Perinatal Mortality in the Netherlands:

perinatal audit and fetal biometry

Paul A.O.M. De Reu

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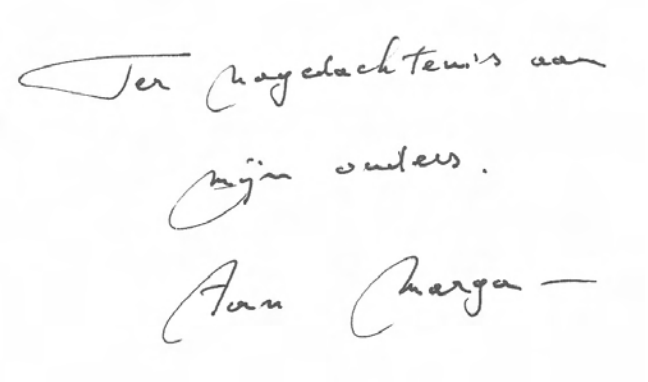
Ter nagedachtenis aan
mijn ouders.
Ann Margaret

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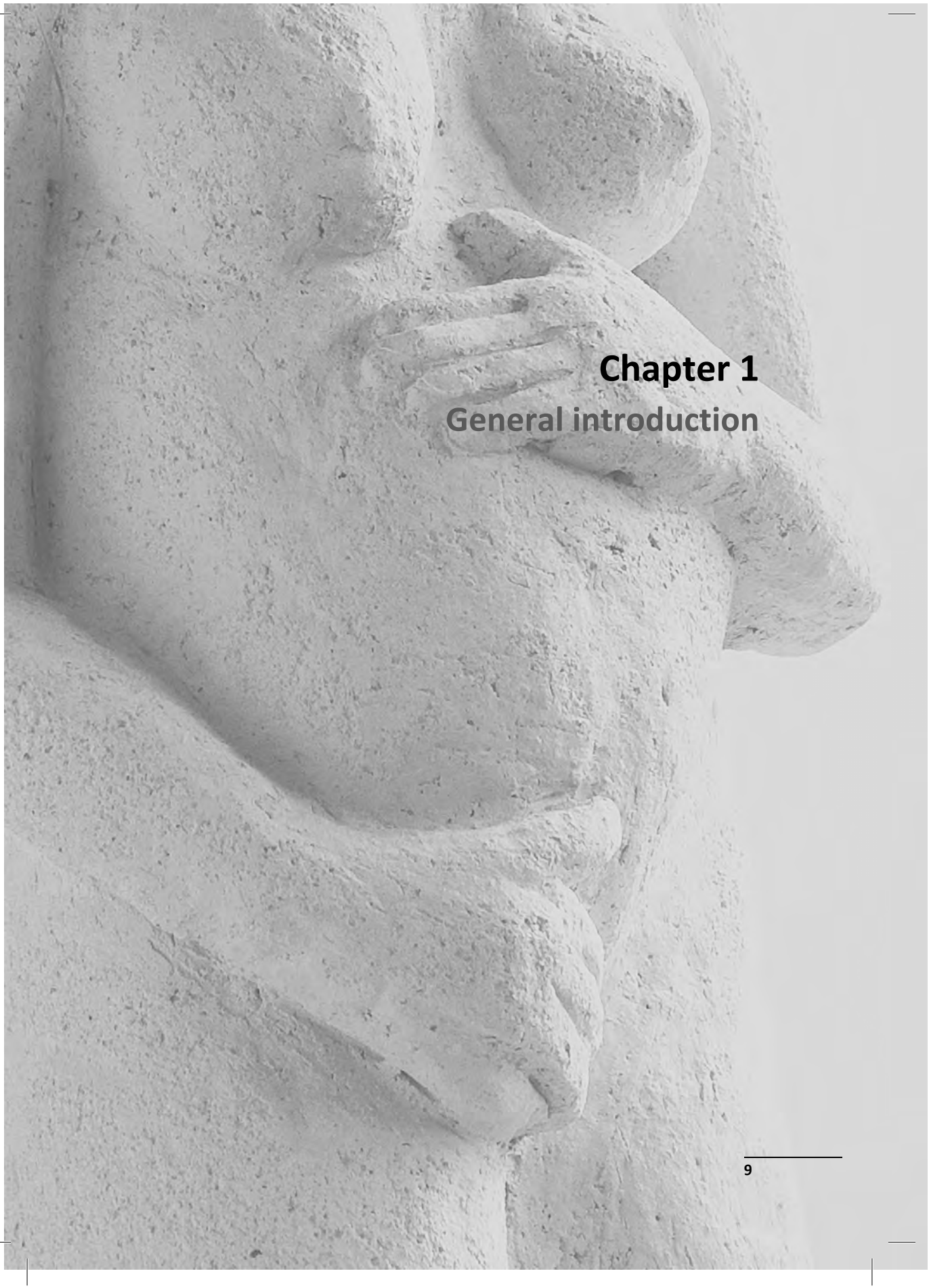

Chapter 1
General introduction

The health status of a population and/or the quality of the perinatal health care system is often based on the data on perinatal mortality and morbidity. Congenital anomalies, very preterm birth and stillbirth, often associated with fetal growth restriction, are the most common determinants [1]. Maternal age, parity, multiple pregnancies and life style factors such as smoking are the most common risk factors. [2-6].

The possible relation of these factors on perinatal mortality is the justification for the here presented studies.

1.1 Gestational age

Gestational age (GA) is expressed in completed days or completed weeks. Traditionally, GA is measured from the first day of the last normal menstrual period (LNMP). However, it is imperative to define GA as precisely as possible. For that reason it may be preferable to determine the exact GA based upon two matching measurements: LNMP and one (late) first trimester ultrasound measurement of the crown-rump-length (CRL) or, if LNMP is not known or not reliable, upon two independent ultrasound measurements before the 20th week of pregnancy [7, 8].

1.2 Perinatal mortality – perinatal mortality rates

Perinatal mortality is defined as the sum of fetal mortality and neonatal mortality. The fetal mortality rate is defined as the number of fetal deaths at or after 22 completed weeks of gestation (≥154 days) in a given year, expressed per 1000 live and stillbirths in the same year. Neonatal deaths are subdivided into early neonatal deaths (at 0-6 days after live birth) and late neonatal deaths (at 7-27 days after live birth). The neonatal mortality rate is defined as the number of deaths during the neonatal period at or after 22 completed weeks of gestation in a given year, expressed per 1000 live births in the same year (figure 1).

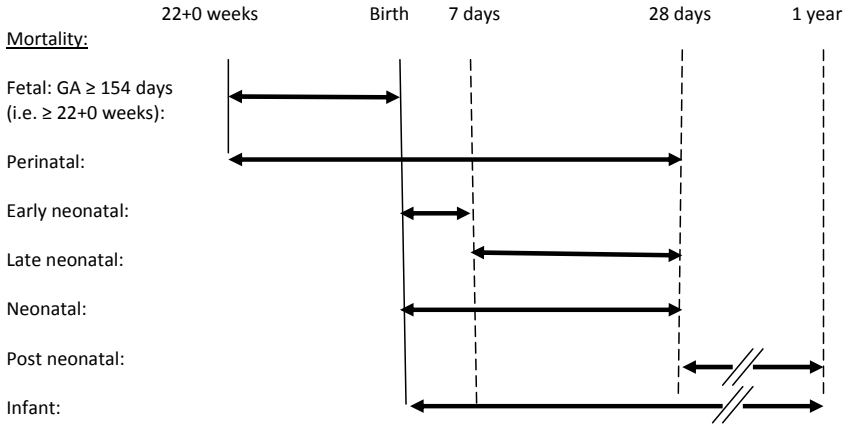

Figure 1: Schematic overview of perinatal and infant mortality.

1.3 The perinatal healthcare system in the Netherlands

With almost 30% home deliveries, the Dutch perinatal healthcare system is quite different from those in other Western countries. The system is based upon risk selection: community midwives and general practitioners (GP's) provide perinatal primary care for the low risk cases while secondary and tertiary perinatal care (cases with elevated risk or possible pathology) is provided by secondary/tertiary care

midwives, obstetricians and neonatologists in general hospitals or in university/third level hospitals [9-11]. During the last decades, a considerable number of studies criticizing the system as well as supporting it have been published [12-18]. Ignorance with this system led, especially outside the Netherlands, to prejudged conclusions, mostly focusing on the risks of home deliveries [19].

In a number of studies in which aspects of perinatal care in the Netherlands were investigated [15, 20-22], a relation between the Dutch perinatal healthcare system and perinatal mortality could not be demonstrated while, more recently, it became evident that home deliveries are relatively safe as mortality and morbidity are comparable with low-risk "home-like" deliveries in hospitals under supervision of a community midwife [23]. The conclusions of this study are in line with an earlier prospective study from North America in 2005 [24].

However, the less rapid decrease in perinatal mortality rates in the Netherlands as compared to other European countries in the early eighties until this moment, is food for thought [25-29] and the question still remains whether aspects of this system, more precisely our so called "obstetrical-chain-care", are related to the relatively high perinatal mortality.

During the last decades, the Dutch reproductive population showed some important changes compared with many other European countries, e.g. an increasing number of women with advanced maternal age, a high percentage non-Western women, multiple pregnancies and mothers with unhealthy lifestyle [30, 31]. However, these risk-factors can only explain the high Dutch perinatal mortality in part. Quality of care still plays a substantial role [32]. As a consequence, the question "what are we doing wrong or what can we improve in our perinatal healthcare system?" is still pertinent because in our country nearly 10‰ of all children die before, during or shortly after birth (table 1).

Table 1: Perinatal mortality rates in the Netherlands 2001 – 2007.
(GA = 22+0 weeks till and including 28th day after delivery)

Year	PNM-rate
2001	11.7 ‰
2002	11.4 ‰
2003	10.6 ‰
2004	10.4 ‰
2005	10.5 ‰
2006	9.8 ‰
2007	9.7 ‰

Source: Netherlands Perinatal Registry (PRN)

Recently, the discussion to what extent our "obstetrical-chain-care" might be responsible for the less favourable perinatal outcome, revived as a result of the reports on perinatal mortality rates in different countries of the European Union in 1999/2000 and 2004. These were published in the European perinatal Health Re-

port (PERISTAT) in 2004 and 2008 respectively (the complete reports are available on www.europeristat.com) [26 - 29]. From these reports it became clear that the Netherlands was among the countries with the highest perinatal mortality rates in Europe. Especially fetal mortality is substantially higher than in most other countries (figures 2 and 3).

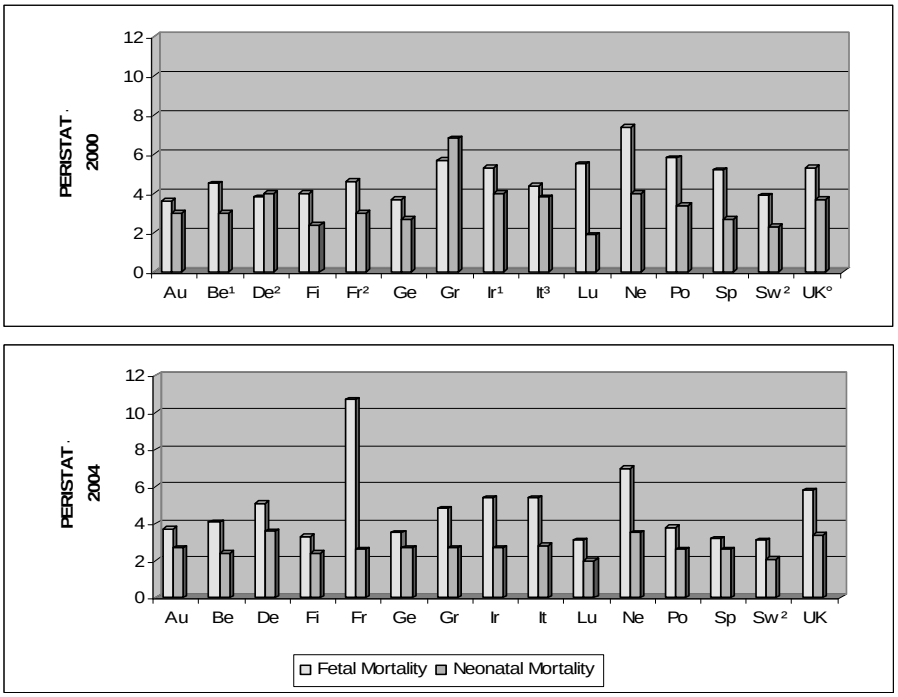

Figure 2: Fetal and neonatal mortality rates in Europe – PERISTAT results 1999/2000 and 2004.
[1] = GA ≥ 22 weeks and ≥ 500 grams; [2] = GA ≥ 28 weeks; [3] = GA ≥ 180 days; [°] = England and Wales, Northern Ireland and Scotland all GA ≥ 24 weeks

1.4 Reliability of perinatal mortality data

Perinatal mortality is classically underreported and this is an international problem: especially stillborns and children less than 500 grams are often not reported [33 - 36]. As shown in earlier studies, under-registration is mostly due to under-reporting by the physicians involved [37 - 40]. Underregistration by the Dutch Central Bureau of Statistics (CBS) was also proven by several studies during the past decades: from 31% in 1975 it decreased to 14.3% in 1985 and, at least, 8.1% in the period 1983 – 1992 [13, 37, 41]. In one of the most recent studies on perinatal mortality in three Dutch regions in 2003 - 2004, an underregistration of even 19% was found [42] which is remarkably higher than in the earlier mentioned studies. This observation

may lead to the assumption that true perinatal mortality rates may still be (much) higher than officially published.

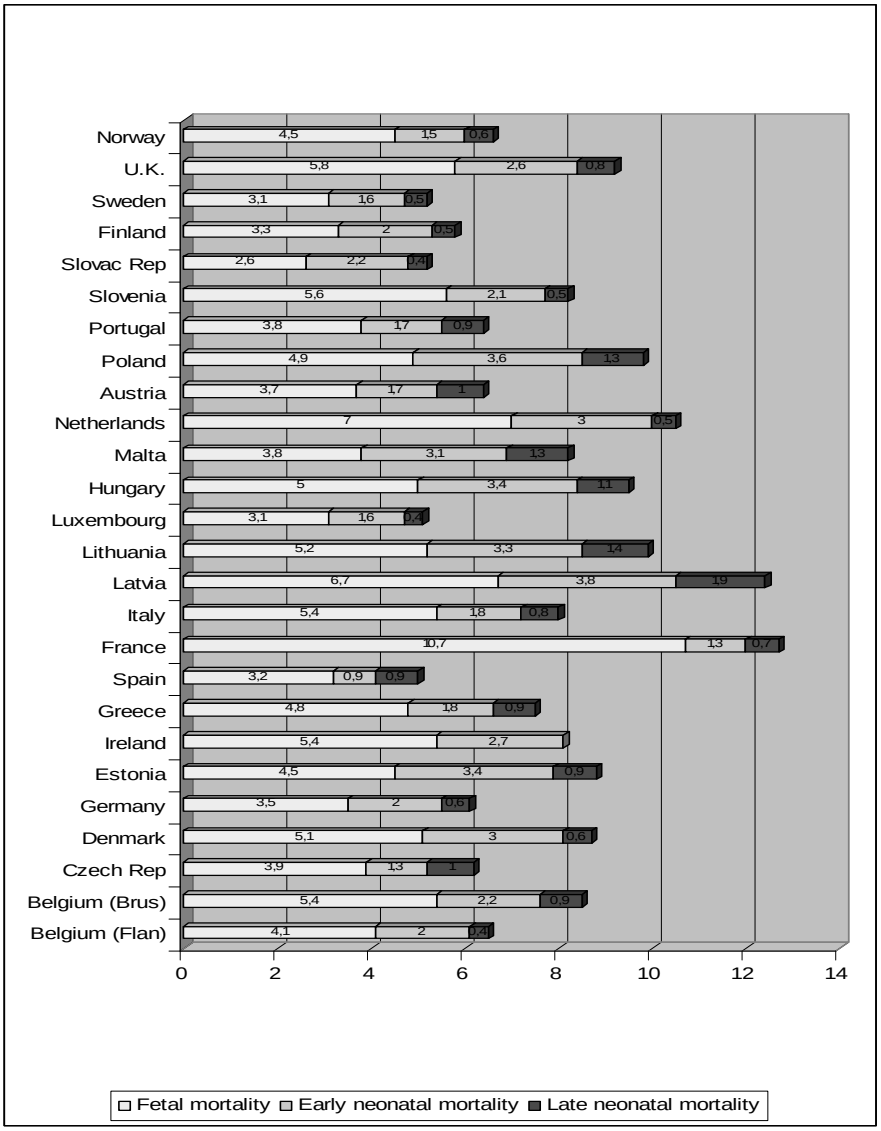

Figure 3: Fetal and neonatal mortality rates (‰) in Europe – PERISTAT results 2004.
Sweden: GA ≥ 28 weeks; Hungary: GA ≥ 24 weeks.

In 1992, the WHO introduced the 10th revision of the International Classification of Diseases (ICD-10) a new directive in which perinatal mortality has been defined as fetal death or stillbirth from 22+0 weeks of gestation (i.e. ≥154 days) and neonatal

death in the first week of life (7 x 24 hours). At present, perinatal mortality rates are calculated from 22+0 weeks of gestation until 28 days after delivery, thus including late perinatal mortality. It is difficult to understand that these criteria, already proposed in 1986 by Macfarlane et al. [43], are still not used in all industrialized countries.

Since national databases often do not correspond with the intended registration, WHO-criteria can not always be met. Therefore, a 100% comparability between countries of the European Union is still not possible [44]. For the PERISTAT reports, in 1999 / 2000 only 8 of the 17 participating countries were able to provide perinatal mortality data according to the international accepted WHO-guidelines while in the 2004-report, 2 of the 31 participating countries were still not able to do so (figures 2 and 3).

1.5 Classification of perinatal mortality by cause of death

Scientific research on perinatal mortality starts at the beginning of the 20th century when two separate studies were published proposing a classification of perinatal death, by J.W. Williams [45] and by L.E. Holt and E.C. Babbit [46], respectively. They revealed nearly equal perinatal mortality rates of 7.1% and 7.2% in study populations where perinatal mortality was considered from 28+0 weeks of gestation (≥ 196 days) until 14 days after delivery.

Since then, a considerable number of classification models for assessment of causes of perinatal mortality have been published. An overview of the most important classifications is shown in table 2.

In 1919 McQuarrie [47] published a classification of eight items. In his view the definition of perinatal mortality was restricted to death occurring between the 30th week of pregnancy – as cut-off point of the 'period of possible viability' – until twelve hours after birth. Within those boundaries, McQuarrie found a mortality rate of 3.6%. He also drew attention to cases with multiple factors leading to perinatal death. In that respect he questioned that the presence of a single factor, e.g. toxemia, may not always be the only cause of a specific perinatal death. In fact, he was the first author to recognize that in some cases treatment itself may cause perinatal death.

A similar opinion was ventilated a few years later in an audit study concerning all cases of perinatal mortality from London, Glasgow, Liverpool, Edinburgh and Cardiff [48]. In this study of 1,673 cases, the authors demonstrated that in at least 25% of the cases mortality was "*due to accidents and complications associated with manipulation by midwife or doctor at birth, whether by forceps or version or in other ways"*.

Table 2: Classifications of perinatal mortality.

Author	Study	Ref.
Holt LE, Babbitt EC	Institutional mortality of the new-born.	JAMA 1915;64:287-90
Willams JW	The limitations and possibilities of perinatal care.	JAMA 1915;64:95-101
McQuarrie JG	Fetal death.	JAMA 1919;73:1574-6.
Browne FJ	Classification of stillbirths and neonatal deaths.	BMJ 1922;Sep:590-3
Holland EL, J.E. Lane-Claypton JE	A clinical and pathological study of 1.673 cases of death-births and neonatal deaths.	Med.Research.Council HM Stationery – 1926
Serbin WB	A report on 320 fetal postmortems at the Chicago lying-in hospital.	Am J Obs Gyn 1927;29:682-5
D'Esopo DA, Marchetti AA	The causes of fetal and neonatal mortality.	Am J Obs Gyn 1942;44:1-22
MacGregor AR	The pathology of still-birth and neonatal death.	BMB 1946;4:174
Labate JS	A study of the causes of fetal and neonatal mortality on the obstetric service of Bellevue hospital.	Am J Obs Gyn - 1947;54:188-200
Baird D, Walker J, Thomson AM	The causes and prevention of stillbirths and first week deaths.	J Obs Gyn Br Emp 1954;61:433-48
Bound JP, Butler NR, Spector WG	Classification and causes of perinatal mortality – I.	BMJ 1956;Nov:1191-6
Bound JP, Butler NR, SpectorWG	Classification and causes of perinatal mortality – II	BMJ 1956;Dec:1260-5
Naeye RL	Causes of perinatal mortality in the US collaborative perinatal project.	JAMA 1977;238(3):228-9
Wigglesworth JS	Monitoring perinatal mortality: a pathophysiological approach.	Lancet 1980;II:684-6
Autio-Harmainen H et al.	Causes of neonatal deaths in a pediatric hospital neonatal unit.	Acta Paediatr Scand 1983;72:333-7
Hovatta O et al.	Causes of stillbirth: a clinicopathological study of 243 patients.	BJOG – 1983;90:691-6.
Morrison I, Olsen J.	Weight-specific stillbirths and associated causes of death: an analysis of 765 stillbirths.	Am J Obstet Gynecol – 1985;152:975-80
Cole SK et al.	Classifying perinatal death: an obstetric approach.	BJOG - 1986;93:1204-12
Hey EN et al.	Classifying perinatal death: fetal and neonatal factors.	BJOG - 1986;93:1213-23
Duley LMM	A validation of underlying cause of death, as recorded by clinicians on stillbirth and neonatal death certificates.	BJOG - 1986;93:1233-35
Macfarlane A, Cole S, Hey EN	Comparisons of data from regional mortality surveys.	BJOG 1986;93:1224-32
Whitfield CR et al.	Perinatally related wastage – a proposed classification of primary obstetric factors.	BJOG 1986;93(7):694-703
Wildschut HIJ et al.	Fetal and neonatal mortality: a matter of care? Report of a survey in Ciraçao, Netherlands Antilles.	BMJ 1987;295:894-8.

Author	Study	Ref.
Keelilng JW et al.	Classification of perinatal; death.	Arch Dis Child 1989;64:1345-51
Georgsdottir I et al.	Classification of perinatal and late neonatal deaths in Iceland. A survey from a defined population.	Acta Obstet Gynecol Scand 1989;68(2):101-8
Magani M. et al.	Stillbirths: a Clinicopathological survey	Ped Path - 1990;10:363-74
Rushton DI	West Midlands perinatal mortality survey 1987. An audit of 300 perinatal autopsies.	BJOG - 1991;98:624-7.
Langhoff-Roos J et al.	Potentially avoidable perinatal deaths in Denmark and Sweden 1991.	Acta Obstet Gynecol Scand 1996;75(9):820-5
Patel N.	Round Table - Perinatal Mortality	Eu J Obstet Gynecol Reprod Biol 1991;41:17-26
Raghuveer G.	Perinatal deaths: relevance of Wigglesworth's classification.	Paed Perinat Epid. - 1992;6:45-50
Settatree RS, Watkinson M.	Classifying perinatal death: experience from a regional survey.	BJOG - 1993;100:110-21
Alberman E et al.	A new hierarchical classification of causes of infant deaths in England and Wales.	Arch Dis Childh - 1994;70:403-9
De Reu PAOM et al.	Perinatal audit on avoidable mortality in a Dutch rural region: a retrospective study.	Eu J Obstet Gynecol Reprod Biol 2000;88:65-9
de Galan-Roosen AEM et al.	Fundamental classification of perinatal death. Validation of a new classification system of perinatal death.	Eu J Obstet Gynecol Reprod Biol 2002;1103:30-6
Korteweg FJ et al.	The Tulip classification of perinatal mortality: introduction and multidisciplinary inter-rater agreement.	BJOG – 2006;113:393-401

All these early classifications had one thing in common: the cause of death was related to maternal diseases or to obstetrical accidents only. When post mortem and histological examinations became more common, the assessment of etiology of the causes of death was also based on clinico-pathological findings. Obviously one became more interested in the "how" and "why" of perinatal death. From that time on, the cause of death was based on the available evidence.

For instance Browne [49] classified 153 cases of neonatal death (out of 400 cases of perinatal mortality) and based the class "traumatic" on the detection of cerebral hemorrhage, suprarenal hemorrhage or other detected injuries.

Following this approach, Serbin [50] was able to identify the cause of death on apparently all cases investigated in his study group. In 320 autopsies from which 172 were excluded having a birth-weight of less than 1500 grams, he detected 45 cases of intracranial hemorrhage, 66 cases of asphyxia, 13 cases of lethal congenital malformations, 2 cases of neonatal sepsis and 4 cases of pneumonia. For obvious reasons he strongly promoted to perform a post mortem examination in any case of

perinatal mortality remarking: *"they are instructive from the obstetricians point of view as well as of pathologic interest".*

The more one recognized primary causes of perinatal death, the more secondary and underlying causes became important. D'Esopo and Marchetty [51] analyzed 1,000 cases of perinatal death in two New York hospitals between 1935 and 1941 and proved that perinatal death was often the result of a compilation of factors. They tried to decrease perinatal mortality focusing on possible preventive measurements in order to avoid, where possible, an increase of (for that time "dangerous") Cesarean Sections (*an increasing cesarean section rate reaches a point where it costs too many mothers for the prospect of saving a proportionately smaller number of babies*). To that purpose, they searched for primary and secondary causes of death and identified particular items possibly related to perinatal death: ethnicity (there *was a higher fetal death rate in "Negro's" than in "Whites"*), parity (*death rate was similar in multi and primiparous*), maternal age (*the most appropriate age to bear children was between 20 and 24 years of age while women over 30 years had higher mortality rates than younger ones*), prolonged labor (*if labor exceed thirty hours, the chances for the fetus to survive decreased*), method of delivery, position of the baby at the onset of labor and inferior birth-weight. A number of these factors were considered to be predisposing for asphyxia, birth injury, congenital pneumonia and preterm labor. Moreover, two conclusive advises were rather progressive for that time (1942): firstly that asphyxiated babies should preferably be treated before delivery in order to avoid hurry in delivering these babies (*a more judicious use of oxygen and ether anesthesia in cases where the fetus begins to show early signs of distress in utero might have prevented fatal asphyxia*) and secondly that the fetal heart rate should be observed frequently for half-an-hour after rupture of membranes.

In 1946, the pathologist MacGregor [52], analyzed 1,071 post mortem results in Edinburgh : 453 cases of still-births and 618 cases of neonatal deaths. Four major causes of death were considered to be responsible for over 80% of the cases: developmental defects (20% in still-births and 10.5% in neonatal deaths), asphyxia (37.2% and 13.1% respectively), intracranial hemorrhage (24.1% and 27.6% respectively) and (especially in the cases of neonatal death) infectious diseases (3.2% and 30.7% respectively). Her conclusions differed from those of the study of Labate [53] performed during the same period in New York who concluded that prematurity (27.6%), pulmonary lesions (22.5%) and birth trauma (16.9%) were the three most frequent occurring causes of perinatal death. MacGregor did not classify prematurity as a cause of death although the incidence was even higher in her study group: 54% of all still-births and 70.5% of all neonatal cases were born preterm.

In the following years, histologic examination became more important in the investigation of the causes of perinatal death. One of the first classifications of causes

of perinatal mortality based upon morbid anatomical and histological studies was published in 1956 by Bound, Butler and Spector [54].

In a number of successive papers published between 1941 and 1954 Baird et al. [55] introduced the *"Aberdeen Clinico-pathological Classification"*. The authors emphasize the relation between the apparent cause of death (e.g. dysmaturity) and the underlying cause of these conditions (e.g. placental insufficiency). Within the scope of preventive measurements they stated *"it is more important to prevent immaturity than to improve the technique of delivery of very immature babies"*. Prevention of perinatal death was also the basic assumption of their efforts as they declare in their statement: "*the chief purpose of a classification of deaths is to assist prevention*". Therefore they evolve rules of classification by clinical cause which leave little space for individual assessment.

Their classification consists of an hierarchical arrangement of. initially eight, and later, nine main classes of causes of perinatal death: (1) congenital anomaly; (2) iso-immunization; (3) pre-eclampsia; (4) ante partum hemorrhage; (5) mechanical; (6) maternal disorder; (7) miscellaneous; (8) unexplained and (9) unclassifiable.

Based upon this classification, the authors were able to analyze the data related to maternal age, parity, GA and even the attitude of the obstetrician involved. This hierarchical model is easy to work with, and although some authors later disagreed with this procedure, their classification can be considered to be framework for a great number of studies on this very subject during the whole second half of the XXth century [56, 57]. At the end of 1986, a group of investigators in the United Kingdom attempted to improve the comparability of data on perinatal mortality in different regions. Two studies preceded this attempt by updating the original Aberdeen Classification: a study by Cole et al. [56], focusing on the obstetric approach and a study by Hey et al. [58], focusing on the fetal en neonatal factors.

Nowadays the Aberdeen classification is still actual and is used worldwide to compare causes of perinatal mortality between different regions and countries. It has been applied by several investigators using a modification of their own. For his "Curacao perinatal mortality survey" Wildschut [59] composed a modified classification of eight items in which 'problems of preterm birth' was added. Two years later Georgsdóttir et al. [60] developed a nearly similar modification, without the class preterm birth. Furthermore they divided the unexplained deaths into two different groups: 'normal birth weight' and 'low birth weight'. In 2000, we also used the principles of Baird's classification ourselves, modified by a minor change in the hierarchical order of the items, while we added a number of underlying causes to each item [61].

However, modifications may not always make things easier: Settatree and Watkinson [62] published a study in which four assessors evaluated 451 cases of prenatal death and only reached a *moderated* degree of consensus: (Kappa = 0.55 to 0.58) using the modified Aberdeen classification (original Aberdeen with modifications of

Cole et al. [56] and Hey et al. [58]), while the same group reached *good* consensus (Kappa = 0.62 to 0.67) for the same data now using the New Wigglesworth classification [63].

In this apparently much simpler original pathophysiological classification of Wigglesworth the number of causes of death is reduced to five subclasses: (1) normally formed macerated stillbirths; (2) congenital malformations; (3) conditions associated with immaturity; (4) asphyxial conditions developing in labor and (5) specific conditions other than above. Some authors even suggest that this classification "*can be carried out even if autopsy has not been performed*" [64].

On the other hand, the New Wigglesworth classification leads to an unacceptable large percentage (45%) of unknown/unclassifiable causes [63, 65].

Another approach was advocated by Macfarlane et al. [66]. They compared 726 cases of perinatal death in 1985 in Scotland with 451 cases from the same year in the Northern region. The authors drew attention to a minimal number of indispensable data items in order to be able to derive comparability within different regions: (1) classification by maternal factors, (2) classification by fetal and neonatal factors, (3) multiplicity, (4) birth weight in grams and (5) timing of death. GA at birth was not mentioned in their series because that item was – at that time – unfortunately not recorded for life births in the registration of England and Wales. GA is, among other items, specified by the Steering Group of Health Services Information for collection in England from April 1st 1988 onwards.

In 1986, the authors concluded that clinical information on stillbirths and death certificates was often unreliable and inaccurate. This was confirmed by Duley [67] during the same period, who focused her study on the reliability of death certificates in cases of congenital malformation and respiratory distress syndrome.

In the Netherlands a new approach for the classification of perinatal mortality was introduced in 2002 by de Galan-Roosen et al [65] and further modified by Korteweg et al [68]. This new classification model is called the "*Fundamental Tulip Classification*" and is based upon a three step assessment: (1) the definition of the initial demonstrable pathophysiological entity e.g. the cause and underlying cause of death, (2) the mechanism of death in the sense of the organ failure incompatible with life and (3) the revealing of the origin of that mechanism.

This classification can assist prevention, not only in general, but also in the individual parents who have experienced a case of perinatal mortality. The system may therefore improve possibilities for adequate preconceptional counseling. Moreover, as compared to other classification models, the Fundamental Tulip Classification leads to a very low percentage (7%) of unknown/unclassifiable cases of perinatal mortality [65, 69].

1.6 Perinatal audit

Once the cause of death is determined, the quality of the care provided and the circumstances influencing that quality should be assessed, preferably by a team of independent experts in perinatal care. Such an assessment has to be performed in a Perinatal Audit.

What is audit? Peter M. Dunn gave the following definition [70]: “Perinatal audit is a systematic, critical analysis of the quality of perinatal care, including the procedures used for diagnosis and treatment, the use of resources and the resultant outcome and quality of life for women and their babies”.

The audit procedure includes the identification of the cause of death and will be based upon national standards of care. If such evidence is not available, ‘best practice’ i.c. expert opinion or generally accepted practice as used by the majority of professionals, may be considered as standard care. In that view, perinatal audit is a dynamic process offering a twofold result: firstly it will reveal if current protocols were respected, secondly the value and the efficiency of these protocols may be assessed and, if necessary, adjusted. In short, assessment on the presence of substandard care factors (SSF) by the caregivers, by the pregnant woman herself and by the organization of care have to be followed by improvement of (local, regional or national) policies in order to decrease specific categories of perinatal mortality (figure 4).

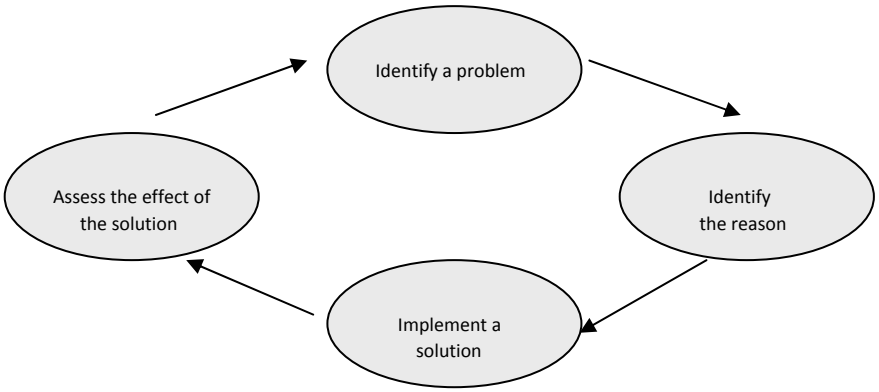

Figure 4: The audit spiral (by Peter M. Dunn).

Assessment of causes of perinatal mortality in general is the relatively easy part. Assessment in terms of avoidability or presence of substandard care appears to be a very difficult task. A considerable number of caregivers may feel threatened in respect to the quality of the care provided since avoidability of death or presence of SSF may be confused with negligence. However, negligence assumes a question of guilt for which the criteria exist on juridical level.

Avoidability however, is focused on measures that can be taken to prevent death in comparable situations in the future. Moreover, avoidability may help to clarify in what area(s) improvement is needed to decrease perinatal mortality.

For that reason, the privacy of caregivers involved in perinatal mortality cases, has to be protected the same way that the privacy of the patient is protected (if not, caregivers no longer will be motivated to participate in the audit process).

1.7 Fetal growth deviation

Identification of determinants of perinatal mortality is an important issue on the way to prevention. Growth deviations play a substantial role in cases of perinatal mortality, intrauterine growth restriction (IUGR) in particular [71 - 73]. Although most small-for-gestational-age (SGA)-children are constitutionally small and otherwise healthy, caregivers should follow fetal growth and, in case of possible retardation, try to distinguish between constitutional smallness and IUGR [74]. If we can detect IUGR in an early stage in pregnancy, we might be able to decrease perinatal mortality in this category substantially.

In the Netherlands, midwives and GP's assess fetal growth in low risk pregnancies by conventional methods (i.e. palpation of the uterus and/or symphysis-fundus height measurement). The poor predictive value of this kind of examination for the detection of growth deviations in SGA was shown by Bais et al [75] in 2004. Fetal biometry assessment by ultrasound examination improves the prediction for the estimated fetal weight (EFW) [76, 77, 78]. However, based upon the conclusions of a number of studies such as the Cochrane review [79] on routine ultrasound examination in late pregnancy, ultrasound examination ≥24 weeks of GA, is still not applied routinely in low-risk pregnancies. Furthermore, one has to realize that the results of international studies, even in case of meta analysis, may not always be applicable in the Dutch perinatal healthcare system (with 30% home deliveries).

