres and the percentage of C-sections.

Table 1: Comparison of maternal characteristics and obstetrical data between 1983 and 1995, in two cohorts of liveborn infants with a gestational age of <32 weeks or birthweight <1500 g

	1983 (*N*=1214)	1995 (*N*=1833)	*P*-value
Mean age in years (S.D.)	27.3 (4.9)	29.9 (4.9)	<0.01
Age ≥ 30 years	325 (26.8)	970 (52.9)	<0.01
Primiparity	630 (52.0)	1024 (58.5)	<0.01
Non-Dutch	176 (14.6)	262 (14.3)	NS
Multiple pregnancy	188 (15.5)	324 (17.7)	NS
Hypertension	290 (23.9)	574 (31.3)	<0.01
Chorioamnionitis	93 (7.7)	48 (2.6)	<0.01
Prenatal transfer	216 (17.8)	561 (39.1)	<0.01
Born in tertiary centre	433 (35.7)	1112 (60.7)	<0.01
Caesarean section	531 (43.7)	1042 (56.8)	<0.01

Number (%). NS: not statistically significant, $P \geq 0.05$. *Note:* the calculated percentages are based on different totals due to a varying number of missing values per variable.

In Table 2 it can be seen that the mean gestational ages and mean birthweights for this group of infants were similar in 1983 and 1995. The distribution of gestational age and birthweight within this group was different, with relatively fewer infants with a gestational age under 28 weeks and more infants with a birthweight over 1500 g in 1995. In Table 3 the prevalence of short-gestational age and low-birthweights is shown for all live births in 1983 and 1995. The prevalence of livebirths under 28 weeks did not increase significantly. However, the prevalence of livebirths between 28 and 31 weeks increased significantly as did the prevalence of low-birthweight infants and the prevalence of SGA infants.

Table 2: Comparison of infant characteristics and perinatal data between 1983 and 1995, for liveborn infants with a gestational age of <32 weeks or birthweight <1500 g

	1983 (*N*=1338)	1995 (*N*=2066)	*P*-value
Mean gestational age in weeks (S.D.)	30.0 (2.9)	30.0 (2.5)	NS
Mean birthweight in grams (S.D.)	1249 (319)	1270 (344)	NS
Non-vertex position	378 (28.3)	642 (31.4)	0.05
Sex ratio (F/M)	47.1/52.9	47.3/52.7	NS
Multiplets	312 (23.3)	557 (27.0)	0.02
Low Apgar score (<7)	251 (20.5)	401 (19.5)	NS
Mortality			<0.01
Early neonatal death	266 (19.9)	163 (7.9)	
Late neonatal death	74 (5.5)	44 (2.1)	
Survival until discharge	998 (74.6)	1859 (90.0)	
Mechanical ventilation	737 (55.1)	1195 (58.5)[a]	0.05
Mean ventilatory days (S.D.)	8.6 (11.1)	14.2 (15.8)	<0.01
Mechanical ventilation >28 days	46 (3.4)	193 (9.5)[a]	<0.01
RDS	621 (46.4)	677 (33.2)[a]	<0.01
ICH	333 (24.9)	316 (15.5)[a]	<0.01
Sepsis	444 (33.4)	335 (16.4)[a]	<0.01
Subgroup of infants surviving until discharge	N=998	N=1859	
Mechanical ventilation	491 (49.2)	1042 (56.7)[a]	<0.01
Mean ventilatory days (S.D.)	9.7 (11.5)	15.5 (16.5)	<0.01
Mechanical ventilation >28 days	33 (3.3)	192 (10.4)[a]	0.01
RDS	389 (39.0)	551 (30.0)[a]	<0.01
ICH	175 (17.5)	278 (15.1)[a]	NS
Sepsis	333 (33.4)	301 (16.4)[a]	<0.01

Number (%). NS: not statistically significant; P ≥ 0.05. *Note*: the calculated percentages are based on different totals due to a varying number of missing values per variable

[a]: number and percent calculated after extrapolation

Table 3: Prevalence of short- gestational age or low birthweight for livebirths in 1983 and 1995 in The Netherlands

	1983	1995	*P*-value
Total number of livebirths	170.246	190.513	
Gestational age (week)			
<28	255 (0.15)	329 (0.17)	NS
28-31	755 (0.44)	1304 (0.68)	<0.01
Birthweight (g)			
<1000	292 (0.17)	452 (0.24)	<0.01
1000-1499	805 (0.47)	1162 (0.61)	<0.01
SGA status			
VSGA	237 (0.14)	266 (0.14)	NS
SGA	217 (0.13)	409 (0.21)	<0.01
AGA	851 (0.50)	1267 (0.67)	<0.01

Number (%) NS: not statistically significant, $P \geq 0.05$.

Despite changes in obstetrical care, the percentage of infants with a low Apgar score did not change. The percentage of ventilated infants increased and the percentage of prolonged ventilation (> 28 days) almost tripled. In the 12 year period between the two cohorts, the chance of survival until discharge increased from 75 to 90%. The neonatal morbidity parameters, RDS, ICH and sepsis all showed a pronounced decrease. The survival rate for infants with prolonged ventilation increased from 71.7% (33 out of 46 infants) in 1983 to 99.5% (192 out of 193 infants) in 1995. In the group of children surviving until discharge, the decrease in RDS and sepsis was less pronounced but still significant. A small, non-significant decrease was found for ICH in this subgroup of survivors.

Separate data for very preterm (28-31 weeks) and extremely preterm (22-27 weeks) pregnancies and births are shown in Tables 4 and 5. In both the very preterm and the extremely preterm group, maternal age increased considerably over time. In both periods, mothers of extremely preterm infants were more likely to be of non-Dutch origin and to have more multiple pregnancies. Extremely preterm delivery is associated

less often with hypertension, but two to three times more often with chorioamnionitis. In both groups, similar trends were observed over time, with more hypertension during pregnancy and less chorioamnionitis in 1995 than in 1983. The increase in antepartum referrals, resulting in more births in tertiary centres, was even more pronounced in the extremely preterm pregnancies. In both groups, an increase was observed in the number of caesarean sections. The increase over time was higher in the extremely preterm pregnancies but, in both years, the percentage of C-sections was lower in the extremely preterm pregnancies than in the very preterm pregnancies.

Table 4: Comparison of maternal characteristics and obstetrical data between 1983 and 1995 in very preterm (28-31 weeks) and extremely preterm (22-27 weeks) pregnancies.

	1983 (very preterm *N*=663)	1995 (very preterm *N*=1132)	*P*-value	1983 (extremely preterm *N*=227)	1995 (extremely preterm *N*=277)	*P*-value
Mean age (S.D.)	27.3 (4.8)	29.9 (5.0)	<0.01	27.0 (4.9)	29. 6 (5.0)	<0.01
Age ≥ 30 years	176 (26.5)	599 (52.9)	<0.01	55 (24.2)	149 (53.8)	<0.01
Primiparity	327 (49.5)	614 (57.2)	<0.01	94 (41.4)	142 (53.4)	<0.01
Non-Dutch	91 (13.8)	159 (14.1)	NS	39 (17.3)	57 (20.7)	NS
Multiple pregnancy	104 (15.7)	182 (16.1)	NS	39 (17.2)	60 (21.7)	NS
Hypertension	119 (17.9)	327 (28.9)	<0.01	11 (4.8)	36 (13.0)	<0.01
Chorioamnionitis	58 (8.8)	28 (2.5)	<0.01	31 (13.7)	19 (6.9)	0.02
Prenatal transfer	126 (19.0)	396 (35.0)	<0.01	56 (24.7)	123 (44.4)	<0.01
Born in tertiary centre	246 (37.1)	766 (67.7)	<0.01	110 (48.5)	220 (79.4)	<0.01
Caesarean section	259 (39.1)	598 (52.8)	<0.01	29 (12.8)	92 (33.2)	<0.01

Number (%). NS: not statistically significant, P ≥ 0.05. *Note:* the calculated percentages are based on different totals due to a varying number of missing values per variable.

Intra-uterine growth retardation was less common in the extremely preterm infants (Table 5). Although mortality rates in extremely preterm babies are higher than in very preterm babies, the observed decrease was most pronounced in the group of extremely

preterm babies over this 12 year period. In extremely preterm infants, the percentage of mechanical ventilation increased and a third of them needed prolonged ventilation. In those who survived until discharge, 50% were ventilated for more than 28 days. Also in the very preterm group, a significant increase in prolonged ventilation was visible over this time period.