Estimation of fetal size by ultrasound measurements is however not a straightforward task, and since 1975 a number of investigators has attempted to predict fetal weight based upon measurements of fetal parts as variables in regression formulas [80 - 85]. The most frequent used formulas are shown in table 3. In these formulas, fetal gender and maternal parity are not taken into account. However, length and weight are sex-dependent up from the 25th week of pregnancy [86].

Table 3: Most used formulas for the prediction of fetal weight.

Author	Formula
Campbell et al [80]	$Log_e EFW = -4.564+0.282*AC-0.00331*AC$ [in cm]
Shepard et al [82]	$Log_{10} EFW = 1.2508+0.166*BPD+0.046*AC-0.002646*AC*BPD$ [in cm]
Hansmann et al [85]	$EFW = -0.001665958(TAD)^3 + 0.4133659(TAD)^2 – 0.5580294(TAD) – 0.01231535(DBP)^3 + 3.7020000(DBP)^2 – 330.18110(DBP) – 0.49371990(GA)^3 = 55.958061 (GA)^2 – 2034.3901(GA) = 32768.19$ [in mm]
Hadlock et al [83]	$Log_{10} EFW = 1.326-0.300326*AC*FL+0.0107*HC+0.0438*AC+0.158*FL$ [in cm]
Mertz et al [84]	$EFW = -3200.40479-157.07186*AC+15.90391*BPD^{2}$ [in cm]

Notes: BPD = Biparietal diameter. HC = head circumference. AC = Abdominal circumference. FL = Femur length.

In 2004 Schwärtzler et al [87] found small but consistent gender-related differences for biparietal diameter (BPD), head circumference (HC) and abdominal circumference (AC) from the 15th week of gestation on, while Schild et al [88] constructed gender-specific fetal weight estimation formulas in which a mean absolute percentage error of 6.8% was found which was significantly lower as compared to established formulas (in 2002) showing percentage errors of 7.7 to 9.5%.

For girls: $= -4035.275 + 1.143 \times BPD^3 + 1159.878 \times AC^{1/2} + 10.079 \times FL^3 – 81.277 \times FL^2$ [in cm].

For boys: $= 43576.579 + 1913.853 \times \log_{10} BPD + 0.01323 \times HC^3 + 55.532 \times AC^2 – 13602.664 \times AC^{1/2} – 0.721 \times AC^3 + 2.31 \times FL^3$ [in cm]

Gardosi et al. introduced "*customized antenatal growth charts*" [89, 90]. In these charts a number of variables such as maternal ethnic origin, weight at first antenatal visit, length, parity, fetal gender and even maternal smoking habits are taken into account for the assessment of the individual EFW. Using these customized fetal growth charts makes it possible to distinguish more easily between constitutional smallness and true IUGR in individual cases.

However, apart from the growth charts used, one has to realize that inter-observer variability between trained examiners still plays a role in the final assessment for EFW: a 2 mm variance for distances (BPD, FL) and a 6-8 mm variance for circumferences (AC, HC) was proven by Chang et al [91]. Consequently, an 8 mm variance in AC-measurement is nearly equal to ½ SD and may lead to a difference in gestational length of 1 to 1½ week (figure 5). If used in a formula (e.g. the Hadlock formula), a 14 – 20% deviation for EFW prediction should be taken into account. If in the same pregnancy different growth chards are used by different caregivers (which may occur within the Dutch obstetrical-chain-care), it becomes almost impossible to assess fetal growth properly.

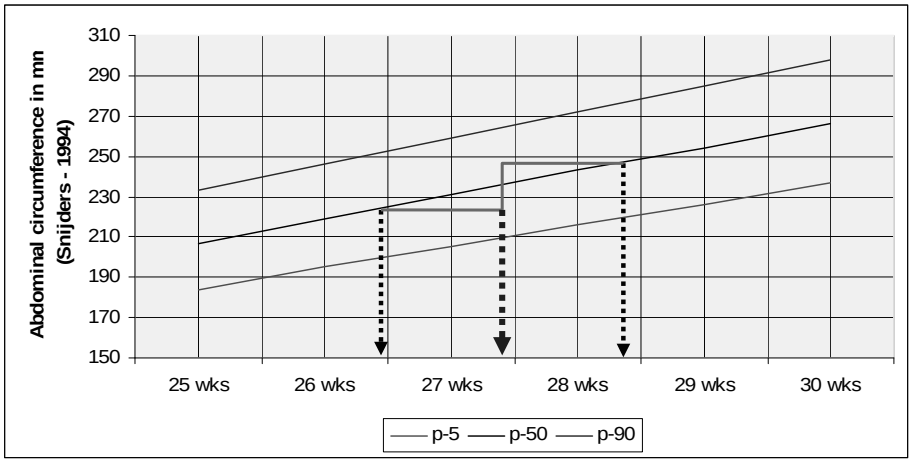

Figure 5: Possible measurement deviation by individual examiners.

1.8 Aims of this thesis

Based on the background, presented in this introduction, we set out to answer the following questions in this thesis:

- Does the Dutch perinatal healthcare system, especially the preservation of out of hospital care and home deliveries, lead to preventable perinatal mortality ? (chapter 2)
- To what extent is substandard care responsible for perinatal mortality in the Netherlands ? (chapter 3)
- Is nationwide perinatal audit in the Netherlands feasible on a yearly basis and if so, what are the practical possibilities and the limits ? (chapter 3)
- Is it possible to identify aspects of regular perinatal care as insufficient and probably responsible for avoidable perinatal mortality ? (chapters 4 and 5)
- Does perinatal mortality in multiplets increase the total perinatal mortality and should this lead to reconsider the actual care provided in this group (chapter 6)
- Is it possible to improve early detection of fetal growth deviations in low-risk pregnancies? (chapters 7 to 9)

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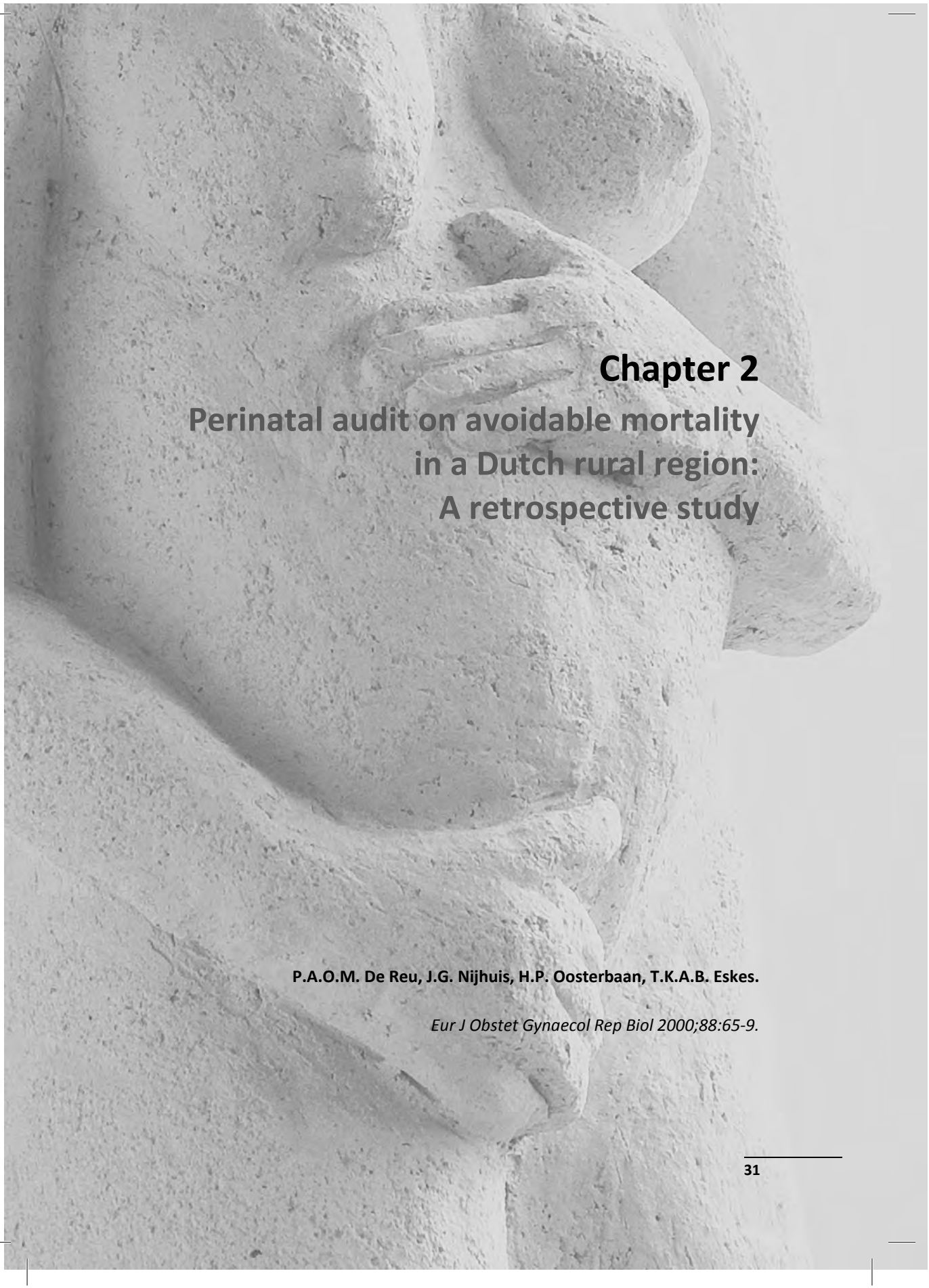
Part I
Auditing Perinatal Mortality



Chapter 2

Perinatal audit on avoidable mortality in a Dutch rural region: A retrospective study

P.A.O.M. De Reu, J.G. Nijhuis, H.P. Oosterbaan, T.K.A.B. Eskes.

Eur J Obstet Gynaecol Rep Biol 2000;88:65-9.

Abstract

Objective: To analyze the mode and cause of perinatal mortality.
Setting: a Rural Dutch region.
Study design: Over a two-years period (1994-1995), data were collected in the 's Hertogenbosch region. A perinatal audit group investigated and classified the cause of death in an "intention to treat" and consensus model. We then analyzed who was responsible for the patient at the moment perinatal death occurred, or became inevitable.
Results: Out of 8,509 newborns, 73 died between the 24th week of pregnancy till the 7th day post-partum (8.58 promille). Twenty-three cases (31.5%) were classified as probably or possibly avoidable. In the primary health care group (midwives, general practitioners) 6 out of 32 (18.75%), in the secondary care group (obstetricians) 15 out of 35 (44.86%) and in the tertiary care group 1 out of 4 (25.00%) were judged as probably or possibly avoidable. The degree of consensus in the perinatal audit committee was high (Kappa = 0.9).
Impact: The analysis of perinatal mortality identifies causes and may help to improve perinatal health care.
Conclusion: In this study 31.55% of perinatal mortality was avoidable in three levels of care. Intra uterine growth retardation, congenital malformations and ante partum hemorrhage were the most determinant factors for perinatal mortality. The Dutch obstetrical care system as such, e.g. home deliveries, did not effect the perinatal mortality rate. Perinatal mortality rates presented by the Dutch Central Bureau of Statistics still shows a slight underregistration.

Key-words: Avoidable Perinatal Mortality; Classification of perinatal death; Perinatal audit; Home delivery; Midwifery.

Introduction

In the Netherlands, pregnancy and delivery are considered physiological events that require medical intervention only when the patient is either at increased risk of complications during pregnancy or delivery, or if a complication occurs.

Based on this principle, in 1993, midwives and general practitioners (GP's) provided prenatal care in more than 50 % of all pregnant women and conducted all home deliveries (32% of all women delivered at home). Almost 40% of all deliveries were attended by midwives, nearly 10% by general practitioners and over 50% by obstetricians [1].

Increasing attention from various parts of the western world is focused on this system as this large number of home deliveries (±60,000/year) is accompanied by a very low rate of obstetrical interventions, while over-all perinatal mortality is below 10‰ (e.g. 8.6 ‰ in 1994 and 7.6 ‰ in 1995 (Source: Dutch Central Bureau of Statistics)).

Nevertheless, the safety of this system is often discussed by obstetricians and midwives in the Netherlands and abroad [2]. Some authors suggest that this very system of home deliveries might be responsible for the less rapid decrease in perinatal mortality as compared to neighboring countries [3].

In the present study we analyzed all cases of perinatal mortality in the 's Hertogenbosch region over a two-years period with respect to the degree of avoidability. We also examined if and to what extent typical aspects of the Dutch obstetrical care system can be held responsible for this mortality, and if measures could be taken to obtain a further reduction of perinatal mortality in the Netherlands.

Methods and material

The obstetric data of all children from mothers of the ´s-Hertogenbosch region, born between 01-01-1994 and 31-12-1995, were retrospectively collected and stored in a DBASE-IV file. For this purpose all midwives and GP's were asked to supply data of their full obstetric population over this period. They were classified by level of care and by place of birth. In addition, data of all hospital deliveries within the region were collected. Similar data were obtained from mothers and children referred to general hospitals and tertiary centers outside the study region. Likewise, 350 children from outside this region, referred to the ‘s Hertogenbosch hospitals were excluded from the study. Inclusion was based upon the postal-codes of the home-addresses of the mothers. All participants were also requested to supply the data of all children of at least 24 weeks of gestation that were stillborn or died within the first postnatal week (perinatal mortality).

The rate of several obstetric interventions of all deliveries was calculated.

All cases of perinatal mortality were classified on the basis of the Aberdeen Clinico-pathological Classification [4]. For each classification group, we also tried to identify the underlying cause of death (Table – I).

Table I: Modified Aberdeen clinico-pathological classification of causes of perinatal death.

Cause of death	Underlying cause
1 - Congenital malformations	1.1. Chromosomal defects
	1.2. Neural tube defects
	1.3. Cor vitium
	1.4. Other non chromosomal defects
2 - Ante partum hemorrhage	2.1. Placental abruption
	2.2. Placenta praevia
	2.3. Others / unknown
3 - Hypertension	3.1. Pre-exist. Hypertension
	3.2. Pregnancy-induced hypertension
	3.3. HELLP-syndrome
	3.4. Pre-eclampsia
4 - Asphyxia	4.1. During pregnancy
	4.2. During labor
	4.3. Neonatal
	4.4. Others
5 - Preterm birth	5.1. P.P.R.O.M.
	5.2. Infection
	5.3. Multiplets
	5.4. Others
	5.5. Unknown
6 - Other known causes	6.1. Infection
	6.2. Iso-immunisation
	6.3. Maternal disease
	6.4. Umbilical cord complication
	6.5. Birth trauma
	6.6. Others
7 - Unknown cause	7.1. Insufficient data
	7.2. Insufficient diagnostics
	7.3. Despite all possible diagnostics

A perinatal audit group, consisting of a midwife, a GP actively engaged in obstetrics, a consultant obstetrician, a neonatologist and a pathologist was asked to assess all cases of perinatal mortality and classify them according to the following subdivision: 'definitely avoidable', 'probably avoidable', 'possibly avoidable', 'definitely not avoidable' or 'undetermined'.

Before assessment, all cases of perinatal mortality were processed into anonymous reports.

Following earlier research [5] the assessments were made individually and exclusively with regard to the expertise of each committee member (e.g. the pathologist only assessed cases in which an autopsy and/or histological examination of the placenta was performed).

During a plenary session of the perinatal audit group, the various opinions and points of view of the individual members were discussed. On the basis hereof, a number of assessments was adjusted. After evaluation of each case it was established whether 'consensus', 'consensus-1' or 'no consensus' had been reached.

The coefficient of agreement between the assessments on avoidability of perinatal mortality of the different members was calculated according to Cohen's Kappa [6].

In each case we determined the moment that perinatal death occurred or became inevitable - in this study referred to as the "fatal moment" - and which caregiver was responsible for the patient at that time.

Birth weight of all cases of perinatal mortality was compared with the Dutch growth centiles according to Kloosterman [7].

In order to check the data on completeness, the Dutch Central Bureau of Statistics (C.B.S.) was requested to supply the perinatal mortality rates of the above mentioned population over the same period [8].

Results

With the exception of the GP's (estimated number of deliveries: <50) and two neighbouring hospitals (estimated number of deliveries: ≤ 120) that were unable to classify the deliveries by postal-code, all care givers supplied the requested data.

Data of 8,509 children (8408 deliveries) were collected: 8,310 singletons, 95 twins and 3 triplets. The perinatal mortality rate was 8.58‰ (n = 73): 25 girls (15 primiparous and 10 multiparous), 46 boys (29 primiparous, 16 multiparous and in 1 case parity was unknown) and two children of unknown gender (1 first and 1 multip). Three children had a birth weight < 500 grams. Over the same period the C.B.S. registered 69 cases (> 499 grams) of perinatal mortality. If perinatal mortality was calculated from the 28th week of pregnancy, PNM-rate was 5.77‰ (n = 49).

Initially 5,994 (70.44%) women attended primary health care workers. Of these, 5,982 were seen in an independent midwifery practice and 12 had their intake in a GP-practice. Of this group 57.4% delivered in primary care: 2496 (41.7%) at home and 938 (15.7%) in a hospital. A total of 2,548 women was referred to a secondary or tertiary hospital during pregnancy or labor.

Birth was spontaneous in 6,964 (81.8%) of all deliveries. In 629 (7.4%) women a ventouse extraction and in 201 cases (2.4%) a forcipal extraction was performed, while 709 (8.3%) were delivered by caesarean section (CS).

Classification by causes of death according the modified Aberdeen Clinicopathological Classification:

Thirteen children (17.81%) died of congenital defects. Two of them had chromosomal anomalies, 2 had anencefalus, 1 Dandy Walker malformation, 4 cases had a cardiac malformation and the remaining 4 cases were classified as "other non chromosomal malformations".

In 10 cases (13.70%) perinatal death was attributed to ante partum haemorrhage (APH), 8 of which due to placental abruption.

In 6 cases (8.22%) perinatal death was the result of hypertensive complications in pregnancy: one case with HELLP syndrome and 5 cases with pre-eclampsia.

Perinatal death was the result of asphyxia in 8 cases (10.96%): in 7 of these cases also an Intra Uterine Growth Retardation (IUGR) was found, there was one case of neonatal asphyxia.

Seventeen children (23.29%) died from the consequences of premature birth. In 9 cases premature birth was preceded by preterm premature rupture of membranes (PPROM). In 5 of these cases a vaginal infection was established: in 2 cases a group ß-haemolytic streptococ was cultured, while in the other 3 cases a Gardnerella, a Candida albicans and Escheria coli was found. Two children died after accidental rupture of membranes during a cerclage procedure. Two children died as a result of twin-to-twin transfusion. In one case (without PPROM) premature delivery was possibly caused by a ß-haemolytic streptococ infection. In 5 cases, no explanation for the premature birth could be established.

Eleven cases (15.07%) with 'other known causes' were identified: 5 children died as a result of an umbilical cord complication, one child died as the result of an infection (acute chorio-amnionitis), one case was diagnosed as post maturity in pregnancy diabetes. In 2 cases the underlying cause was a maternal disease: in one case this involved a necrotizing fibroid and in one case a maternal placental floor infarction [9]. In one case a possible viral infection in combination with low socio-economic patterns of the mother were involved and finally in one case a triplet pregnancy was complicated by a "Twin Reversed Arterial Perfusion (= TRAP)-sequence" [10] between one child and an acardiac fetus with a length of 6 cm. In 8 cases (10.96%) the cause of death remained unknown: in 5 of these cases insufficient data were available (in most cases absence of an autopsy who was refused by the parents). In 3 cases the cause of death remained unknown despite extensive investigations:

Classification in terms of avoidability of mortality:

With regard to avoidability of mortality, consensus was reached for 65 cases. In 6 cases consensus-1 was reached, and these cases were classified according to the majority of the assessors. In two cases no consensus was reached. No case was classified as 'definitely avoidable'. Five cases (= 6.84%) were assessed as 'probably

avoidable', 18 cases (= 24.65%) as 'possibly avoidable', 41 cases (= 56.16%) as 'definitely not avoidable' and 7 cases (= 9.58%) as 'undetermined'.

After the consensus meeting the degree of agreement in assessments among the different members of the committee was calculated and resulted in an average Kappa Value (κv) of .90.

Fatal moment

Primary care contained 32 cases, 5 of which were possibly avoidable and 1 probably avoidable (18.75%). The secondary group contained 35 cases, 11 of which were possibly avoidable and 4 of which probably avoidable (44.86%) and the tertiary care group contained 4 cases, one of which was possibly avoidable (25.0% of avoidability).

In one case no prenatal care had taken place and in another (classified as possibly avoidable) the client has acted against the advice of the health care official.

Birth weight

The birthweight of 38.4% (n = 28) of the children was $\leq$ 10th centile and in 23.3% (n = 17) birthweight was ≤ 2.3th centile according to the Dutch growth scales [7].

In the group probably or possibly avoidable, these percentages were even higher (47.8% (n = 11) and 30.4% (n = 7), respectively).

Discussion

In the present study, a perinatal audit is presented on 73 cases (8.58‰) of perinatal mortality in 8,509 births.

Perinatal mortality is classically underreported. The Dutch CBS reported 69 cases and 4 (5%) were missing. As was earlier reported this underregistration is mostly due to an under reportation by the physicians involved [11]. However, this percentage seems to improve over the years as compared to earlier reports where 31.0% [12] and later 14.3% of missing values were reported.

Nearly 18% of the mortality was caused by serious congenital defects. With the exception of one child that died as a result of the complications of cardiac surgery all these cases were classified as 'definitely not avoidable'.

Obviously, a number of these defects could have been diagnosed prior to the viable stage. Our findings are in line with data in the literature: in 1982, Davies [13] reported 12.4% in a series of 105 cases in Mexico. In Curacao, Wildschut [14] found 28 cases in a series of 223 cases (= 12.55%) while Duley [15] presented a series of 590 cases with 96 cases (= 16.27%) of congenital defects. Combier [16], Bekaert [17] and Gulbransen [18] however, even established rates of 21, 30 and 31% respectively. In view of the two cases of anencephaly, the mortality rate in our group of

congenital anomalies might have been lowered if prophylactic measures like preconceptional suppletion of folic acid [19] had been taken.

Although as yet no clear benefit in terms of perinatal mortality until yet can be discerned to result from the use of ultrasound [20, 21], one could speculate that routine application of echoscopic examination at the end of the first trimester of pregnancy might likewise have effected in a substantial reduction of this category.
In this respect the introduction of preconceptional consultation and counseling, especially in the case of nulliparae, might be important.

The highest rate of avoidable mortality but one was found in the APH-group*:* 5 out of 10 cases (50%). In one case death could be attributed to the patient herself (refused adequate care), while in one case the primary health care-giver and in three cases hospital care workers gave substandard care. With the exception of one case in which the avoidability was contributed to the delayed arrival of the anesthesiologist at the operation theatre, in all other cases of possibly/probably avoidable mortality in the APH-group, growth retardation was also observed: 7 cases (70%) had a birth weight ≤ P-10. Also in this group, preconceptional suppletion of folic acid might have had an effect in the reduction of perinatal mortality [22]. The mortality rate of this group might also have been reduced if the IUGR and the possible placental insufficiency, had been diagnosed earlier (earlier transfer to second care-level and/or more sufficient monitoring and/or more accurate therapy in case of suboptimal fetal condition). In the hypertension-group, for 2 out of 6 children (33,3%) perinatal mortality was avoidable. In this group 5 out of 6 (83,3%) had a birth weight ≤ P-10.

The highest rate of avoidable perinatal deaths was observed in the cases classified under asphyxia: 5 out of 8 cases (62.5%) while 7 of them had a birth weight ≤ P-10. Avoidability in this group was demonstrated 4 times in secondary health care level and 1 time in primary health care level. More accurate intervention in this group, especially in cases with IUGR, might reduce perinatal mortality.
Nearly a quarter of the cases of mortality was caused by premature birth, often (7 times = 41%) preceded by PPROM In this group, 5 out of 17 cases (29.4%) were classified as probably or possibly avoidable.

In 35.3% of the whole group (6 out of 17) an infection might be responsible for the premature birth. The possible effect of an antenatal screening procedure on, and/or therapeutic measures against, vaginal infections of all pregnant women at the beginning of the second half of the pregnancy still needs to be evaluated [23]. In this group SGA was not relevant (2 out of 17 ≤ P-10).

In nearly one-third of the total group, mortality was possibly or probably avoidable (23 cases out of 73). The conclusion that one in three children might not have died if optimal care had been provided at least suggests that perinatal mortality can still be lowered in our region to approximately 25%. Of all cases, primary health care was involved in 6 cases (= 26.09%). Eskes [24] found a lower percentage of 22.53%

of avoidable mortality, while the Wormerveer survey [25] demonstrated avoidability 21 out of 53 cases (= 39.62%). In a more recent publication Coria-Soto [26] found an average avoidable mortality rate of 44.47% in Mexico.

The obstetric intervention rates in the Netherlands and in our region are extremely low compared to nearly all other industrial countries. The low percentage of interventions in Holland can be seen as a side effect of an obstetrical system with home deliveries. One could ask if this attitude also has to be held responsible for a number of cases of perinatal death. However, this does not seem to be the case. A comparison with the Flanders (Belgium) perinatal survey (comparable in socio-economic status, urbanization, infrastructure and health care facilities, but no home-deliveries) over the same period [17] shows no significant difference in perinatal mortality despite an almost doubled intervention rate (table – II).

Table II: Comparison of intervention data and perinatal mortality rate between study group and Flanders

	Ventouse	**Forceps**	**CS**	**PNM**	
				N	**o/oo**
Study group	7.4 %	2.4 %	8.3 %		
> 500 gr.				70	8.23
> 1000 gr.				42	4.94
Flanders	12.4 %	1.5 %	14.0 %		
> 500 gr.				975	7.66
> 1000 gr.				672	5.28

In conclusion

A consensus committee is capable to analyze and classify cases of perinatal mortality retrospectively with a high degree of accuracy and consensus (κv 0.9). In this study 23 out of 73 cases (31.5%) were classified as probably or possibly preventable. Avoidability varied between the various obstetrical care-givers, but our data are to limited to allow any firm conclusions in this respect. Mode and cause of death could mostly be identified and classified. This might lead to preventive measures. Special attention to fetal growth e.g. ultrasound observation in the early thirth trimester of pregnancy, and in time referral to hospital care followed by adequate intervention to referred cases might lead to a further reduction of perinatal death in the Netherlands.

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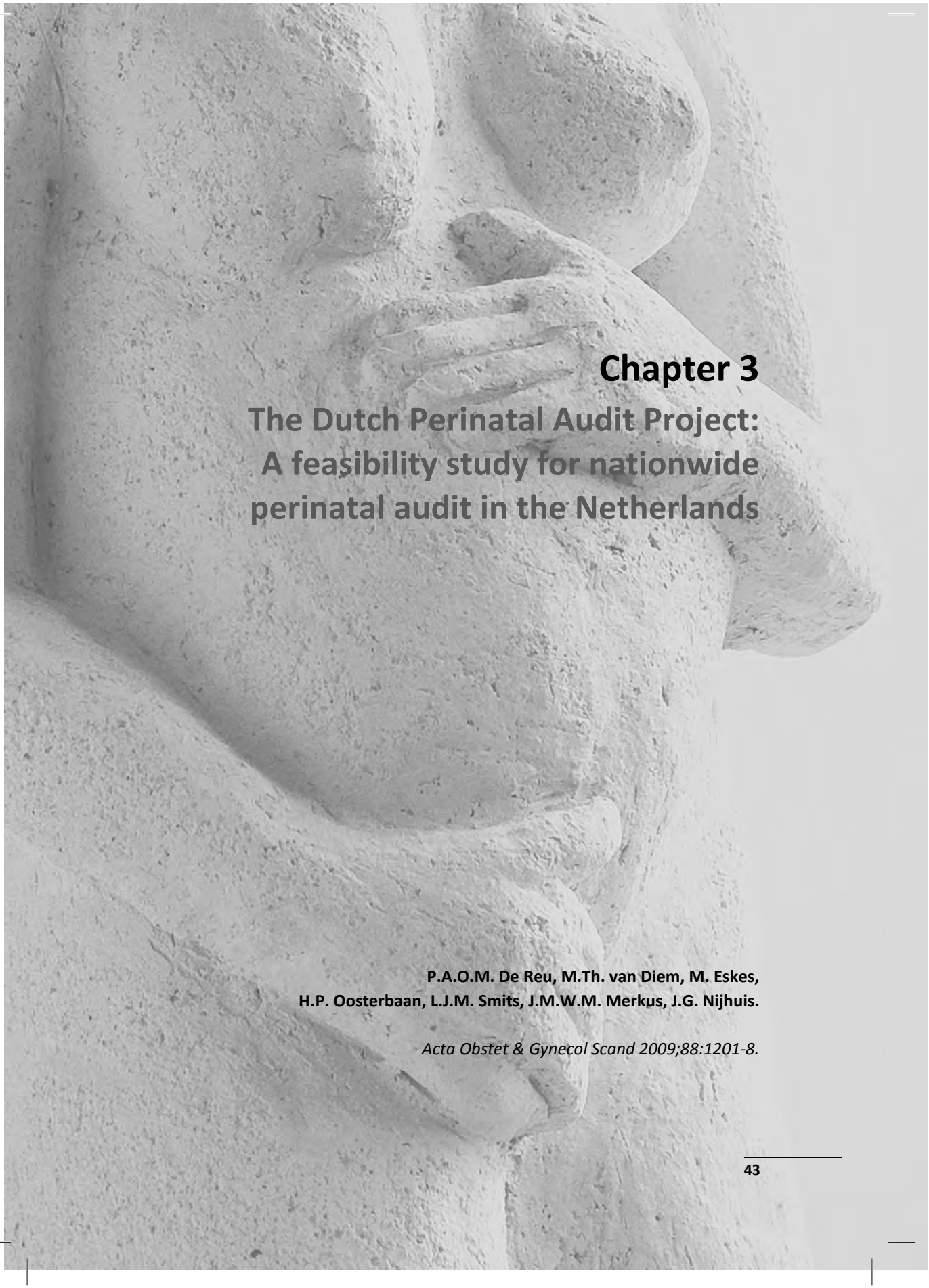

Chapter 3

The Dutch Perinatal Audit Project: A feasibility study for nationwide perinatal audit in the Netherlands

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Abstract

Objective: Investigate feasibility for nationwide perinatal mortality audits in the Netherlands.
Study design: Over a one-year period, data of all cases of perinatal mortality were collected. Six perinatal audit panels of professionals within perinatal care investigated and classified causes of death, and identified the presence of substandard factors (SSF).
Results: Out of 22,189 newborns, 228 cases of perinatal mortality were audited. Placental pathology, congenital anomalies and preterm birth were the main causes of perinatal death. SSF by caregivers were identified in 72 cases (32 %). Almost 20% of the cases were not reported.
Conclusions: In the Netherlands perinatal audit is well supported by all groups of caregivers. It reveals usable facts and findings in quality assessment in perinatal care. This audit showed that in 9% of the cases perinatal death was related to SSF and potentially avoidable. However, immediate reporting of cases of perinatal death apart from regular registration in the perinatal database proved to be inaccurate. Once a nationwide audit-program is realized, in which data from the different caregivers will be collected in a single database instead by collection by linkage afterwards, this problem should be solved.
Local audits will start from 2009. This audits will assess mortality cases within their respective areas and may initiate adjustments for perinatal care and optimize quality of care and inter-professional collaboration. Yearly nationwide audits will focus on specific items (e.g. post-term deliveries) and may well offer an opportunity for development or adjustment of national guidelines.

Key-words: Feasibility study, perinatal audit, perinatal mortality, substandard care.

Introduction

During the first half of the previous century, it was assumed that the Netherlands had the lowest perinatal mortality rates in the western world [1]. However, between 1970 and 1984 perinatal mortality in the Netherlands decreased less rapidly compared to other western countries [2]. In 1999 and 2004 perinatal mortality in the Netherlands was even one of the highest in 25 states of the European Union [3, 4]. Compared with many other European countries, during the last decades, the Dutch reproductive population showed some important changes such as an increasing number of women with advanced maternal age, high percentage non-western women, multiple pregnancies and mothers with unhealthy lifestyle [5]. However, these risk-factors can only explain the high Dutch perinatal mortality in part. The quality of care may also play a role [6].

As stated in 1993 by the Workshop of the European Association of Perinatal Medicine, perinatal audit is considered to be an important instrument to improve the quality of care [7]. Such audits have been routinely performed in Norway since 1986 and in the United Kingdom since 1992. The audits in the United Kingdom have been known as CESDI (Confidential Enquiry into Stillbirths and Death in Infancy) and since 2003 as CEMACH (Confidential Enquiry into Maternal and Child Health). The conclusions of the Norwegian audits led to appropriate educational trainings for professionals in perinatal medicine and better interdisciplinary communication and cooperation [8]. As a consequence, perinatal mortality decreased from 13.8‰ in 1976-1980 to 7.7‰ in 1992-1997. Especially perinatal mortality in cases with intrauterine growth restriction (IUGR), congenital anomalies, infections and placental pathology decreased significantly [9]. Therefore, the implementation of perinatal audits was recognized as an important tool for the improvement of perinatal care in Norway [10].

In the past a number of regional perinatal audit studies have been performed in the Netherlands [11, 12, 13]. Before starting a national program, professional organizations in perinatal care performed a feasibility study for perinatal audit with the involvement of representatives of all professional caregivers in perinatology [14]. The study was called LPAS (Landelijke Perinatale Audit Studie = National Perinatal Audit Study) and was funded by the Health Care Insurance Board (CvZ). The aim of this study was to investigate the feasibility of a perinatal audit on a nationwide scale executed by professionals in the perinatal field. Consequently our study was focused specifically on the feasibility, reliability and completeness of data.

Material and methods

In three different regions in the Netherlands – Amsterdam and suburbs, the central region of the province of Noord-Brabant and the Zuid-Limburg region – all cases of perinatal mortality were collected by caregivers during a one year period (2003-2004). The study was approved by the medical-ethical committees of all hospitals involved.

These regions comprise large and smaller cities, mixed ethnic populations, villages and rural areas and have all levels of medical care facilities. The regions covered approximately 12% of the Dutch population. Perinatal death was defined according to the WHO-definition: all cases of stillbirth or neonatal death from 22 completed weeks of pregnancy (154 days) onwards, or birth-weight ≥ 500 grams (if gestational age was not known) or crown-heel length ≥ 25 cm (if birth weight was also unknown), up to and including the 28th day after birth [15].

Perinatal care in the Netherlands is based upon a three level care-system in which midwives and general practitioners (GP's) provide primary-care for the low risk cases, while secondary and tertiary perinatal care is provided by obstetricians and neonatologists in general or tertiary-care hospitals [16, 17].

All professionals involved in perinatal care reported all cases of perinatal death, encountered in their practices, using a case report form. If necessary, they were asked to give additional information. Finally, anonymous structured narratives and case documents were composed for assessment by the members of the audit groups. Six audit groups, all consisting of a primary care (community) midwife, a secondary care midwife, a GP, a secondary and a tertiary care obstetrician, a secondary and a tertiary care pediatrician/neonatologist and a perinatal pathologist were formed. Each audit group was headed by an independent chairperson. The audit groups classified the cause of death, using three different classifications: the *Modified Aberdeen* classification [18], the *Extended Wigglesworth* classification [19] and the *Fundamental Tulip* classification [20]. The Modified Aberdeen classification as well as the Extended Wigglesworth classification are hierarchical classification models, composed to reveal the obstetrical and/or neonatal causes of perinatal death and are generally used in international comparisons. The Fundamental Tulip Classification was developed in the Netherlands to give more insight in the pathophysiological process leading to death and is therefore more suitable [21]. In addition the audit groups identified the presence of substandard care factors (SSF) at three different levels: the professional, the organization of care and the patient.

SSF on caregiver's level tells us in what way the perinatal care provided was below current standards. In the Netherlands, standard care is defined in the '*Verloskundig Vademecum*' (Obstetric Manual, http://www.cvz.nl/resources/verloskundig-vademecum_2003_tcm28-18807.pdf) and in guidelines for perinatal care, developed by the professional organizations of midwives, obstetricians (http://-

www.nvog.nl/professionals/richtlijnen/perinatologie) and pediatricians (http://-www.nvk.pedianet.nl/index.htm/richtlijnen). In absence of appropriate guidelines, *best practice* (expert opinion or generally accepted practice as used by the majority of professionals) was considered as standard care.

In addition the relation between the SSF and the cause of perinatal death was assessed according to the following subdivisions: unlikely, possible, probable or very probable. As most members of the audit groups were participating in such an audit for the first time, a short training program, consisting of a plenary discussion on seven cases, was introduced. This training specifically focused on the classification of death causes, the identification of SSF and the ability to discriminate levels of relation between SSF and perinatal death.

Table 1: Main characteristics in PRN for 2003 and 2004 versus LPAS study population.

Main characteristics	Netherlands 2003/2004		LPAS regions (*)	
	N	(%)	N	(%)
Primiparous	173,215	(46.2)	11,334	(51.1)
Multiparous	201,119	(53.7)	10,830	(48.8)
Parity unknown	361	(0.1)	25	(0.1)
Singletons	359,523	(95.9)	21,257	(95.8)
Multiplets	15,172	(4.1)	932	(4.2)
Boys	192,512	(51.4)	11,334	(51.1)
Girls	181,822	(48.5)	10,830	(48.8)
Gender unknown	361	(0.1)	25	(0.1)
Pre-term (< 37 wks)	59,120	(15.8)	4,342	(19.6)
Post-term (> 42 wks)	39,494	(10.5)	2,586	(11.7)
LBW (< 2500 gr)	53,318	(14.2)	3,628	(16.4)
NBW (2500-4500 gr)	300,218	(80.1)	17,624	(79.4)
HBW (>4500 gr)	20,928	(5.6)	930	(4.2)
Birth weight unknown	231	(0.06)	7	(0.03)
Perinatal deaths	4,033	(1.076)	239	(1.077)
Total	374,695	(100)	22,189	(100)

Source: Netherlands Perinatal Registry and LPAS-study

PRN = Netherlands Perinatal Registry; LPAS = National Perinatal Audit Study; LBW = low birth weight; NBW = normal birth weight; HBW = heavy birth weight.

* Amsterdam and suburbs, the central region of the province of Noord-Brabant and the region Zuid-Limburg

Consensus was considered to be reached if at least 75% of the assessors agreed. In order to judge if the pilot regions were representative, we collected appropriate data from the national Dutch perinatal database (Netherlands Perinatal Registry (PRN)) for the period of the study. This database is composed of three linked registries (midwifery, obstetrics and neonatology/pediatrics registry) and covers ± 94% of all deliveries in the Netherlands (www.perinatreg.nl).

At the end of the perinatal audit meetings, each individual member of the audit groups was requested to complete an evaluation form with a personal assessment about the procedures followed.

Finally, at the end of the whole process, hospital and individual administration of the care-givers involved, were checked meticulously by two members of the LPAS secretariat in order to identify possible missing cases of perinatal mortality.

Results

Deliveries of 22,189 children were registered in the PRN-database during the study period in the three study regions : 21,257 singletons (95.8%) and 932 twin children (4.2%). Main characteristics of the perinatal data in PRN and those of the LPAS-study population are shown in table 1.

Caregivers reported 239 cases of perinatal death (PNM rate = 10.8 per 1,000) of which 147 were cases of fetal death (61.5%) and 92 neonatal deaths (38.5%). In four cases, the information was inadequate for analysis. The seven cases used for initial training of the audit groups were excluded for the final analysis. Consequently 228 cases were left for audit. Fifty nine more cases of perinatal death were found afterwards by an additional search in the hospital administration and in primary care practices. This means that almost 20% were not reported (table 2).

Table 2: Perinatal mortality in different regions by LPAS and PRN.

	Total births	LPAS		PRN	
		Perinat.deaths	PNMR (‰)	Perinat.deaths	PNMR (‰)
Amsterdam	10,394	105	(10.1)	119	(11.6)
Noord Brabant	7,851	82	(10.4)	106	(13.5)
Zuid Limburg	3,944	52	(13.2)	52	(13.2)
Total	22,189	239	(10.8)	277	(12.5)
Missing		59 = 19.8%		21 = 7.1%	

Source: LPAS-study and Netherlands Perinatal Registry (PRN)
PNMR = Perinatal Mortality Rate.

An overview of assessment of causes of death in the different classification systems is shown in table 3. Using the *The Modified Aberdeen Classification*, the *Extended Wigglesworth Classification* and the *Fundamental Tulip Classification* the perinatal audit groups reached consensus in 94%, 93% and in 97% of the cases respectively. Most cases of perinatal mortality were related to placental pathology (37%), congenital anomalies (22%) and preterm birth (15%).

Table 3: Assessments of cause of death by different classifications.

Classification model: →	Aberdeen		Wigglesworth		Tulip	
Cause of death ↓	n	(%)	N	(%)	n	(%)
Congenital anomalies	45	(19.7)	47	(20.6)	49	(21.5)
Iso-immunisation	0	-				
Pre-eclampsia	10	(4.4)				
Antepartum hemorrhage	20	(8.8)				
Mechanical (*)	17	(7.5)				
Maternal disorder	19	(8.3)				
Infection			14	(6.1)	12	(5.3)
Immaturity / prematurity			25	(11.0)	33	(14.5)
Intrapartum asfyxia, anoxia, trauma			25	(11.0)		
Placental pathology / umbilical cord complications					84	(36.8)
Accident or non intra-partum trauma			1	(0.4)		
Miscellaneous / other specific causes	14	(6.1)	10	(4.4)	12	(5.3)
Unexplained antepartum fetal death			79	(34.6)		
Unexplained	86	(37.7)	1	(0.4)	32	(14.0)
Unclassifiable	3	(1.3)	9	(3.9)		
No concensus	14	(6.2)	17	(7.5)	6	(2.6)
Total	228	(100)	228	(100)	228	(100)

Source: LPAS-study

* e.g. death from uterine rupture, birth trauma or intrapartum asphyxia associated with problems as disproportion or breach deliveries.

A total of 139 SSF was identified over the three different levels defined (table 4): 109 cases with one, and 15 cases with two SSF. In 65 of the total of 72 cases in which SSF were found at the caregivers level (in 10 cases, two SSF were found), consensus could be reached on the relation between SSF and perinatal death. In 22 cases (34%) the relation was assessed to be unlikely, in 23 cases (35%) as possibly, in 15 cases (23%) as probably and in five cases (8%) as very probably.

In cases of SSF by the patients (n=46), the items that occurred most frequently were tobacco abuse, obesity (body mass index (BMI) ≥ 30) and consanguinity. In the organization of care (n=11), assessors repeatedly found inadequate or unclear arrangements between patients and care-givers e.g. in cases of decreased fetal movements, minor blood loss and preterm contractions.

Table 4: SSF by level of care.

Number of cases in which consensus was reached according level of care		One SSF found		Two SSF found	
		Cases	(%)	Cases	(%)
Caregiver	158 cases	62	(39.2)	10	(6.3)
Organization	208 cases	11	(5.3)	0	-
Patient	173 cases	36	(20.8)	5	(2.9)

Source: LPAS-study.
SSF = Substandard factors

Transfer from secondary to tertiary care level was not performed although in at least three cases transfer was indicated according to the national guidelines. No transport- or capacity-problems in obstetric as well as in neonatology units leading to an unfavorable perinatal outcome or to perinatal death were reported. Special attention was given to the cases (n=20) where the relation between SSF (n=21) and perinatal death was (very) probable. We categorized SSF in these cases into four major groups: 1- the risk-problem was not recognized, insufficiently recognized or too late (n=10), 2- the risk-problem was recognized but not reacted or too late or managed adequately (n=7), 3- the management was not in line with current protocols (n=3) and 4- other (n=1) (table 5). In five of these cases (25%), the underlying cause for SSF was probably related to late evening and/or night shifts. Finally, although 41% of all cases of perinatal death occurred in children of non-Dutch mothers, we noticed that 18 of the SSF-cases (90%) occurred in Dutch mothers while in one case ethnicity was not known.

Based upon the results of the evaluation forms distributed at the end of the audit meetings, the members of the audit groups considered the audit performed, although time consuming, highly instructive and essential for the detection of week points in all levels of care, that need improvement in order to decrease situations leading to perinatal mortality.

Although discharge letters, especially from obstetricians, were often incomplete, the overall composition of the case documents was assessed to be useful and highly workable. Moreover, the multidisciplinary composition of the audit groups proved to be ideal for solid foundations in assessments.

However, in view of the workload, time investment and financial input, a yearly nationwide audit on all cases of perinatal death was not considered feasible.

Table 5: Classification of SSF.

Class	Subclass		Examples	SSF
1 -Risk problem is not recognized as such	1a- No or inadequate diagnosis in cases of increasing risk.		- no US in case of BMI ≥ 30 - decreasing fetal condition not recognized during delivery (CTG) - no action in spite of pre-eclampsia. - severe deceleration during 3 minutes, nevertheless send home until next day.	N=4
	1b- Unnecessary delay in diagnostic actions		- suspicion of IUGR – referral postponed - no action in case of IUGR (32 wks).	N=2
	1c- Insufficient action in diagnostic research.		- no action in case of PROM and not engaged head - confirmation of IUGR – inadeq. action - diastolic pressure 105 mm – no action - no further diagnostic actions in spite of decreasing fetal condition (CTG only).	N=4
2 -Risk problem is recognized but not adequately treated	2a- Unnecessary delay in therapeutic actions		- 7 hours postponed action in primary care in case of preterm labor (33wk) - 3½ hours delay for CS (Saturday) - neonatal infection - start antibiotic therapy 24 hrs postponed - delay of 40 minutes in case of decreasing fetal condition (CTG) of 2nd twin	N=4
	2b- Insufficient therapy.	No therapy provided	- no active treatment in spite of preterm labor	N=1
		Wrong therapy provided	- wrong choice of assisted delivery	N=1
		Not adequately provided	- false route intubation (intubation performed by anesthesiologist in absence of pediatrician)	N=1
3 - Conduct	Not in line with current protocols or generally accepted 'best practice'		- referral from obstetrician to midwife at 42+1 wks of gestation. - care provided by GP in case of history of repeated (3x) severe IUGR - high risk patient sent home by mistake (resident) – no further actions afterwards.	N=3
4 -Other:			- overstimulation ovulation induction resulting in quadruplet followed by fetocide of 2 embryo's at 13+2 wks.	N=1

SSF = Substandard factor

Discussion

This study aimed to investigate feasibility of a nationwide perinatal audit. It reveals a number of important items regarding perinatal mortality. As shown in table 1 the chosen sample was representative for the Netherlands. Only a difference in preterm born babies between the data of the Netherlands and those of LPAS (15.8 vs. 19.6%) was found.

All data used in this article were extracted from two databases (i.e. the PRN and the database of the LPAS) which gives a high reliability for this study. The latter was composed by all caregivers involved in perinatal care, all of whom were highly motivated. Nevertheless under-registration of 7.1% and 19.8% were found in the PRN and LPAS databases respectively . This is remarkably higher than in studies that were carried out previously in our country [12, 22-24]. Consequently, the most probable perinatal mortality rate in this population is 298/22,189 = 13.4‰. This observation may lead to the assumption that under-registration in perinatal mortality was probably underestimated in the past and true perinatal mortality rates are even higher than officially published. However, for years, under-registration has proven to be an international problem: especially stillborns and children < 500 grams are often not reported [9, 25-27].

Even in a well-motivated group, immediate reporting of every case of perinatal death apart from regular registration in the perinatal database appeared to be inaccurate. The under-reported perinatal mortality cases in the LPAS study are difficult to explain and they were found at the primary, secondary and tertiary care-levels. Differences found between the LPAS and PRN-data are show in table 2. There was a considerable difference (30.5%) in mortality rate between the three regions (range 10.10 – 13.18). In the Amsterdam and Noord-Brabant regions 14 and 24 cases respectively of perinatal death were not reported. Only in Zuid-Limburg, reports of perinatal mortality showed no difference between the two databases used (52 cases in both LPAS and PRN-records).

Differences in Noord-Brabant (24 cases) may be due to the fact that in that particular region there is no third level hospital, and for that reason a considerable number of high risk pregnancies had to be transferred to a hospital out of the study-region. In those cases, PRN-data may be more reliable as this databank covers the whole nation. Babies, born outside the region are included here, as registration is based upon the postal code of the residence of the mother at the time of delivery. For the missing cases of the Amsterdam group we could not find a plausible reason. Nevertheless one has to be aware that this databank still does not cover the whole Dutch perinatal field as 40% of the pediatricians working in general hospitals and all GP's (responsible for ± 5% of all births) do not participate in this registration (remark: all NICU's do participate).

Once a nationwide audit-program is realized in which data from the different caregivers will be collected in a single database instead of collection by linkage afterwards from three different databases, this problem should be solved.

The LPAS was especially designed to evaluate the development of an audit model for professionals in perinatal care. All participants considered the audit as an instructive exercise and were highly motivated to build out this evaluation model nationwide. With respect to the classification of cause of death, the investigation of the pathophysiological mechanisms and the origin of these mechanisms demands specialized know-how from a team of clinicians (midwives, GP's, obstetricians and neonatologists) as well as from trained perinatal pathologists and genetic specialists. Although the latter did not participate in the present study they may be of additional value in individual cases in future audits e.g. in the cases of children with multiple congenital malformations or dysmorphisms.

The assessment of SSF proved to be complicated. In most cases the presence of SSF by care givers was based upon existing national guidelines [16], while in the absence of appropriate guidelines the 'best practice'-rule was used. However, different assessors identified different (sometimes controversial) kinds of SSF in individual cases. This diversity in assessment demonstrates that the use of a classification model as we propose in this article might simplify the assessment for SSF in provided care for future audits (table 5).

Perinatal audit is a time consuming activity demanding specialized know-how from trained assessors. A training program for audit-assessors is mandatory and should be initiated to reach more uniform and comparable conclusions. Each case took approximately five hours of secretarial work to make it presentable for audit. In addition the composition of written reports (of the audit) took another three hours per case. For 1,800 cases in the Netherlands this exercise would take at least 12,000 hours each year. For this reason a yearly audit of all perinatal mortality cases nationwide will be far too expensive.

Although the LPAS project was conducted as a feasibility study on a limited sample, some of the findings were of special interest.

On the caregivers side we found that the majority of SSF are not the result of a failure in diagnosis or therapy. In half of all cases (probably / very probably related to perinatal death) a relation was found with a reticent attitude of professionals in all care-levels. Moreover, weekend, late evening and night shifts seem to have played a role in at least five cases while unclear arrangements and protocols between caregivers of different levels of care are often the initial factor in the chain of events leading to perinatal death.

For the assessment of SSF by patients and/or organization of care, clear definitions are often inexistent. In some cases, SSF and 'risk-factors' were confounded. For this reason we did not pay full attention on these two levels in this article. However, in nearly 20% of all cases assessed, SSF were found in the behavior of the

pregnant women themselves: smoking habits and obesity were assessed as the most common factors with a possible impact on perinatal death [28]. For that reason, more attention should be given to pre-conceptional counseling on life style habits.

Decreased fetal movements, minor vaginal blood loss and other alarm symptoms too often led to a catastrophic outcome as no (timely) contact was sought with the responsible caregiver, or by lack of good arrangements. For that reason, it is imperative that caregivers instruct their patients more adequately on how to handle in such situations. Although transfer- or capacity-problems in obstetric as well as in neonatology units were not reported, one cannot exclude that this might have played a role in three cases where, according to the Dutch guidelines (http://www.nvog.nl/professionals/richtlijnen /perinatologie), transfer was indicated. The reason why such a transfer was not performed was not mentioned in the LPAS reports. Lack of time or no adequate reaction on signs and symptoms of threatening preterm labor could be excluded as possible reason. In a recent Dutch study it was shown that 312 pregnant women in one year were transferred to a tertiary perinatal centre outside their own region since admission nearby was not possible. In seven cases even transfer abroad had to be organized [29]

As a result of this study the government has decided to start a nationwide perinatal audit starting this year. However, a nationwide perinatal audit on all cases of perinatal death on a yearly base is not yet feasible for both practical and financial reasons. Therefore, local audits will assess mortality cases inside their own area. Moreover such audits may initiate more easily and rapidly local adjustments on perinatal care protocols and optimize quality of care and inter-professional cooperation. These audits on smaller numbers of cases will probably suffer from lack of power to provide clinically significant conclusions. Audits focused on specific topics (e.g. all cases of perinatal death in term or post-term deliveries, growth restricted children) may offer an opportunity for a nationwide study and development of new guidelines of policy review.

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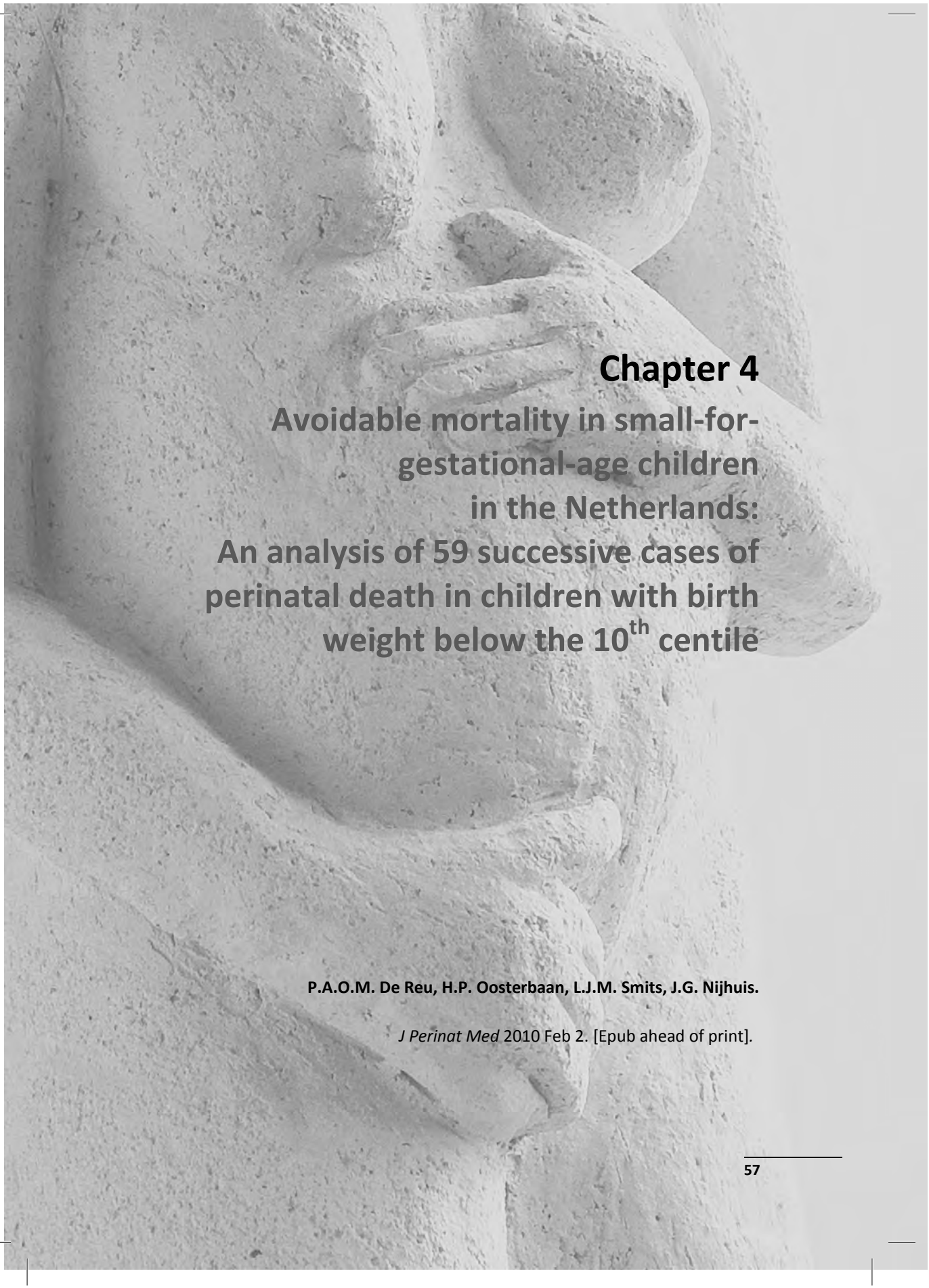

Chapter 4

Avoidable mortality in small-for-gestational-age children in the Netherlands: An analysis of 59 successive cases of perinatal death in children with birth weight below the 10th centile

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Abstract

Objective: To analyze avoidable perinatal mortality in small-for-gestational-age (SGA) children.

Methods: All SGA-children (≤10th percentile) among 22,189 newborns delivered after 25 weeks' gestation (175 days), from three regions of the Netherlands during 2003-2004 were evaluated. Cases of perinatal mortality were identified and assessed in a consensus model by perinatal audit groups for cause of death and the presence of substandard care factors (SSF). We analyzed all singleton SGA-cases with and without SSF for avoidable perinatal mortality.

Results: Out of 20,927 singletons, 2,396 newborns were SGA. Of those 59 died perinatally (2.46%) and 55 of which were assessed by perinatal audit groups. SSF by caregivers were found in 22 cases (40%). In 16 of these cases (29%) the relation to the perinatal death was considered possible or (very) probable. Of the cases without SSF by caregivers, 15 cases (25%) could possibly have been avoided: in 13 cases an avoidable condition and in two cases avoidable death were identified. Failure in the correct and timely diagnosis of fetal growth restriction appears to be an important issue in all cases of perinatal mortality in SGA-children. Before referral growth restriction was suspected only in 22% of all SGA cases during the third trimester of pregnancy.

Conclusions: More adequate action by caregivers could decrease perinatal mortality in nearly 1/3 among SGA-children. Adjustments in pregnancy monitoring, especially in low risk pregnancies, such as routine ultrasound biometry examination, may improve the accuracy in the detecting growth deviations and decreasing the number of possibly avoidable cases of perinatal mortality in this category.

Introduction

Low birth weight (LBW), small-for-gestational-age (SGA) and intrauterine growth restriction (IUGR) are terms often used to describe the same phenomenon: 'physiological or pathological growth of a fetus resulting in birth weight at or below the 10th centile of all newborns'. The expression 'LBW' is commonly used for newborn children weighing <2500 grams. However, gestational age (GA), gender and parity are not taken into account using this definition.

SGA relates birth weight to these variables and classifies birth weights below the 10th centile and in cases of 'severe SGA' birth weights below the 2.3rd centile. SGA can be the result of several causes, such as genetic inheritance, infections, congenital anomalies and placental insufficiency. When insufficient growth causes SGA, a diagnosis of IUGR is made. It is well known that both perinatal morbidity and mortality are significantly higher in SGA-children compared to children with birth weights appropriate-for-gestational-age (AGA). SGA-children may have more difficulties during the first day in adaptation to their extra-uterine life, they are at increased risk of stillbirth, hypoxia, and severe complications during the early and late neonatal period [7, 9, 28]. Disturbed intrauterine growth may also have a negative impact on health in adult life [3, 18, 21, 22, 25, 32].

In the Netherlands, perinatal mortality is remarkably high compared to the majority of the other countries of the European Union [5, 33]. The obstetrical care is organized in a three level care-system: community midwives and general practitioners (GP's) provide perinatal primary-care for the low risk cases and operate in an out-of-hospital setting whereas secondary and tertiary perinatal care is provided by obstetricians and neonatologists in general or university/third level hospitals respectively (obstetrical-chain-care) [4, 36]. Nearly 30% of all deliveries take place at home. Recently, it became evident that home deliveries are relatively safe as mortality and morbidity are equal to the low-risk "home-like" deliveries in hospital under supervision of a community midwife [20]. Consequently, the question arises if this system itself, more precisely our "obstetrical-chain-care" system, might be related to the relatively high perinatal mortality especially in cases of SGA.

Between April 2003 and May 2004, a National Perinatal Audit Study (LPAS) has been performed in the Netherlands in which all cases of perinatal mortality in three different Dutch regions (comprising ~ 12% of the total population) were collected. Causes of death, presence of substandard care factors (SSF) and possible relation of SSF to perinatal death were assessed by six audit panels consisting of a community midwife, a hospital midwife, a general practitioner, a gynaecologist, a neonatologist and a neonatal pathologist. For details, we refer to earlier published articles [12, 14, 15] and to the LPAS report as published in 2007 (www.cvz.nl/resources/-rpt0511_lpas_tcm28-17810.pdf).

In summary, out of 22,189 births in three different Dutch regions, 239 cases of perinatal death were reported. SSF appeared to be (very) probably responsible for at least 9% of the cases of perinatal mortality. Moreover, of 172 perinatal mortalities >25 completed weeks of pregnancy, birth weight was ≤ 10th percentile in 65 (38%).

In the present study we sub-analyzed all cases of perinatal mortality in singleton pregnancies with birth weight ≤ 10th percentile from the LPAS database to identify the cause in avoidable cases.

Patients and methods

In the LPAS database, we identified all cases with GA ≥ 25 weeks (175 days) and birth weight ≤ 10th percentile based upon the recently published new Dutch national birth weight reference charts [35]. Cases with GA of <25 weeks could not be assessed for birth weight characteristics since these charts only start at this GA-limit.

All SGA-children of singleton pregnancies in the regions investigated within the same period were recorded and served as controls. Of those, children with GA < 175 days or > 315 days (unlikely GA) were excluded from the study. For this purpose, data from the national Dutch perinatal database (Netherlands Perinatal Registry - PRN-foundation-www.perinatreg.nl) were used. In all cases of perinatal mortality in SGA children, previous perinatal mortality, causes of death, ethnic origin, birthweight, gender, parity, maternal age and selection for transfer between different care levels and hospitals were recorded. Causes of perinatal death were classified according to the TULIP classification [23] and assessed by the LPAS panels as described earlier.

Referrals between different care levels were noted. For each referral, the medical reason, the instance when the decision was taken and time until subsequent action, were taken into account. The presence of SSF as assessed by the LPAS-perinatal audit panels, was noted. However, since SSF indicate a deviation from nationwide accepted procedures only, we also investigated possible avoidable mortality in cases without SSF. To this end, we categorized avoidable according to a study of Herman et al [19] over two scales: either it's a matter of 'avoidability of condition (AvC)' if the condition leading to death could have been avoided, or 'avoidability of death (AvD)' if death could have been prevented once the condition was present.

Cases considered to have conditions or situations with a quality of life below an acceptable level were treated as a separate group and referred to them as 'Voluntarily Accepted or Induced Perinatal Death' (VAIPD). After all, such cases of perinatal death are due to termination of pregnancy (TOP), no treatment or active induction of death. Nationwide agreements for these protocols are laid down by the Dutch

association of pediatrics [13] whereas more recently, the Dutch Society of obstetrics and gynecology introduced guidelines for treatment in cases of preterm labor at the onset of the second half of pregnancy (www.nvog.nl/professionals/richtlijnen/ perinatology/dreigende vroeggeboorte).

Finally, for each case, we tried to identifie the moment when perinatal death occurred or became inevitable and defined this as the fatal moment (FM) similar to a previous study [10]. Especially in cases of mortality related to fetal growth restriction, this moment is important in view of possible preventive actions in future obstetrical care and to answer the question: when and where did it go wrong?

Results

Of the 22,189 births collected from the PRN-database, 21,257 were singletons of which 20,948 were born between 25 and 45 weeks of pregnancy. In 21 cases, birth weight centile could not be determined (birth weight unknown (n=14), gender unknown (n=9), maternal parity unknown (n=1) whereas in 3 cases 2 variables were missing). Finally, 20,927 births remained for analysis. In 2,396 children, birth weight was ≤ 10^{th} percentile (11.45%) while in 657 cases it was ≤ 2.3^{rd} percentile (3.14%). In the LPAS study, 239 perinatal mortalities were reported. Of these, 172 took place after 25 completed weeks of pregnancy and 65 cases (38%) had birth weights ≤ 10^{th} percentile (59 singletons and 6 twin-children). In 40 of these children birth weight was even ≤ 2.3^{rd} percentile (35 singletons and 5 twin-children). Consequently perinatal mortality rate for all singleton SGA-children with birth weight ≤ 10^{th} percentile was calculated as 59/2,396 = 2.46% and for those with birth weight ≤ 2.3^{rd} percentile it was 35/657 = 5.33% (table 1).

Table 1: Perinatal mortality rates in singletons ≥ 175 days of gestation.

	n	†	PNM-rate (%)	95% CI	RR	95% CI
All ≥ 25 weeks GA	20,927	172	0.822	0.706-0.951	1 (ref)	
≤ p-10	2,396	59	2.462	1.896-3.143	3.002	2.24-4.02
≤ p-2.3	657	35	5.327	3.797-7.251	6.481	4.55-9.24

PNM-rate = Perinatal Mortality rate; RR = Relative Frisk; CI = Confidential Interval; GA = Gestational age; † = number of perinatal deaths

Maternal age, ethnicity and perinatal mortality:

Data of maternal age were available for 2,396 SGA births. In comparison to mothers between 26 and 35 years of age, mothers older than 35 showed an increase perinatal mortality: RR = 1.97 (1.11 – 3.51) among SGA ≤ 10^{th} percentile and RR = 1.65 (0,79 – 3.42) among SGA ≤ 2.3^{rd} percentile (table 2). Perinatal mortality among mothers below 26 years of age was slightly increased but did not differ substantially

from mothers of intermediate age. Maternal ethnicity was known for 2,376 SGA births but was not associated with perinatal mortality.

Characteristics of LPAS cases:
Since most members of the LPAS audit groups participated for the first time in such an audit, a short training program, consisting of a plenary discussion on 7 cases, was introduced. Those cases, of which 4 were SGA, were excluded from the final LPAS-analysis.

Parity was known in 58 out of 59 investigated mortality cases, 34 were first born children (57.6%) and 24 were children of multiparas (40.6%). Birth weight of previous children was known in 21 mothers in the latter group. In 13 of them (62%) at least 1 of the previous children had birth weight ≤ 10th percentile.

In five cases (8.5%) an earlier case of perinatal mortality was found. In one case only, IUGR as well as preterm birth could have been related to a maternal condition (uterine fibromas). In one case the cause of the previous death was unknown. In three other cases no relation between the actual and the previous perinatal death was found. However, in three of these five cases birth weight of previous perinatal deaths was ≤ 10th percentile, whereas in one case it was unknown.

Table 2: Maternal age, ethnicity and perinatal mortality among SGA children.

	≤ 10th percentile				≤ 2.3rd percentile			
	n	% †	RR	95% CI	n	% †	RR	95% CI
Maternal age								
≤ 25 years	594	2.36	1.14	0.61–2.13	173	4.62	0.95	0.42-2.14
26 – 35 years	1,449	2.07	1	Ref	370	4.86	1	Ref
> 35 years	353	4.25	1.97	1.11-3.51	114	7.89	1.65	0.79-3.42
Ethnicity								
Dutch	1,509	2.19	1	Ref	424	5.19	1	Ref
Other	867	2.42	1.08	0.63-1.86	227	4.85	0.93	0.46-1.89

% † = % deceased; RR = Relative Risk; CI = Confidence Interval

In 32 cases (54%) with birth weights ≤ 10th percentile the cause of perinatal death was due to placental disorders. In 25 of them (78%) death occurred during pregnancy. The second major group consisted of 16 cases with congenital anomalies (27%). However, a total of 18 cases had congenital anomalies (31%) but two of them died of placental disorders and were not categorized as death due to congenital anomaly. All other causes, inclusive the group "unknown", comprised 12% of the cases (n=7).

An overview of all SGA-cases according the Fundamental Tulip classification is given in table 3.

Table 3: causes of death according the Fundamental TULIP-classification.

Cause of death	N	Sub classification		n
Congenital anomaly	16	Chromosomal defect	Numerical	8
			Structural	1
			Micro deletion	
		Syndrome	Monogenic	1
			Other	3
		Central nervous system		1
		Heart and circulatory system		2
		Respiratory system,		
		Digestive system		
		Urogenital system		
		Musculoskeletal system		
		Endocrine / metabolic system		
		Neoplasm		
		Other	Single organ	
			Multiple organ	
Placenta *	32	Placenta bed pathology		24
		Placental pathology	Development	4
			Parenchyma	1
			Localization	1
		Umbilical cord complication		1
		N.O.S.		1
Prematurity / immaturity	1	P.P.R.O.M.		
		Preterm labor		
		Cervical dysfunction		
		Iatrogenous		
		Multiplets		
		N.O.S.		1
Infection	1	Transplacental		1
		Ascending		
		Neonatal		
		N.O.S.		
Other	1	Fetal hydrops of unknown origin		
		Maternal disease		
		Trauma	Maternal	
			Fetal	
		Out of the ordinary		1
Unknown	4	Despite thorough investigation		2
		Important information missing	Lack of diagnostics	2
			Results not offered	
No assessment by LPAS	4			4
Total				59

* In 2 cases of mortality due to placental pathology 'trisomia-21' was diagnosed after birth.
N.O.S. = Not Otherwise Specified; PPROM = Preterm Premature Rupture Of Membranes.

Among all cases of SGA children, assessors found 22 SSF (37%) by caregivers (table 4). in 16 of them, SSF were related to perinatal death: in 7 cases the relation to perinatal death was assessed as 'possible' (3 SSF provides by a midwife and 4 by an obstetrician), in 7 cases as 'probable' (1 case of attendance by a GP, 2 by a midwife and 4 by an obstetrician) whereas in 2 cases the attendance of the midwife was assessed substandard and very probably related ro perinatal death. In 6 cases the relation between SSF and perinatal mortality was assessed to be unlikely.

SSF related to perinatal death were categorized into three major groups: 1- the problem was not recognized at all, was insufficiently recognized or too late recognized (n=7), 2- the problem was recognized but was not managed or managed too late or inadequate (n=8), 3- management was not in line with current protocols (n=2) (in one case the problem was not recognized either) (table 5).

Moreover, in 10 cases the impact of one or two SSF from the care receiver (i.c. the pregnant woman) may be considered to contain a possible or probable relation to perinatal death: drug (tobacco) abuse (n=5), severe obesity (n=2) and refusal for adequate care (n=3).

Table-4: Avoidability in SGA cases:

Causes of death	n	No SSF		SSF by caregiver				No SSF by caregiver				Av. cases	
		n	(%)	Rel. unlik.	(%)	PNM relat.	(%)	AvC.	(%)	AvD	(%)	n	(%)
Congenital	16	10	(63)	5	(31)	1	(6)	6	(38)	0	-	7	(44)
Placenta	32	18	(56)	0	-	14	(44)	4	(13)	2	(6)	20	(63)
Preterm	1	0	-	0	-	1	(100)	0	-	0	-	1	(100)
Infection	1	0	-	1	(100)	0	-	0	-	0	-	0	-
Others	1	1	(100)	0	-	0	-	0	-	0	-	0	-
Unknown	4	4	(100)	0	-	0	-	3	(75)	0	-	3	(75)
All	55	33	(60)	6	(11)	16	(29)	13	(24)	2	(4)	31	(53)
Not assessed	*4*	*4*	-	-	-	-	-	*0*	-	*0*	-		

SSF = Substandard care factor.; Rel. unlik. = Relation between SSF and perinatal death is unlikely; PNM relat. = A relation is possible / probable or very probable between SSF (by caregiver) and perinatal death; No SSF = No SSF by caregiver; AvC = Avoidability of condition; AvD = Avoidability of death; Not assessed = not assessexd by LPAS audit groups – No AvC or AvD either.

Avoidability of Condition (AvC), Avoidability of Death (AvD) and Voluntarily Accepted or Induced Perinatal Death (VAIPD).

We considered avoidable all 16 perinatal deaths related to SSF by caregivers disclosed by LPAS assessors. In 28 of the remaining 43 cases (all cases including the 4 that were not assessed by the LPAS-audit groups), no elements of avoidability of perinatal mortality were found. Consequently, perinatal deaths of children with birth weight ≤ 10^{th} percentile were considered unavoidable in 28 cases (47%).

Table 5: Classification of substandard care factors in SGA-cases.