Table 5: Comparison of infant characteristics and perinatal data between 1983 and 1995 in very preterm (28-31 weeks) and extremely preterm (22-27 weeks) liveborn infants

	1983 (very preterm *N*=755)	1995 (very preterm *N*=1304)	*P*-value	1983 (extremely preterm *N*=255)	1995 (extremely preterm *N*=329)	*P*-value
Mean gestational age in weeks (S.D.)	29.7 (1.1)	29.8 (1.1)	NS	26.0 (1.1)	26.1 (1.0)	NS
Mean birthweight in grams (S.D.)	1352 (322)	1354 (355)	NS	927 (211)	886 (195)	0.02
Birthweight in categories (g)			0.04			NS
<1000 g	99 (13.1)	205 (15.7)		159 (62.4)	233 (70.8)	
1000-1499	417 (55.2)	648 (49.7)		94 (36.9)	95 (28.9)	
≥ 1500	239 (31.7)	451 (34.6)		2 (0.8)	1 (0.3)	
SGA status			0.04			NS
VSGA	50 (6.6)	75 (6.1)		9 (4.0)	15 (5.2)	
SGA	96 (12.7)	209 (17.0)		16 (7.0)	33 (11.4)	
AGA	607 (80.6)	947 (76.9)		202 (89.0)	242 (83.4)	
Non-vertex position	221 (29.3)	403 (31.2)	NS	80 (31.4)	119 (36.7)	NS
Sex ratio (F/M)	45.0/55.0	45.8/54.2	NS	45.1/54.9	40.7/59.3	NS
Multiplets	196 (26.0)	354 (27.1)	NS	67 (26.3)	112 (34.0)	0.04
Low Apgar score (<7)	124 (17.8)	242 (18.6)	NS	98 (45.4)	121 (37.2)	NS
Mortality			<0.01			<0.01
Early neonatal	108 (14.3)	64 (4.9)		139 (54.5)	87 (26.4)	
Late neonatal	39 (5.2)	21 (1.6)		24 (9.4)	19 (5.8)	
Survival until discharge	608 (80.5)	1219 (93.5)		92 (36.1)	223 (67.8)	

	1983 (very preterm *N*=755)	1995 (very preterm *N*=1304)	*P*-value	1983 (extremely preterm *N*=255)	1995 (extremely preterm *N*=329)	*P*-value
Mechanical ventilation	478 (63.3)	842 (65.1)[a]	NS	180 (70.6)	269 (83.5)[a]	<0.01
Mean ventilatory days (S.D.)	7.7 (8.5)	11.7 (13.0)	<0.01	11.8 (14.7)	24.6 (20.2)	<0.01
Mechanical ventilation >28 days	18 (2.4)	82 (6.3)[a]	<0.01	26 (10.2)	108 (33.5)[a]	<0.01
RDS	419 (55.5)	449 (34.7)[a]	<0.01	155 (60.8)	192 (59.6)[a]	NS
ICH	203 (26.9)	221 (17.1)[a]	<0.01	103 (40.4)	83 (25.8)[a]	<0.01
Sepsis	278 (36.9)	205 (15.9)[a]	<0.01	76 (30.8)	87 (27.0)[a]	NS
Subgroup of infants surviving until discharge	*N*=608	*N*=1219		*N*=92	*N*=223	
Mechanical ventilation	349 (57.4)	773 (63.9)[a]	<0.01	79 (85.9)	193 (88.9)[a]	NS
Mean ventilatory days (S.D.)	8.0 (7.7)	12.2 (13.3)	<0.01	19.6 (16.3)	32.0 (18.9)	<0.01
Mechanical ventilation >28 days	9 (1.5)	82 (6.8)[a]	<0.01	22 (23.9)	108 (49.8)[a]	<0.01
RDS	298 (49.0)	400 (33.1)[a]	<0.01	55 (59.8)	121 (55.8)[a]	NS
ICH	120 (19.7)	214 (17.7)[a]	NS	36 (39.1)	54 (24.9)[a]	<0.01
Sepsis	209 (34.4)	189 (15.6)[a]	<0.01	46 (50.5)	68 (31.3)[a]	<0.01

Number %. NS: not statistically significant, $P \geq 0.05$. *Note:* the calculated percentages are based on different totals due to a varying number of missing values per variable.

[a]: number and percent calculated after extrapolation

The morbidity in very preterm infants decreased. In the extremely preterm children, only the percentage of intracranial haemorrhage decreased significantly. The rates of RDS and neonatal sepsis were similar. In infants who survived until discharge, we did not find any decrease in the percentage of very preterm children with intracranial

haemorrhage, but there was a significant decrease in the percentage of this morbidity in the extremely preterm infants.

Table 6: Multivariate analysis: odds ratio comparing 1995 - 1983 for various outcome measures in the absence or presence of specific risk factors

Outcome variable	Subcategories (defined by risk factors) in which "time period-effects" are significantly different	Adjusted for …$	Time period effect 1995 vs 1983 OR	
			Not adjusted for GA/BW* (95% C.I.)	Adjusted for GA/BW*
In-hospital mortality	No hypertension or chorioamnionitis	[a]	0.3 (0.2-0.4)	0.3
	Hypertension present		0.6 (0.4-1.0)	0.4**
	Chorioamnionitis present		0.8 (0.4-1.8)	0.5
Birth in or referral to NICU	No chorioamnionitis	[b]	2.7 (2.3-3.2)	3.3**
	Chorioamnionitis present		8.1 (3.2-21)	7.6**
Caesarean section	All patients	[c]	1.7 (1.5-2.1)	1.7**
AS < 7	No chorioamnionitis	[d]	0.7 (0.6-0.8)	0.7**
	Chorioamnionitis present		1.4 (0.7-2.7)	1.1
RDS	All patients	[e]	0.6 (0.5-0.7)	0.6**
Intercranial haemorrhage	All patients	[f]	0.6 (0.5-0.7)	0.6**
Sepsis	All patients	[g]	0.4 (0.3-0.5)	0.4**

($) risk factors not mentioned as "adjusted for" were removed from the model because they were not significant at the 10% level (backward elimination).

[a] Adjusted for parity, hypertension, chorioamnionitis, foetal position

[b] Adjusted for hypertension, chorioamnionitis, SGA status, foetal position

[c] Adjusted for ethnicity, multiple pregnancy, hypertension, SGA status, foetal position

[d] Adjusted for parity, chorioamnionitis, SGA status, foetal position

[e] Adjusted for ethnicity, parity, multiple pregnancy, SGA status, maternal age, place of birth

[f] Adjusted for hypertension, SGA status, place of birth

[g] Adjusted for hypertension, chorioamnionitis, place of birth

* Main analysis without adjustment for gestational age or birthweight and extra column where adjusted estimates are given so the amount of possible confounding by gestational age and birthweight can be taken into account when interpreting the data.

** Adjusted estimate is significantly different from 1 ($P<0.05$).

Multivariate logistic-regression analyses with various outcome measures comparing 1995 - 1983 are tabulated in Table 6. If the interaction of the time period effect with any perinatal risk factor in the model was significant, time period effects are stated separately for those risk-factor categories. Since, for example, there was an effect modification (interaction) for “hypertension” for the relation between time period and mortality, hypertension is not only used as a possible confounder in the logistic regression model but is also used to show the time period effect, both in the presence and in the absence of hypertension. Mortality in infants born from mothers with hypertension decreased over time (OR=0.6), but not as much as the mortality in mothers without hypertension (OR= 0.3). When adjusted also for gestational age and birthweight mortality in mothers with hypertension decreased even more over time (OR=0.4). If chorioamnionitis was present the decrease in mortality was small (OR=0.8). This decrease was more pronounced (OR=0.5) when also adjusting for gestational age and birthweight.

The chance of being refered to, or born in, a tertiary centre increased threefold (OR=2.7) for the children of mothers without chorioamnionitis. For children of mothers with chorioamnionitis this increase was much higher (OR = 8.1). The increase over time in C-sections was similar for all infants (OR = 1.7). The majority of infants had a better condition at birth, represented by the Apgar score, and less neonatal morbidity. The OR for a low Apgar score increased only in the small proportion of infants with chorioamnionitis.

Comment

We described changes in two virtually complete cohorts of very preterm infants born in The Netherlands in 1983 and 1995. The study describes outcome for infants who were admitted to the neonatal units. A shortage of data meant that children who were born dead or could not be resuscitated were not taken into consideration. The outcome for the total population of very preterm infants may therefore, in reality, be less favourable than our study indicates.

The number of livebirths with a gestational age of less than 32 weeks or a birthweight of less than 1500 g increased from 1423 to 2151. As the total number of livebirths in the country only increased in the same period from 170,246 to 190,513 [13], there was a proportional increase of livebirths with a gestational age of less than 32 weeks or a birthweight of less than 1500 g from 0.84% in 1983 to 1.13% in 1995. This increase is mainly accounted for by the 28-31-week category (0.44% - 0.68%) and the SGA group (0.13% - 0.21%).

One reason for the increase in preterm births may be the well-documented higher risk of preterm labour, hypertensive disorders and multiple gestation for pregnancies at a later maternal age [14,15]. In the Dutch population, the mean maternal age at the birth of the first child increased from 26 years in 1983 to 28.6 years in 1995. This means that women in The Netherlands are among the oldest mothers in the Western world [13]. In our study, maternal age was even higher than in the general population and the increase in mean age was similar to that in the general population. In accordance with the literature, we also found that pregnancies were more often complicated by hypertension, but that there was no statistically-significant increase in multiple births.
On the other hand, the incidence of chorioamnionitis, another possible cause of preterm delivery [16] fell in this 12-year period. Preterm deliveries took place more often in a tertiary centre and more Caesarean sections were performed. Information about preterm stillbirths was not available for the 1983 cohort and so it was not possible to examine the question of whether these changes in obstetrical care and an increased belief in the viability of preterm children led to a reduction in stillbirths and therefore an increase in preterm livebirths.