Class	Subclass		Examples *of* Cases	N Cases
1 -Risk factor not recognized as such	1a- Inadequate diagnosis in cases of increasing risk.		• no ultrasound in case of BMI > 45 • no action in case of vag. bleeding (>24 wks) • and no action ether i.c.o. contractions (25 wks) • no ultrasound in case of BMI > 30 and • tobacco abuse • decreasing fetal condition (on CTG) not • recognized during labor	4
	1b- Unnecessary delay in diagnostic actions		• referral 5 weeks after first suspicion for • IUGR	1
	1c- Insufficient action in diagnostic research.		• No hosp. admission nor adequate diagn. • measurements taken i.c.o. signs of P.E. • no action at all (sec.care) i.c.o. serious • hypertension	2
2 -Risk factor recognized but not adequately treated	2- Unnecessary delay in diagnostic or therapeutic actions		• 1 week delay for referral after IUGR • diagnosis in primary care and another • week delay for subsequent hospital visit. • delay of 6½ hours for referral to hosp. i.c.o. • preterm labor at home • refrerral postponed (2 wks) i.c.o. IUGR	3
	3- Insufficient diagnosis or therapy.	No diagn/therapy provided	• no IUGR diagnosed (US) in case of high • risk (diabetic) pregnancy • correct referral not accurately handled in • secondary care • no referral i.c.o. diagnosed IUGR at 32 wks	3
		Wrong diagn/therapy provided	• high risk patient sent home by mistake – no • further actions	1
		Therapy not adequately provided	• no hospital administration i.c. of complete • growth stop	1
3 - Conduct	Not in line with current protocols or generally accepted 'best practice'		• application of therapies / prescription of • medications not in use in actual medicine • pregnancy with history of 3x IUGR conducted • by GP (no US controls)	2 (*)

* 2 SSF in one of these cases

AvC was found in six cases with congenital anomalies including five in which the anomaly was not detected by early second half of pregnancy ultrasound (US). In the other case, prenatal care was unjustifiably provided by a GP (history of three severe

IUGR – prenatal care by obstetrician indicated) and no US investigation at all was performed during pregnancy. In all these cases, no (further) treatment was decided after the 22nd week of pregnancy or after delivery (VAIPD) whereas TOP had been another option (therefore no "perinatal" mortality).

In another nine cases without SSF, elements of avoidability could clearly be demonstrated: in three cases, components in provided care could possibly have led to death (AvD): in one case IUGR was not recognized (IUFD at GA = 37 wks) following the common Dutch protocols (no routine US in late pregnancy). At that time, in one case minimal diagnostic measurements in case of decreased fetal growth and minor vaginal bleeding at 38 weeks were performed while more extensive investigations could have prevented perinatal death (AvD). Finally in one case fetal blood sampling during labor failed repeatedly leading to a significantly delayed Cesarean Section resulting in an adverse condition (AvC) at birth and ultimately neonatal death.

In the remaining six cases, AvC was demonstrated as a result of the behavior of the care receivers: in three cases, severe tobacco abuse may have possibly contributed to the suboptimal placental function whereas in three other cases perinatal care was refused or delayed by the patient.

Consequently a total of 31 cases may be considered as possibly avoidable (53%).

Finally, in nine cases, caregivers decided to give no treatment during the perinatal period: five cases of lethal congenital anomalies, two during the second half of pregnancy in case of severe HELLP-syndrome and two during the neonatal period. These cases we referred to as VAIPD.

Referrals

In 14 cases, pregnancy was conducted in secondary or tertiary care level only. In two cases no care was given at all while in the remaining 43 cases care was initially conducted by a community midwife (n=42) or a GP (n=1). Of those, 27 cases were referred during the third trimester of pregnancy (≥ 28 completed weeks) or after birth (n=1). In 6 cases the patient was referred to an obstetrician for (a suspicion of) IUGR (22%). In 21 cases (78%) IUGR was not suspected at referral (eight cases of SGA ≤ 10th percentile and 13 cases of SGA ≤ 23rd percentile). In 13 of the latter cases (62%) the patients were referred because of fetal death.

Fatal moment and mortality related to inadequacy in the "obstetrical-chain-care"

FM could be determined in 56 of the cases. In 13 cases (22%) it occurred during embryogenesis (7 chromosomal defects, 5 lethal (multiple) congenital malformations, 1 M.Steinert). In 17 cases (29%) it occurred during the period that the midwife was the responsible caregiver, in 23 cases (39%) during obstetricians care (14 times in a secondary hospital and 9 times in a tertiary hospital), whereas in 3 cases (5%) when the newborn was under tertiary neonatal care.

In two cases only, perinatal death might be the result of inadequacies related to the obstetrical-chain-care. In both cases referral to secondary care or adequate treatment in secondary care was delayed whereas in one case the patient was unjustifiable referred back to primary care.

Discussion

As already mentioned, in the LPAS-study, SGA was present in 38% of all cases of perinatal death. This percentage is exactly the same as we found in an earlier perinatal mortality audit study we performed in 1994-1995 [10]. Obviously the contribution of SGA to perinatal mortality did not decrease in our country during the last decade.

Advanced maternal age (≥35 years), is associated with increased perinatal morbidity and mortality [1, 16, 30, 34]. Comparable results were found in this study (figure 1). However, if maternal age was stratified in 5 years age categories, both the younger and the older group show an increased prevalence of SGA prevalence (figure 2). The increased risk for SGA in the first group (< 21 years) might be related to factors such as tobacco- or drug-abuse and lower social class while the increased risk in the 'older age'-group (> 40 years) is more likely due to age-related effects such as hypertension [6, 24, 26, 27, 31]. Ravelli et al [29] also showed, in an analysis of perinatal mortality in the Netherlands between 2000 and 2006, a significant increase below 25 and above 35 years.

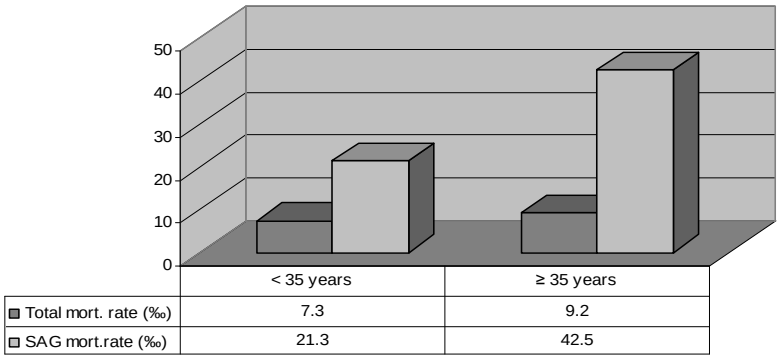
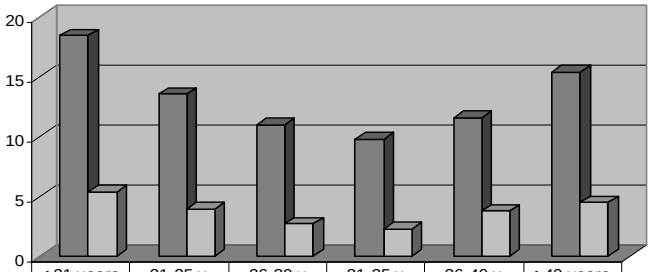


Figure 1: Total and SGA mortality rate at birth by maternal age < or ≥35 years of age.

In our study population, Dutch and non-Dutch mothers showed neither significant differences in the incidence of SGA nor in perinatal mortality in the SGA-group. However, one has to realize that due to restrictions, the Dutch PRN-data system, does not reveal the real ethnicity of the pregnant women since the 'non-Dutch'

group is composed of Caucasian, Mediterranean, Asian, African women etc. For that reason, the risk-levels for incidence of SGA and perinatal mortality in mothers of different ethnic categories in our study are not fully reliable.



	< 21 years	21-25 y	26-30 y	31-35 y	36-40 y	>40 years
% SGA ≤ p-10 at birth	18.5	13.6	11	9.8	11.6	15.4
% SGA ≤ p- 2.3 at birth	5.4	4	2.7	2.3	3.8	4.5

Figure 2: SGA-at birth stratified by maternal age.

Previous deliveries of SGA-children were often found in our study group (62%). Therefore, woman with previous SGA should be considered as at increased risk for repeated SGA and monitored accordingly.

The majority of SGA mortality cases were caused by placental disorders. Placenta bed pathology often occurs successively and should be considered as an increased risk for subsequent pregnancies [17]. For that reason histological investigation of the placenta in all cases of perinatal mortality and fetal death from 14 weekas is strongly advisable.

This audit, although relatively small, yields some important findings. Quality of care in cases of restricted growth has a considerable impact on survival chance and risk of death. When fetal growth is already disturbed, timely decision making with adequate fetal monitoring and accurate action may be crucial for a lifetime 'quality of life' of the individual child . If investigated systematically as it is the case in perinatal audits, SSF occur regularly in daily practice and are equally balanced between caregivers of different levels and care units. The fact that FM occurred most often when the patient was under secondary care may partly be due to the increased complexity in this particular group: community midwives provide care to the low risk cases whereas the more complex high risk cases are treated in hospitals. On the other hand, the more caregivers are involved in a particular case, the more consultations between different caregivers (nurses, midwives, residents, obstetricians and neonatologists) will take place. This increases the risk of miscommunication between these caregivers and more essential information may be forgotten to pass on.

Once the cause of death is determined, assessment on the presence of SSF and its possible relation to perinatal mortality is a starting point in the audit process. However, deaths occurring in spite of the absence of SSF should not a priori be considered as unavoidable as was assessed in other studies [8]. Protocols may be insufficient, regional and even national agreements may be inadequate whereas unexpected coincidences may lead to unfortunate decisions by caregivers. In this view, the question arises why the caregiver in that particular case acted the way he/she did and could another decision have changed the outcome?

Following the Dutch conventional protocols in prenatal care, IUGR (≥ 28 weeks of pregnancy) was not detected in four out of five cases at the moment of referral, while no SSF were found in 2/3 of the cases. In more than half of them fetal death occurred before referral.

It is obvious that restricted growth often remains undetected by conventional methods (e.g. palpation of the uterus only) as was performed during the LPAS-study and still is in daily practice in the Netherlands. Our findings on this matter are in line with the conclusions of other authors [2]. We already demonstrated that the SGA at birth can be predicted with a much higher sensitivity by routine use of ultrasound biometry at the onset of the third trimester of pregnancy [11]. Introduction of this procedure as a standard procedure in prenatal care in the Netherlands might in future reduce perinatal mortality in cases of growth restriction.

Conclusion

Caregivers cannot avoid SGA or IUGR. However, early detection of IUGR may lead to timely intervention and treatment. Thus prenatal care in the second half of pregnancy should focus on the detection of possible growth deviations espscially in low risk pregnancies. Since SGA is still observed in 38% of all perinatal deaths, reduction of mortality in this group could substatially decrese ther total perinatal mortality in the Netherlands. However, larger scale, preferably nationwide, perinatal audit of all SGA cases has to be performed to confirm these recommandations.

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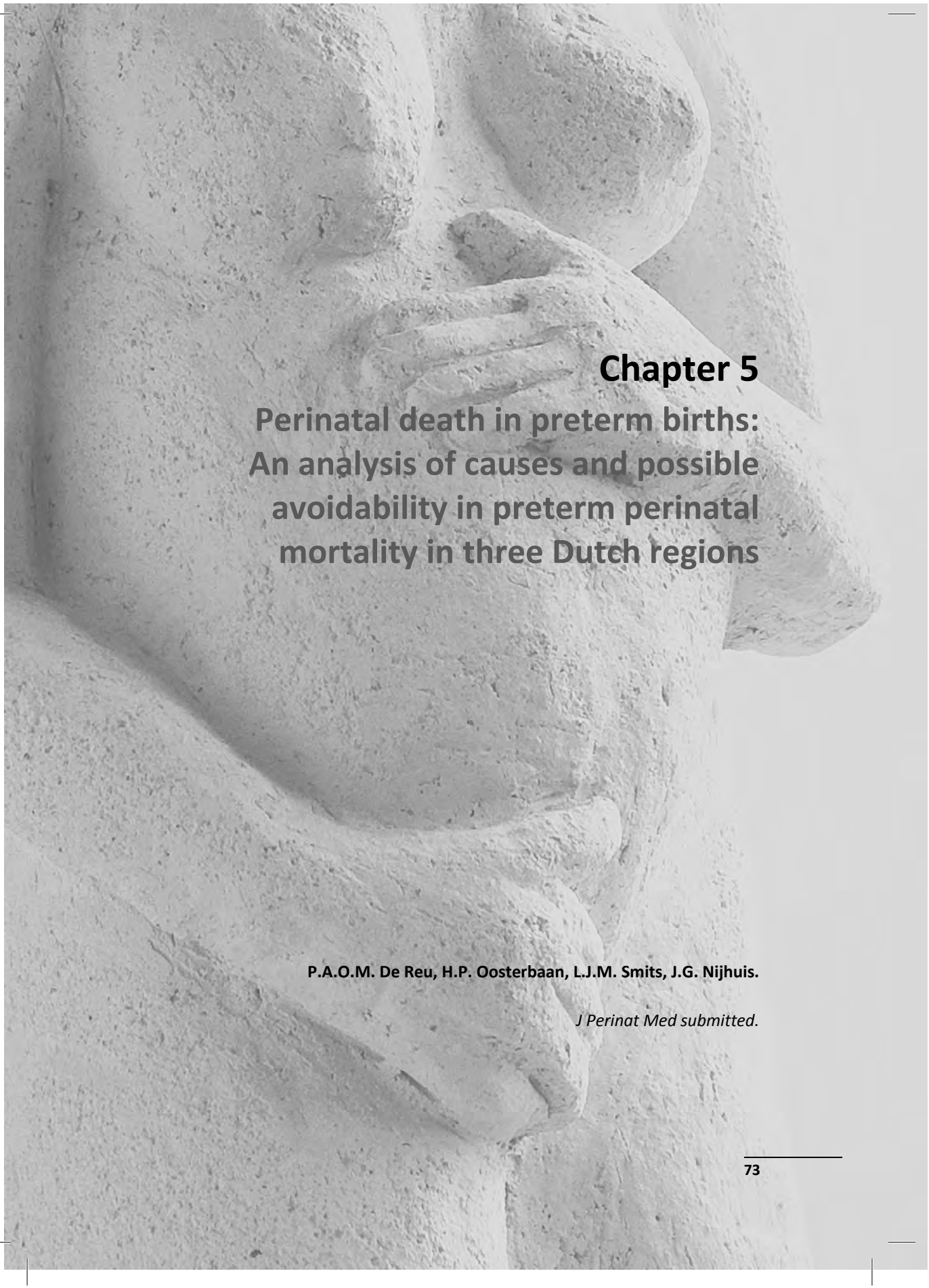

Chapter 5

Perinatal death in preterm births: An analysis of causes and possible avoidability in preterm perinatal mortality in three Dutch regions

P.A.O.M. De Reu, H.P. Oosterbaan, L.J.M. Smits, J.G. Nijhuis.

J Perinat Med submitted.

Abstract

Objective: To analyze avoidability of preterm birth and perinatal mortality in preterm born children.
Setting: Three regions within the Netherlands.
Study design: For this study, we combined data of a perinatal mortality audit study with data of its source population (n=22,189; year of birth 2003-2004). For the perinatal audit study, all cases of perinatal mortality had been assessed by multi disciplinary teams of professionals in perinatal care in a consensus model for cause of death and the presence of substandard care factors (SSF). We restricted our analysis to children born between 22+0 and 37+0 weeks of pregnancy (≥ 154 and <259 days) and evaluated both avoidability of preterm birth and of preterm perinatal mortality (PPM).
Results: Of 1,885 preterm born children, 166 died perinatally (PPM 8.81%). High risk conditions were small-for-gestational-age (PPM 17.9%), previous perinatal mortality (21.1%), non Dutch origin (PPM 12.3%) and maternal age between 20 and 26 years (PPM 13.4%). In 16% of the cases perinatal death was related to SSF by caregivers. In 22.6% of the cases perinatal death was considered to be avoidable.
Conclusions: More adequate preconceptional care, more appropriate actions by caregivers and care receivers in case of early signals of possible preterm labor may prevent 1 of every 10 cases of preterm delivery while perinatal mortality in this category might be reduced with more than 20%.

Introduction

In cases of perinatal mortality, reported percentages of prematurity vary, depending on definition, between 20 and 70% [1, 4, 5, 14, 17, 18, 21, 23, 25]

Although considerable progress has been made in the prevention of prematurity and the reduction of the harmful effects of being born prematurely (e.g. the administration of tocolytic drugs and administration of corticosteroids for lung maturity), perinatal mortality is roughly 30 times more likely among preterm than in term born babies (table 1).

Table-1: Perinatal mortality in term and preterm births in the Netherlands.

	Gest. age	N	Fetal mortality		Neonatal mortality		Perinatal mortality	
			N	‰	N	‰	N	‰
2003	154–258 days	14,658	957	65.3	453	33.1	1,410	96.2
	≥ 259 days	176,766	413	2.3	209	1.2	622	3.5
2004	154–258 days	14,081	906	64.3	378	28.7	1,284	91.2
	≥ 259 days	168,198	367	2.9	166	9.9	533	3.2
2005	154–258 Days	13,652	861	63.1	451	35.6	1,312	96.1
	≥ 259 days	163,904	373	2.3	180	1.1	553	3.4
2006	154–258 days	13,546	860	63.5	363	28.6	1,223	90.3
	≥ 259 days	162,640	331	2.0	171	1.1	502	3.1
2007	154–258 days	13,121	806	61.4	401	32.6	1,207	92.0
	≥ 259 days	15,3007	53	3.5	116	7.6	169	1.1

Source: the Netherlands Perinatal Registry (2003 - 2007).

Between April 2003 and May 2004, an audit study on perinatal mortality in three different Dutch regions was performed. This study was called National Perinatal Audit Study (LPAS - Landelijke Perinatal Audit Studie) and was initiated by the professional groups involved in perinatal care and the Dutch Health Care Insurance Board ('*College Voor Zorgverzekeringen*' CVZ).

In the present article, we analyzed the data of all deceased children born preterm (n=166) from this LPAS study, as well as their source population. We aimed to answer the following questions: is there an increased risk of preterm perinatal mortality (PPM) in certain demographic groups, what events led to mortality in preterm

born children alive at the onset of labor and what measures can be taken to reduce preterm birth and PPM based on the present study?

To this end, we investigated PPM on the level of Avoidability of Condition (AvC): "was preterm delivery avoidable?" and on the level of Avoidability of Death (AvD): "could death have been avoided once premature birth occurred or became inevitable?" Moreover, we investigated in the impact on perinatal mortality of the different care levels within the Dutch perinatal care system.

Patients and Methods

Our study population was a sub-set of all cases of perinatal death (n=235) reported in the LPAS study over a one-year period in three different Dutch regions. For details we refer to articles published earlier [6, 10, 11] and to the original LPAS report as published in 2007 (www.cvz.nl/resources/rpt0511_lpas_tcm28-17810.pdf). The source population of the LPAS study were all children born in the regions of central Noord-Brabant province and the southern part of the province of Zuid-Limburg between April 1st 2003 until March 30th 2004 and all children born in the Amsterdam region between May 1st 2003 until April 30th 2004. Data of the source population were obtained from the national Dutch perinatal database (Netherlands Perinatal Registry (PRN) – www.perinatreg.nl), which covers approximately 93% of all births in the Netherlands.

According to the WHO-guidelines, preterm birth was defined as all live- or stillbirth between gestational age (GA) of 22+0 and 36+6 weeks of pregnancy (≥ 154 and <259 days). The cases of PPM identified in the LPAS-study, were categorized for the timing of death: fetal deaths (IUFD); intra partum deaths (IPD); early neonatal deaths (END = within the first 7 days of life) and late neonatal deaths (LND = between the 7th and the 29th day of life). Previous perinatal mortality, causes of perinatal death, ethnic origin, birth-weight, gender, parity, GA at delivery, maternal age, transfer to another care-level (transfer from first to second or tertiary obstetric or neonatal care-level or vice versa) and conclusions based upon pathological findings and/or autopsy results were noted. For each transfer, the medical reason, the moment the decision for transfer was made and the interval between this decision and subsequent arrival at the next level of care was evaluated.

Causes of perinatal death were based upon the assessment of the audit panels of the LPAS study according to the Fundamental TULIP classification [16].

Presence of substandard factors (SSF) as assessed by the perinatal audit committees of LPAS, was also evaluated and classified in categories as we described earlier [6]: (i) the problem was not recognized at all, was insufficiently recognized or too late recognized, (ii) the problem was recognized but was not managed or man-

aged too late or inadequate, (iii) management was not in line with current protocols and (iiii) other.

Moreover, we investigated avoidability of perinatal mortality in all cases (with and without SSF) according to a study of Herman et al [13]: AvC and AvD. In addition we identified cases of perinatal death due to termination of pregnancy (TOP) or abstention of treatment. Such cases were labeled as Voluntarily Accepted or Induced Perinatal Death (VAIPD). Assessment of the indications for the latter group was based upon a protocol, published by the Dutch association of pediatricians in 1992 and current protocols in the Netherlands [9, 20].

We further stratified our study-population in 3 subgroups based upon GA at the moment of birth: from 22+0 till 24+6 weeks (day 154 up to and including day 174); from 25+0 till 31+6 weeks (day 175 up to and including day 223) and from 32+0 till 36+6 weeks (day 224 up to and including day 258). These subgroups were chosen because active management in cases of GA ≤ 25+0 weeks (e.g. cesarean section (CS) and/or neonatal intensive care) is only performed in the Netherlands in situations where a realistic chance to survive and an acceptable quality of life is expected. In addition, in cases of GA between 25+0 and 32+0 weeks, delivery in a tertiary care level hospital with a Neonatal Intensive Care Unit (NICU) is mandatory [9].

Multiplets and all children born before 25 weeks could not be classified for birth weight characteristics according to the current Dutch birth weight charts since these charts cover data of singletons with GA from at least 175 days (25+0 weeks) only [24]. Finally we identified the 'fatal moment' (FM) e.g. the moment that perinatal death occurred or became inevitable, for each case as described in an earlier study [7].

Results

Prevalence of preterm birth, time of death and GA stratification

The source population consisted of 22,189 children: 21,257 singletons (95.8%) and 932 children of multiplets (4.2%). A total of 1,885 children were born prematurely (8.5%): 1,440 singletons (6.8%) and 445 children of multiplets (47.7%). Of those, 166 died perinatally (PNM-rate = 88.1‰): 141 singletons (PNM-rate = 97.9‰) and 25 children of multiple pregnancies (PNM-rate = 56.2‰). There were 103 cases of fetal death (62.0%) of which 10 TOP and four cases of abstention of treatment, and 63 cases of neonatal death (38.0%) of which eight TOP and 20 cases of abstention of treatment. Consequently in 42 cases (24.1%) perinatal death was accepted before or early after delivery (=VAIPD's).

Birth weight characteristics

The birth weight characteristics of 1,382 preterm born singletons of GA ≥ 25 completed weeks (175 – 258 days) were calculated. Perinatal death was reported in 93 cases (= 6.7%). In 207 cases the birth weight was ≤ 10^{th} percentile (15.0%) of which 37 died (17.9%): 27 IUFD, three during delivery, one in the early neonatal period and six during the late neonatal period. Of the 1,086 appropriate of gestational age (AGA)-children (79%), 53 died (4.9%): 30 IUFD, four during delivery and 19 in the early neonatal period. Finally 89 children (6.4%) were large for gestational age (LGA) of which three died in the early neonatal period (3.4%).

Previous perinatal mortality

Of all mothers in our study group, 71 were multiparous. Fifteen of these women (= 21.1%) had a history of perinatal mortality (two had two previous cases of perinatal mortality). A relation between the actual and the previous mortality was found in two cases only: in one case the mother had a repeated early HELLP-syndrome (induction of labor in a very preterm stage on the basis of a deterioting maternal condition), while in the other case the parents were consanguine and for the third time a child with Ellis van Creveld Syndrome was born.

Ethnic back ground, preterm birth, and PPM

In 21,761 cases of the PRN data, GA at birth and ethnic origin of the mothers was known. About one-third of the children were born to mothers of non-Dutch origin. Preterm birth rates in children of mothers of Dutch and non-Dutch origin were comparable: 8.7% and 8.3% respectively (table 2). In 152 of the 166 PPM-cases of the LPAS group, ethnicity was registered. Among children born preterm, mortality differed according to maternal ethnic background with 12.3% in children of mothers of non-Dutch origin and 6.5% in those of Dutch mothers: RR=1.88 (95% confidence interval = 1.46 – 2.43).

Table-2: Preterm perinatal mortality among children of mothers of Dutch and non-Dutch origin.

Ethnicity	Total born		Preterm born		IUFD		Preterm †		Total PPM	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Dutch	15,133	(68.2)	1,322	(8.7)	39	(29.5)	47	(36.6)	86	(6.5)
Non-Dutch	6,628	(29.9)	547	(8.3)	36	(65.8)	31	(60.7)	67	(12.3)
Unknown	428	(1.9)	16	(3.7)	7	-	6	-	13	-
All	22,189	(100)	1,885	(8.5)	82	(43.5)	84	(46.6)	166	(8.8)

IUFD = Intrauterine fetal deaths; Preterm † = Preterm neonatal mortality; PPM = Preterm perinatal mortality

Maternal age, preterm birth, and PPM

GA and maternal age were known for 21,901 children in the source population (288 missing), Maternal age was unknown in one case of PPM. Preterm birth rates were nearly equal across maternal age groups (table 3) and varies between 8% (36-40 years) and 9% (21-25 years). The highest PPM was observed in children from mothers of 21 to 25 years of age in all GA categories (13% versus <9% in all other categories).

Causes of perinatal mortality

In the LPAS-study, seven cases (4.2%) of preterm born babies were used for initial training of the members of the audit groups and not used for the final analysis while in another seven cases assessors couldn't reach consensus on the cause of death (table 4) .

Assessment of death-causes performed by de LPAS audit-groups according the TULIP-classification showed 24 cases (14.5%) of congenital anomalies. Placental dysfunction was the cause of death in 61 cases (36.7%). At least 28 of them (45.9%) were growth retarded. Nine (5.7%) children died as a consequence of infections, 33 children from the effects of prematurity itself (19.9%), eight were classified in the group 'others' (4.8%) and in 17 cases (10.2%) the cause of death remained unknown.

Table-3: Preterm perinatal mortality by maternal age.

Maternal age	All <37 wks		22+0 / 24+6 wks			25+0 / 31+6 wks			32+0 / 36+6 wks			22+0 / 36+6 wks		
	N	**%**	**N**	**†**	**%**	**N**	**†**	**%**	**N**	**†**	**%**	**N**	**†**	**%**
14 – 20 yrs.	990	8.28	4	4	100	17	3	17.7	61	0	0	82	7	8.5
21 – 25 yrs.	3,150	8.98	18	16	88.9	51	13	25.5	214	9	4.2	283	38	13.4
26 – 30 yrs.	6,668	8.77	18	11	61.1	89	14	15.7	478	11	2.3	585	36	6.2
31 – 35 yrs.	7,998	8.55	31	25	80.7	102	21	20.6	551	15	2.7	684	61	8.9
36 – 40 yrs.	2,793	8.09	5	4	80.0	36	9	25.0	185	5	2.7	226	18	8.0
> 40 yrs	299	8.36	0	2	??	3	1	33.3	22	2	9.1	>25	5	2.0
Unknown	288	-	?	1	-	?	-	-	?	-	-	288	1	0.3
Total	22,186	8.45	76	63	82.9	298	61	20.5	1,511	42	2.8	1,885	166	8.8

Table-4: Causes of death according to the Fundamental TULIP-classification.

Cause of death	Fetal deaths		Neonatal deaths		All preterm born	
	N	(%)	N	(%)	N	(%)
Congenital anomaly	13	(12.6)	11	(17.5)	24	(14.5)
Placenta	50	(48.5)	11	(17.5)	61	(36.7)
Prematurity / immaturity	9	(8.7)	24	(38.1)	33	(19.9)
Infection	7	(6.8)	2	(3.2)	9	(5.4)
Other	1	(1.0)	7	(11.1)	8	(4.8)
Unknown	16	(15.5)	1	(1.6)	17	(10.2)
No consensus	2	(1.9)	5	(7.9)	7	(4.2)
Not assessed	5	(4.5)	2	(3.2)	7	(4.2)
Total	103	(100)	63	(100)	166	(100)

Table-5a: Substandard factors in Preterm perinatal mortality cases

		Substandard care factors (SSF) – (Consensus: 75%)											
Causes of death	N	None		Care giver				Care receiver				All cases with ≥ 1 SSF	
		N	(%)	Rel. unlik	(%)	PNM relat.	(%)	Rel. unlik	(%)	PNM relat	(%)	N	(%)
Congenital	24	19	(79.2)	3	(12.5)	0	-	2	(8.3)	2	(8.3)	5	(20.8)
Placenta	61	40	(65.6)	3	(4.9)	17	(27.9)	-	-	5	(8.2)	21	(34.4)
Preterm	33	24	(72.7)	2	(6.1)	5	(15.6)	-	-	2	(6.1)	9	(27.3)
Infection	9	8	(88.9)	1	(11.1)	0	-	-	-	-	-	1	(11.1)
Others	8	3	(37.7)	1	(12.5)	3	(37.5)	-	-	3	(37.5)	5	(62.5)
Unknown	17	10	(50.8)	2	(11.8)	2	(11.8)	2	(11.8)	2	(11.8)	7	(41.2)
No consensus	7	5	(71.4)	1	(14.3)	0	-	-	-	1	(14.3)	2	(28.6)
Not assessed	(7)	-	-	-	-	-	-	-	-	-	-	-	-
All	159	109	(68.6)	13	(8.2)	27	(17.0)	4	(2.5)	15	(9.4)	50	(31.4)

SSF = Substandard care Factor; **None** = number of cases without substandard factors; **Relation unlikely** = there is no relation between SSF and perinatal death; **PNM related** = A relation is possible / probable or very probable between SSF (by caregiver or care receiver) and perinatal death.

In 9 cases there were SSF by care giver as well as by care receiver.

Table-5b: Avoidable Preterm perinatal mortality cases

Causes of death	N	Avoidability assessment in preterm perinatal mortality (PPM)											
		None		AvC		AvD		VAIPD				Avoid. cases	
		n	(%)	Care giver	Care receiv	Care giver	Care receiv	TOP	%	Abst	%	N	%
Congenital	24	22	(91.7)		2			13	(54.2)	3	(12.5)	2	(8.3)
Placenta	61	43	(70.5)	2	4	15	1	1	(1.6)	4	(6.6)	18	(29.5)
Preterm	33	26	(78.8)	5	2			-	-	11	(33.3)	7	(21.2)
Infection	9	9	(100)					-	-	-	-	0	(0)
Others	8	3	(37.7)		3	3		1	(12.5)	-	-	4	(50.0)
Unknown	17	13	(76.5)	1	2	1		-	-	-	-	4	(23.5)
No consensus	7	6	(85.7)		1			1	(14.3)	4	(57.1)	1	(14.3)
Not assessed	(7)	-	-	-	-	-	-	-	-	-	-	-	-
All	159	121	(76.1)	8	14	19	1	18	(11.3)	24	(15.1)	36	(22.6)

AvC = Avoidability of condition; AvD = Avoidability of death; VAIPD = Voluntarily accepted or induced perinatal death; TOP = Termination of Pregnancy; Abst. = Abstention of (further) treatment.
In 3 cases (placenta) there was AC (care receiver) and AD (care giver)
In 1 case (placenta) there was AD (care receiver) and AD (care giver)
In 2 cases (other) there was AC (care receiver) and AD (care giver)

SSF and avoidability of perinatal mortality

In 109 of the 159 cases of PPM (69.0%) assessed, obstetrical and neonatal care was considered adequate. In 50 cases (31.4%) one or more SSF were identified (table 5a). In 27 cases (16.3%) in which SSF by caregivers were found, a relation to perinatal death was considered as possible (19x), probable (6x) or very probable (2x) and all were found in both community care as well as in hospital care (table 6). In seven cases the seriousness of the situation was not recognized which in four cases led to inadequate diagnosis and three times to delayed or insufficient actions. In nine cases diagnostic or therapeutic actions were taken too late or inadequately although the risk was identified timely. In six cases standard protocols were not followed while in another five cases, the SSF were related to incompliance with national guidelines or unclear arrangements between caregivers and/or patients (inefficiency in the obstetrical-chain-care).

In eight of the PPM-cases (5.0%) AvC and in 19 cases (11.9%) AvD could be demonstrated (table 5b). In six of these, the patients' behavior contributed to AvC also. Moreover, in 15 cases, elements of avoidability by the mother were found. This occurred in six cases with SSF and in nine of the 109 cases without SSF (8.3%): eight times there was AvC and in one case there was AvD. Consequently a total of 36 cases (22.6%) of PPM may be considered to be avoidable.

Table 6: Classification of SSF.

Class	Subclass		In this study	SSF
1 -Risk problem is not recognized as such	1a- No or inadequate diagnosis in cases of increasing risk.		• in case of increasing risk for preterm birth • in case of increasing blood pressure • in case of minor blood loss at GA ≥ 24 weeks • misjudged fetal presentation (cluneus)	n=7
	1b- Unnecessary delay in diagnostic actions		• in case of referral for IUGR: (too long interval between prenatal visits) • delay > 1week in decision for referral to higher care-level in case of serious IUGR	
	1c- Insufficient action in diagnostic research.		• no biometry evaluation in case of IUGR (clinically observed)	
2 -Risk problem is recognized but not adequately treated	2a- Unnecessary delay in diagnostic / therapeutic actions		• delay > 1week in subsequent arrival in case of referral to appropriate care level i.c.o. IUGR • delay in referral 2nd to 3rd level in case of HELLP in 2nd trimester of pregnancy • delay for induction of labor (or CS) in case of IUFD of 1 child in twin pregnancy • delay of > 30 minutes for emergency CS in case of serious fetal distress • delay for induction of labor (or CS) in case of IUFD of 1 child in twin pregnancy	n=9
	2b- Insufficient therapy.	No therapy provided	• no hospital admission nor any other intervention in case of complete growth stop.	
		Wrong therapy provided	• (operative) vaginal delivery in cases that SC should have been performed	
		Inadequate therapy provided	• delay of > 30 minutes for emergency CS in case of serious fetal distress	
3 - Conduct	Not in line with current protocols or generally accepted 'best practice'		• therapies / medication prescription not in use in actual medicine • care level inappropriate to risk level	n=6
4 -Other:			• confusion (e.g. for appointments) due to linguistic problems. • substandard performance related to late evening and/or night shifts. • complication(s) related to performed therapy (e.g. preterm homebirth after amniocenthesis, infection after cervical cerclage)	n=5

SSF = Substandard factor

Fatal moment

The fatal moment (FM) could be determined in 162 of the cases (in four cases no prenatal care at all was given). In 21 cases lethal pathology already arose during the embryonic period (20 cases), while in one case a massive feto-maternal transfusion as a result of a traffic accident caused IUFD.

FM without avoidable death (n=114) occurred in 42 cases during midwifery care, in 69 during obstetrical care and in three cases during neonatal care. Finally FM in the 27 avoidable cases with SSF by caregivers occurred in eight cases during midwifery care, in 18 cases during secondary/tertiary obstetrical care and in one case during neonatal care.

Discussion

SGA (33.3% of all singletons with GA ≥ 175 days), congenital anomalies (25%) and previous perinatal mortality (21%) were the most important determinants in this study-group.

Of all preterm born children, SGA children show an 17.9 % chance for PPM, which is more than 3 times higher than in all other cases together (LGA and AGA = 4.7 % PPM).

Although a possible relation between the previous and actual perinatal mortality was found in two cases only, a chance for repeated perinatal mortality of 21% may be enough reason to intensify perinatal care in all women with a history of PPM.

Ethnic origin is often considered a risk factor for perinatal mortality and preterm birth [1]. Although the prevalence of preterm birth in mothers of Dutch and non-Dutch origin was comparable in our population, PPM was nearly twice as high in the non-Dutch group.

Finally, it is known that both low and high maternal age are associated with elevated rates of preterm birth, growth restriction and perinatal mortality [3, 15]. In our study, we found highest PPM in mothers between 21 and 25 years of age. In this group, a decrease in perinatal mortality may be realized on both avoidability fields: firstly by decreasing the number of preterm births and secondly by decreasing mortality in cases where preterm delivery occurred of became inevitable.

A number of authors showed a possible relation between the mothers professional occupation and preterm delivery [12, 19, 22]. In an earlier study, we already showed that within this particular age group the amount of SGA is also increased as compared to all other age groups [8]. In the Netherlands, a considerable number of women postpone their (first) pregnancy for educational reasons (e.g. university

training programs) of career. As a consequence, a considerable part of young mothers belong to the working class, and often show often a less healthy lifestyle while another (also considerable) part often has a lower socio-economic status [12]. Both groups should thus be considered as 'elevated risk-groups' and need special attention with preconceptional advise on lifestyle issues and eventual changes in their professional occupation.