The stable percentage of extremely preterm livebirths (<28 weeks) admitted to a neonatal ward confirms that perinatologists in The Netherlands are among the most conservative where treatment at the limits of viability is concerned [17,18,19]. In the same period, however, there was a marked increase in the intensity of both obstetric and neonatal management, probably focusing on the more mature babies. The absolute number of such infants has increased considerably, partly explaining the shortage of

intensive-care capacity. The increase in the number and relative percentage of 28-31-week livebirths is impressive (0.44% - 0.68%).

The reduction in chorioamnionitis and severe intra-uterine growth retardation and the policy of concentrating perinatal care in a small number of tertiary centres contributed to improving the chances of survival. Unfortunately, the alleged positive effect of administering antenatal-steroids could not be studied because antenatal-steroid use is not registered in the national databases. Mortality in preterm babies of mothers with hypertension decreased by a factor of 0.6 compared to a reduction by a factor of 0.3 in mothers without hypertension. A better condition at birth is reflected by a decrease in low Apgar scores, except in the presence of chorioamnionitis. Intracranial haemorrhages were also significantly reduced, especially in the extremely preterm group, in the children who were discharged alive, notwithstanding the advanced technological possibilities for diagnosing ICH. The increased intensity of neonatal care is illustrated by the percentage of prolonged ventilation (over 28 days), that almost tripled. These changes contributed to a decrease in mortality, especially in the extremely premature infants. In this subgroup, mortality in 1995 was almost half that in 1983.

Although the morbidity percentage for the very preterm and extremely preterm infants who were discharged alive fell considerably, it should be noted that the total number of severely-ill extremely and very preterm children needing intensive care increased. This is due to the simultaneous increase in the percentage of preterm births and the higher number of total births in the population. In our study, we found that, in the subgroup of infants surviving until discharge, there was also a marked decrease in severe neonatal infections, respiratory disorders and neurological damage that play a role in later developmental disturbances. On the basis of these short-term outcomes, it seems possible that the combination of a conservative policy in extremely preterm infants and aggressive obstetric and neonatal management in more mature babies accompanying a pronounced decrease in neonatal morbidity also improves the developmental prospects for individual preterm babies. The future for these babies may therefore be less bleak than in the past.

On the other hand, there is also some concern that the pronounced increase in prolonged ventilatory support and the persistently high incidence of RDS, ICH and sepsis, especially in extremely preterm infants, may increase the risk of developmental problems. The results of long-term follow-up in the 1983 cohort show that preterm birth has life-long implications: at 14 years of age, 28% of the survivors were in special education and only 30% was without physical problems or learning disabilities [5]. This is similar to the results of other long-term follow-up studies of adult or adolescent VLBW survivors [20-23]. Studies of more recent preterm cohorts found that the increased survival of very low birthweight infants is not accompanied by a decrease in late sequelae [24-26], possibly because the increased survival of more immature and sicker babies may lead to an increase in developmental disturbances [27,28].

Long-term follow-up through to school age and adulthood of preterm infants is needed to investigate the consequences of intensive obstetrical and neonatal care. It is only with an adequate knowledge of the sequelae that it will be possible to decide whether intensive treatment of extremely preterm neonates is medically and ethically justified at the cost of considerable increases in the utilisation of expensive resources.

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Chapter 9

Discussion

High-quality clinical databases are essential for clinical practice, research and audit, as well as for the management of health care services. They enable us to monitor for example effects of medical developments and effects of demographic changes in the population. This calls for continuous data registration, as an important role in perinatal and neonatal health care is played by information on pregnancy, labour, puerperium, and the health of the mother and newborn.

This need for data registration is especially relevant in the Netherlands, where the maternity care system differs from those in most other Western developed countries. Not only is a key role in this played by independent midwives, there is also a high percentage of planned home births. To continuously evaluate Dutch obstetric care, the continuous registration of data is needed.

At present, however, the Netherlands has no single national system for registering extensive and detailed perinatal and neonatal information. Although there are several registers containing perinatal data, most contain only limited information; those that are detailed do not have national coverage. In this thesis we have investigated whether it was possible to create one single perinatal database representative of all Dutch births on the basis of the existing separate professional perinatal and neonatal registers. This combined database could then form the basis for extensive perinatal epidemiological research.

The creation of a linked and extrapolated database based on the separate perinatal and neonatal registers

This thesis describes a method for creating a single perinatal database of all Dutch births by combining three databases: the National Perinatal Database for primary care by independent midwives (LVR-1), the National Perinatal Database for secondary care by obstetricians (LVR-2), and the National Neonatology Database of paediatricians (LNR). The first step was to link these registers, using a combination of variables and defined criteria to identify all the records in the different registers containing information on the same newborn. This was necessary because referral between the different caregivers often means that a child appears in more than one register. Since fewer than

100% of obstetric caregivers participate in the registers, the next step was to extrapolate the data. The final step consisted of defining new variables in the combined database on the basis of the variables containing similar information in the separate registers.

Reliability of separate databases

The registers used are routine registers in which standard answer categories are defined per item. Open-ended questions are not incorporated. In general, the completeness and accuracy of collected data depends both on the method of collecting and on the specific variables. One of the points of discussion regarding questionnaire information concerns the extent (if any) to which recall bias influences the data collected. [1-5] In contrast, however, one of the major issues with data from routine registers is whether information is underreported. [6-8]

A 1996 pilot study attempted to determine reliability (including underreporting) within LVR-1 and LVR-2. [9] Since then, no study has systematically investigated the potential magnitude of underreporting for all variables. As in other routine registers, the degree of underreporting in LVR and LNR depends on the variables examined. Underreporting of certain variables is determined by the time of registration, i.e. within a week after birth for the LVR and within one month of birth for the LNR.

This is illustrated in the following example from a comparative study published in 1993, which showed that routine LVR data reported a first-week mortality that was 30% lower than that stated in a specific project on Preterm and Small for Gestational Age Infants (POPS). [10] The discrepancy was explained by the fact that if neonatal death occurred after the LVR form had been completed, the data on this subject were left unchanged. In other words, because most LVR forms are filled in shortly after birth, and because no correction is made if a change occurs later in the first week, the registered perinatal death until 7 days postpartum usually represents labour-room death. Since most of these underreported deaths *will* be recorded in the LNR, it is self-evident that the LNR and LVR records should be linked.

A similar mechanism plays a role in the underreporting of certain congenital malformations.[11] When time is needed to make a final diagnosis (to confirm a chromosomal abnormality with additional tests, for example) the diagnosis will often be too late for inclusion in the register. A different explanation for the underreporting of congenital malformations is that certain malformations, such as congenital heart malformations, will not result in admission to a neonatal intensive care unit and therefore in a LNR registration, but will lead instead to admission to a cardio-surgical intensive care unit that does not yet participate in the LNR.

Yet another factor determining the reliability of the registers is the registration of incorrect values. Here, a distinction can be made between two types of error: those that record impossible values, and those that, while incorrect, nonetheless fit within the range of accepted values. It goes without saying that the latter are harder to detect. Over the years, registrations in the LVR or LNR have – according to caregiver and the year of registration – been made either electronically or on paper. By 2004, electronic registration had become standard for all participating caregivers. To check for obvious errors and impossible values, the electronic registration programs incorporate routine checks. [12] To the extent that they reduce the percentage of obvious errors, these checks, together with the checks performed afterwards by the holder of the registers, guarantee a certain data quality.

More difficult to prevent are erroneous values that lie within the range of accepted values. The registration of a number of items is known to be unreliable, including 'ethnicity of the mother', 'referral from primary care of the midwife to secondary care of the obstetrician', 'the moment of referral' and 'the reason for referral'. [9;12;13] If we are to prevent the differences of interpretation that underlie this type of incorrect registration, clear unambiguous definitions will be needed. Such errors will also be reduced by unequivocal instructions on filling in the variables and by continuous training of the caregivers who produce the data.

Enhancing the usefulness of the data to the caregivers who produce them is believed to be a strong motivating factor for accurate registration. Caregivers use the LVR and LNR

data to extract discharge letters for other healthcare providers and to create personal overviews. [14] The same data is also used to provide caregivers with feedback in the form of monthly and annual overviews on their own practices. All such activities are parts of an attempt to enhance caregivers' involvement in the registers, and thereby to stimulate accurate data entry. [13;15] Elferink et al. reported that, over the years since the LVR started, the quality of data has indeed steadily improved. [12]

In conclusion, the reliability of the separate LVR and LNR registers depends both on the degree of underreporting and on the percentage of incorrect registrations. These two factors differ for the various variables. For all studies performed on the basis of these registers, it is important to determine the impact of these factors and the potential bias they generate. In this respect, the study design of the study is important. This might, for example, be seen when comparing the pregnancy outcomes of two groups of children. When data for these two groups are both extracted from the routine LVR register, the potential bias will be less than it would be if data on one group originated from a specific questionnaire, and data on the other was drawn from the routine LVR register. If data for both groups was extracted from the routine register, underreporting and incorrect registration would be assumed to be random, and not to differ between the two groups of children. Such an assumption would be less likely in a study design with different methods of data collection.

Linkage of the separate registers will actually increase the reliability of the data, since underreporting or incorrect values in a record in one register may be completed or corrected by data on the same item in the corresponding record in one of the other registers.

Validity of the linked and extrapolated database

Besides the reliability of the separate registers, the methods used to link and extrapolate these registers into one single database also determine the overall validity of the linked register. These methods consisted of the three steps outlined here:

Step 1: Linkage of the separate registers,
Step 2: Extrapolation of the linked database for non-participation,
Step 3: Defining new variables in the linked database.