In this study, 42 of the PPM-cases (50%) were VAIPD: in 18 cases TOP was performed by GA ≥22 completed weeks while in 24 cases one decided for abstention of treatment (before or after birth). In this group, mortality itself was unavoidable. However in at least 11 cases abstention for (further) treatment was decided after the 22nd week of pregnancy or after delivery (between GA ≥22 wks and 28 days after birth) whereas TOP before the 22nd week of pregnancy had been an alternative option (therefore no "perinatal" mortality).

In 22 cases (13.8%) preterm birth itself might have been avoided if caregivers (n=8) or patients (n=14) should have reacted (more) adequately on initial signals of imminent preterm labor. In 20 cases (12.3%) mortality could have been avoided in cases of inevitable preterm birth (in 6 cases there was a combination of AvC and AvD). Consequently more than 1 in every 5 cases of PPM could have been avoided (22.6%). Focused on all children without (lethal) congenital anomalies, mortality could possibly or probably have been avoided in 34 cases out of 135 healthy children (25.2%).

Conclusions

Immediate and appropriate actions by caregiver and care receiver in case of early signals of possible preterm labor may prevent 1 of every 10 cases of preterm delivery while perinatal mortality in this category may be reduced with more than 20%.

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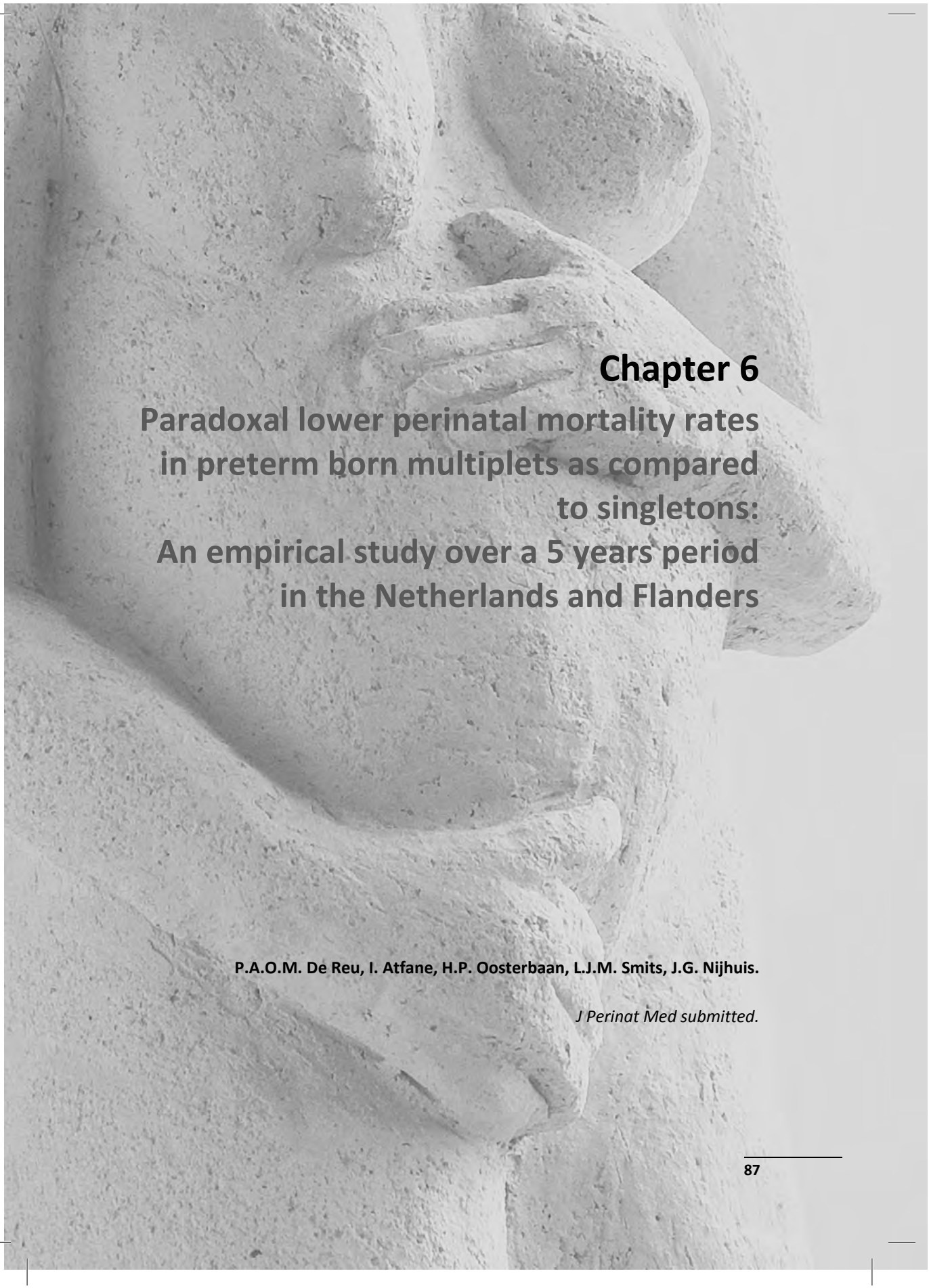

Chapter 6

Paradoxal lower perinatal mortality rates in preterm born multiplets as compared to singletons: An empirical study over a 5 years period in the Netherlands and Flanders

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Abstract

Background: The high incidence of multiple pregnancies is suggested as one of the possible reasons for the relatively high perinatal mortality in the Netherlands. However, the yearly published overview of perinatal care in the Netherlands, shows that perinatal mortality in children of preterm born multiplets is substantially lower than in singletons. This intriguing finding led to study perinatal mortality differences in both groups.

Methods: We analysed perinatal mortality rates in preterm and term born singletons and multiplets over a five years period in the Netherlands and Flanders.

Results: Fetal mortality in preterm born singletons was two to three times higher as compared to multiplets. After 37 completed weeks of pregnancy the opposite was found. In case of singletons a minor increase in perinatal mortality was noticeable at gestational age (GA) ≥ 280 days while in case of multiplets, a substantial increase is shown at GA ≥ 259 days.

In the Netherlands, a perinatal mortality rate of 6.12% in preterm born multiplets, versus 10.97% in preterm born singletons was found. In term born singletons the perinatal mortality rate was 0.59% in multiplets versus 0.27% in singletons. Perinatal data of Flanders showed comparable differences in mortality rates: 4.64% versus 6.51% in preterm and 0.52% versus 0.17% in term born children.

Conclusions: Our findings suggest that prenatal care in singleton pregnancies might benefit from more frequent consultations as is done in multiplets. In case of multiple pregnancies the induction of labour and delivery around 37+0 - 37+6 weeks might further decrease perinatal mortality.

Introduction

In the Peristat-I study 1999 the highest perinatal mortality was found in the Netherlands as compared with 15 other European countries [1]. In the recently published Peristat–II study it became clear that in 2004, the perinatal mortality rate in the Netherlands had only slightly improved, i.e. a decrease of 8%. Furthermore, perinatal mortality was still remarkably high, now compared with 26 other European countries. Only France and Latvia had higher mortality rates (the complete reports are available on www.europeristat.com) [2, 3]. These confronting data once more led to much discussion in the Netherlands.

During the last decade, in the Netherlands a perinatal mortality of nearly 10 out of every 1000 children born after 22 weeks of pregnancy was found (table 1). However, Buitendijk and Nijhuis [4] showed that the overall perinatal mortality rates of all children born in the Netherlands after 22 weeks of pregnancy between 2000 and 2006 were even higher.

Table 1: Perinatal mortality rates in the Netherlands 2001 – 2007.
(GA = 22+0 weeks till and including 28th day after delivery)

Year	PNM-rate
2001	11.7 ‰
2002	11.4 ‰
2003	10.6 ‰
2004	10.4 ‰
2005	10.5 ‰
2006	9.8 ‰
2007	9.7 ‰

Source: Netherlands Perinatal Registry (PRN)

More recently, we suggested that perinatal mortality is probably even higher than the officially published mortality rates [5]. Possible explanations for the high perinatal mortality in the Netherlands can be the increased number of immigrate families (> 18%), the relatively high number of older pregnant women (over 20% of women ≥ 35 years) and the higher incidence of multiple pregnancies (multiple birth rate > 20/1000) [6]. Ravelli et al. [7] showed that in the Netherlands maternal age and non-western ethnicity are less important risk factors for perinatal mortality than expected. A significantly higher overall perinatal mortality was found in multiple pregnancies as compared to singletons. However, in the yearly published data on perinatal care in the Netherlands, the opposite was shown for perinatal mortality in premature born singletons compared to multiplets (www.perinatreg.nl). This phenomenon was observed already by other authors as a secondary outcome [8] but, to the best of our knowledge, never investigated in detail. In this study we describe

the phenomenon in two separate samples over five years from the Netherlands and Flanders (the Dutch speaking part of Belgium) and speculate on possible explanations.

Methods

Data of all children born after 22+0 completed weeks of pregnancy (≥154 days) in the Netherlands and Flanders over the years 2003 up to and including 2007 were extracted from the National Dutch Perinatal Database (Netherlands Perinatal Registry (PRN) (www.perinatreg.nl/ jaarboeken_zorg_in_nederland)) and from the Flemish Study-centre for Perinatal Epidemiology (SPE) (www.zorg-en-gezondheid.be-/cijfers.aspx) and stratified in preterm (≤ 258 days) and term (≥ 37+0 weeks of gestation) born groups.

The Netherlands and Flanders are comparable in population composition, urbanization, medical facilities, and level of education. Moreover, in both countries a reliable and complete database is available. But they have a different perinatal care system: in Flanders nearly 100% of the obstetrical care is provided by obstetricians in secondary or tertiary care hospitals while in the Netherlands, prenatal care is initially provided in more than 80% by community midwives and general practitioners. When risk factors are recognised or arise, pregnant women will be referred to an obstetrician [9].

According to the WHO criteria, prematurity was defined as gestational age (GA) ≥154 days (22+0 weeks) up to 258 days (36+6 weeks), stillbirth as death before birth while neonatal death as mortality between life birth and 28 days after birth. Fetal mortality rate is defined as the number of stillborns per 1000 newborns. Neonatal mortality rate as the number of all life born children that die within 28 days after delivery per 1000 live born. Perinatal mortality is the sum of the fetal and neonatal mortality.

We calculated fetal, neonatal and perinatal mortality rates of singletons and infants from multiplets in both study populations (table 2). In addition, we calculated perinatal mortality rates, relative risk (RR) and additive risk (AR) for preterm and term born babies per gestational week at the time of birth for the Dutch population (table 3).

Tabel-2: Perinatal mortality in the Netherlands and Flanders for singletons and multiplets

	GA		Number of newborns		Fetal mortality				Live born		Neonatal mortality				Perinatal mortality			
			Flan.	Neth.	Flan.	%	Neth.	%	Flan.	Neth.	Flan.	%	Neth.	%	Flan.	%	Neth.	%
2003	P	Sing	3,674	10,866	177	4.82	858	7.90	3,497	10,008	69	1.97	389	3.89	246	6.70	1,247	11.48
		Mult	1,406	3,792	36	2.56	99	2.61	1,370	3,693	27	1.97	132	3.57	63	4.48	231	6.09
	T	Sing	54,419	170,246	71	0.13	366	0.21	54,348	169,880	29	0.05	205	0.12	100	0.18	571	0.34
		Mult	901	3,879	4	0.44	16	0.41	897	3,863	0	0	11	0.28	4	0.44	27	0.70
	Unknown			2,641			32	-		2,609			21	-			53	-
2004	P	Sing	4,011	10,587	185	4.61	806	7.61	3,826	9,781	73	1.91	317	3.24	258	6.43	1,123	10.61
		Mult	1,231	3,494	19	1,54	100	2.86	1,212	3,394	34	2.81	113	3.33	53	4.31	213	6.10
	T	Sing	53,311	162,049	58	0.11	16	0.01	53,253	162,033	27	0.05	181	0.11	85	0.16	197	0.12
		Mult	798	3,658	3	0.38	12	0.33	795	3,646	2	0.25	5	0.14	5	0.63	17	0.46
	Unknown			2,491			18			2,473			15				33	
2005	P	Sing	4,001	10,263	147	3.67	759	7.40	3,854	9,504	81	2.10	382	4.02	228	5.70	1,141	11.12
		Mult	1,274	3,389	20	1,57	102	3.01	1,254	3,287	31	2.47	134	4.08	51	4.00	236	6.96
	T	Sing	57,971	158,807	70	0.12	342	0.22	57,901	158,465	26	0.04	186	0.12	96	0.17	528	0.33
		Mult	968	3,490	2	0.21	14	0.40	966	3,476	1	0.10	8	0.23	3	0.31	22	0.63
	Unknown			1,607			17			1,590			17				34	
2006	P	Sing	4,143	10,323	190	4.59	770	7.50	3,953	9,553	70	1.77	339	3.55	260	6.28	,1109	10.74
		Mult	1,338	3,223	28	2,09	90	2.79	1,310	3,133	26	1.98	94	3.00	54	4.04	184	5.71
	T	Sing	59,490	158,088	83	0.14	301	0.19	59,407	157,787	31	0.05	181	0.11	114	0.19	482	0.30
		Mult	961	3,339	3	0.31	14	0.42	958	3,325	2	0.21	6	0.18	5	0.52	20	0.60
	Unknown			1,213			16			1,197			14				30	
2007	P	Sing	4,054	10,193	223	5.50	730	7.16	3,831	9,463	79	2.06	381	4.03	302	7.45	1,111	10. 90
		Mult	1,329	2,928	38	2,86	76	2.60	1,291	2,852	46	3.56	90	3.16	84	6.32	166	5.67
	T	Sing	60,652	155,755	67	0.11	283	0.18	60,585	155,472	33	0.05	140	0.09	100	0.16	423	0.27
		Mult	989	3,156	5	0,51	11	0.35	984	3,145	2	0.20	7	0.22	7	0.71	18	0.57
	Unknown			1,402			53			1,349			16				69	
All	P	Sing	19,883	52,232	922	4.64	3,923	7.51	18,961	48,309	372	1.96	1,808	3.74	1,294	6.51	5,731	10.97
		Mult	6,578	16,826	141	2.14	467	2.78	6,437	16,359	164	2.55	563	3.44	305	4.64	1030	6.12
	T	Sing	285,843	804,945	349	0.12	1,308	0.16	285,494	803,637	146	0.05	893	0.11	495	0.17	2201	0.27
		Mult	4,617	1,7522	17	0.37	67	0.38	4,600	1,7455	7	0.15	37	0.21	24	0.52	104	0.59
	Unknown			9,354			100			9,218			83				219	

Tabel 3. Comparison Fetal / Neonatal mortality in singletons and multiplets - PRN: 2003 t/m 2007

GA	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
All singl.	859	947	487	576	685	849	976	1047	1470	1837	2545	3903	6363	10225	19467	46872	120172	199540	236523	156780	45058
Fetal †	622	626	261	274	241	227	206	180	171	170	168	171	186	210	208	276	348	336	335	262	72
Life born	237	321	226	302	444	622	770	867	1299	1667	2377	3732	6177	10015	19259	46596	119824	199204	236188	156518	44986
Neonat †	235	315	209	158	108	113	84	86	89	64	57	63	72	87	112	107	189	182	186	180	80
Fet.M-rate	72,41	66,1	53,59	47,57	35,18	26,74	21,12	17,19	11,63	9,25	6,6	4,38	2,92	2,05	1,07	0,59	0,29	0,17	0,14	0,17	0,16
Neo.M.rate	99,16	98,13	92,48	52,32	24,32	18,17	10,91	9,92	6,85	3,84	2,4	1,69	1,17	0,87	0,58	0,23	0,16	0,09	0,08	0,12	0,18
All mult.	155	180	143	185	210	272	319	465	520	861	1297	1834	2684	3695	5378	7598	5314	2138	15549	100	20
Fetal †	70	66	36	26	21	11	12	19	15	25	23	25	38	29	47	29	20	6	10	1	0
Life born	85	114	107	159	189	261	307	446	505	836	1274	1809	2646	3666	5331	7569	5294	2132	15539	99	20
Neonat †	84	113	101	77	50	54	45	47	38	33	34	33	35	34	34	36	31	35	28	0	0
Fet.M-rate	45,16	36,67	25,17	14,05	10	4,04	3,76	4,09	2,88	2,9	1,77	1,36	1,42	0,78	0,87	0,38	0,38	0,28	0,06	1	0
Neo.M.rate	98,82	99.12	94,39	48,43	26,46	20,69	14,66	10,54	7,52	3,95	2,67	1,82	1,32	0,93	0,64	0,48	0,59	1,64	0,18	0	0
Attributable Risk %[1] (F)[2]	-27,25**	-29,44**	-28,42**	-33,56**	-25,18**	-22,69**	-17,34**	-13,11**	-8,75**	-6,35**	-4,83**	-3,02**	-1,51**	-1,27**	-0,19	-0,21*	0,09	0,11	-0,08**	0,83	-0,16
Relative Risk[3] (F)[2]	0.62**	0.55**	0.47**	0.30**	0.28**	0.15**	0.18**	0.24**	0.25**	0.31**	0.27**	0.31**	0.48**	0.38**	0.82	0.65*	1.30	1.67	0.45**	5.98	0
Attributable risk %[1] (N)[4]	-0,33	0.99	1,91	-3,89	2,13	2,52	3,75	0,62	0,67	0,12	0,27	0,14	0,16	0,06	0,06	0,25**	0,43**	1,55**	0,1**	-0,12	-0,18
Relative Risk[3] (N)[4]	1.00	1.01	1.02	0.93	1.09	1.14	1.34	1.06	1.10	1.03	1.11	1.08	1.14	1.08	1.10	2.07**	3.71**	17.97**	2.29**	0	0

GA = Gestational Age; Fetal † = Number of fetal deceased children; Neonatal † = Number of neonatal deceased children; Fet.M.rate = Fetal mortaqlity rate; Neo.M.rate = Neonatal mortality rate; PRN = Dutch Perinatal Regustry.

1: Risk among multiplets – risk among singletons; 2: Fetal mortality; 3: Risk among multiplets / risk among singletons; 4: Neonatal mortality; *: p<0.05; **: p<0.01.

Results

The total study population consisted of 1,211,446 newborns in the Netherlands (860,117 singletons and 34,348 children from multiplets) and of 316,921 newborns in Flanders (305,726 singletons and 11,195 children from multiplets).

Over a period of five years (2003-2007), the overall perinatal mortality rate decreased from 11.12‰ to 10.30‰ in the Netherlands and increased from 6.84‰ to 7.36‰ in Flanders. The decrease in the Netherlands was found in all categories observed. In Flanders, a decrease was found in term born singletons only (table 2).
Overall perinatal mortality in children from multiplets was higher than in singletons, but perinatal mortality rates in preterm born children from multiplets were lower than in preterm born singletons. In the Netherlands, over the total study period, a perinatal mortality rate of 6.12% in preterm born children from multiplets was found, versus 10.97% in preterm born singletons (RR, 0.56; 95%-CI, 0.53-0.59), while in term born singletons the perinatal mortality rate was 0.59% in children from multiplets versus 0.27% in singletons (RR, 2.17; 95%-CI, 1.84-2.56). The ratio of relative risks was 0.26 (95%-CI, 0.22-0.31; $p<0.05$). Perinatal data of Flanders showed comparable differences in mortality rates: 4.64% versus 6.51% in preterm children from multiplets and preterm singletons, respectively (RR, 0.71; 95%-CI, 0.64-0.79), and 0.52% versus 0.17% in term children from multiplets and term singletons, respectively (RR, 3.00; 95%-CI, 2.13-4.23). Here, the ratio of relative risks was 0.24 (95%-CI, 0.17-0.34; $p<0.05$).

The total neonatal mortality in both countries is, in general, higher in children from multiplets than in singletons except in the Netherlands in the years 2006 and 2007. On the other hand, fetal mortality is two to three times higher in preterm born singletons as compared to children from multiplets (figures 1 to 3) which lead to the higher perinatal mortality in the singleton group. As shown in table 3, the switch occurs after 37 completed weeks of pregnancy (259 days).

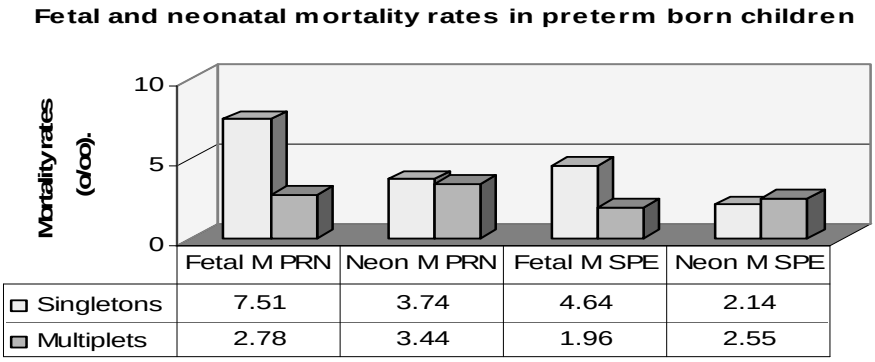

Figure 1a: Neonatal and perinatal mortality rates in singletons and twins 22–42 weeks of pregnancy 2003-2007.
Source: Netherlands Perinatal Registry (PRN)

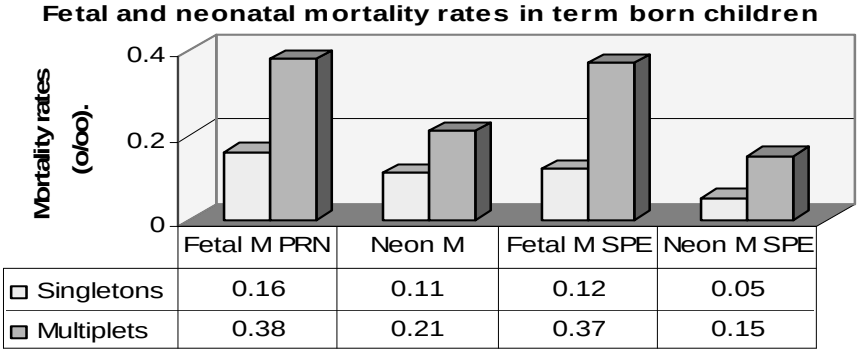

Figure 1b: Fetal, neonatal and perinatal mortality rates in singletons and twins 22–42 weeks of pregnancy 2003-2007.
Source: Netherlands Perinatal Registry (PRN)

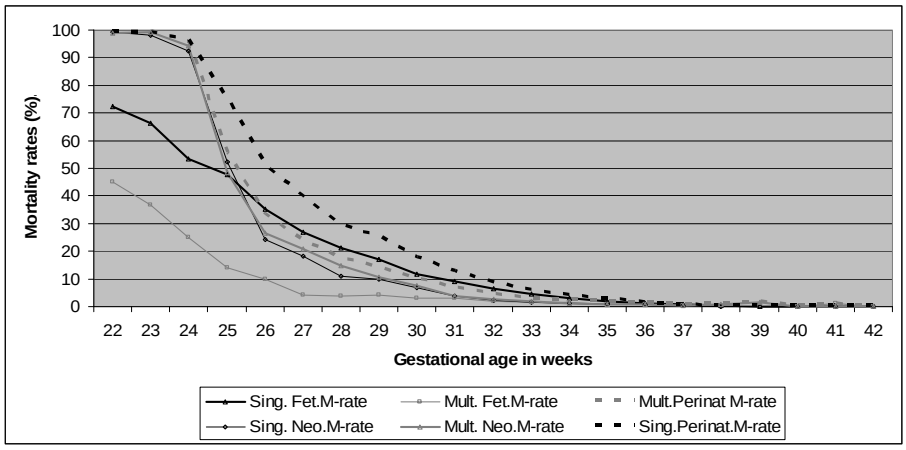

Figure 2: Fetal, neonatal and perinatal mortality rates in singletons and twins 22–42 weeks of pregnancy 2003-2007.
Source: Netherlands Perinatal Registry (PRN)

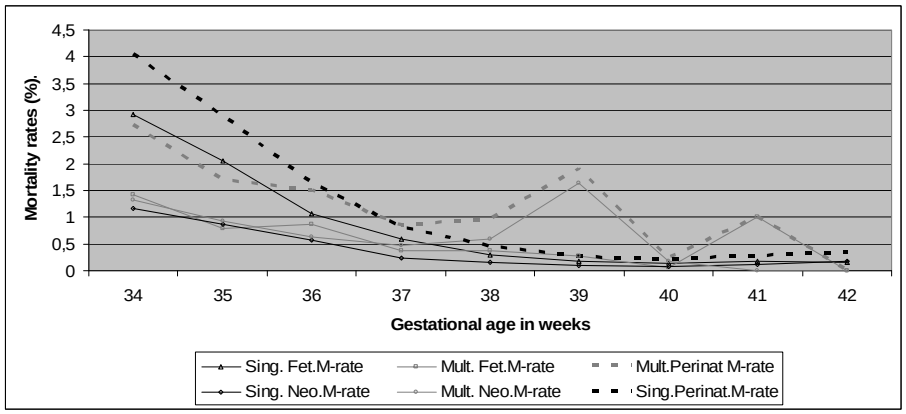

Figure 3: Fetal, neonatal and perinatal mortality rates in singletons and twins 34–42 weeks of pregnancy (2003–2007).
Source: Netherlands Perinatal Registry (PRN)

Discussion

Literature on fetal mortality in premature multiple pregnancies, compared to singleton pregnancies is scarce. In one study from Korea, the perinatal mortality rate in twin children was lower in neonates with gestational age above 29 weeks and birth weight ≥1000 grams compared to singletons [10]. Unfortunately no distinction was made between fetal and neonatal mortality or between term and preterm pregnancies.

Alexander et al [11] investigated fetal and neonatal mortality rates for singleton and multiple births in the United States over the years 1985-1988 and 1995-1998. Fetal mortality decreased in all groups (singletons and multiplets). In their study, fetal mortality rate including early fetal mortality rate (GA ≥20+0 and <27+0 weeks) and late fetal mortality rate (GA ≥27+0 weeks) as well as neonatal mortality rate remained higher for multiplet children. Between 1995 and 1998, twin children showed an approximately four times higher perinatal mortality as compared with singletons. In higher order multiplets perinatal mortality risk increased even nearly nine times. However, the highest fetal mortality rates were found for singletons with GA < 37 weeks and/or less than 2500 grams as compared to multiplet children. Nevertheless, the overall risk of fetal death as a proportion of the total deliveries proved to be lowest for singletons.

Draper et al [7] analyzed the survival chances of early preterm born children (22 to 32 weeks gestation) and calculated the odds ratio for birth weight and gestational age related survival for multiple birth compared with singleton infants as 1.4 (1.1 – 1.8). In this study, only infants known to be alive at the onset of labour, or when it was decided to deliver, were included and no data on fetal death are presented.

Since the 1970's the number of multiple pregnancies has risen (www.perinatreg.nl). This is likely the result of an increasing percentage of women postponing their offspring and the impact of assisted reproduction techniques [12]. In the Netherlands 3.5% of all newborns in 2007 were children from multiplets (6,122 out of 173,434 – source: PRN). The proportion of preterm deliveries in the multiplet infant group was 47.8% compared to 6.1% in the singleton group. Moreover, it is known (and shown once more in our data) that perinatal mortality is roughly 30 times higher among preterm born babies than among term born ones (table 2).

Consequently, one might expect that multiplets have a substantial impact on the total perinatal mortality: in the term group this effect is increasing while in the preterm group it is decreasing. Therefore it is important to investigate whether the lower preterm fetal mortality in multiplets may, at least in part, be due to possible differences in prenatal care.

One can speculate on possible explanations for this intriguing finding and try to explain the possible protective mechanisms responsible for the lower fetal death rate in multiple pregnancies with GA < 37+0 weeks (259 days). It is known that multiple pregnancies have a different antenatal and clinical management than singleton pregnancies [13, 14]. In the Netherlands midwives and GP's manage low risk singleton pregnancies in their own practice and a substantial number of these mothers aim to deliver at home. Multiple pregnancies on the other hand are managed by obstetricians and delivered in hospital. Their antenatal care provides more consultations with frequent ultrasound assessments of fetal growth and assessment of fetal

wellbeing (e.g. cardiotocography and Doppler flow of the umbilical artery, cervical length measurement).

The higher frequency of ultrasound guidance in multiple pregnancies enables to earlier detect IUGR resulting in earlier interventions [13]. It is known that IUGR is often missed in singletons especially if no ultrasound biometry is made during the second half of pregnancy [15, 16]. If growth restriction occurs in multiple pregnancies, management (timely induction of labour, which is the case in nearly 30% of all preterm deliveries in multiplets [14]) is comparable to IUGR-detected singletons. This might reduce the risk for fetal death of the growth restricted twin fetuses, also in cases of discordant growth. Besides, the caesarean section (CS) rate is significantly higher in preterm as well as in term born children of multiplets as compared to preterm born singletons (table 4). In addition, the clarification of inherent, and thus-far unknown, protecting mechanisms in multiple pregnancies may also be of importance.

On the other hand, a number of life born (co-)twins may die neonatally as a consequence of the (early) preterm delivery, which may partly explain the high neonatal mortality-rates in preterm life-born multiplet children. However, this hypothesis has not yet been tested in a quantitative manner.

Perinatal mortality rates decrease in singletons and multiplets until the 37th week of pregnancy. From that moment on, perinatal mortality in singletons shows a further decrease while in multiplets this is not the case (figure 3). Based upon this observation one may conclude to not further postpone delivery from that moment (between 37+0 and 37+6 weeks (GA = 259 and 266 days)).

In conclusion: There is indirect evidence supporting more frequent use of technical means in prenatal care in singletons comparable to daily practice in multiplets. The possible role of tocolysis, the extra use of ultrasound observations, planned induction of labour or planned caesarean section may be important features in the diagnosis and treatment for elevated-risk singletons as it is current in cases of multiple pregnancies.

More research is necessary to investigate the nature of the differences in perinatal mortality between singleton and multiple pregnancies. It is of interest to see whether these findings are comparable in other European countries or if they are specific for the Netherlands and Flanders.

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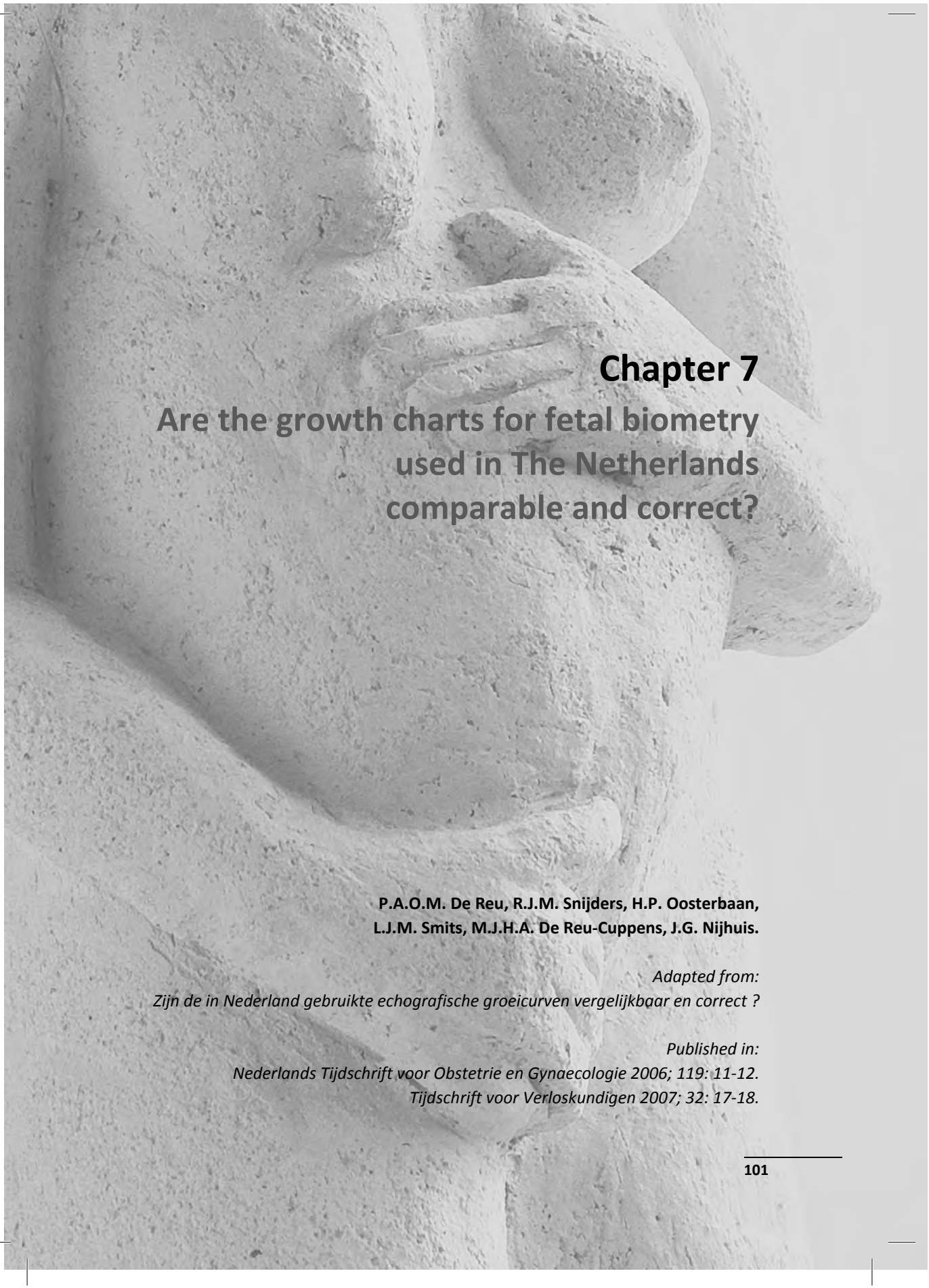
Part II

Third trimester fetal biometry: check for assessment of fetal growth



Chapter 7

Are the growth charts for fetal biometry used in The Netherlands comparable and correct?

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Zijn de in Nederland gebruikte echografische groeicurven vergelijkbaar en correct ?

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One of the most important aspects of antenatal care is the monitoring of fetal growth. This can be done by the ultrasonographic measurements of the fetus ("biometry"). In general, fetal biometry includes the measurement of crown-rump length (CRL), biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL).

In fact, in a substantial number of pregnancies, the early diagnosis of intrauterine growth restriction (IUGR) highly depends on a correct and accurately performed biometry. The significance of this accuracy is particularly demonstrated when the biometrical results are plotted on related reference charts.

To obstetrical caregivers it is most important to speak the same language concerning fetal growth estimation also in relation to the ultrasound evaluation.

Especially in this respect it became evident that we had a problem in the Netherlands for many years: at least four different reference curves are being used: the reference charts published by Chitty et al [1-4], the reference charts published by Snijders and Nicolaides in 1994 [5], reference charts from 1992 also attributed to Nicolaides and often called 'the NVOG-reference charts' [6] and, finally the reference charts of Snijders as presented in the Dutch manual 'Ultrasound in Obstetrics and Gynecology' of 2003 [7].

In theory it shouldn't be a problem when all caregivers consequently stick to identical charts for each individual patient. If on the contrary, different caregivers use different growth charts, the effect might lead to confusion (figures 1 and 2).

Thus it is possible that, when one caregiver makes a diagnosis of fetal growth restriction based on "his" fetal growth chart, the other caregiver using another fetal growth chart decides that the measurements are within the normal range. This not only leads to confusion among caregivers but also might upset pregnant women unnecessarily.