Step 1: Linkage of the separate registers
To link the three separate registers, all duplicate records on a child were identified in the different registers. This was intended to prevent any double counting that might generate incorrect perinatal statistics. As referral is more likely in complicated high-risk perinatal situations, double registrations are also more common within high-risk pregnancies and deliveries. Incomplete identification of double records may, therefore, seriously affect the reliability of the statistics generated.

Because no unique identifier is available in these registers, duplicate records were identified by using a combination of defined mother-and-child variables. The main selection criterion for this combination was that it had to be sufficiently able to discriminate between two similar records on the same child and two similar records on two different children. In other words, the variables had to be sufficiently informative without being too susceptible to errors.

The combination of variables used in the described linkage procedure was conservative and strict, meaning that there was only a low risk of incorrectly linking two records on two different children. However, it was inherent to this choice that double records on the same child might nonetheless remain unidentified. On average, 36% of children were found to have duplicate records in the LVR-1 and LVR-2 in the years from 1995 to 2000. On average, 91% of the children registered in the LNR could be linked to their corresponding LVR birth record. Non-matching was explained mainly by the fact that the corresponding births had been assisted by midwives or obstetricians who did not yet participate in LVR-1 or LVR-2; this was accounted for by the extrapolation for non-participants. In the different search steps, only one variable of the defined combination was allowed to be discrepant or missing at a time. It is possible that records on the same child differed with regard to more than one identifying variable. However, in

order to minimize the risk of labelling the records of two different children as identical, we chose not to allow more than one difference.

The choice of variables and the specific criteria included in the additional searches were essential choices that determined the result of linkage. National and international epidemiological studies often use similar linkage methods (i.e. ones using a combination of several variables and defined specific criteria) to determine whether records refer to the same entity. [16-20] This linkage method is referred to as 'statistical linkage'. Within these methods a distinction can be made between a deterministic and a probabilistic method of linking. A combination of these two methods was used during the generation of the linked perinatal database described in this thesis.

Step 2: Extrapolation of the linked database for non-participation

To be properly representative of all Dutch births, the linked database had to be extrapolated to correct for the small percentage of births taking place with non-participating caregivers. In 2000, 8% of midwifery practices (n=37) did not participate in LVR-1. With respect to LVR-2, 4% of general (level I) hospitals (n=3) did not register births under their care. Neither did registration in the years from 1995 to 2000 include births that took place under the care of the few Dutch general practitioners (GPs) who were still active in obstetrics. For the year 2000, the births under care of a GP were assumed to be around 7% of all births. Births not included in the registers due to non-participation were by definition low risk births. To prevent an overestimation of pathology in the linked database, it was therefore necessary to extrapolate the data by assigning weighing factors according to level of care.

The extrapolation was performed at the level of hospital or midwifery practice. It was assumed that, annually, non-participating hospitals and midwives assist approximately the same number of births as participating hospitals and midwives at the same level of obstetric care. It was not feasible to determine the exact number of missing births per hospital or practice per registration year. For the first year of the linkage, 1995, we made a detailed investigation of the size of the missing hospitals and midwifery

practices. As the non-participants included both small and large general hospitals, the distribution of the number of births was similar to that at participant general hospitals. Our subsequent extrapolation at general hospital level assumed an average hospital size. The method appropriate to the midwifery practices was less obvious, since a solo practice with one midwife working fulltime may report more births in one year than a group practice in which all midwives work part-time. As the number of missing births could not be predicted on the basis of the type of midwifery practice, it was assumed that, on average, missing practices performed the same number of births as the ones that registered data.

In the extrapolation step that assigned weighing factors according to the level of care of the missing hospitals and midwifery practices, it was assumed that these hospitals and practices did not differ from the registering hospitals and practices with regard to their population characteristics and to the perinatal care they provided. This assumption was plausible, as participation depends mainly on logistic factors such as the availability of hospital staff and working computer programs, and thus less on factors such as population characteristics.

It was assumed that GPs who did not register in the database accounted for the difference between the number of births reported nationally by Statistics Netherlands and the number of births in the linked and extrapolated database, taking account of different lower limits of registration. Bearing this assumption in mind, we estimated that an average of 6% of all Dutch births had taken place under the responsibility of a GP in the 1995-2000 period. [21] In 2000, this figure was estimated to be around 7%. Other sources report estimates of 10% for 1991, 9% for 1993, and 7.8% for 1998. [14;22;23] These percentages show that the number of births assisted by GPs has decreased over the years. Our estimates confirm this. An important check on our linkage and extrapolation methodology was provided by the agreement between previously published percentages of GP births and the percentage we ourselves had estimated. In the near future, the extrapolation step we describe will no longer be necessary, as participation in the registers by the various caregivers is increasing every year and will soon cover 100% of births.

Step 3: Defining new variables in the linked database

Once the separate registers had been linked, it had to be decided how new variables should be defined in this database on the basis of the variables that code similar items in the separate registers. The method of combining the information from the separate variables differed per variable, and assumptions had to be made for each newly created variable. Some variables were averaged; others were created by taking the lowest or highest value; yet others first used the information from LVR-2, completing it if necessary with information from LVR-1. Variables with information missing from one register were completed with information on the same variable from another register. A more general coding in one variable was completed with a more specific coding in one of the other registers. In this way, different assumptions underlay the creation of each new combined variable.

Although no 'gold standard' is available against which we could check the correctness of our methods for linkage and extrapolation and for the combination of variables, it was possible to compare our data with that reported in other sources. As discussed in Chapter 3, we examined the reliability of the new perinatal database by comparing calculated mortality rates from this database with mortality rates published by Statistics Netherlands as derived from the Dutch civil registers, the primary source for Dutch perinatal and neonatal mortality rates. Overall, the mortality rates were similar, demonstrating the validity of our methodologies and thus of the resulting mortality data. Any differences could easily be attributed to the design of the registers. If this is examined in greater detail, we see that the linked and extrapolated professional database reported more perinatal deaths (1.2 per 1000 births) than Statistics Netherlands. This relative underreporting in the national statistics was found to apply especially to immature newborns born close to the lower legal limit of registration and to the lower limit of viability. [24] This suggests that these births are often not notified to the civil registers. On the other hand, fewer late neonatal deaths (0.3 per 1000 live births) were registered in the linked professional database than in the civil registers. As the obstetric LVR only registers care (and therefore deaths) within the first week postpartum, registered late deaths were all derived from the neonatal LNR register. Late

neonatal deaths occurring outside a paediatric department (for example, at home, or in other hospital departments such as surgical departments), are not registered in the LNR, and are therefore not included in the linked LVR/LNR database. This was confirmed by studying the underlying cause of death for the underreported death cases in the LVR/LNR database. This comparison of mortality rates confirmed that the linkage and extrapolation method applied to the three separate LVR and LNR registers thus created a reliable database representative for all births in the Netherlands.

In 1993, the last year in which Statistics Netherlands reported these statistics, planned home births accounted for 32% of births in the Netherlands. [25] In chapter 4 we described how we used the linked and extrapolated database to calculate the percentage of planned home birth in the 1995-2000 period, arriving at 31.6% for 1995 and 30.3% for 2000. The percentages derived from the linked and extrapolated LVR/LNR database are similar to those previously reported by Statistics Netherlands, thereby confirming the validity of the new perinatal database. Comparisons of the prevalence of congenital malformations resulting from the linked and extrapolated LVR/LNR database with prevalences reported by the EUROCAT register also confirm that the prevalences of congenital malformations resulting from the perinatal database are reliable. When the prevalences were not similar, differences could be easily explained, for example when malformations were not visible shortly after birth and therefore not registered well enough in the LVR. [11]

In conclusion, the methods used for linkage and extrapolation appear to have been valid. The literature contains reports of similar linkage methods based on probability-matching using a combination of variables in the absence of a unique identifier. The statistics calculated on the basis of this linked perinatal database agree with those derived from other data sources.

It is thus possible to create one single perinatal database representative of all Dutch births on the basis of the existing separate registers. Missing and incorrect data in the separate registers can be completed and corrected by information from the other registers. For future research question, the specific way to apply the linked perinatal

database should be accurately determined. As long as its limitations are borne in mind, the linked database can be used for a broad field of perinatal epidemiological research, as it contains detailed information on pregnancy, delivery, puerperium and the newborn for all births in the country.

Future methods of perinatal database linkage

Linkage procedures can be extended by methods such as blocking, multiple imputation and attributed weights. [26-29] In the search for double records, all the variables used in our linkage method have the same importance. In the future, however, the linkage procedure could be refined, for example by applying different weights to discrepant or missing information in the search variables. These weights might be dependent on the clinical relevance of a possible discrepancy. For example, a discrepancy in gender might receive a higher weight than a difference of one day in gestational age. For each possible match, a sum score of all attributed weights could then be calculated. The higher this sum score, the lower the probability that the records referred to one and the same individual. This method of weighing allows the researcher the flexibility to vary the emphasis placed on any of the variables involved in the matching criterion.

In 2002, the Netherlands Perinatal Registry was founded by the Royal Dutch Association of Midwives (KNOV, *Koninklijke Nederlandse Organisatie voor Verloskundigen*), the Dutch Society for Obstetrics and Gynaecology (NVOG, *Nederlandse Vereniging voor Obstetrie en Gynaecologie*) and the Paediatric Association of the Netherlands (NVK, *Nederlandse Vereniging voor Kindergeneeskunde*). The Netherlands Perinatal Registry is concerned with the future organisation and use of the perinatal and neonatal registers. During 2004, they developed a linkage method for combining the registration year 2001 of the LVR-1, LVR-2 and LNR registers. This consisted of a probabilistic method based on assigning weights and determining a cut-off point based upon them. Results based on this method have not yet been published. Therefore, it is currently too early to report on any divergences between this method and the method described and applied in this thesis. This will have to be verified by comparing the different methods and assumptions underlying the two methods of linkage, and the outcomes each produces.

Other variables not yet collected in the registers could be used to search for duplicate records. At present, the perinatal and neonatal registers do not include data, such as maternal first name, surname, place of birth, or address. As this kind of information is unique per person, registration of such variables would facilitate linkage. On the other hand, it is more prone to misspelling; similarly, addresses tend to change over time. Using this kind of information instead of more anonymous information also raises the issue of privacy, which might be compromised if linkage were based on it. The right balance should therefore be found between reliable data linkage and protection of the patient's privacy.

If an identification number was available in these registers, the linkage of the perinatal databases would be much easier, less time-consuming, and thus less costly. Since 1994 it has in principle been possible, when referring a pregnant woman from the midwife to the obstetrician, for the LVR-2 to use the code of the midwifery practice and the patient number allocated to the patient in LVR-1. In practice, however, these numbers have not been copied onto the LVR-2 form after referral. For the registration years 1994 and 1995, for example, it was reported that these LVR-1 numbers were available in only 6% of all referrals to the LVR-2. [9] They are therefore inappropriate for linkage of the LVR-1 and LVR-2.

As other countries have unique national identification numbers attributed to each individual person in that country, it is easier to link different databases on the basis of that number. At birth, Scandinavian countries assign unique personal identification numbers to all residents. [30] The UK also has a system in which a unique personal identification number is allocated per person. [31] Within the perinatal period, such a number could be used to identify a child on every form (computerised and otherwise) filled out by the different care providers, both during the perinatal period and later in life. This would have clear benefits in terms of facilitating data linkage and therefore epidemiological research. The introduction of such a number in the Netherlands may directly be linked to future implementation of electronic patient files. [32-34] Currently, however, no such identification number exists in the Netherlands. Although a so-called *Burger Service Nummer* (BSN) may be introduced in the near future. It is not yet clear

whether this will be assigned directly at birth, or after a few days, when the birth is registered at the municipality. In the latter situation, the number will be allocated too late for inclusion as an identifier in the perinatal registers.

To avoid the described linkage of the three registers in the future, these separate registers might be converted into one central, computerised perinatal database, to which all caregivers involved in obstetric care would have access, and in which they would register their given obstetric care. Given the options now inherent to the internet, it would be relatively easy to create such a central perinatal database. The benefit would be that all the perinatal information already registered by caregivers would be available for other caregivers.

Use of the linked perinatal registers

This thesis has provided examples of perinatal epidemiological research that illustrate the numerous opportunities for research created by the linked national perinatal database. Chapter 4 demonstrates the use of this database as a monitoring tool for planned home births in the Netherlands. [35] As this is a country where an exceptionally high percentage of women give birth at home, it is somewhat unfortunate that, since 1993, Statistics Netherlands has no longer issued annual report on this percentage. Using the linked and extrapolated perinatal database, we thus calculated the home-birth percentages for the 1995-2000 period. At the beginning of this period, this percentage decreased slightly, from 31.6% in 1995 to 29.1% in 1998. In the following years it stabilised around one third of Dutch births. Even though more women started their pregnancy care with a midwife in primary care in the year 2000 than in the year 1995, the percentage home births did not increase. This was due to a concomitant increase in referrals during pregnancy and delivery to secondary obstetric care, which was especially noticeable during pregnancy. To establish whether this tendency was positive or negative, more elaborate research will be needed on the reasons for this increase in referrals.

Of relevance to the home birth percentage described in Chapter 4 is the study of maternal demographic factors and the probability of a home birth covered in Chapter

5. [36] Whether a baby is born at home in the Netherlands is determined partly by the risk of being referred from the midwife to the obstetrician, and partly by whether the pregnant woman chooses a home delivery or a short-stay hospital delivery under the care of a midwife. In all age groups, the percentage of home births in primiparous women is lower than in multiparous women. This is due primarily to the higher referral percentage of primiparous women to the obstetrician. In both groups of women, the percentage of home births is low in the youngest age group (i.e. under 25 years). This is explained not by a higher number of referrals to the obstetrician but by a high percentage of midwife-supervised short-stay hospital births. A higher percentage of midwife-supervised hospital births is also observed in non-Dutch women than in Dutch women, explaining the higher percentage of home births observed in the Dutch group. There are fewer home births in large towns than in smaller towns or rural areas. We therefore conclude that if the home births are to be promoted, special attention has to be focused on non-Dutch women, a growing group in the Netherlands. Furthermore, young pregnant women and women living in large towns need to receive special attention, as these groups all tend to choose a short-stay hospital birth over a planned home birth.

Ethnic differences have also been observed in the prevalence of congenital malformations (Chapter 6). [37] In this study, five registration years (1996-2000) of the perinatal database were merged to create a database large enough (n=881,800) to study the relatively small prevalences of congenital malformations, especially per ethnic group. The most striking result of this study was the observation that Mediterranean (Turkish and Moroccan) women have a 20% higher risk than Dutch women of bearing a child with a congenital malformation. This increased risk was observed in different organ systems. As the Mediterranean group is the largest and fastest growing group of immigrants in the Netherlands, this is an important finding. Ethnic differences in congenital malformations may provide a valuable basis for etiological studies, and prove useful to health care advice and planning.

Chapter 7 examined children born after In Vitro Fertilisation (IVF), another group that may have a higher risk of congenital malformations. [38] Due to demographic changes

such as an increasing maternal age, and due to new developments in assisted reproduction techniques, the number of children conceived after IVF will continue to grow in the years ahead. In this group it is therefore essential to monitor pregnancy outcomes and long term follow-up. In our study we found a slightly higher risk of malformations in IVF children. However, this disappeared after account was taken of differences in maternal characteristics, IVF mothers were older and of lower parity, between the IVF and control mothers. It was therefore concluded that the small increased risk of malformations observed in the IVF children was caused by differences in maternal characteristics and was not the result of any aspect of the IVF procedure. The strength of our study over earlier studies was the fact that we were able to use the same data source – i.e. the perinatal database – for both the IVF and naturally conceived children. With regard to the IVF children, it was possible to compare specific questionnaire information with the congenital malformations registered in their birth records in the perinatal database.

The last study included in this thesis compared obstetric and neonatal care and the survival of preterm infants (gestational age < 32 weeks or birthweight < 1500 grams) between 1983 and 1995 (Chapter 8). [39] In this 12-year period, obstetric and neonatal management changed, with increases in prenatal transfer, caesarean sections and the percentage of ventilated infants. In the same period, the chance of survival for these preterm infants increased from 75 to 90% and the neonatal morbidity parameters, RDS, ICH and sepsis, all decreased. On the other hand, in the same period, the prevalence of preterm births increased. It was concluded that short-term neonatal outcomes for preterm infants improved between 1983 and 1995. However, long-term follow-up into adulthood is necessary to investigate the potential health effects of the changed intensiveness of obstetric and neonatal care. Recently, a Dutch study of very preterm infants at five years of age reported that not only the survival of preterm infants has increased over time, but also the incidence of disabling cerebral palsy. [40]

Future use of the linked perinatal registers

Many caregivers and researchers have long been aware there would be many advantages to linking the separate perinatal and neonatal registers. These people

expressed the hope that a single source would soon provide them with a full overview of perinatal care in the Netherlands. [41-43] As stated above, such a perinatal database would have a variety of potential applications. The studies described in this thesis represent only a small part of all of the research that the linked perinatal database might make possible.

The database might be used to generate various types of perinatal statistics and to study the relationship between potential risk factors and specific pregnancy outcomes. Since total perinatal care is overviewed in one database, it is possible to study the care of pregnant women together with the resulting outcomes. As an example, this thesis has remarked upon the increase seen in referrals from the midwife to the obstetrician. To evaluate whether or not this increase is desirable, it would be possible to study the given reasons for referral and to relate them to pregnancy outcomes after referral.

The perinatal database might also be used as a control population when studying specific populations such as premature newborns or newborns conceived after hormone therapy or In Vitro Fertilisation. Similarly, for purposes of international comparisons, it might also serve as a reference population for all Dutch births. In this respect, the linked perinatal database of 1999 has already served as a source for extracting perinatal statistics for international comparison. Financed by the European Union, this involved a joint project called PERISTAT, which took place in 2003. Conducted by 15 European countries, this set out to define a uniform set of perinatal core indicators that could be used for reliable international comparisons. [44]

The described linkage method has been repeated annually, thus making perinatal databases available over several registration years. In this way, the databases can be used as a monitoring tool, for example to monitor the prevalence of certain pregnancy outcomes over time. In this respect, until now, the linked perinatal databases for 1995-2002 have been used to monitor the overall and specific prevalence of congenital malformations. [45] The primary goal of this project, which is financed by the Ministry of Health, is to determine the baseline prevalence of a variety of congenital malformations such that possible changes in these prevalences can rapidly be detected over time. The

databases can thus be used as a monitoring tool. It might be used to study annual percentages of preterm or multiple births, and to relate possible variations to changes in demographic factors or changing medical developments.