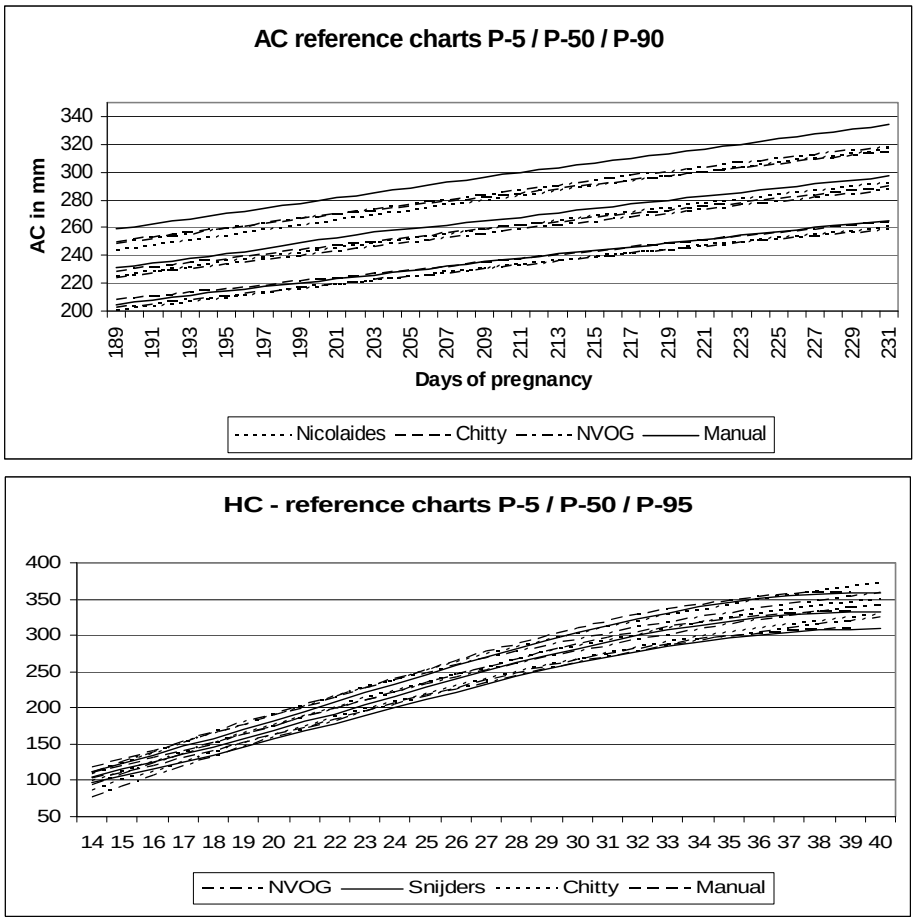
In the Netherlands the – so called – NVOG-charts (for BPD, AC, HC and FL) are most commonly used as they are used in the software of most ultrasound machines. Those charts were said to be based on the results of a transversal study of 1992 (n=40) from the obstetrical department of professor Nicolaides in London. The data plotted on these charts (which are normally sent to midwives or obstetricians who requested the examination) suggest that they were published by Nicolaides in 1992. However, it proved to be impossible for us to retrieve that particular publication. Finally it turned out that Nicolaides never published those reference charts in 1992 (Nicolaides, personal communication).

In fact, nothing is wrong with these charts but their origin is at least rather vague.

Besides, other reference charts, published in the Dutch textbook 'Ultrasound in Obstetrics and Gynecology' [7] are also in use. In this case we may speak of a real mistake.

These reference charts are said to be based on a publication of Snijders and Nicolaides published in 1994. However, when we compare the data in the textbook

with the data of the original publication, it became evident that the duration of pregnancy differs 3½ days for each measurement.



Figures 1 and 2: Different reference charts for HC and AC used in the Netherlands in 2006.
Notes: AC = Abdominal Circumference HC = Head Circumference NVOG = Reference charts of the Dutch Society of Obstetrics and Gynecology Snijders = Reference charts of Snijders and Nicolaides [5] Chitty = Reference charts of Chitty et al [2, 3] Manual = Reference charts of Snijders and Nicolaides as published in the Dutch manual [7].

This is caused by the fact that the average values of for instance 20+0 and 20+6 weeks of pregnancy as published in the original paper, are presented in the text-book as the value for 20+0 weeks of pregnancy.

The differences between those four reference charts also increase considerably. The 95th centile AC at 40th week of pregnancy in the original Snijders and Nicolaides-reference chart is 389 mm, while in the NVOG-reference chart it is only 369 mm. A difference of 2 cm! For the 5th percentile the difference is 'only' 1,1 cm (310 mm vs.

299 mm) but such a difference at that specific time in a pregnancy might be significant, especially when referring to IUGR.

In order to obtain uniformity and mutual comparability it is imperative that in the whole of the Netherlands, the same validated reference charts are used in all ultrasound machines and in all documents. This will contribute to more clarity for caregivers and less confusion for pregnant women.

The authors of this article do not want to suggest the use of any specific growth charts for application in the Dutch perinatal services. They only want to draw attention to the existing relevant differences between reference charts in use in the Netherlands and the vague origin of the NVOG-reference charts.

In addition, they want to make clear to obstetricians and midwives that the current indistinctness in this matter might confuse caregivers and distress pregnant women unnecessarily.

The working party on fetal ultrasound of the NVOG has been recently informed about our findings and will soon advise as to which reference charts should be used in the Netherlands.

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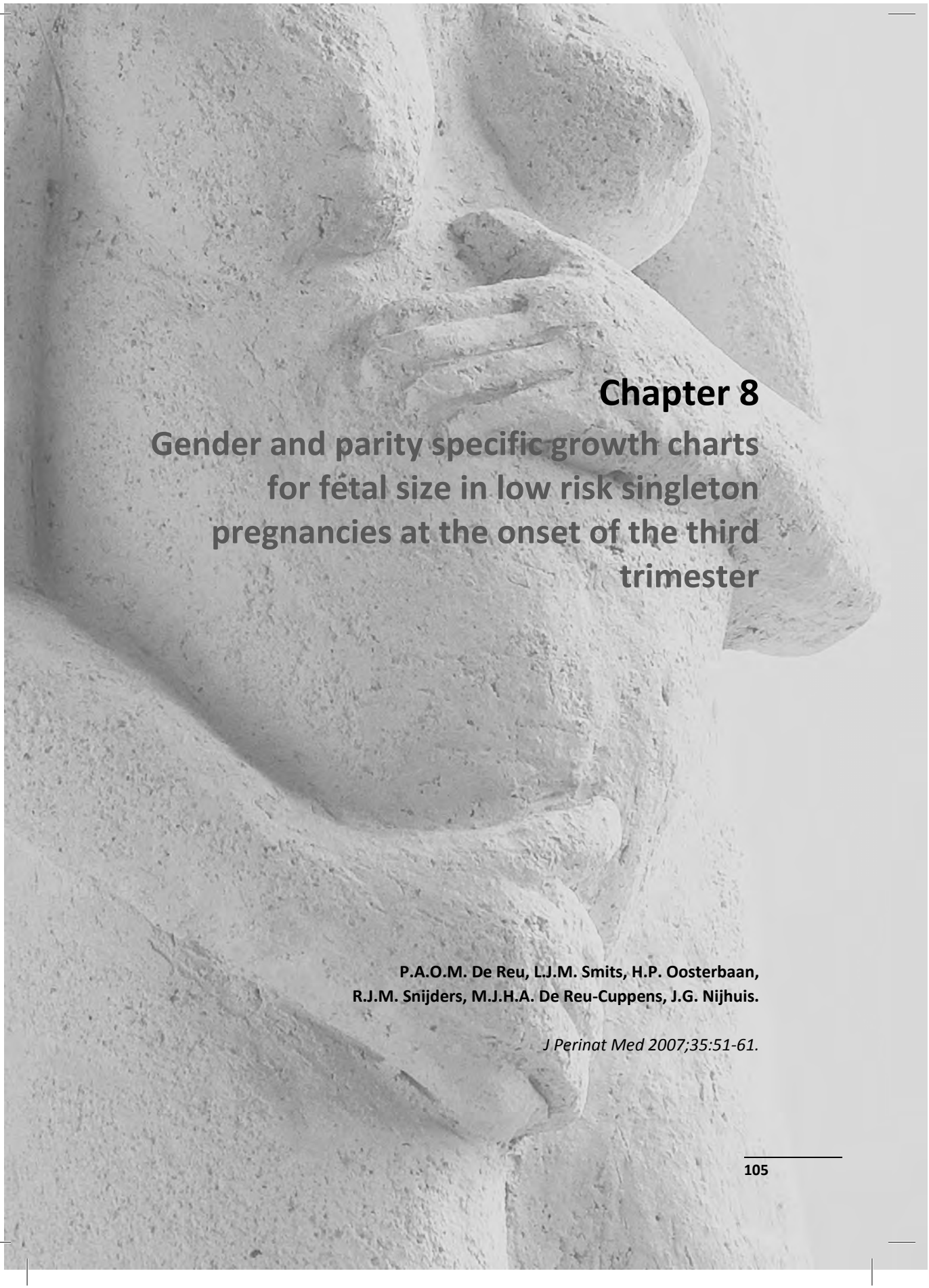

Chapter 8

Gender and parity specific growth charts for fetal size in low risk singleton pregnancies at the onset of the third trimester

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Abstract

Objectives: To determine fetal growth in low risk pregnancies at the beginning of the third trimester and to assess the relative importance of fetal gender and maternal parity.
Setting: Dutch primary care midwifery practice.
Study design: Retrospective cohort study on 3641 singleton pregnancies seen at a primary care midwifery centre in the Netherlands. Parameters used for analysis were fetal abdominal circumference (AC), fetal head circumference (HC), gestational age, fetal gender and maternal parity. Regression analysis was applied to describe variation in AC and HC with gestational age. Means and standard deviations in the present population were compared with commonly used reference charts. Multiple regression analysis was applied to examine whether gender and parity should be taken into account.
Results: Between the 27th and the 33rd week of pregnancy the fetal AC and HC increased significantly with gestation (AC $r^2 = 0.3652$, $p < 0.0001$; HC $r^2 = 0.3301$, $p < 0.0001$). Compared to some curves, our means and standard deviations were significantly smaller (at 30+0 weeks AC mean = 258 mm, SD = 13 mm; HC mean = 281 mm, SD = 14 mm) but corresponded well with other curves. Fetal gender was a significant determinant for both AC ($p < 0.0001$; ß = 0.01403) and HC ($p < 0.0001$; ß = 0.01674). Parity contributed significantly to AC only but the difference was small (ß = 0.00464).
Conclusion: At the begining of the third trimester, fetal size is associated with fetal gender and, to a lesser extent, with parity. Some fetal growth charts (e.g. Chitty et al.) are more suitable for the low-risk population in the Netherlands than others.
Key-words: Abdominal circumference, fetal growth, gender differences, head circumference, normal ranges, parity, ultrasound.

Introduction

In the Netherlands, prenatal care is provided by several professionals: midwives and general practitioners (GP's) operating at home and in hospital (primary care) and obstetricians (secondary and tertiary care). Over 85% of the pregnant women initially visit a midwife or GP for prenatal care. From booking onwards, the pregnant population is classified in low-risk, medium-risk or high-risk groups. Either the midwife or the GP will decide to which risk group a pregnant woman belongs according to the Dutch Perinatal Care List [10]. When a risk factor is identified or suspected at booking, or during the course of pregnancy, pregnant women will be referred to an obstetrician for detailed assessment and specialized care. Currently, about 40% of the pregnant women in the Netherlands deliver under guidance of a midwife or GP, and nearly 30% of all children are born at home [8]. This policy has always been seen as typically Dutch. However, out-of-hospital deliveries as well as prenatal care provided by midwives were re-introduced during the last decades in an increasing number of industrialized western countries (e.g. Canada, the U.K. and France).

In an earlier study we have demonstrated that the baby was small for gestational age in almost 50% of all cases of avoidable perinatal deaths [7]. For a safe home delivery it is important to exclude fetal growth restriction as well as excessive fetal growth, since both are known to be associated with increased perinatal morbidity and mortality [6]. As a consequence, a care-system like ours demands appropriate perinatal controls and observation of intrauterine growth in order to detect growth deviations as early as possible during pregnancy. These women must be referred to an obstetrician in time for further follow-up and detection analysis and subsequent therapy.

So far most primary care providers monitor fetal growth by abdominal palpation of the uterus only. Abdominal palpation has a rather low sensitivity for growth deviation [1, 2]. Although ultrasound application also has its limits in the detection of growth deviation [3, 18], this technique might improve the early diagnosis of both intrauterine growth retardation and excessive growth.

The "Verloskundig Centrum Midden Brabant" (Midden Brabant Midwifery Care Centre) is a primary care midwifery unit in which, contrary to the common national policy in midwifery care in the Netherlands until 2003, the routine use of ultrasound during pregnancy has already been established since 1982. Prenatal ultrasound examinations are routinely performed at the end of the first trimester (week 11 – 14) and at the beginning of the third trimester of pregnancy (week 27 – 33).

In the current study we have derived reference charts for Head Circumference (HC) and Abdominal Circumference (AC) for uncomplicated singleton pregnancies that were examined in our midwifery practice between 27+0 and 33+0 weeks of pregnancy. Means and standard deviations were compared to reference charts currently used. This is specifically of interest because no published curves are based

on data derived from a low-risk group only. Additionally, we assessed whether it would be useful to take into account two parameters that are known to affect size at birth: gender and parity [9,11].

Methods

Data of pregnant women, booked for prenatal primary care at our midwifery practice between 1993 until 2003, were collected retrospectively. The study focused on all singleton pregnancies of Caucasian women who were still under our care at the 27th week of gestation. All data included in the study were derived from patients without risk factors or any pathology at the onset of the third trimester. Gestational age was assessed by ultrasound examination between the 10th and 14th week using the crown-rump length reference curve of Robinson and Fleming [14]. Gestational age was adjusted if the expected date of delivery, based on the first day of the last menstrual period, differed more than 7 days from the expected date based on the crown-rump length.

Third-trimester ultrasound examinations were scheduled between week 27+0 and 33+0 of pregnancy (189 – 231 days). All scans were performed by one of six trained midwife-sonographers using a standard protocol. HC (outer-outer) was measured at the level of the septum cavum pellucidum. AC was measured in a transverse section at the level of the stomach and the bifurcation of the main portal vein. Information of parity was collected at the first visit, and fetal gender was determined at birth. During the 11-years study period the following ultrasound machines were used: Toshiba Sal-20 linear array scanner (Toshiba; Tokyo, Japan); Pie Data Scanner 150-S (EsaotePie; Maastricht, the Netherlands); Toshiba Capasee SSA 220S (Toshiba; Tokyo, Japan) and Aloka 100-S (Aloka; Okinawa, Japan).

For each case, the following data were stored in an Excel file: parity (primiparous=0, multiparous=1), gestational age (in days), AC (in mm), HC (in mm) and gender (girl=0, boy=1).

Our method of constructing gestational age specific reference charts was similar to that previously employed by Snijders and Nicolaides [16]. First, we stabilized variance of the AC and HC across the gestational age spectrum by means of logarithmic transformation. Then we compared, for both AC and HC, three models: one with gestational age as a linear term only, one with the linear and quadratic terms, and one with the linear, quadratic and cubic terms. If the quadratic and cubic terms did not improve the original linear model (an independent correlation with $p<0.05$ and increase in variance explained) the linear model was chosen as the model with the best fit. Otherwise, the cubic or both the cubic and the quadratic term were maintained in the model.

Because our measurements were done within a restricted range of gestational ages (189-231 days), the model with the best fit might show biologically implausible upward or downward deviations at the extremes. If that was the case, we chose the second best model with sufficient biological plausibility. After choosing the appropriate models for predicting the (transformed) HC and AC, we used them to calculate (transformed) gestational age-specific means and centiles.

The following formula for the calculation of (transformed) centiles was used [15]: (transformed) centile = (transformed) mean + K * mean of the (transformed) residuals where K was the corresponding centile of the Gaussian distribution (e.g. K=1.645 for calculation of 5^{th} and 95^{th} centiles). In order to produce reference ranges in the original (untransformed) units, we applied anti-logarithmic transformation to the transformed means and centiles.

Mean and 5^{th} and 95^{th} percentiles for fetal AC and HC in our population were compared to reference values commonly used in Dutch perinatal centres (Snijders and Nicolaides [16], Chitty et al. [4, 5]).

The effect of maternal parity and fetal gender was assessed by adding both parameters to a multiple regression model. If parity or gender had a significant independent effect on fetal size (i.e. $p<0.05$), we maintained the variable in the model. Otherwise the parameter was omitted.

For all statistic procedures, SAS for windows version 8.02 was used (SAS-institute inc., Cary, North Carolina).

On the basis of the resulting models, we constructed, where appropriate, gender- and parity-specific growth charts (tables 1 – 6).

Results

During the study-period, a total of 5,067 pregnant women were seen for prenatal care in our midwifery practice. Data of 1,426 (28.1 %) pregnancies were excluded from analysis for the following reasons:

- non-Caucasian background (n = 224);
- multiple pregnancy (n = 59);
- miscarriage < 16+0 weeks (n = 544);
- no scan performed during first and/or third trimester of pregnancy (n = 110);
- data not fully documented (i.e. prints not available) or biometry not reliable (n = 389);
- diagnosis of perinatal death or fetal anomaly before 28^{th} week (n = 7);
- transfer to a consultant obstetrician before the 28th week of gestation because a risk-factor was identified (n = 40);
- no outcome data available (n = 25);
- scan performed outside the studied gestational age range (n = 28).

Data from the remaining 3,641 pregnancies were used for analysis. The model with the best fit for the association between AC by gestational age contained both the quadratic and the cubic term of gestational age. This model yielded a reference curve that flattened towards nearly horizontal at the right extreme, which we considered biologically implausible before the 34th week of pregnancy.

The next best model demonstrated a linear increase (ln AC = 4.43323 + 0.005334 * gestational age (r^2 = 0.3652, p (model) < 0.0001) table 1). The explained variance of this model was only marginally lower than that of the more complex model (r^2 = 0.3652 vs r^2 = 0.3669).The association between HC and gestational age was best described by ln(HC) = 3.84750 + 0.01355 * gestational age – 0.00002390 * gestational age^2 ((r^2 = 0.3301, p (model)< 0.0001).

In figures 1 and 2, the mean and 5th and 95th centiles of HC and AC in our population are compared with values reported by Snijders and Nicolaides [16] and Chitty et al [4, 5].

From 28 weeks onward (196 days) our HC measurements became smaller than those reported by Snijders and Nicolaides [16], but they compared well with those reported by Chitty et al [4]. The difference from the Snijders and Nicolaides curve increased with gestational age reaching 20 mm (= 2 wks) at 33 weeks.

At 27 weeks our mean AC measurement compared well with the mean reported by both Snijders and Nicolaides [16], and Chitty et al. [5]. Our 5th centile was similar to that reported by Chitty et al. [4] but higher than the 5th centile reported by Snijders and Nicolaides [16]. At 33 weeks, our mean and 95th centiles were smaller than the values reported by Snijders and Nicolaides (9 mm = 1 wk) [16], but similar to those reported by Chitty et al [5].

Both fetal gender and maternal parity turned out to be statistically significant determinants for AC (figures 3 – 6). Inclusion of gender and parity led to the following model: ln(AC) = 4.42281 + 0.0534 * gestational age + 0.00464* parity + 0.01403 * gender (r^2 = 0.3788 ; p (parity) = 0.0049 ; p (gender) < 0.0001).

Gender, but not parity, was a statistically significant determinant for HC (figure 7). The gender-adjusted model was: ln(HC) = 3.83480 + 0.01360 * gestational age – 0.00002403 * gestational age^2 + 0.01674 * gender (r^2 = 0.3664 ; p (gender) < 0.0001.

Table 1: Abdominal Circumference (AC) for boys in primiparae.

Pregn weeks	Pregn. days	Observations	P-5	P-25	P-50	P-75	P-95
27	189						
	190						
	191	2	215.8	226.5	234.2	242.1	254.1
	192	3	217.0	227.7	235.4	234.4	255.5
	193	1	218.1	228.9	236.7	244.7	256.8
	194	7	219.3	230.1	238.0	246.1	258.2
	195	8	220.5	231.4	239.2	247.4	259.6
28	196	16	221.7	232.6	240.5	248.7	261.0
	197	26	222.8	233.8	241.8	250.0	262.4
	198	25	224.0	235.1	243.1	251.4	263.8
	199	25	225.2	236.3	244.4	252.7	265.2
	200	30	226.4	237.6	245.7	254.1	266.6
	201	54	227.6	238.9	247.0	255.4	268.0
	202	44	228.9	240.2	248.3	256.8	269.5
29	203	48	230.1	241.4	249.7	258.2	270.9
	204	52	231.3	242.7	251.0	259.5	272.3
	205	50	232.6	244.0	252.3	260.9	273.8
	206	46	233.8	245.3	253.7	262.3	275.3
	207	46	235.1	246.7	255.0	263.7	276.7
	208	48	236.3	248.0	256.4	265.1	278.2
	209	46	237.6	249.3	257.8	266.6	279.7
30	210	42	238.8	250.6	259.2	268.0	281.2
	211	50	240.1	252.0	260.6	269.4	282.7
	212	41	241.4	253.3	261.9	270.9	284.2
	213	31	242.7	254.7	263.3	272.3	285.7
	214	29	244.0	256.0	264.8	273.8	287.3
	215	23	245.3	257.4	266.2	275.2	288.8
	216	17	246.6	258.8	267.6	276.7	290.4
31	217	15	247.9	260.2	269.0	278.2	291.9
	218	3	249.3	261.6	270.5	279.7	293.5
	219	12	250.6	263.0	271.9	281.2	295.0
	220	13	251.9	264.4	273.4	282.7	296.6
	221	3	253.3	265.8	274.8	284.2	298.2
	222	8	254.6	267.2	276.3	285.7	299.8
	223	8	256.0	268.6	277.8	287.2	301.4
32	224	8	257.4	270.1	279.3	288.8	303.0
	225	3	258.8	271.5	280.8	290.3	304.6
	226	6	260.1	273.0	282.3	291.9	306.3
	227	0	261.5	274.5	283.8	293.5	308.0
	228	2	262.9	275.9	285.3	295.0	309.6
	229	2	264.3	277.4	286.8	296.6	311.2
	230	1	265.7	278.9	288.4	298.2	312.9
33	231	2					

Table 2: Abdominal Circumference (AC) for boys in multiparae.

Pregn weeks	Pregn. days	Observations	P-5	P-25	P-50	P-75	P-95
27	189	2	214.5	225.1	232.8	240.7	252.6
	190	0	215.7	226.3	234.1	242.0	254.0
	191	2	216.8	227.5	235.3	243.3	255.3
	192	8	218.0	228.7	236.5	244.6	256.6
	193	4	219.5	230.0	237.8	245.9	258.0
	194	3	220.3	231.2	239.1	247.2	259.4
	195	12	221.5	232.4	240.3	248.5	260.8
28	196	27	222.7	233.7	241.6	249.9	262.2
	197	20	223.9	235.0	242.9	251.2	263.6
	198	29	225.1	236.2	244.2	252.5	265.0
	199	40	226.3	237.4	246.0	253.9	266.4
	200	35	227.5	238.7	246.8	255.2	267.8
	201	47	228.7	240.0	248.2	256.6	269.3
	202	50	229.9	241.3	249.5	258.0	270.7
29	203	48	231.2	242.6	250.8	259.4	272.2
	204	48	232.4	243.9	252.2	260.7	273.6
	205	61	233.6	245.2	253.5	262.1	275.1
	206	67	234.9	246.5	254.9	263.5	276.6
	207	44	236.1	247.8	256.2	265.0	278.0
	208	50	237.4	249.1	257.6	266.4	279.5
	209	46	238.7	250.5	259.0	267.8	281.0
30	210	48	240.0	251.8	260.4	269.2	282.5
	211	26	241.2	253.1	261.8	270.7	284.0
	212	33	242.5	254.5	263.2	272.1	285.5
	213	44	243.8	255.9	264.6	273.6	287.1
	214	31	245.1	257.2	266.0	275.0	288.6
	215	23	246.4	258.6	267.4	276.5	290.2
	216	25	247.8	260.0	268.8	278.0	291.7
31	217	14	249.1	261.4	270.3	279.5	293.3
	218	10	250.4	262.8	271.7	281.0	294.8
	219	9	251.8	264.2	273.2	282.5	296.4
	220	9	253.1	265.6	274.6	284.0	298.0
	221	14	254.5	267.0	276.1	285.5	299.6
	222	20	255.8	268.4	277.6	287.0	301.2
	223	5	257.2	269.9	279.1	288.6	302.8
32	224	10	258.6	271.3	280.6	290.1	304.4
	225	4	260.0	272.8	282.1	291.7	306.1
	226	2	261.3	274.2	283.6	293.2	307.7
	227	1	262.7	275.7	285.1	294.8	309.3
	228	1	264.1	277.2	286.6	296.4	311.0
	229	2	265.6	278.7	288.2	298.0	312.7
	230	0	267.0	280.2	289.7	299.6	314.4
33	231	1	268.4	281.7	291.2	301.2	316.0

Table 3: Abdominal Circumference (AC) for girls in primiparae.

Pregn weeks	Pregn. days	Observations	P-5	P-25	P-50	P-75	P-95
27	189						
	190						
	191	2	212.8	223.3	230.9	238.8	250.6
	192	3	213.9	224.5	232.1	240.1	251.9
	193	2	215.1	225.7	233.4	241.3	253.2
	194	5	216.2	226.9	234.6	242.6	254.6
	195	9	217.4	228.1	235.9	243.9	256.0
28	196	20	218.6	229.3	237.2	245.2	257.3
	197	17	219.7	230.6	238.4	246.5	258.7
	198	14	220.9	231.8	239.7	247.9	260.1
	199	35	222.1	233.1	241.0	249.2	261.5
	200	31	223.3	234.3	242.3	250.5	262.9
	201	28	224.5	235.6	243.6	251.9	264.3
	202	32	225.7	236.8	244.9	253.2	265.7
29	203	46	226.9	238.1	246.2	254.6	267.1
	204	41	228.1	239.4	247.5	255.9	268.6
	205	40	229.3	240.6	248.8	257.3	270.0
	206	60	230.5	241.9	250.2	258.7	271.4
	207	38	231.8	243.2	251.5	260.1	272.9
	208	45	233.0	244.5	252.8	261.4	274.3
	209	39	234.3	245.8	254.2	262.8	275.8
30	210	50	235.5	247.1	255.6	264.3	277.3
	211	41	236.8	248.5	256.9	265.7	278.8
	212	32	238.0	249.8	258.3	267.1	280.3
	213	31	239.3	251.1	259.7	268.5	281.8
	214	24	240.6	252.5	261.1	270.0	283.3
	215	24	241.9	253.8	262.5	271.4	284.8
	216	11	243.2	255.2	263.9	272.9	286.3
31	217	12	244.5	256.5	265.3	274.3	287.8
	218	11	245.8	257.9	266.7	275.8	289.4
	219	11	247.1	259.3	268.1	277.3	290.9
	220	6	248.4	260.7	269.6	278.7	292.5
	221	6	249.8	262.1	271.0	280.2	294.1
	222	5	251.1	263.5	272.5	281.7	295.6
	223	3	252.4	264.9	273.9	283.2	297.2
32	224	1	253.8	266.3	275.4	284.8	298.8
	225	4	255.1	267.7	276.8	286.3	300.4
	226	1	256.5	269.2	278.3	287.8	302.0
	227	2	257.9	270.6	279.8	289.3	303.6
	228	8	259.3	272.1	281.3	290.9	305.2
	229	1	260.6	273.5	282.8	292.5	306.9
	230	0	262.0	275.0	284.4	294.1	308.5
33	231	2	263.4	276.4	285.9	295.6	310.1

Table 4: Abdominal Circumference (AC) for girls in multiparae.

Pregn weeks	Pregn. days	Observations	P-5	P-25	P-50	P-75	P-95
27	189	1	211.5	222.0	229.5	237.3	249.0
	190	1	212.7	223.2	230.8	238.6	250.4
	191	1	213.8	224.3	232.0	239.9	251.7
	192	3	214.9	225.5	233.2	241.2	253.1
	193	5	216.1	226.8	234.5	242.5	254.4
	194	9	217.2	230.0	235.7	243.8	255.8
	195	10	218.4	229.2	237.0	245.1	257.6
28	196	26	219.6	230.4	238.3	246.4	258.5
	197	31	220.8	231.6	239.5	247.7	259.9
	198	29	221.9	232.9	240.8	249.0	261.3
	199	38	223.1	234.1	242.1	250.3	262.7
	200	36	224.3	235.4	243.4	251.7	264.1
	201	37	225.5	236.6	244.7	253.0	265.5
	202	45	226.7	237.9	246.0	254.4	266.9
29	203	68	227.9	239.2	247.3	255.7	268.4
	204	44	229.2	240.5	248.7	257.1	269.8
	205	50	230.4	241.8	250.0	258.5	271.2
	206	52	231.6	243.0	251.3	259.9	272.7
	207	49	232.9	244.3	252.7	261.3	274.2
	208	44	234.1	245.7	254.0	262.7	275.6
	209	50	235.4	247.0	255.4	264.1	277.1
30	210	45	236.6	248.3	256.7	265.5	278.6
	211	38	237.9	249.6	258.1	266.9	280.1
	212	38	239.6	251.0	259.5	268.3	281.6
	213	31	240.4	252.3	260.9	269.8	283.1
	214	36	241.7	253.6	262.3	271.2	284.6
	215	23	243.0	255.0	263.7	272.7	286.1
	216	24	244.3	256.4	265.1	274.1	287.6
31	217	18	245.6	257.7	266.5	275.6	289.2
	218	17	246.9	259.1	267.9	277.1	290.7
	219	14	248.3	260.5	269.4	278.5	292.3
	220	18	249.6	261.9	270.8	280.0	293.9
	221	5	250.9	263.3	272.3	281.5	295.4
	222	3	252.3	264.7	273.7	283.0	297.0
	223	7	253.6	266.1	275.2	284.6	298.6
32	224	5	255.0	267.5	276.7	286.1	300.2
	225	5	256.3	269.0	278.1	287.6	301.8
	226	3	257.7	270.4	279.6	289.1	303.4
	227	1	259.1	271.9	281.1	290.7	305.0
	228	2	260.5	273.3	282.6	292.2	306.7
	229	3	261.9	274.8	284.1	293.8	308.3
	230	2	263.3	276.3	285.7	295.4	309.6
33	231	1	264.7	277.7	287.2	297.0	311.6

Table 5: Head Circumference (HC) for boys.

Pregn weeks	Pregn. days	Observations	P-5	P-25	P-50	P-75	P-95
27	189	2	246.1	254.6	260.7	266.9	276.1
	190	0	247.2	255.8	261.9	268.1	277.3
	191	4	248.3	256.9	263.0	269.3	278.5
	192	11	249.4	258.0	264.1	270.4	279.8
	193	5	250.5	259.1	265.3	271.6	281.0
	194	10	251.6	260.2	266.4	272.8	282.2
	195	20	252.6	261.3	267.6	274.0	283.4
28	196	43	253.7	262.4	268.7	275.1	284.6
	197	46	254.8	263.5	269.8	276.3	285.8
	198	54	255.8	264.6	270.9	277.4	287.0
	199	65	256.8	265.7	272.0	278.5	288.1
	200	65	257.9	266.8	273.1	279.6	289.3
	201	101	258.9	267.8	274.2	280.7	290.4
	202	94	259.9	268.9	275.3	281.9	291.6
29	203	96	260.9	269.9	276.4	282.9	292.7
	204	100	261.9	271.0	277.4	284.0	293.8
	205	111	262.9	272.0	278.5	285.1	294.9
	206	113	263.9	273.0	279.5	286.2	296.0
	207	90	264.9	274.0	280.5	287.2	297.1
	208	99	265.8	275.0	281.5	288.3	298.2
	209	92	266.8	276.0	282.6	289.3	299.3
30	210	92	267.7	277.0	283.6	290.3	300.3
	211	76	268.7	277.9	284.5	291.3	301.4
	212	64	269.6	278.9	285.5	292.3	302.4
	213	85	270.5	279.8	286.5	293.3	303.4
	214	60	271.4	280.6	287.4	294.3	304.4
	215	46	272.3	281.7	288.4	295.3	305.4
	216	42	273.2	281.7	288.4	295.3	305.4
31	217	29	274.0	283.5	290.3	297.2	307.4
	218	13	274.9	284.4	291.2	298.1	308.4
	219	21	275.8	285.3	292.1	299.0	309.3
	220	22	276.6	286.1	293.0	299.9	310.3
	221	17	277.4	287.0	293.8	300.8	311.2
	222	28	278.3	287.9	294.7	301.7	312.1
	223	13	279.1	288.7	295.6	302.6	313.1
32	224	18	279.9	289.5	296.4	303.5	313.9
	225	7	280.7	290.3	297.3	304.3	314.8
	226	8	281.4	291.1	298.1	305.2	315.7
	227	1	282.2	291.9	298.9	306.0	316.6
	228	3	282.9	292.7	299.7	306.8	317.4
	229	4	283.7	293.5	300.5	307.6	318.2
	230	1	284.4	294.2	301.2	308.4	319.1
33	231	1	285.1	295.0	302,0	309.2	319.6

Table 6: Head Circumference (HC) for girls.

Pregn weeks	Pregn. days	Observations	P-5	P-25	P-50	P-75	P-95
27	189	1	242.0	250.4	256.3	262.4	271.5
	190	1	243.1	251.5	257.6	263.6	272.7
	191	3	244.2	252.6	258.6	264.7	273.9
	192	6	245.3	253.7	259.8	266.0	275.1
	193	7	246.3	254.8	260.9	267.1	276.3
	194	14	247.4	255.9	262.0	268.3	277.5
	195	19	248.4	257.0	263.1	269.4	278.7
28	196	46	249.5	258.1	264.2	270.5	279.9
	197	48	250.5	259.2	265.3	271.7	281.0
	198	43	251.6	260.2	266.4	272.8	282.2
	199	73	252.6	261.3	267.5	273.9	283.3
	200	67	253.6	262.3	268.6	275.0	284.5
	201	65	254.6	263.4	269.7	276.1	285.6
	202	77	255.6	264.4	270.7	277.2	286.7
29	203	114	256.6	265.4	271.8	278.2	287.8
	204	85	257.5	266.5	272.8	279.3	288.9
	205	90	258.5	267.5	273.8	280.4	290.0
	206	112	259.5	268.5	274.9	281.4	291.1
	207	87	260.5	269.4	275.9	282.4	292.2
	208	89	261.4	270.4	276.9	283.5	293.2
	209	89	262.3	271.4	277.9	284.5	294.3
30	210	95	263.3	272.4	278.8	285.5	295.3
	211	79	264.2	273.3	279.8	286.5	296.4
	212	70	265.1	274.2	280.8	287.5	297.4
	213	62	266.0	275.2	281.7	288.5	298.4
	214	71	266.9	276.1	282.7	289.4	299.4
	215	47	267.8	277.0	283.6	290.4	300.4
	216	35	268.6	277.9	284.5	291.3	301.4
31	217	30	269.5	278.8	285.4	292.2	302.3
	218	28	270.3	279.7	286.3	293.2	303.3
	219	25	271.2	280.5	287.2	294.1	304.2
	220	24	272.0	281.4	288.1	295.0	305.1
	221	11	272.8	282.2	289.0	295.9	306.1
	222	8	273.6	283.1	289.8	296.7	307.0
	223	10	274.4	283.9	290.7	297.6	307.9
32	224	6	275.2	284.7	291.5	298.4	308.7
	225	9	276.0	285.5	292.3	299.3	309.6
	226	4	276.8	286.3	293.1	300.1	310.5
	227	3	277.5	287.1	293.9	300.9	311.3
	228	6	278.2	287.8	294.7	301.7	312.1
	229	4	279.0	288.6	295.5	302.5	313.0
	230	2	279.7	289.3	296.2	303.3	313.8
33	231	3	280.4	290.1	297.0	304.1	314.5

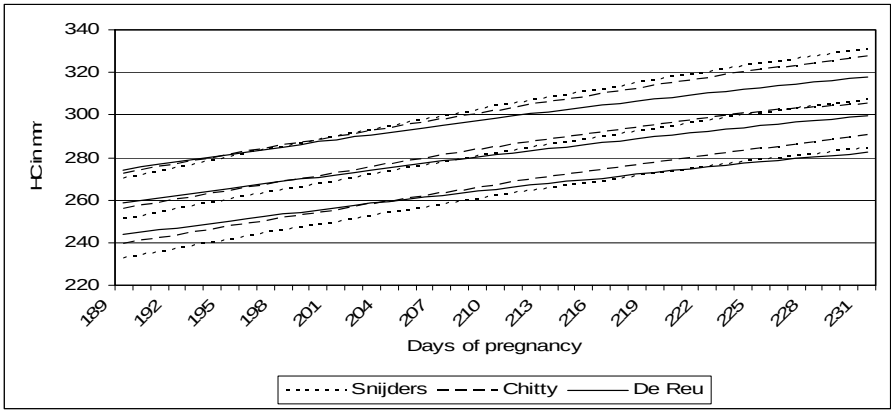

Figure 1: Head circumferences (all) compared with values reported by Snijders and Nicolaides and by Chitty et al.