Linking information already available in existing databases is a creative way of increasing research options, and when resources are scarce (as they are at present), is certainly more cost-effective than starting a new data collection. When one uses the perinatal database for future research, it should always be considered whether it is the appropriate data source for investigating the research hypothesis in question. [46;47] In other words, it should always be considered whether the research fits with the objectives of the perinatal database.

The linkage described in this thesis concerns the linkage of the three registers within one registration year. In the future, consecutive registration years could be linked. This would make it possible to match a particular woman's subsequent pregnancies, thereby creating person-based obstetric histories. Similarly, linkage might also take place with other data sources. This is necessary for a variety of purposes, such as analysing the associations between socio-economic indicators, or parental exposure to various workplace hazards and unfavourable birth outcomes. Linking the perinatal database and the Dutch Cancer Register might also help answer various questions relating to childhood cancers.

As the use of this perinatal database will increase, it may become essential to scrutinise the reliability and representativeness of the data it contains. There are several reasons perinatal information may not have been registered adequately, including lack of staff, lack of personal involvement, a low priority to data provision, doubts about the quality of data, and technical or logistical problems. [48] Caregivers must be convinced of the importance and the usefulness of the data they register. Only incentives will make it possible to overcome the problems outlined above, and thus to register perinatal and neonatal data more accurately. Routine year-on-year linkage will help produce more

accurate data, which in turn will enhance the productive and meaningful use of the register, and thereby stimulate caregivers to register data more thoroughly.

Conclusion

The registration of perinatal and neonatal information is essential to monitor the health of newborns, to detect potential risk factors in the perinatal period, and to evaluate perinatal and neonatal care. At present, however, there is no single surveillance system or registration system for recording the full spectrum of pregnancy outcomes in the Netherlands. This thesis has demonstrated that is it possible to create a single national perinatal database on the basis of the existing separate Dutch perinatal and neonatal registers. By applying methods of linkage and extrapolation, such a database has been created. Comparison with external data sources has also confirmed its reliability.

This thesis has presented a broad range of epidemiologic research based on the linked perinatal database. Potentially this database provides an important basis for clinical practice, research, audit, and education, and also for managing and assessing perinatal health care services.

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Summary

Each year, over 200,000 children are born in the Netherlands. If their health is to be properly monitored, potential perinatal risk factors detected, and perinatal and neonatal care evaluated, it is essential that full perinatal and neonatal information is registered. This enables evaluation of a wide range of factors and their health effects: medical developments such as assisted reproductive techniques and the treatment of premature infants, as well as demographic changes such as the increasing maternal age of first-time mothers and the increasing proportion of women from ethnic minorities.

As **Chapter 1** describes, the Netherlands has no single national system for registering full and detailed perinatal information on births. However, unique resources for generating such information are contained in two national perinatal registers, LVR-1 and LVR-2, and a neonatal register, LNR. To date, these have been used separately for recording detailed data on pregnancy, delivery, puerperium and on newborns admitted to a paediatric ward. LVR-1 is used by midwives, LVR-2 by obstetricians, and LNR by paediatricians. Due to frequent referrals between the different caregivers, the information they contain partly overlaps.

This thesis examines the option of using the separate registers as a basis for a single national perinatal and neonatal database covering all births in the Netherlands. First, we describe the method used to create a single database. Next, we establish the reliability of the database thus created. Finally, we demonstrate possible applications of this database in perinatal epidemiological research.

Chapter 2 describes the three existing registers. To create one single database on the basis of these registers, the overlapping information between the registers had to be identified and linked. It was not possible to perform this linkage by identifying duplicate records across the registers on the basis of a unique number per registered newborn, as the registers do not feature such a number. Thus, the search for duplicate records had to be performed by using a combination of overlapping variables. To choose the most useful variables and to determine the discrepancies that could be tolerated within them, we consulted obstetric caregivers involved in daily practice. Their clinical insight and knowledge of the registers were essential to identify the best choice of variables and to

define proper criteria. Using these variables and defined criteria, we identified duplicate records in a number of consecutive searches in the LVR-1 and LVR-2 registers. We used aggregation to reduce (and thus link) these duplicates. Linkage of the registers for the year 2000 showed that 39% of the children had been registered more than once in LVR-1 and LVR-2. Using similar methods, we linked the LNR records to their LVR-1 or LVR-2 birth records.

Because a small percentage of caregivers do not yet participate in either register, not all Dutch births are included in the LVR registers. The degree of participation in the LNR also depends on the level of care. A linked database that does not take this into account will inevitably overrate perinatal problems, as non-participation affects only two categories: 1. some low-risk pregnancies and births in level I hospitals and primary care (i.e. births covered by midwives and GPs); and 2. less severely ill newborns in some general paediatric departments. On the basis of the participation rate of the level of care recorded during delivery or during neonatal care, we applied weighting factors to extrapolate the database and thus to correct for this non-participation.

Once the registers had been linked, it had to be decided how similar variables from the separate registers should be combined into one overall variable within the linked database. In general, the method for combining depended on the content of the variable and the specific research question.

Chapter 3 describes how we determined the reliability of the perinatal and neonatal database thus created. Mortality rates calculated on the basis of the new database were compared with those published by Statistics Netherlands (CBS) on the basis of civil registers. The mortality rates were similar, demonstrating the validity of the linkage and extrapolation methods used, and thus of the mortality data they generated. It was possible to explain any differences, such as the under-reporting of perinatal deaths in the civil register (1.2 per 1,000 births), especially within the subgroup of immature newborns born close to the lower legal limit of registration.

Chapters 4 to 8 describe applications of the linked and extrapolated perinatal database. In **Chapter 4**, we calculate the percentage of Dutch planned home births over the 1995-2000 period. This shows that, after a slight decrease at the beginning of this period, the percentage stabilised at around one third of all Dutch births. A larger number of women started their pregnancy care with a midwife in primary care. However, due to an increase in referrals to secondary obstetric care during pregnancy and delivery, the percentage of planned home births did not increase during this period.

In **Chapter 5** we examine the relationship between maternal demographic factors and home births supervised by midwives, calculating the probability that women with different demographic profiles will have a planned home birth. In all age groups, the percentage of planned home birth was lower in primiparous women than in multiparous women (23.5% versus 42.8%). Further, women under 25 years of age had the lowest percentage of home births. In non-Dutch women the percentage was lower than in Dutch women (17.3% versus 36.5%). In large cities fewer home births took place than in small cities and rural areas.

Chapter 6 compares the prevalence of congenital malformations between different maternal ethnic groups in the Netherlands, using a five-year national birth cohort containing 881,800 births. The following maternal ethnic groups were distinguished: Dutch; Mediterranean (Moroccan/Turkish); other European; Black; Hindustani and Asian. The risk for a Mediterranean woman of having a child with a congenital malformation was 20% higher than for a Dutch woman (age-adjusted odds ratio (OR)=1.21 [95% confidence interval (C.I.): 1.16-1.27]). This increased risk was observed in various organ systems and types of malformations. For multiple malformations, for example, the age-adjusted OR was 1.80 [95% C.I.: 1.47-2.20]. The Black group showed a significantly increased risk of skeletal and muscular malformations (age-adjusted OR=1.76 [95% C.I.: 1.53-2.02]), with a risk of polydactyly that was six times higher than in the Dutch group.

In **Chapter 7** we determine whether or not children conceived by means of in-vitro fertilization (IVF) have an increased risk of congenital malformations. In the crude

analysis, the risk of any malformation in IVF children appeared to be 20% higher than that in naturally conceived children. However, after correction for differences regarding factors such as maternal age between the IVF and control population, the risk is similar (OR=1.03 [95% C.I.: 0.86-1.23]). The higher apparent risk in IVF children thus appeared to be attributable to differences in maternal characteristics rather than to the IVF procedure.

In **Chapter 8** we evaluate the changes that took place between 1983 and 1995 with regard to obstetric and neonatal care for very preterm and extremely preterm infants. This care changed over time, with a higher number of deliveries in tertiary centres (35.7 versus 60.7%), an increase in Caesarean-sections (43.7 versus 56.8%) and prolonged artificial ventilation (3.4 versus 9.5%). Survival until discharge increased from 75 to 90%, and neonatal morbidity parameters decreased. However, follow-up is still needed to investigate the long-term effects brought about by changes to the intensiveness of obstetric and neonatal care.

In **Chapter 9** we discuss the results of this thesis and draw conclusions. To date, there has been no single national registry in the Netherlands that makes it possible to monitor perinatal health care. By using methods of linkage and extrapolation, we created a single perinatal database for all Dutch births based on the separate LVR-1 and LVR-2 perinatal registers and LNR neonatal registers.

The validity of the database depends both on the reliability of the separate registers used and on the correctness of the methods used to create it. The reliability of the separate LVR and LNR registers itself depends on the degree of underreporting and on the percentage of incorrect registrations. These factors differ per variable. If the usefulness of the data were enhanced, the caregivers who produce this data would no doubt be stimulated to enter their own data more accurately. In this respect, linkage increases the reliability of the data, as underreported or incorrect data in the separate registers can be completed and corrected by information from the other registers.