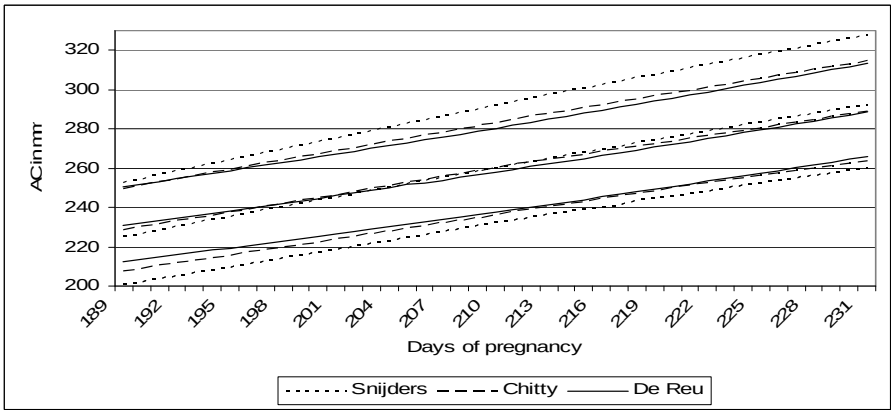

Figure 2: Abdominal circumferences (all) compared with values reported by Snijders and Nicolaides and by Chitty et al.

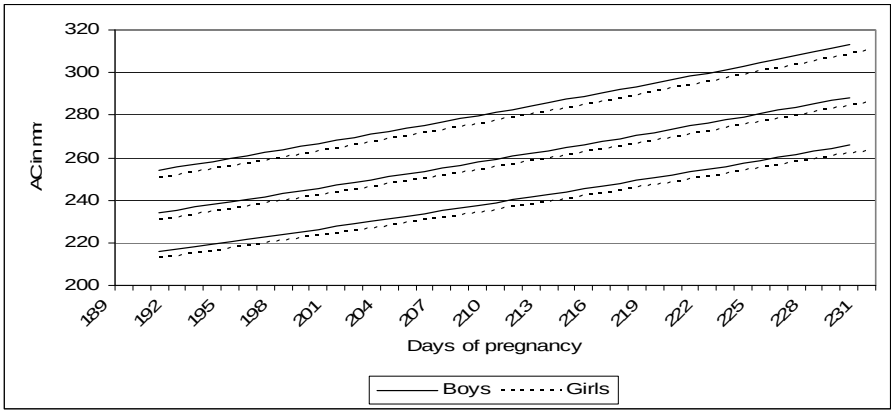

Figure 3: Abdominal circumference for boys versus girls in primiparae.

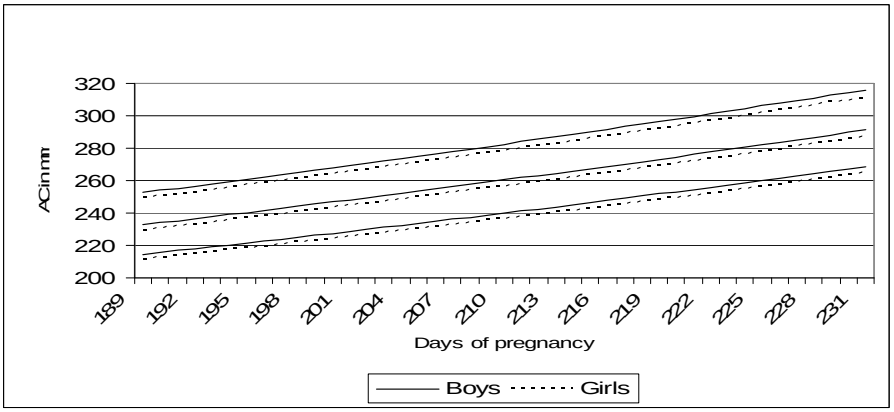

Figure 4: Abdominal circumference for boys versus girls in multiparae.

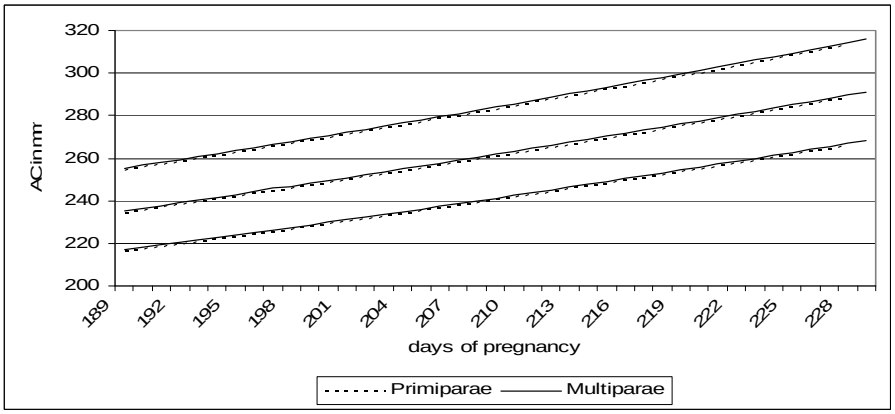

Figure 5: Abdominal circumference for boys: primiparae versus multiparae.

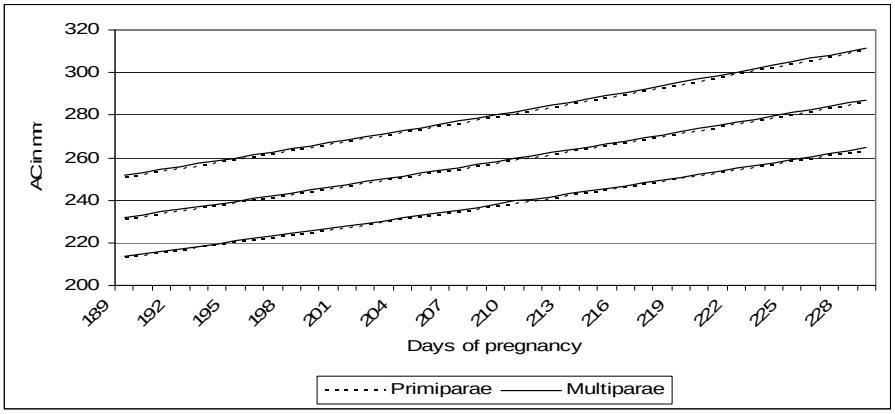

Figure 6: Abdominal circumference for girls: primiparae versus multiparae.

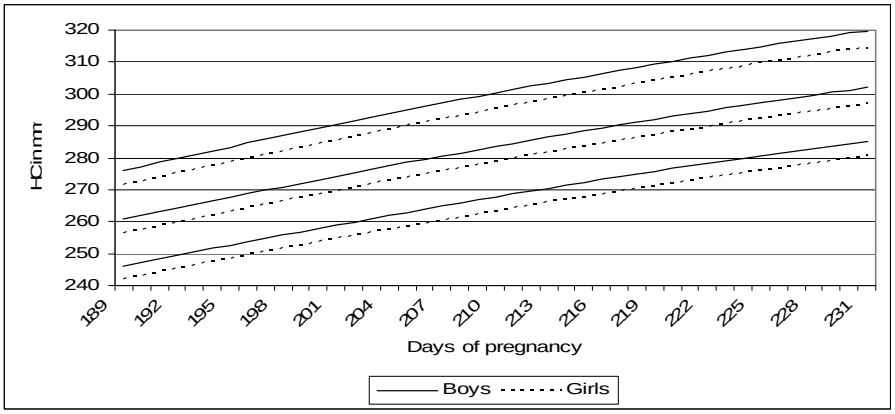

Figure 7: Head circumference for boys versus girls.

Discussion

Fetal growth abnormalities are highly correlated with perinatal morbidity and mortality [7]. An ultrasound examination early in the third trimester may provide accurate information on fetal size and as a consequence it may facilitate early diagnosis of impaired or excessive fetal growth. This information could be of great importance in risk selection and the decision about the location and mode of delivery.

It is known from studies on live born infants that boys are heavier than girls and that first-born infants weigh on average less than infants subsequently born [9, 11]. The hypothesis that gender affect size even before birth has been confirmed in

several studies [12, 13]. Yet these parameters are not routinely taken into account when fetal growth is assessed.

In the present study mean values of AC and 95th centile of the HC were smaller than the ones presented by Snijders and Nicolaides [16]. Also the standard deviations were smaller. Our means and standard deviations compare well with those presented by Chitty et al. [4, 5]. Moreover the reference ranges presented by Chitty et al. are valid already from the 10th week of gestation onwards, whereas the Snijders and Nicolaides curves only start at the 14th week. Therefore we consider the reference ranges of Chitty et al. more appropriate for use within the Dutch population than the Snijders and Nicolaides reference ranges.

In this article, we choose to define the 5^{th} and 95^{th} centiles in order to compare easily with the reference values of the above mentioned authors.

Until now, sonographers have rarely taken fetal gender into account. Data from the present study indicate that for optimal assessment of fetal growth it may be important to take fetal gender, and to a lesser extend, fetal parity into account. These findings are in line with the findings of Schwärtzler et al. [17] who also demonstrated that in male fetuses the biparietal diameter (BPD), fetal abdominal circumference (AC) and head circumference (HC) are significantly larger than in female fetuses, whilst the femur length (FL) is not significantly different.

Comparison of prenatal size of first and subsequently born children demonstrated that there is a small difference in AC but not in HC. To our knowledge no studies on this subject have been performed before.

Our data demonstrate that the difference in the measurements of a male or a female fetus at a certain gestational length and parity might be relevant.

We conclude that, in the third trimester, fetal size is significantly associated with fetal gender and, to a lesser extent, with parity. In a prospective ongoing study we are now investigating whether the present data are indeed helpful to select those fetuses, which are at risk for growth deviation near term, and should therefore get extra attention, and thus should be referred to the obstetrician.

Acknowledgements

We would like to thank Lian Rijkers, Mariëtte Frerichs-Pauw, Manon van Mil and Helma Tichelman-Brands for their sonographic contribution.

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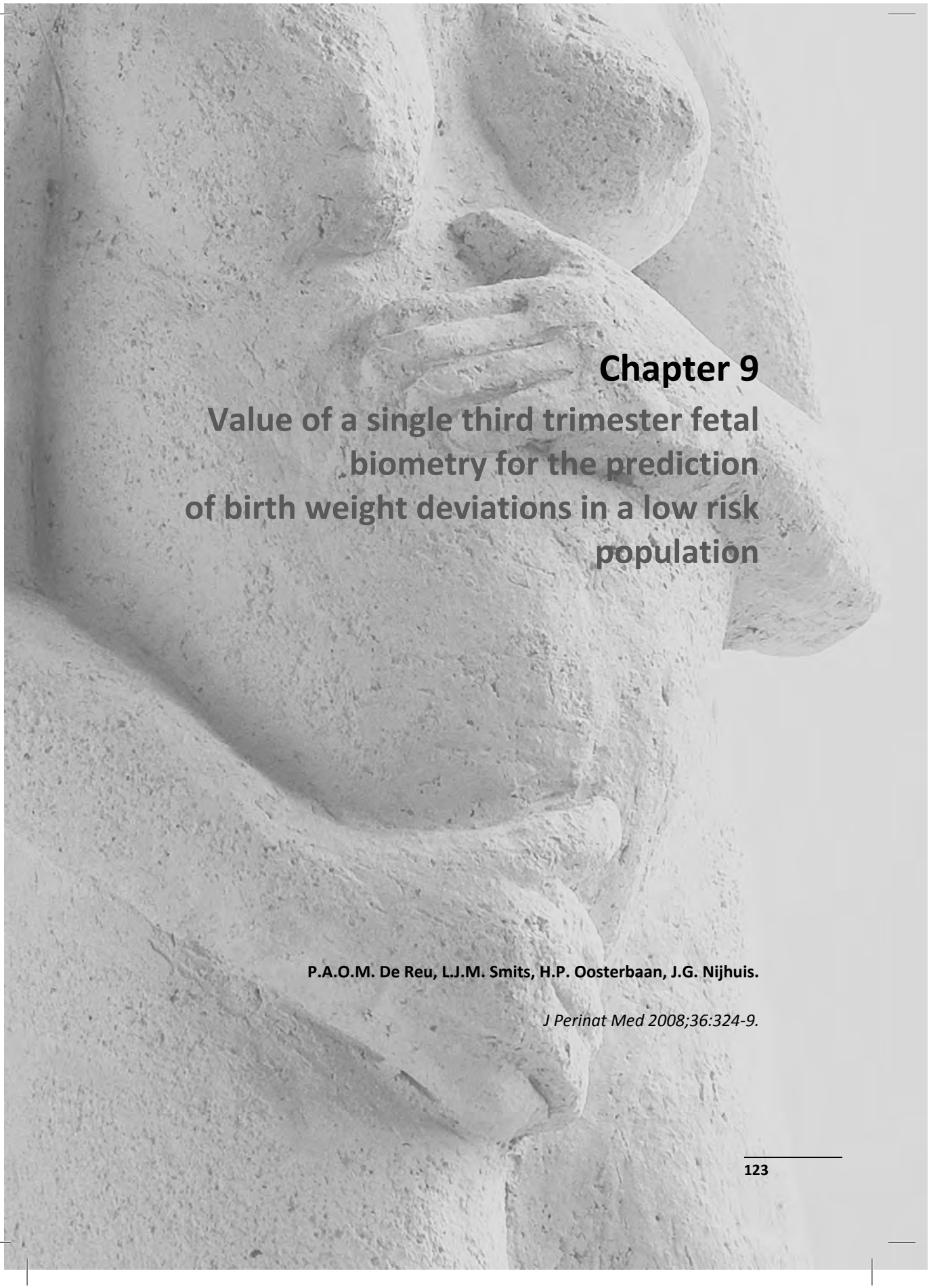

Chapter 9

Value of a single third trimester fetal biometry for the prediction of birth weight deviations in a low risk population

P.A.O.M. De Reu, L.J.M. Smits, H.P. Oosterbaan, J.G. Nijhuis.

J Perinat Med 2008;36:324-9.

Abstract

Objective: To analyze the value of a single ultrasound biometry examination at the onset of the third trimester of pregnancy for the detection of small-for-gestational-age (SGA) and large-for-gestational-age (LGA) at birth in a low risk population. The aim of this study was to develop a simple and useful method for the detection of growth deviations during pregnancy in primary care (midwife or general practitioner) practices.

Setting: A Dutch primary care midwifery practice.

Study design: In an earlier study, we developed parity and sex specific fetal growth charts of abdominal circumference (AC) and head circumference (HC) on the basis of ultrasound data of a low-risk midwifery population in the Netherlands. In the present study, we calculated sensitivity, specificity and predictive values at different cut-off points of AC and HC for the prediction of growth deviations at birth. Patients booked for perinatal care between January 1st 1993 and December 31st 2003 (n=3,449) were used for the identification of promising cut-off points (derivation cohort) and those admitted between January 1st 2004 and December 31st 2005 (n=725) were used to evaluate the performance of these cut-offs in an independent population (validation cohort). For the determination of SGA and macrosomia at birth, we used the recently published Dutch birth weight percentiles.

Results: Most promising cut-offs were AC ≤25th percentile for the prediction of SGA (birth weight ≤10th percentile) and AC ≥75th percentile for the prediction of macrosomia (birth weight ≥90th percentile). Within the validation cohort these cut-offs performed slightly better than in the derivation cohort. For the prediction of SGA, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 53% (95%-CI: 49%-58%), 80% (95%-CI: 80%-83%), 25% (95%-CI: 23%-29%), and 93% (95%-CI: 93%-94%), respectively. The false positrive rate was 74%. For the prediction of macrosomia, the values of these parameters were 63% (95%-CI: 59%-69%), 79% (95%-CI: 78%-81%), 22% (95%-CI: 20%-26%), and 96% (95%-CI: 95%-97%), respectively. Here the false positrive rate was 77%. No cut-offs were found that predicted extreme birth weight deviations ≤2.3rd percentile; ≥97.7th percentile) sufficiently well.

Conclusions: In a low risk population, we could predict future growth deviations with a higher sensitivity and in a significant earlier stage (at the onset of the third trimester in pregnancy) than with the use of conventional screening methods (i.e. palpation of the uterus only and fundus-symphysis measurement). Sonographic measurement of fetal abdominal circumference enables to detect more than half of cases of SGA at birth and more than two-thirds of cases of macrosomia with acceptable false-positive rates. We suggest that fetuses with biometry results below the 25th percentile or above the 75th percentile at the onset of the third trimester of pregnancy should be more intensively investigated in order to distinguish between

pathology (e.g. IUGR or macrosomia) and physiology and to decide about the appropriate level of further perinatal care.

Key-words: Effectiveness of antenatal screening; intrauterine growth restriction; large-for-gestational-age; macrosomia; prenatal care; small-for-gestational-age; ultrasound measurement.

Introduction

In the Netherlands, approximately 80% of the pregnant women start their prenatal care at a midwifery practice or at a general practitioner (GP) office [34]. Pregnancies are then divided into low-, medium- and high-risk. Low risk pregnant women obtain perinatal care in an out-of hospital care-unit whereas the majority will deliver at home (nearly 30% of all births in the Netherlands). In low-risk cases, midwives and GP's assess fetal growth by conventional methods such as palpation of the uterus or by symphysis-fundus measurement [2].

Until recently, technical aids such as ultrasound, were not used in our country for routine controls in low risk pregnancies, and were applied only in cases where an elevated risk was found or suspected, based upon the Dutch list of obstetrical indications for Perinatal care [5] (e.g. suspicion for multiplets, abnormal position of the fetus, growth deviations), medical history or clinical examination. Ultrasound for specific risk-screening (nuchal translucency measurement and mid-pregnancy assessment (18 – 23 weeks scan) of the fetus) became available for all pregnant women since 2007 only.

This seems to be paradoxal in our separated care-system, where accuracy of selection and the use of nationwide protocols are considered to be essential for the quality and the results of the perinatal care offered.

It is well known that both intrauterine growth restriction (IUGR) and macrosomia are associated with increased perinatal morbidity and mortality [9, 17, 18, 20, 24, 26, 32].

In a recent study, Bais et al [2] showed that, in a low-risk group, the prenatal detection of small-for-gestational-age (SGA) children at birth by conventional methods is rather disappointing. For the prediction of SGA $\leq 10^{th}$ percentile sensitivity was 21% and specificity 96%. The majority of cases were not detected before the end of pregnancy. Moreover, one can presume that prediction of large-for-gestational-age (LGA) at birth by physical examination may not give better results in terms of sensitivity and specificity. However, studies on the detection of macrosomia are mostly performed at the end of pregnancy or at the onset of labor [1, 4, 6, 7, 8, 21, 23, 25, 30, 36].

In an earlier study, we developed gender and parity specific fetal growth charts of abdominal circumference (AC) and head circumference (HC) on the basis of ultrasound data of a low-risk population in the Netherlands [11].

In the present study, we investigated whether growth deviations present at the time of birth (SGA and LGA) could be predicted accurately already in early third trimester of pregnancy by means of a one-step ultrasound biometry examination. To this end, we calculated sensitivity, specificity and predictive values for the detection of SGA and LGA at birth at different cut-off points of AC and HC in order to evaluate the discriminative power of a one-step ultrasound biometry assessment at the onset of the third trimester of pregnancy. First we determined which growth percentile of AC or HC had the best predictive test characteristics. For this task we used the same population as was used for the construction of the mentioned growth charts (derivation population). Then we validated these cut-offs within an independent population (validation population).

Patients and Methods

Patients booked for perinatal care in our midwifery practice between January 1st 1993 and December 31st 2003 (n=3,449) were used for the determination of the most promising biometrical cut-off values to the prediction of SGA and LGA at birth (derivation cohort). Those admitted between January 1st 2004 and December 31st 2005 (n=725) were used to validate the chosen cut-offs.

All data included in the study were derived from singleton pregnancies of Caucasian women without risk factors or pathology at the onset of the third trimester. Excluded were patients where no scans were performed at the end of the first trimester or at the onset of the third trimester and cases with incomplete data (e.g. missing gender, AC or HC).

Gestational age was confirmed by ultrasound examination between the 10th and 14th week using the crown-rump length (CRL) reference curve of Robinson and Fleming [29]. If the expected date of delivery, based on the first day of the last menstrual period, differed more than seven days from the expected date based upon these measurements, gestational age was adjusted. Third-trimester ultrasound examinations were scheduled between 27 and 33 (189 – 231 days) weeks. Information of parity was collected at the first visit, and fetal gender and birth weight were determined at birth. All scans were performed by one of six trained midwife-sonographers using a standard protocol. The biometric results were compared and discussed regularly and, if necessary reassessed and corrected, in order to exclude possible inter-observer differences.

In all cases with an ultrasonographic suspicion of growth deviations, additional measures were taken e.g. advise to change lifestyle (stop smoking, reduce burden

activities etc.), laboratory tests to investigate possible diabetes and referral to an obstetrician in order to decide about the appropriate level of perinatal care. However, the effects of these actions on the perinatal outcome in these cases were not part of this study.

Individual birth weight percentiles adjusted for sex, maternal parity and gestational age were calculated for all children based upon the recently published Dutch birth weight scales [35]. They were then categorized as SGA, appropriate-for-gestational-age (AGA) and LGA. Moderate SGA was defined as a birth weight between p-2.3 and ≤ p-10 and severe SGA as birth weight ≤ p-2.3. Likewise moderate LGA was defined as a birth weight between ≥ p-90 and p-97.7 and severe LGA as birth weight ≥ p-97.7.

All biometric results for AC and HC were categorised as lower as or higher than the chosen centile cut-offs: ≤ p-5, ≤ p-10, ≤ p-25, ≥ p-75, ≥ p-90, and ≥ p-95.

Based upon these cut-offs we divided all cases as expected small-for-gestational-age (ESGA) and expected large-for-gestational-age (ELGA) respectively. The remaining group (> p-25 and < p-75) was identified as expected appropriate-for-gestational-age (EAGA).

We first determined the most promising cut-off values for SGA and LGA in the derivation cohort based upon AC and HC biometry. Sensitivity, specificity, positive and negative predictive values and the fractions of women with positive tests were calculated.

A cut-off value was considered to be 'promising' if sensitivity was at least 50% and predictive value of the positive test at least 20%. We did not construct ROC curves, as these plot sensitivity against 1-specificity, and do not give direct information about predictive values.

Cut-off values with the best performance were then applied to the validation cohort in order to evaluate the stability of the parameters. For all statistical procedures, SAS for windows, version 9.1 was used (SAS-institute inc., Cary, North Carolina).

Results

During the study-period (1993 – 2005), a total of 6,040 pregnant women were booked for prenatal care in our practice. Based upon the criteria mentioned, 1,618 cases in the derivation cohort and 248 in the validation cohort were excluded. Main characteristics of both cohorts are shown in table 1.

Table 1: Main characteristics of both deviation and validation cohort.

Main characteristics		Derivation cohort		Validation cohort	
		n	%	n	%
Gender	♂	1,772	51.4	361	49.8
	♀	1,677	48.6	364	50.2
Parity	Primiparous	1,618	46.9	328	45.2
	Multiparous	1,831	53.1	397	54.8
Preterm born		122	3.5	28	3.9
Postterm born		215	6.2	27	3.7
SGA ≤ p-10		387	11.2	68	9.4
AGA		2,777	80.5	582	80.3
LGA ≥ p-90		285	8.3	75	10.3
Total		3,449	100	725	100
GA at birth (days)		278.7 (SD = 10.9)		279.1 (SD = 10.7)	
Birth weight (grams)		3,429.6 (SD = 530.7)		3,493.7 (SD = 527.9)	

SGA = Small-for-Gestational-Age; AGA = Appropriate-for-Gestational-Age; LGA = Large-for-Gestational-Age; GA = Gestational Age; SD = Standard Deviation.

Table 2a shows the test characteristics for different outcomes and different cut-offs of AC and HC within the derivation sample. For the prediction of SGA (birth weight ≤ p-10), a cut-off of AC ≤ p-25 gave the most promising results, with a sensitivity of 53%, a specificity of 80%, a positive predictive value (PPV) of 25%, a negative predictive value (NPV) of 93% and a false positive rate of 74%. None of the other cut-offs yielded a sensitivity higher than 50% together with a PPV above 20% for this outcome.

Table 2a: Test-characteristics for the prediction of Small-for-Gestation-Age (SGA) and Large-for-Gestational-Age (LGA) in the derivation cohort (n=3449).

	SGA ≤ p-2.3					SGA ≤ p-10				
	Sens.	Spec.	PPV	NPV	%test+	Sens.	Spec.	PPV	NPV	%test+
AC ≤ p-5	0.24	0.97	0.19	0.97	0.04	0.17	0.98	0.47	0.90	0.04
AC ≤ p-10	0.36	0.93	0.14	0.98	0.08	0.28	0.94	0.37	0.91	0.08
AC ≤ p-25	0.62	0.78	0.09	0.98	0.24	0.53	0.80	0.25	0.93	0.24
HC ≤ p-5	0.13	0.96	0.09	0.97	0.05	0.13	0.96	0.30	0.90	0.05
HC ≤ p-10	0.24	0.92	0.09	0.97	0.09	0.23	0.93	0.29	0.91	0.09
HC ≤ p-25	0.48	0.78	0.07	0.98	0.23	0.42	0.80	0.21	0.92	0.23

	LGA ≥ p-90					LGA ≥ p-97.7				
	Sens.	Spec.	PPV	NPV	%test+	Sens.	Spec.	PPV	NPV	%test+
AC ≥ p-75	0.63	0.79	0.22	0.96	0.24	0.68	0.77	0.06	0.99	0.24
AC ≥ p-90	0.35	0.93	0.31	0.94	0.10	0.45	0.91	0.09	0.99	0.10
AC ≥ p-95	0.22	0.96	0.34	0.93	0.05	0.33	0.95	0.12	0.99	0.05
HC ≥ p-75	0.49	0.79	0.17	0.95	0.23	0.52	0.77	0.05	0.99	0.23
HC ≥ p-90	0.26	0.92	0.24	0.93	0.09	0.38	0.92	0.08	0.99	0.09
HC ≥ p-95	0.16	0.96	0.29	0.93	0.05	0.25	0.96	0.11	0.98	0.05

Sens = sensitivity; Spec = specificity; PPV = positive predictive value; NPV = negative predictive value; AC – Abdominal circumference; HC = head circumference

Table 2b: Test-characteristics for the prediction of Small for gestation Age (SGA) and Large for gestational Age (LGA) in the validation cohort (n=725).

	SGA ≤ p-2.3					SGA ≤ p-10				
	Sens.	Spec.	PPV	NPV	%test+	Sens.	Spec.	PPV	NPV	%test+
AC ≤ p-25	0.68	0.84	0.12	0.99	0.18	0.59	0.87	0.32	0.95	0.18

	LGA ≥ p-90					LGA ≥ p-97.7				
	Sens.	Spec.	PPV	NPV	%test+	Sens.	Spec.	PPV	NPV	%test+
AC ≥ p-75	0.69	0.80	0.29	0.96	0.25	0.88	0.76	0.08	0.99	0.25

Sens = sensitivity; Spec = specificity; PPV = positive predictive value; NPV = negative predictive value; AC – Abdominal circumference.

For SGA (birth weight ≤ p-2.3), a sensitivity of 62% was reached at a cut-off of AC ≤ p-25, but concomitant positive predictive value was low (9%).

For the prediction of LGA (birth weight ≥ p-90), a cut-off of AC ≥ p-75 gave the best results, with a sensitivity of 63%, a specificity of 79%, a PPV of 22%, a NPV of 96% and a false positive rate of 77%. None of the other cut-offs yielded a sensitivity higher than 50% together with a PPV higher than 20% for this outcome. For LGA (birth weight ≥ p-97.7), both AC ≥ p-75 and HC≥ p-75 yielded sensitivities above 50% (namely, 68% and 52%, respectively) but associated PPV's were low (6% and 5%, respectively).

Within the validation cohort, the two chosen cut-offs performed equally well as (and sometimes slightly better than) in the derivation cohort (table 2b).

Table 3 shows test parameters for the two cohorts combined, including 95%-confidence intervals. The fractions of women with positive tests were 0.22 for AC ≤ p-25 and 0.24 for AC ≥ p-75.

Table 3: Test-characteristics for the prediction of Small for gestation Age (SGA) and Large for gestational Age (LGA) in the two cohorts combined (n=4174).

	SGA (≤ p-10)		LGA (≥ p-90)	
	Value	95%-CI	Value	95%-CI
Sensitivity	53%	49 - 58 %	64%	59 - 69 %
Specificity	81%	80 - 83 %	80%	78 - 81 %
Positive predictive value	26%	23 - 29 %	23%	20 - 26 %
Negative predictive value	93%	93 - 94 %	96%	95 - 97 %

Discussion

The results of this study indicate that a single routine biometry examination may double the probability of detection of growth restriction resulting in SGA (≤ p-10) compared with the conventional methods (physical examination) as is common practice in out of hospital obstetric care systems [2, 31, 33]. Unfortunately we were

not able to compare our detection rates for LGR (63% for ≥ p-90 and 68% for ≥ p-97.7) with most other studies since increasing growth was investigated at the end of pregnancy only [1, 4, 6, 7, 8, 21, 23, 25, 30, 36]. The only study on this particular subject showed lower sensitivity (21% for SGA and 56.5% for LGA) and PPV (33.3% for SGA and 23.2% for LGA) compared to our results but higher specificities (96.6% for SGA and 81.8% for LGA) and NPV's (93.9% for SGA and 95% for LGA) [3]. However, the objective of that study was to estimate fetal weight ultrasonographically calculated between 28 and 34 weeks of pregnancy and to compare these results with birth weight at term. The results showed low PPV's in cases of SGA and LGA but not in case of AGA. Therefore the authors concluded that routine early fetal weight estimation in low risk pregnancies is probably not justified. Apparently fetuses with normal growth between 28 and 34 weeks of pregnancy in most cases continue their physiological growth potential. On the other hand, fetal growth already disturbed (LGA or SGA) before the 34th week of pregnancy often shows a further upward or downward turnoff [4]. The goal of our study was not to predict birth weight in itself but to predict possible deviations at term (≤ p-10 or ≥ p-90) already in an early stage.

In the latter study as well as in ours, the selection is already made before the 34th week (day 238) of pregnancy. At this time referral to an obstetrician and interventions such as lifestyle advises, fetal surveillance or timely induction of labour are still possible in order to deliver the baby in the best possible condition [27, 28].

Alternatively, the use of our study-protocol may also lead to a considerable number of false positive cases. Using AC ≤ p-25 as cut-off for the prediction, for each SGA-baby ≤ p-10, three women without fetal growth deviation are unnecessary intensively investigated and probably worried (false positive rate = 74%). In case of LGA ≥ p-90 detection, the false positive rate is even somewhat higher: 77%.

However, the false positive rate using this protocol is remarkable lower than in case of conventional methods as presented in the study of Bais et al [2] where 324 false positive cases in a total of 350 suspected SGA-referred patients were found (false positive rate = 93%). Moreover, the false positive rates found in our study are acceptable since the aim of the check-up is to isolate the majority of cases with high probability for SGA and LGA at birth. In addition, subsequent investigations may reveal the presence or absence of growth deviations on a pathological basis.

It should be noted that, in the Bais et al. study, the Dutch scales of Kloosterman [19] were used, and Dutch newborns are on average heavier than half a century ago [35]. General increase in birth weight may lead to an increase of the total number of SGA-children and to a small increase of sensitivity for the Bais study. However, we believe that these differences in cut-off values are too small to influence our final conclusions.

Although official intervention protocols for possible growth restrictions based upon ultrasound biometry results only were not (yet) existing during the study pe-

riod**,** changes in lifestyle (stop smoking, reduce burden activities etc.) were advised in suspected cases. Therefore, an intervention-bias may have played a role in our study-group, since these actions may have caused a downward bias of sensitivity [12, 14, 22].

In our opinion, an ultrasound examination between the 28th and 33rd week of pregnancy may be seen as an initial marker for growth deviations but not as an early diagnosis of IUGR or macrosomia. ESGA and ELGA are risk-categories of fetuses that demand a specific management. They have to be considered as elevated risk-cases until the opposite is proven. Therefore, once a case is labeled as ESGA or ELGA, a procedure to identify possible underlying pathology should be initiated.

In case of ESGA, the care-giver wants to know which of these cases is indeed growth restricted and which is not. In case of suspected excessive growth at the onset of the third trimester of pregnancy ELGA may reveal an underlying problem of another category. For instance pregnancy induced diabetes as well as diabetes type-1 should be excluded [16]. Biometric results ≥ p-75 may also have an important impact on the decision about the most appropriate place of the delivery since an increased risk for shoulder dystocia, brachial plexus injury, prolonged labor, asphyxia, postpartum hemorrhage and operative delivery may exist.

Early detection of fetal growth deviations is important for timely management and clinical decision making since growth deviations remain a major problem in the antenatal and neonatal period. A substantial number of cases of fetal death are growth retarded [10]. In these cases the growth restriction in general may be considered as an ultimate signal of a serious fetal problem. Unfortunately these signals are not always discovered timely or often inadequately handled.

Although some authors contest the accuracy of screening routines based on ultrasound investigations [3, 13, 15], this particular procedure may improve early detection of risk groups in community obstetrical care systems as we demonstrated in the present study.

Therefore we suggest in cases of ESGA ≤ p-25 that serial biometry surveillance and monitoring be perormed. If fetal growth shows a normal increase, the case may be considered as physiological. On the other hand if fetal growth shows a downward turn-off, the case must be considered at risk and referral for further clinical management is indicated. Further investigation may confirm or reject the presence of a pathological development and an increase of risk.

In addition we also suggest adopting an increasing test-protocol in all cases of biometry ≥ p-75. Presence of diabetes (type-1 or pregnancy induced) should always be investigated for every case and, in addition, birth weight should be calculated as exact as possible at the end of pregnancy in order to minimize the complications and consequences of macrosomia [20, 21, 23, 32].

Conclusions

In a low risk population, we were able to predict future growth deviations with a higher sensitivity and at a significant earlier stage (at the onset of the third trimester in pregnancy) than with the use of conventional screening methods (i.e. palpation of the uterus only and fundus symphysis-measurement). Sonographic measurement of fetal abdominal circumference enables to detect more than half of cases of SGA at birth and more than two-thirds of cases of macrosomia with acceptable false-positive rates (74-77%). We suggest that fetuses with biometry results below the 25^{th} centile or above the 75^{th} centile at the onset of the third trimester of pregnancy should be investigated more intensively in order to distinguish between pathology (e.g. IUGR or macrosomia) and physiology and to decide about the appropriate level of further perinatal care. Future research is needed to investigate the impact of this protocol and possible interventions on perinatal morbidity and mortality.