Because complicated perinatal situations make referral more likely, they tend to lead to double registrations. Incomplete identification of double records within the linkage method may in this way seriously affect the reliability of generated statistics. Two crucial factors determine the result of the linkage: the variables used to identify duplicate records, and the definition of the specific criteria used to search for possible links.

To be representative of all Dutch births, the linked database was extrapolated to 100% births so as to correct for the small percentage of births that take place under the auspices of caregivers who do not yet participate in the existing LVR-1, LVR-2 and LNR registers. Because these represent low-risk births, weighing factors used for the extrapolation were assigned on the basis of the level of care, thereby reducing the risk of overestimating pathology in the linked database.

Although no “gold standard” is available to validate the linked perinatal database, comparison with data reported from other sources provides useful information. Mortality rates calculated on the basis of this database were similar to those published by Statistics Netherlands (CBS). The differences observed could be explained by the design of the registers compared. As the prevalences calculated for factors such as planned home births and congenital malformations were comparable with statistics from other data sources, the methods we used appear to be valid. We conclude that it is possible to use the existing separate professional registers as the basis for a single perinatal database recording all Dutch births.

This linked perinatal database provides considerable opportunity for a range of far-reaching applications. For every new research question, the specific way to use the linked database has to be accurately determined. Provided its limitations are fully taken into account, it is possible to use the linked database for a wide range of perinatal epidemiological research, since it contains detailed information on pregnancy, delivery, puerperium and on all babies born in the Netherlands.

Samenvatting

Jaarlijks worden in Nederland ruim 200.000 kinderen geboren. Om de gezondheidstoestand van pasgeborenen te monitoren om potentiële risicofactoren die hun gezondheid bedreigen op te sporen en om na te gaan of de zorg rond zwangerschap en geboorte goed is, is het nuttig om uitgebreide perinatale en neonatale informatie te registreren. Hiermee kan ook worden gekeken wat het gezondheidseffect is van veranderingen in behandeling zoals de behandeling van onvruchtbaarheid of de behandeling van te vroeg geborenen. Ook het effect van demografische veranderingen in de maatschappij zoals de steeds latere leeftijd waarop vrouwen hun eerste kind krijgen of de toename van het aantal allochtone zwangeren kan hiermee in kaart gebracht worden.

Zoals in **hoofdstuk 1** wordt beschreven, bestaat er op dit moment geen landelijke registratie met uitgebreide en gedetailleerde perinatale gegevens van alle pasgeborenen in Nederland. Wel bestaan er drie gescheiden landelijke registraties die ieder een deel van de gegevens over zwangeren en pasgeborenen en de verleende zorg registreren. Dit zijn:

- de Landelijke Verloskunde Registratie eerste lijn (LVR-1),
- de Landelijke Verloskunde Registratie tweede lijn (LVR-2) en
- de Landelijke Neonatologie Registratie (LNR).

Hierin registreren respectievelijk verloskundigen, gynaecologen en kinderartsen uitgebreide informatie over zwangerschap, bevalling en kraambed, en specifieke gegevens over pasgeborenen opgenomen op een kinderafdeling. Omdat zwangeren bij complicaties door de verloskundige naar de gynaecoloog worden verwezen en omdat van alle opgenomen pasgeborenen naast de gegevens van de kinderarts ook door de verloskundige of gynaecoloog geregistreerde gegevens over de zwangerschap en bevalling bestaan, overlappen de geregistreerde gegevens in deze registraties vaak.

In dit proefschrift zijn deze gescheiden registraties gebruikt voor het creëren van één landelijk bestand met perinatale en neonatale gegevens van alle Nederlandse pasgeborenen. Allereerst, wordt de hiervoor gebruikte methode uitgelegd. Daarna is de

betrouwbaarheid van het gecreëerde bestand onderzocht en tot slot zijn een aantal epidemiologische toepassingen van dit landelijke perinatale bestand beschreven.

In **hoofdstuk 2** worden de drie aparte registraties beschreven en de methode om deze te koppelen tot één landelijk perinataal gegevensbestand. Hiervoor zijn drie stappen nodig:

- het in de verschillende registraties identificeren van records behorende bij dezelfde zwangere en hetzelfde kind
- het corrigeren voor het niet volledig zijn van de perinatale bestanden doordat een klein deel van de zorgverleners niet deelneemt
- het combineren van vergelijkbare perinatale gegevens uit de verschillende registraties

Voor het koppelen van records behorende bij hetzelfde kind is in de genoemde registraties geen uniek nummer beschikbaar. Dubbele records zijn daarom gezocht op basis van een combinatie van identificerende variabelen die in alle registraties worden vastgelegd. Bij het keuzeproces van de meest bruikbare en discriminerende variabelen zijn in de praktijk werkzame zorgverleners geraadpleegd. Hun kennis van de praktijk samen met gedegen kennis van de registraties hebben geleid tot de beste keuze van te gebruiken variabelen en nog te accepteren verschillen binnen deze variabelen. Aan de hand van deze variabelen en gedefinieerde discrepanties zijn eerst in een aantal zoekrondes dubbele records in de LVR-1 en LVR-2 geïdentificeerd en gekoppeld op basis van een toegekend uniek nummer. Vervolgens zijn de LNR records van pasgeborenen met een vergelijkbare methode aan hun LVR-1 of LVR-2 geboorterecords gekoppeld. In het registratiejaar 2000, blijkt 39 procent van de geregistreerde pasgeborenen meer dan één keer voor te komen in de LVR-1 en LVR-2.

Correctie voor het niet geheel volledig zijn van de bestanden, door niet deelnemen van alle bij de verloskunde betrokken zorgverleners is nodig, omdat niet-deelname samenhangt met het niveau van de zorg. Deelname aan de LVR-1 is in de loop van de onderzoeksperiode toegenomen van 89 procent van de verloskundigenpraktijken in 1995 tot 92 procent in 2000. Huisartsen registreerden in deze periode (nog) niet in de LVR. In

de LVR-2 is de deelname van opleidingsklinieken volledig en nam die van de algemene niet-opleidingsziekenhuizen tussen 1995 en 2000 toe van 84 tot 96 procent. Ook de deelname van kinderartsen in de LNR is onvolledig en afhankelijk van het niveau van zorg, waarbij in de Neonatale Intensive Care Units (NICU) de registratie gedurende de onderzoeksperiode wel volledig was, maar de overige kinderartsenpraktijken slechts voor de helft deelnamen. Hier dient rekening mee gehouden te worden omdat anders een overschatting gemaakt zou worden van perinatale problemen. De niet-deelname is namelijk beperkt tot laag risico zwangerschappen en bevallingen en tot de opgenomen pasgeborenen met iets minder ernstige problemen aangezien alle NICUs in de LNR participeren maar niet alle algemene kinderafdelingen. Gebaseerd op het deelnamepercentage van het geregistreerde zorgniveau tijdens de bevalling of tijdens neonatale opname zijn wegingsfactoren toegepast om het perinatale bestand te extrapoleren en hiermee te corrigeren voor de niet-deelname van een aantal zorgverleners.

Naast het koppelen en extrapoleren is per variabele bepaald hoe deze vanuit de aparte registraties samengevoegd kan worden tot één nieuwe variabele in het gekoppelde perinatale bestand. Het gaat hierbij enerzijds om variabelen die theoretisch in alle drie de bestanden gelijk zouden moeten zijn, maar die in de praktijk kunnen verschillen. Zo kunnen er bijvoorbeeld kleine verschillen bestaan in het geregistreerde geboortegewicht doordat de ene zorgverlener het gewicht bijvoorbeeld afrondt. Anderzijds zijn er gegevens die ook werkelijk per registratie kunnen verschillen. Een voorbeeld hiervan is het overlijden van een pasgeborene aan het eind van de eerste levensweek: het kind is nog in leven als de gynaecoloog de gegevens over de bevalling registreert maar gestorven als de kinderarts de neonatale gegevens registreert. De gekozen manier waarop variabelen worden samengevoegd is afhankelijk van de inhoud van de variabele en de specifieke onderzoeksvragen.

Hoofdstuk 3 beschrijft hoe betrouwbaar het nieuwe landelijke bestand is door de berekende sterftecijfers te vergelijken met sterftecijfers zoals gepubliceerd door het Centraal Bureau van de Statistiek (CBS). Deze blijken goed vergelijkbaar, gevonden verschillen zijn verklaarbaar uit het verschil in doel van de registraties. Zo is bij het CBS

de sterfte bij veel te vroeg geboren kinderen op de grens van levensvatbaarheid lager dan in het perinatale bestand, omdat aangifte bij de burgerlijke stand rond deze grens (ten onrechte) niet altijd gebeurt. Anderzijds is de sterfte in de eerste levensweek lager in het perinatale bestand, omdat bijvoorbeeld kinderen met een ernstige aangeboren afwijking met een hoog risico op overlijden meestal worden opgenomen op een kinder Intensive Care, waar geen LNR registratie plaatsvindt.

De laatste hoofdstukken beschrijven toepassingen van het landelijke perinatale bestand bij epidemiologisch onderzoek naar het percentage thuisbevallingen in Nederland (hoofdstuk 4 en 5), naar de kans op aangeboren afwijkingen in verschillende etnische groepen (hoofdstuk 6), naar de kans op aangeboren afwijkingen na In Vitro Fertilisatie (IVF, hoofdstuk 7) en naar veranderingen in de zorg voor te vroeg geborenen (hoofdstuk 8).

In **hoofdstuk 4** blijkt dat zwangeren in de periode 1995-2000 hun zwangerschapszorg vaker beginnen in een eerstelijns verloskundigenpraktijk. Dit leidt echter niet tot een stijging van het aantal thuisbevallingen omdat het aantal verwijzingen naar de tweede lijn tijdens de zwangerschap en de bevalling sterk gestegen is in deze periode. Het percentage thuisbevallingen in Nederland is, na een lichte daling in het begin van deze periode, gestabiliseerd rond de 30 procent van alle Nederlandse geboorten.

In **hoofdstuk 5** is bekeken welke zwangeren meer kans hebben op een thuisbevalling onder leiding van een verloskundige. Leeftijd, etnische achtergrond en woonplaats (stad of platteland) blijken (nog steeds) grote invloed te hebben. Het percentage thuisbevallingen is in alle leeftijdsgroepen voor de eerste zwangerschap (primiparae) lager dan voor latere zwangerschappen (multiparae), namelijk 23.5% versus 42.8%. Zwangeren jonger dan 25 jaar bevallen het minst vaak thuis. Het percentage thuisbevallingen bij niet-Nederlandse vrouwen is lager dan bij Nederlandse vrouwen (17.3% versus 36.5%) en in grote steden wordt minder vaak thuis bevallen dan in kleine steden of op het platteland.

Hoofdstuk 6 vergelijkt het voorkomen van aangeboren afwijkingen in verschillende etnische groepen op basis van 881.800 geboortes. Hiervoor zijn vijf jaarbestanden samengevoegd. Etnische groepen die in de LVR worden onderscheiden zijn: Nederlands; Mediterraan (Turks en Marokkaans); ander Europees; Negroïde; Hindu en Aziatisch. De kans op een kind met een aangeboren afwijking is voor een Mediterrane zwangere 20 procent groter dan voor een Nederlandse zwangere (leeftijd gecorrigeerde odds ratio (OR)=1.21 [95% betrouwbaarheidsinterval (B.I.): 1.16-1.27]). Dit verhoogde risico is zichtbaar bij verschillende orgaansystemen en specifieke afwijkingen. De leeftijd gecorrigeerde OR voor multipele afwijkingen is bijvoorbeeld 1.80 [95% B.I.: 1.47-2.20]. Een Negroïde zwangere heeft een verhoogd risico op afwijkingen van het skelet- en spierstelsel (leeftijds gecorrigeerde OR=1.76 [95% B.I.: 1.53-2.02]), waaronder een zes keer grotere kans op polydactylie in vergelijking met een Nederlandse zwangere.

Hoofdstuk 7 toont aan dat kinderen geboren na In Vitro Fertilisatie (IVF) geen verhoogd risico op aangeboren afwijkingen hebben. In de ongecorrigeerde analyse lijkt de kans op een afwijking bij IVF kinderen weliswaar 20 procent hoger dan bij natuurlijk verwekte kinderen. Wanneer gecorrigeerd wordt voor verschillen, bijvoorbeeld in de leeftijd van de moeder, is het risico niet meer verhoogd (OR=1.03 [95% B.I.: 0.86-1.23]). Het gevonden risico bij IVF kinderen berust dus niet op de IVF procedure maar op verschillen in karakteristieken van de moeder.

In **hoofdstuk 8** zijn veranderingen in de obstetrische en neonatale zorg voor te vroeg geborenen en veel te vroeg geborenen tussen 1983 en 1995 geëvalueerd. Deze zorg is met de tijd veranderd met onder andere een hoger aantal bevallingen in de derde lijn (35.7 versus 60.7%), een toename in het aantal keizersneden (43.7 versus 56.8%) en meer langdurige kunstmatige beademing (3.4 versus 9.5%). De overlevingskans tot ontslag is in deze periode gestegen van 75 tot 90%, en de neonatale morbiditeit is gedaald. Follow-up blijft echter noodzakelijk om de lange termijn effecten van deze verandering in intensiteit van obstetrische en neonatale behandeling goed te kunnen inschatten.

Tot slot (**hoofdstuk 9**) is de conclusie dat het ontbreken van een landelijke registratie van alle geborenen in Nederland gecompenseerd kan worden door het samenvoegen van de perinatale bestanden LVR-1, LVR-2 en LNR. Deze bestanden kunnen op een gestandaardiseerde wijze gekoppeld en geëxtrapoleerd worden, waardoor een betrouwbaar bestand met perinatale gegevens ontstaat, dat representatief is voor alle geborenen in Nederland.

Hierbij is de betrouwbaarheid van het nieuwe perinatale bestand afhankelijk van de juistheid van de toegepaste methoden en van de betrouwbaarheid van de aparte registraties, die bepaald wordt door de mate van onderrapportage en invulfouten. De onderrapportage en invulfouten verschillen per variabele. Het vergroten van de bruikbaarheid van de vastgelegde gegevens voor de zorgverlener, stimuleert deze om nauwkeuriger te registreren. Koppeling van de verschillende registraties vergroot bovendien de betrouwbaarheid van de data doordat onderrapportage of invulfouten in de aparte registraties aangevuld en verbeterd kunnen worden door informatie uit de andere registraties.

Gecompliceerde perinatale situaties en (mogelijke) perinatale problemen verhogen de kans op een verwijzing en daardoor op dubbele registratie. Het onvolledig identificeren van dubbele records tijdens de koppelingsprocedure kan hierdoor de betrouwbaarheid van gegenereerde epidemiologische gegevens beïnvloeden. Anderzijds leidt het ten onrechte identificeren van dubbelen eveneens tot onbetrouwbaarheid. Daarom zijn twee factoren cruciaal voor het bepalen van het resultaat van de koppeling: de gebruikte variabelen om dubbele records te identificeren en het vaststellen welke verschillen binnen deze variabelen nog geaccepteerd kunnen worden en daarmee welke specifieke criteria per koppelingsronde gebruikt moeten worden.

Om representatief te zijn voor alle geboorten in Nederland is een extrapolatie toegepast die corrigeert voor (nog) niet aan de LVR-1, LVR-2 of LNR deelnemende zorgverleners. Omdat deze niet-deelname zich beperkt tot laag risico geboortes, zijn wegingsfactoren toegekend per geregistreerd niveau van zorg. Dit vermindert de kans op het overschatten van pathologie.

Er bestaat geen gouden standaard waarmee het gecreëerde perinatale bestand te valideren is. Vergelijking met data uit andere bronnen, zoals de gepubliceerde sterftecijfers van het CBS of oudere gegevens over thuisbevallingen in Nederland of (regionale) gegevens over het voorkomen van aangeboren afwijkingen bevestigen de validiteit van de toegepaste methode. Concluderend, is het dus mogelijk om op basis van de aparte perinatale en neonatale registraties (LVR-1, LVR-2 en LNR) één betrouwbaar en representatief bestand te genereren voor alle geboortes en geborenen in Nederland.

Dit gekoppelde en geëxtrapoleerde bestand vormt de basis voor uiteenlopende onderzoekstoepassingen. Bij elke nieuwe onderzoeksvraag zal nauwkeurig bepaald moeten worden hoe dit bestand gebruikt kan worden. Als hierbij rekening gehouden wordt met de gemaakte aannames en beperkingen van dit bestand, biedt het een rijke bron met gedetailleerde informatie over zwangerschap, bevalling en kraambed van alle geborenen in Nederland.

Curriculum Vitae

Sabine Anthony werd geboren op 28 januari 1971 te Strasbourg (Frankrijk). In 1989 behaalde zij haar eindexamen VWO aan het Rijnlands Lyceum te Oegstgeest. In datzelfde jaar startte zij de studie Biomedische Wetenschappen aan de Rijksuniversiteit Leiden. Tijdens deze studie liep zij stages bij de afdeling Jeugd en Gezondheid van het NIPG-TNO (huidige TNO Kwaliteit van Leven) te Leiden, bij de afdeling Reumatologie van het Academisch Ziekenhuis Leiden (huidige LUMC), bij de afdeling Fibrinolyse en Proteolyse van het Gaubius Laboratorium IVVO-TNO (huidige TNO Kwaliteit van Leven) te Leiden en bij de Laboratoire d'Epidémiologie van de Faculté de Médecine, Université Louis Pasteur te Strasbourg. Haar afstudeerstage doorliep zij op de afdeling Chronische Ziekten en Milieuhygiëne van het RIVM te Bilthoven. In 1995 behaalde zij haar doctoraalexamen. In 1994 startte zij een Master of Science opleiding in Klinische Epidemiologie aan The Netherlands Institute of Health Sciences (NIHES) te Rotterdam die zij in 1995 afrondde. Van 1995 tot 1997 werkte zij als Clinical Research Associate op de afdeling Biometrie gevestigd te Leiden van Clin-Pharma Research AG (Zwitserland).
Sinds 1997 werkt zij als wetenschappelijk medewerker bij de sector Voortplanting en Perinatologie, divisie Jeugd van TNO Preventie en Gezondheid (sinds januari 2005 TNO Kwaliteit van Leven, Businessunit Jeugd, Preventie en Bewegen) te Leiden. Hier verricht zij onderzoek dat onder andere heeft geresulteerd in dit proefschrift.