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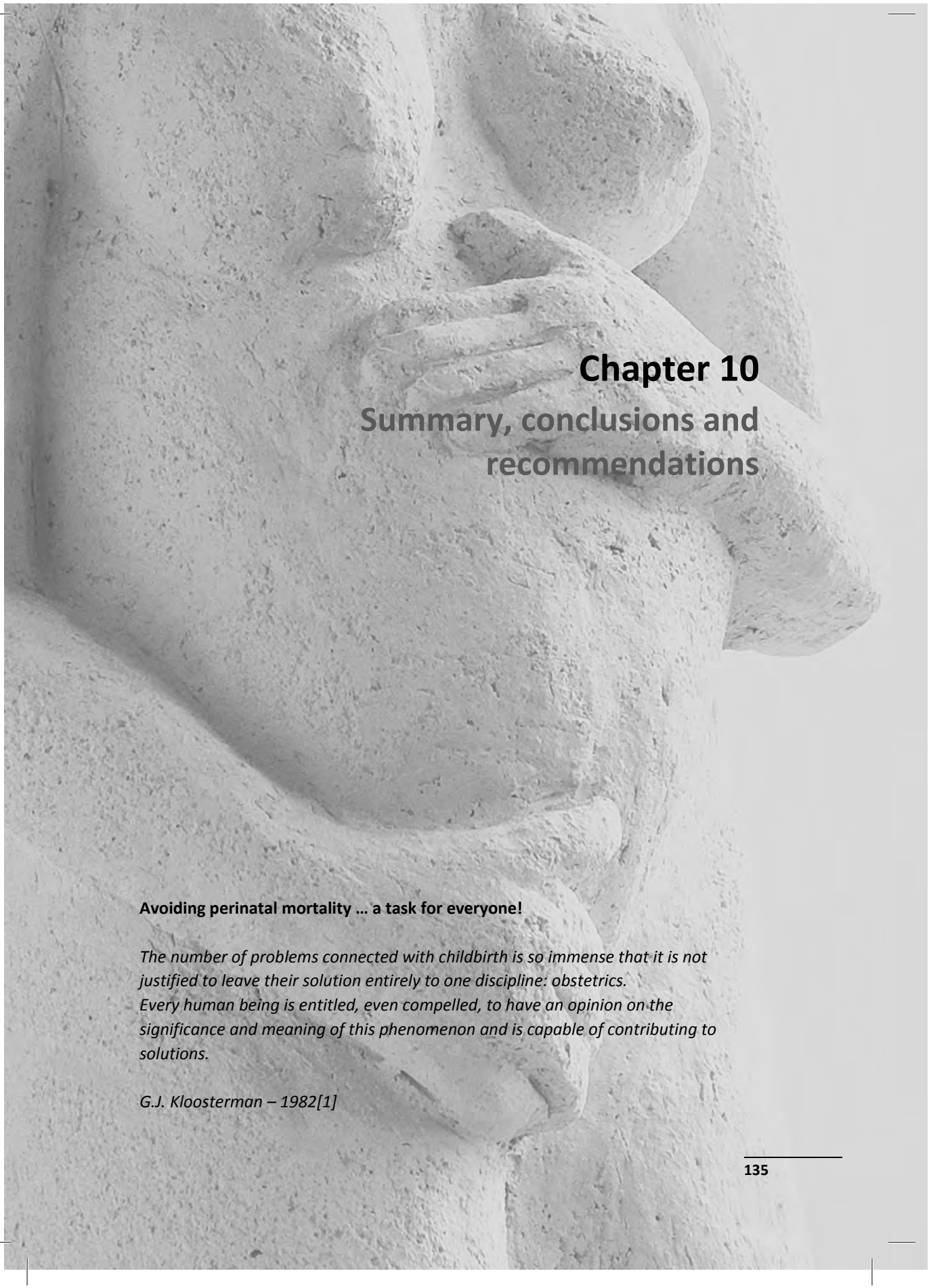

Chapter 10
Summary, conclusions and recommendations

Avoiding perinatal mortality … a task for everyone!

The number of problems connected with childbirth is so immense that it is not justified to leave their solution entirely to one discipline: obstetrics.
Every human being is entitled, even compelled, to have an opinion on the significance and meaning of this phenomenon and is capable of contributing to solutions.

G.J. Kloosterman – 1982[1]

Not only for parents but also for midwives, general practitioners (GP's), obstetricians and neonatologists, most cases of perinatal mortality are tragic events with enormous impact. For the pregnant woman, her partner and the perinatal caregiver(s), the death of a child around birth often also results in a feeling of failure and even sometimes of guilt. It's obvious that questions arise where things went wrong and whether the care provided has been sufficient or not according to current standards.

This feeling of guilt increases when the results of the local (national) perinatal care performed are not as good as in neighboring regions or countries. Moreover, as a substantial part of cases of perinatal mortality occurs in healthy children (as is the case in most IUGR-children), questions may arise about the quality and efficiency of the care provided.

However, as the Romans already recognized more than 2000 years ago: "*omnia comparatio claudicat*" (every comparison falls short), international comparisons may not always prove what they intend to [2]. Within the European Union, differences in the registration of perinatal care, regional infrastructure, population composition etcetera are so varying that the presented data in reports such as PERISTAT may tell more about all those issues together than about the quality of one single item (i.c. the quality of perinatal care) only. In fact, perinatal mortality statistics are the result of a range of factors on which the quality of perinatal care is depending. Nevertheless, in two subsequent investigations with an interval of 5 years, perinatal mortality in the Netherlands appeared to be far from good, and in the highest range of the countries of the European Union [3, 4].

In this thesis, we attempted to make a critical appraisal of aspects of the Dutch perinatal healthcare system in relation to perinatal mortality.

In **chapter 1** we define the phenomenon of perinatal mortality, and highlighted the difficulties in comparison of perinatal mortality rates between different countries as caused by variables in population composition and the reliability of perinatal mortality figures. Classification models as presented by different authors during the past century, successively led to an investigation-model for perinatal audit with three crucial questions for the assessment of provided perinatal care: what, when and why? Finally the impact of fetal growth deviations on perinatal mortality as well as pitfalls in reliability of fetal weight prediction are mentioned.

In **chapter 2** we describe a pilot study on avoidability of perinatal mortality in the region of 's Hertogenbosch. Determination of causes of perinatal death was based upon a modified Aberdeen Classification in which a minor change in the hierarchical order was made and précised causes of death arranged in subgroups (e.g. we excluded iso-immunisation, pre-eclampsia and maternal disorder as separated groups and allocated them as subgroup-items). Avoidability of perinatal mortality was as-

sessed by a team of professionals involved in perinatal care and showed a high degree of consensus (κv = 0.9) between the different assessors. We also determined the time that perinatal death occurred or became inevitable and defined this as the 'fatal moment'.
This study revealed two remarkable findings:

- in 32% of the cases perinatal death was assessed to be avoidable to a certain degree while;
- 38% of the deceased children were Small-for-Gestational-Age (SGA) ≤ p-10.

In **chapter 3** we describe the LPAS-study (the Dutch National Perinatal Audit Study). This study analyzed and assessed perinatal mortality over a one year period in three separate Dutch regions between 2003 and 2004. LPAS was meant as a feasibility study to investigate the possibility of a nationwide perinatal audit program in the Netherlands.

To this end, all cases of perinatal mortality in the areas chosen were collected and assessed by perinatal audit groups composed of different professionals involved in perinatal care. Assessment was made for the cause of death based upon three different classifications. In addition the presence (or absence) of substandard care factors (SSF's) was assessed on three levels: that of the care provider(s), of the care receiver (= patient) and of the organization of care. Finally the relation between the SSF and perinatal death was identified.

We presented the results of the study in the frame of the total study population (n= 22,198). The total perinatal mortality rates within the three regions were calculated using the LPAS data (10.8‰) and the national Dutch perinatal registry (PRN) data (12.5‰).

In the LPAS study an under-registration of perinatal mortality cases of 19.8% was found while in the PRN data the under-registration was 7.1%. In 72 cases a total of 82 SSF's by caregivers was found. They were equally divided between the different groups of caregivers. In 20 cases a relation between the SSF's (n=21) and perinatal mortality was assessed to be (very) probable (9%).
We categorized all identified SSF's into 4 groups:

- the risk-problem was not, insufficiently or too late recognized (n=10);
- the risk-problem was recognized but not, or too late reacted on or managed adequately (n=7);
- management was not in line with current protocols (n=3) and;
- other (n=1).

Moreover, 38% of all deceased children in the LPAS-population were SGA ≤p-10 which was exactly the same as we found 10 years earlier (chapter 2). The LPAS study demonstrated that a nationwide perinatal audit on all cases of perinatal death on a yearly base is not yet feasible for both practical and financial reasons. However, local audits may assess mortality cases inside their own area and may initiate more

easily and rapidly local adjustments in the quality of care and may optimize inter-professional cooperation. Audits focused on specific topics (e.g. unexplained mortality in term born babies) may offer an opportunity for a nationwide study and may lead to the development of new guidelines of policy review.

In **chapters 4 and 5** we further analyze the perinatal mortality cases of SGA (chapter 4) and preterm born children (chapter 5) from the LPAS-study. In both groups we investigated avoidability of perinatal mortality in all cases with and without SSF. Apart from the cases with SSF related to perinatal death we were able to identify 15 more cases in the SGA-group (n= 59) and 9 more cases in the preterm born group (n=166) in which perinatal mortality may be considered avoidable. In **chapter 4** we demonstrate that in at least 4 cases of SGA children, IUGR most probably could have been detected before fetal death occurred if current policy of prenatal care would focus on the detection of growth deviations i.c. by observing fetal growth routinely by means of ultrasound fetal biometry measurements. Moreover, it became clear that growth assessment by conventional methods in low risk pregnancies (as it is the case in the Dutch perinatal care system) leads to an important underestimation of growth deviations in SGA-children: before referral, IUGR was suspected in 22% of the cases only. The rate of SSF's by caregivers in this group was high (37%). Mortality rate in SGA-children increased significantly if the mother was ≥ 35 years of age (21.3‰ in the mothers < 35 years and 42.5‰ in mothers ≥ 35 years of age). In **chapter 5** we show that in a number of cases preterm birth might have been prevented if the pregnant women would have been aware of the first signs of imminent labor. A reduction of preterm birth could also be reached if caregivers (in primary as well as in secondary/tertiary care) would have acted more adequately in such cases. High maternal age does not appear to play an important role in the incidence of preterm birth or in the mortality rate of preterm born children. However, the group of mothers between 20 an 25 years of age showed a slight, non significant elevated risk for preterm birth (8.98% vs. ≤8.77% (ns)) as well as for perinatal mortality (13.4% vs. ≤8.9% (ns)). Finally, preterm deliveries occurred as often in Dutch and non-Dutch mothers. However, mortality rates in preterm born children of non-Dutch mothers were twice as high as in children of Dutch mothers (6.5% vs. 12.3% - p=0.001).

We conclude that more adequate action by care givers and care receivers may decrease or postpone the number of preterm births and decrease perinatal mortality in this group while adjustment in guidelines for prenatal care may decrease the perinatal mortality in SGA-children.

In **chapter 6** we describe the remarkable phenomenon that perinatal mortality in preterm born children of multiplets in both the Netherlands and Flanders is lower than in singletons of comparable GA. On the other hand, perinatal mortality in mul-

tiplets increases substantially from the 37th week of pregnancy and from this time onwards becomes higher than in singletons. The lower perinatal mortality in preterm born children of multiplets is due to the much lower fetal mortality as compared to singletons (Netherlands: 7.51 vs. 3.74‰ and Flanders 4.64 vs. 1.96‰).
Although we were not able to provide a plausible explanation for this phenomenon, this study leads to two reconsiderations.

- Firstly it forces caregivers to reconsider the quality of care offered in daily prenatal practice and to compare the 'usual' care for singletons with the 'usual' care for multiplets. Further research is needed to conform that this might lead to a decrease of perinatal mortality in the singletons-group.
- Secondly, the significant increase in perinatal mortality rates in children of multiplets from the 37th week of pregnancy onwards, suggests a policy of timed induction of labor before the 38th week of pregnancy (<266 days) in this group.

In **chapter 7** we look at the fact that in nearly 40% of all cases of perinatal mortality, IUGR (birth weight ≤p-10) appears to play a role. This led us to study the 'how' and 'why' of such a substantial part of 'missed' growth retarded fetuses. As a first step, we tried to compare different growth charts used in the Netherlands and discovered inaccuracies and even essential mistakes in the officially published charts [5]. Furthermore, different ultrasound machines contained different growth charts and it became clear that the interpretation of fetal biometry was at least a little chaotic in the Netherlands. For these reasons it was not possible to perform reliable scientific comparison on fetal growth. We drew attention on the existing differences between the different reference charts used in the Netherlands. We suggested that for the benefit of internal comparability it is imperative that validated uniform reference charts have to be used in all equipment and documents.

In **chapter 8,** based on the experience we got from chapter 7, we decided to construct more reliable charts for fetal growth suited for our study population. To this end we used data of abdominal circumference (AC) and head circumference (HC) of all singleton fetuses of Caucasian mothers in our low-risk midwifery practice collected over an 11 years period (n=3641).

Birth weight reference curves are gender and parity specific. However, this distinction is on average not made in biometry assessment by ultrasound for children during their intrauterine life. This is remarkable since we know that fetal morphometry is also gender and parity-depending [6]. In order to improve the assessment of intrauterine growth, we composed gender and parity specific fetal growth charts of AC and HC for a restricted GA-window between 27+0 and 33+0 weeks (189 and 231 days).

The AC measurements showed significant differences between boys and girls, as well as between children of first and successive pregnancies. HC showed a significant difference in gender only.

In **chapter 9** we validated our gender and parity specific growth charts as presented in chapter 8, Sensitivity, specificity and predictive values for growth deviations (SGA ≤p-10 and LGA ≥p-90) were calculated for different cut-off values. The most promising cut off values (AC ≤p-25 for SGA and AC ≥p-75 for LGA at birth) as detected in the derivation cohort (n=3449) were validated in an independent cohort (n=725) and showed a sensitivity of 53% for SGA and 64% for LGA at birth. This is remarkable higher than what was found in case of assessment by conventional methods e.g. palpation of the uterus only (sensitivity for SGA = 21%) [7].

Epilogue

Perinatology is a very complex multidisciplinary medical specialism. On one hand it is focused upon two "patients", a pregnant woman and a growing human being. On the other hand, the care provided is focused on low risk individuals (healthy mothers and children) as well as on high risk (ill) ones. The latter are entitled to receive the best suitable treatment in order to improve their medical condition and fetal outcome, while the first group needs particular specialized conduct focused on the prevention of obstetrical or neonatal risk and unnecessary medical interventions [8].

Since perinatal care in the Netherlands is managed by different caregivers in our health-care-chain, a high degree of cooperation between all professionals involved is indispensable [9]. Although professional interests sometimes may obstruct nationwide agreements in conduct, during the study-period we observed enough willingness between caregivers to improve the inter-professional collaboration while an increasing number of activities are geared to one another.

However, good practice needs appropriate tools. Uniform information for the pregnant woman should be available and as accurate as possible. New IC-technologies were introduced at a great pace in different units in perinatal care. Unfortunately, software in hospitals and out of hospital (midwifery) units are not yet compatible and for that reason a quick consultation in each other's electronic (medical) files is still not possible. Uniform electronic patient-files, admissible for all caregivers involved may decrease this problem and has to be realized as soon as possible. Therefore, the linkage of patient-files between all care-levels is imperative.

Nevertheless, although our perinatal healthcare system still needs improvement, the fact that 85% of the pregnant women start their pregnancy under supervision of a midwife while nearly 30% of the deliveries take place at home support

the opinion that the majority of Dutch women still are satisfied with the options this system offers. In a recent study nearly 80% of the young mothers declared, three years after their delivery, to be (very) satisfied about the course and the coaching during their pregnancy and delivery [10]. On the other hand, we can't ignore that 23.2% of the primiparous and 11.4% of the multiparous are 'unhappy' or 'very unhappy' about it, which is much more than in the United Kingdom [11].

Perinatal mortality rates are considered as an indicator for the quality of care. However, those numbers comprise the top of the iceberg only. Although we did not investigate neonatal morbidity in our study, one cane safely assume that in countries with a high perinatal mortality, perinatal morbidity will also be much higher.

In conclusion

Perinatal mortality in the Netherlands is high as compared with other Western countries. A substantial number of the cases of perinatal mortality are related to SSF and in nearly 1 of 10 cases death is due to SSF by caregivers. Besides, perinatal mortality is avoidable in 1 of every 4 cases of SGA without SSF and in 1 of every 12 preterm born cases without SSF.

The introduction of perinatal audits on local, regional and national level might also improve perinatal care and lead to a substantial decrease of perinatal mortality. Implementation of routine ultrasound biometry at the onset of the third trimester in low risk pregnancies, might improve the detection of impaired fetal growth in an early stage and decrease perinatal mortality in healthy SGA-children. Future research is needed to investigate the impact of our suggestions on perinatal morbidity and mortality.

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Samenvatting, conclusies en aanbevelingen

Voorkomen van perinatale sterfte … een taak voor allen!

The number of problems connected with childbirth is so immense that it is not justified to leave their solution entirely to one discipline: obstetrics.
Every human being is entitled, even compelled, to have an opinion on the significance and meaning of this phenomenon and is capable of contributing to solutions.

G.J. Kloosterman – 1982 [1]

Het overlijden van een kind vóór, tijdens of kort na de geboorte is een ingrijpende, tragische gebeurtenis en laat zowel bij de moeder en haar partner als bij de betrokken zorgverlener(s) een leegte achter en vaak ook schuldgevoel. Men vraagt zich af waar en waanneer het fout ging en of de geboden zorg toereikend dan wel suboptimaal was.

Dit schuldgevoel wordt nog versterkt wanneer ook aangetoond is dat de resultaten van de perinatale zorg in Nederland minder gunstig zijn in vergelijking met de ons omringende landen. Als daarenboven een substantieel aantal van de overleden kinderen gezond blijkt te zijn (zoals vaak in het geval van intra-uteriene groeivertraging) kan – niet onterecht – getwijfeld worden aan de kwaliteit van de geleverde zorg in vergelijking met landen waar de resultaten beter zijn dan de onze.

Het vergelijken van resultaten van gezondheidszorg blijkt echter een moeizame onderneming. Ruim 2000 jaar geleden reeds onderkenden de Romeinen dat iedere vergelijking mank loopt ("*omnia comparatio claudicat*"). Ook nù nog tonen internationale vergelijkingen niet altijd precies datgene aan wat men pleegt aan te tonen [2]. Zo zijn binnen de landen van de Europese Unie registraties van perinatale zorg, infrastructuur, samenstelling van de populatie en dergelijke dusdanig verschillend dat onderzoeksverslagen, zoals in de PERISTAT rapporten, eigenlijk meer vertellen over het complex van al deze variabelen samen dan over de kwaliteit van één enkele variabele (perinatale sterfte) alleen [3, 4]. Daarom dient de perinatale sterfte ratio veeleer beschouwd te worden als het resultaat van een reeks van factoren waar de kwaliteit van de perinatale zorg in belangrijke mate van afhankelijk is. Voor ons in Nederland blijft het desalniettemin toch een vervelende vaststelling dat de perinatale sterfte alhier tot één van de hoogste behoort binnen de landen van de Europese Unie.

In dit proefschrift hebben wij geprobeerd om met een kritische blik diverse aspecten van de Nederlandse perinatale ketenzorg te onderzoeken in relatie tot de perinatale sterfte en voorstellen aan te dragen die mogelijk kunnen leiden tot vermindering van deze sterfte.

In **hoofdstuk 1** beschrijven wij eerst de definities van sterfte vóór, tijdens en kort na de geboorte. Daarnaast wordt aandacht besteed aan de betrouwbaarheid van perinatale sterftecijfers en problemen welke zich kunnen voordoen bij het internationaal vergelijken ervan.

Vervolgens hebben wij de ontwikkeling van de beoordeling van perinatale sterfte onder de loep genomen waarbij een groot aantal bestaande classificaties van oorzaken van sterfte worden besproken. Al deze classificaties hebben uiteindelijk geleid tot de huidige beoordelingsmodellen waarbij de vragen zoals *waaraan, hoe*

en *waardoor* de basis vormen voor perinatale audit zoals wij dit momenteel plegen te doen. Ten slotte wijzen wij in dit hoofdstuk op een aantal valkuilen en beperkingen in de mogelijkheden m.b.t. het beoordelen van de foetale groei.

In **hoofdstuk 2** beschrijven wij een pilot onderzoek naar de vermijdbaarheid van perinatale sterfte in de regio 's Hertogenbosch. De oorzaak van sterfte in al deze casus werd beoordeeld op basis van een door ons gemodificeerde Aberdeen classificatie waarbij wij een paar kleine wijzigingen aanbrachten in de hiërarchische volgorde van sterfteoorzaken en aan de bestaande oorzaken subclassificaties toevoegden. In dit onderzoek werd de vermijdbaarheid van de perinatale sterfte beoordeeld door een panel van deskundigen in de perinatale zorg (verloskundige, huisarts, gynaecoloog, neonatoloog en patholoog) waarbij een zeer goede mate van overeenkomst werd bereikt (κv = 0.9). Voor elke casus werd tevens het "*fataal moment*" vastgesteld, d.i. het moment waarop de sterfte optrad of niet meer was te voorkomen. In deze studie bleek dat in 32% van de gevallen de sterfte (mogelijk) had kunnen voorkomen worden. Bovendien bleek dat 38% van de overleden kinderen een geboortegewicht had op of onder de tiende percentiel.

In **hoofdstuk 3** wordt de LPAS-studie (LPAS = Landelijke Perinatale Audit Studie) beschreven. In deze feasibility-studie voor een mogelijk toekomstige landelijke perinatale audit werd de perinatale sterfte gedurende één jaar in drie verschillende regio's in Nederland (Amsterdam e.o., regio den Bosch – Tilburg en Zuid Limburg) verzameld en beoordeeld door zes audit panels van deskundigen in de perinatale zorg (een eerstelijns en een tweedelijns verloskundige, een (verloskundig actieve) huisarts, een tweede en een derdelijns gynaecoloog, een tweede en een derdelijns neonatoloog en een patholoog). Beoordeeld werden de oorzaak van sterfte en aanwezigheid en impact van substandaard zorgfactoren (SSF) op deze sterfte. De SSF werden zowel bij de zorgverlener, de zorgontvanger als in de organisatie van de zorg onderzocht.

In totaal werden in de onderzoeksperiode 22,198 kinderen geboren in de drie regio's. Hiervan werden 239 casus (perinatale mortaliteit (PNM) ratio = 10.8‰) gemeld door de deelnemende verloskundigen, gynaecologen en neonatologen. In de databank van de PRN stonden echter 277 casus van perinatale sterfte geregistreerd (PNM-ratio = 12.5‰). Na diepgaand onderzoek werd bovendien een onderregistratie van 19.8% in de LPAS en 7.1% in het PRN-data bestand vastgesteld.

Bij 72 sterftecasus werden in totaal 82 SSF gevonden. Deze SSF kwamen voor bij alle zorgechelons. In 20 casus (= 9%) werd een waarschijnlijke tot zeer waarschijnlijke relatie aangetoond tussen de SSF (n=21) en de sterfte.

Wij classificeerden de SSF in 4 hoofdgroepen:

- het risico was niet, onvoldoende of te laat onderkend (n=10);
- het risico was onderkend maar niet, te laat of inadequaat behandeld (n=7);

- de toegepaste behandeling was niet conform de bestaande standaarden (n=3);
- overig (n-1).

Opvallend was dat ook in deze studie 38% van de overleden kinderen een geboortegewicht had ≤ p-10, dus exact hetzelfde percentage SGA-kinderen (≤p-10) als wij 10 jaar eerder hadden gevonden in de pilotstudie in de regio 's Hertogenbosch (hoofdstuk 2).

Uit de LPAS-studie werd geconcludeerd dat een jaarlijkse landelijke audit naar de totale perinatale sterfte in Nederland om praktische en financiële redenen niet mogelijk was. Organisatie van audits waarbij alle perinatale sterfte op locaal niveau wordt geanalyseerd in combinatie met landelijke audits waarbij specifieke sterfte (bij voorbeeld de a terme sterfte) wordt beoordeeld biedt wel een haalbaar alternatief. De resultaten van deze audits kunnen leiden tot het aanpassen van bestaande richtlijnen of zelfs het ontwikkelen van nieuwe richtlijnen.

In de **hoofdstukken 4 en 5** hebben wij de sterfte bij de small-for-gestational-age (SGA)-kinderen (hoofdstuk 4) en bij de prematuur geborenen (hoofdstuk 5) uit het LPAS onderzoek geanalyseerd. In beide groepen onderzochten wij de vermijdbaarheid van de sterfte bij zowel de casus met als zonder SSF. In alle casus zonder SSF werden in de groep SGA-kinderen (n=59) nog eens 15 potentieel vermijdbare sterfte-casus gevonden en in de premature (n=166) groep 9 casus. In **hoofdstuk 4** werd aangetoond dat bij ten minste 4 casus van SGA-kinderen de intra-uteriene groeirestrictie (IUGR) had kunnen worden aangetoond vóór het moment van intra-uteriene vruchtdood indien de foetale groei routinematig echoscopisch was beoordeeld. Gebleken is dat bij laag risico zwangerschappen de foetale groei middels conventionele methodes (palpatie van de uterus) vaak ten onrechte als normaal wordt ingeschat. Slechts in 22% van de casus van SGA-kinderen werd de IUGR onderkend vóór verwijzing naar de 2de lijn. De SSF-ratio bij zorgverleners in deze groep was hoog (37%). Bovendien was de perinatale sterfte ratio bij oudere zwangeren significant verhoogd (21.3% bij moeders < 35 jaar tegen 42.5% bij moeders ≥ 35 jaar). In **hoofdstuk 5** werd aangetoond dat in een aantal gevallen de vroegtijdige partus had kunnen voorkomen worden (of uitgesteld) indien de zwangere de eerste signalen ervan had onderkend en gemeld aan de betrokken zorgverlener. Het aantal vroegtijdige baringen had ook lager kunnen zijn indien zorgverleners in eerste, tweede en derde lijn meer accuraat hadden gereageerd op de vroege signalen van preterme arbeid. Hogere maternale leeftijd was in deze populatie niet van invloed op de frequentie van preterme partus. Desalniettemin bleek een verhoogd risico te bestaan (niet significant) voor zowel het vóórkomen van preterme partus bij moeders in de leeftijd 20 – 25 jaar (8.98% vs. ≤8,77% voor de overige leeftijdscategorieën) als voor sterfte in deze groep (13.4% vs. ≤8.9% voor de overige leeftijdscategorieën). Ten slotte bleek vroeggeboorte niet vaker voor te komen in de groep vrouwen van niet-Nederlandse komaf in vergelijking met de groep Nederlandse zwangeren. Daarte-

genover staat dat de sterfte in geval van vroeggeboorte bij kinderen van niet Nederlandse moeders bijna dubbel zo hoog is als bij kinderen van Nederlandse moeders (6.5% vs. 12.3% - p=0.001).

Concluderend kan gesteld worden dat meer accurate actie bij zorgverleners en zorgontvangers de sterfte bij vroeggeboorte kan verlagen terwijl aanpassing van de richtlijnen voor prenatale zorg (in het 3de zwangerschapstrimester) de sterfte bij SGA-kinderen mogelijk kan reduceren.

In **hoofdstuk 6** hebben wij een verklaring gezocht voor het feit dat, in Nederland evenals in Vlaanderen, de perinatale sterfteratio bij preterm geboren meerlingen substantieel lager ligt in vergelijking met preterm geboren éénlingen terwijl zich, vanaf de 37ste zwangerschapsweek, het omgekeerde voordoet. Gebleken is dat dit vooral een gevolg is van de lagere foetale sterfte bij de meerlingen (In Nederland 7.51% foetale sterfte vs. 3.74% neonatale sterfte en in Vlaanderen respectievelijk 4.64% vs. 1.96%).
Een plausibele verklaring voor dit fenomeen is niet zo maar voorhanden maar deze waarneming leidt wel tot twee overwegingen:

- Op de eerste plaats kan men zich afvragen of de standaard prenatale zorg zoals deze momenteel aangeboden wordt bij éénlingzwangerschappen meer intensief dient te gebeuren vergelijkbaar met de standaard prenatale zorg in geval van tweelingzwangerschappen;
- Op de tweede plaats kan men zich afvragen of de waargenomen stijging in prenatale sterfte bij meerlingen vanaf de 37ste zwangerschapsweek voldoende argument biedt om deze zwangerschappen niet verder dan 37 à 38 weken te laten duren.

In **hoofdstuk 7** tonen wij de resultaten van een vergelijkend onderzoek tussen de diverse gebruikelijke echoscopische groeicurven van de foetale abdominale omtrek (AC) en de hoofdomtrek (HC) in Nederland. Hierbij viel op dat de origine van de meest gebruikte (NVOG-)curven niet correct was aangegeven en slechts matig onderbouwd (ontwikkeld op basis van een onderzoeksgroep van 40 casus). Daarnaast bleken de meetwaarden van de groeicurven, gepresenteerd in het Nederlandse leerboek [5] niet correct weergegeven. Aangezien de software in diverse echoapparaten afhankelijk was van de voorkeur van de fabrikant, concludeerden wij dat op die manier het vervolgen van de foetale groei door verschillende zorgverleners (met verschillende apparatuur) weinig houvast biedt. In dit hoofdstuk vestigden wij de aandacht op deze verschillen en stelden voor om uniformiteit te betrachten in het gebruik van groeicurven zowel t.a.v. de software als t.a.v. de documentatie.

In **hoofdstuk 8** hebben wij, op basis van de vaststellingen in hoofdstuk 7, besloten tot het zelf ontwikkelen van foetale groeicurven. Hiervoor werden de data van een

periode van 11 jaar (1993 t/m 2003) uit onze eigen eerstelijns praktijkgegevens (n=3641) gebruikt. Bij geboortegewichtcurven wordt gedifferentieerd naar geslacht en pariteit. Merkwaardig genoeg gebeurt dit niet bij foetale groeicurven. Daar is nochtans voldoende reden voor aangezien foetale morfometrie geslacht- en pariteit afhankelijk is [6]. Teneinde de beoordeling van de foetale groei te verbeteren hebben wij groeicurven voor AC en HC voor eenlingfoetus van Caucasische moeders geconstrueerd voor de periode tussen 28+0 t/m 33+0 weken (189 en 231 dagen) zwangerschapsduur.

Hieruit bleken voor de foetale AC significante verschillen te bestaan naar geslacht én pariteit. In de HC werden eveneens significante verschillen aangetoond naar geslacht maar niet naar pariteit.

In **hoofdstuk 9** hebben wij de geslacht- en pariteitafhankelijke foetale groeicurven, zoals berekend in hoofdstuk 8 gevalideerd. Sensitiviteit, specificiteit en voorspellende waarden voor groeideviaties (SGA ≤p-10 en LGA ≥p-90) werden berekend voor verschillende afkappunten in het derivatiecohort (n=3449). De meest waardevolle afkappunten hierbij waren AC ≤p-25 voor SGA ≤p-10 bij geboorte en AC ≥p-75 voor LGA ≥p-90 bij geboorte. Deze waarnemingen werden vervolgens beoordeeld in een validatiecohort (n=725) waarbij een sensitiviteit van 53% voor SGA en 64% voor LGA werd waargenomen. Dit is veel gevoeliger dan middels conventionele methode zoals palpatie van de uterus (sensitiviteit voor SGA = 21%) tot nog toe werd bereikt [7].

Epiloog

Perinatologie is een complex multidisciplinair specialisme. Enerzijds gericht op twee "patiënten": de zwangere en het kind. Anderzijds is de zorg toegespitst op zowel laag risico zwangerschappen (gezonde moeders en kinderen ≈ fysiologie) als op hoog risico zwangerschappen (pathologie). De laatste groep heeft "recht" op de best mogelijke behandeling van het pathologisch proces, terwijl de eerste groep "recht" heeft op een gespecialiseerde begeleiding, gericht op het voorkomen van verhoogd obstetrisch of neonataal risico en onnodige medische interventies [8].

Aangezien de perinatale zorg in Nederland zich de laatste decennia als ketenzorg heeft ontwikkeld waarbij verschillende professionals elk binnen hun eigen terrein functioneren, is een intensieve samenwerking tussen deze zorgverleners een absolute voorwaarde om de kwaliteit van de zorg op een hoog peil te houden [9].

Alhoewel beroepsbelangen in sommige gevallen goede landelijke afspraken nog wel eens in de weg kunnen staan, hebben wij in de loop van dit onderzoek een ruime eensgezindheid ervaren in de betrokkenheid van de professionals wanneer het

gaat om het verbeteren van de kwaliteit van zorgverlening door optimaliseren van de onderlinge samenwerking.

Maar optimale samenwerking vereist ook adequate logistiek binnen die praktijkvoering. Een uniform informatiesysteem waarbij alle essentiële gegevens van de zwangere voor alle betrokken zorgverleners direct beschikbaar wordt, is hiervoor een "must". In de voorbije jaren heeft de ICT weliswaar haar intrede gedaan binnen de verloskundige ketenzorg, maar de diversiteit van software programma's hebben tot nog toe weinig bijgedragen in dit proces: snelle inzage in elkaars gegevens blijkt vooralsnog niet mogelijk.

Alhoewel ons Nederlandse verloskundig zorgsysteem haar tekortkomingen heeft, lijkt het er toch op dat de meerderheid van de Nederlandse zwangeren de geboden zorg in hoge mate waardeert: 85% van de zwangeren richten zich bij het begin van hun zwangerschap primair tot de eerstelijns zorgverlener (verloskundige of huisarts) en bijna 30% van de baringen vindt thuis plaats. Daarnaast bleek uit recent onderzoek [10] dat ruim 80% van de jonge moeders, 3 jaar na de geboorte van hun kind, te kennen gaf dat zij tevreden tot zeer tevreden waren over de gang van zaken tijdens hun zwangerschap en bevalling. Anderzijds is het wél zó dat 23.2% van de primiparae en 11.4% van de multiparae er (na 3 jaar nog steeds!) een (zeer) negatieve herinnering aan overhielden. En dit is heel wat meer dan bij voorbeeld in het Verenigd Koningrijk [11].

Ten slotte is belangrijk dat wij er ons van bewust zijn dat de perinatale sterfteratio slechts een bescheiden beeld geeft van het topje van de ijsberg: tegenover iedere casus waarbij het kind is overleden staan een onbekend aantal "survivors" bij wie het (toevallig !!) toch goed ging. Aangenomen mag ook worden dat hoge perinatale sterfte hand in hand gaat met een nóg hogere perinatale morbiditeit.

In conclusie

De perinatale sterfte in Nederland is hoog in vergelijking met vrijwel alle andere Westerse landen. Een substantieel aantal casus van perinatale sterfte wordt (mede) veroorzaakt door SSF en in bijna 1 op 10 gevallen gaat het om SSF in de zorgverlening zelf. Daarnaast blijkt de sterfte vermijdbaar in 1 op 4 gevallen zonder SSF wanneer het gaat om kinderen < p-10 en in 1 op 12 gevallen zonder SSF bij prematuren.

Introductie van perinatale audits op lokaal, regionaal en landelijk niveau kunnen een belangrijke bijdrage leveren aan het terugdringen van de perinatale sterfte. Implementatie van routine echoscopisch onderzoek ter beoordeling van de foetale groei aan het begin van het derde zwangerschapstrimester, kan de detectie en de behandeling van groeivertraagde kinderen gevoelig verbeteren en daarmee ook de perinatale sterfte in deze groep terugdringen.

Verder diepgaand onderzoek is echter noodzakelijk om de resultaten van deze aanpassingen in de verloskundige zorg op hun meritus te beoordelen.

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List of abbreviations

AC	Abdominal Circumference
AGA	Appropriate-for-Gestational-Age
APH	Ante Partum Hemorrhage
AvC	Avoidability of Condition
AvD	Avoidability of Death
BMI	Body Mass Index
BPD	Biparietal Diameter
CBS	Central Bureau of Statistics
CEMACH	Confidential Enquiry into Maternal And Child Health
CESDI	Confidential Enquiry into Stillbirths and Death in Infancy
CI	Confidence Interval
CS	Cesarean Section
CTG	CardioTocoGram
CRL	Crown Rump Length
CVZ	College Voor Zorgverzekeringen (=Health Care Insurance Board)
DCQ	Data Collection Questionnaire
EAGA	Expected-Appropriate-for-Gestational-Age
EFW	Estimated Fetal Weight
ELGA	Expected-Large-for-Gestational-Age
END	Early Neonatal Death
ESGA	Expected-Small-for-Gestational-Age
FIGO	Fédération Internationale de Gynaecologues et Obstétriciens
FL	Femur Length
FM	Fatal Moment
GA	Gestational Age
GP	General Practitioner
HC	Head Circumference
ICD	International Classification of Diseases
IPD	Intra Partum Death
IUFD	Intra Uterine Fetal Death
IUGR	Intra Uterine Growth Restriction
κv	Kappa Value
LBW	Low Birth Weight
LGA	Large-for-Gestational-Age
LND	Late Neonatal Death
LNMP	Last Normal Menstrual Period
LPAS	Landelijke Perinatal Audit Studie

NICU	Neonatal Intensive Care Unit
NOS	Not Otherwise Specified
NPV	Negative Predictive Value
PNM	PeriNatal Mortality
PPM	Preterm Perinatal Mortality
PPROM	Preterm Premature Rupture Of Membranes
PPV	Positive Predictive Value
PRN	Netherlands Perinatal Registry
PROM	Premature Rupture Of Membranes
ROC	Receiver Operating Characteristic
SGA	Small-for-Gestational-Age
SSF	SubStandard (care) Factor
TOP	Termination Of Pregnancy
TRAP	Twin Reversed Arterial Perfusion
US	Ultra Sound
VAIPD	Voluntarily Accepted or Induced Perinatal Death
WHO	World Health Organization

Dankwoord

Na bijna 15 jaar is het eindelijk zover: wat begon als onvrede en irritatie over de té hoge sterfte bij gezonde kinderen is uitgemond in een wetenschappelijke dissertatie waarvan ik hoop dat vooral die kinderen die suboptimaal groeien tijdens hun intra-uteriene periode er baat bij mogen hebben.

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