CLINICAL ASPECTS OF MULTIPLE PREGNANCY.

KLINISCHE ASPECTEN VAN MEERLINGZWANGERSCHAP.

Financial support for publication of this thesis was provided by Organon, Ferring BV, and Abbott BV

Clinical aspects of multiple pregnancy / Job G. Santema
Thesis Rotterdam - with ref. - with summary in Dutch
ISBN 90-9009747-3
Keywords: Multiple pregnancy, maternal complications, fetal death, hypertensive disorders, perinatal outcome

Cover: Photograph by Helmut Swart of their twin born in 1993

CLINICAL ASPECTS OF MULTIPLE PREGNANCY.

KLINISCHE ASPECTEN VAN MEERLINGZWANGERSCHAP.

PROEFSCHRIFT
TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
AAN DE ERASMUS UNIVERSITEIT ROTTERDAM
OP GEZAG VAN DE RECTOR MAGNIFICUS
PROF.DR P.W.C. AKKERMANS M.A.
EN VOLGENS BESLUIT VAN HET COLLEGE VOOR PROMOTIES
DE OPENBARE VERDEDIGING ZAL PLAATSVINDEN OP
WOENSDAG 25 SEPTEMBER 1996 OM 15.45 UUR

DOOR

JOB GERBEN SANTEMA

GEBOREN TE LEEUWARDEN

Promotiecommissie

Promotor	Prof.dr. H.C.S. Wallenburg
Overige leden	Prof.dr. R. Derom Prof.dr. W.H. Birkenhäger Prof.jhr.dr. J.W. Wladimiroff

In memory of my daughter Anna

to Marij, Sjoerd, Marius, Edo

CONTENTS

Chapter 1

GENERAL INTRODUCTION

The natural wonder of multiple pregnancy and birth has fascinated mankind since ancient times and twins figure prominently in legends, folktales and myths. One of the best known traditional stories is that of Romulus and Remus, the twins who were abandoned on the banks of the Tiber and suckled by a she-wolf. Later Romulus founded Rome, the city that still bears his name, after killing his twin-brother. Tales of profound attachment of co-twins, such as Castor and Pollux, as well as those of murderous jealousy, such as between Jacob and Esau, illustrate an early intuitive recognition of the fact that even identical twins have their own personality. A century ago this particular aspect of twinning made Francis Galton realize that twins could also serve as tools for scientific research into the old question of nurture versus nature. His publication "The history of twins, as a criterion of the relative powers of nature and nurture" that appeared in 1875 set the basis for the development of what is now known as the "twin method" in scientific research[47]. The twin method in its simplest form is based on the assumption that the extent to which any given morphologic, biochemical, functional, or behavioral trait or condition exhibits a higher average within-pair similarity in monozygotic than in dizygotic co-twins is a reflection of the extent to which that particular variable is under genetic control[100].

The cause of multiple pregnancy and its clinical hazards have been subject of medical investigation since Hippocrates' time. In particular in the past decade the scientific and clinical interest in multiple pregnancy has expanded rapidly, as shown by the steady rise in the number of publications, for which two main reasons are apparent. First, since approximately 1980 the rate of multiple births in developed countries shows a steady rise. Second, progress in obstetric and neonatal care has created better possibilities for prevention, diagnosis and treatment of maternal, fetal, and neonatal complications associated with multiple pregnancy. The foundation of the International Society for Twin Studies (ISTS) in 1974 in Rome, the city of

Romulus, has made an important contribution to the dissemination of knowledge and stimulation of research in what is called "gemellology", the science of twinning[49].

The incidence of multiple births varies considerably in different parts of the world and has shown important changes over time. This variation is contributed almost exclusively to the occurrence of dizygotic twins, who result from the fertilization of two different oocytes arising in two distinct follicles. The incidence of monozygotic twins, derived from one and the same zygote, appears to be almost constant at 3.5-5 per 1000 maternities everywhere in the world. The slight increase in the monozygotic twinning rate observed during the last two decades in some developed countries, including The Netherlands[99], may be an artefact due to the use of Weinberg's rule to estimate zygosity[37]. Almost a century ago Weinberg postulated that in dizygotic twinning the number of unlike-sex twins will be equal to that of like-sex pairs. Therefore, taking twice the number of unlike-sex twin pairs will provide a fair estimate of the total number of dizygotic twins in a population. Subtracting that number from the total number of twin pairs yields the estimated number of monozygotic twins. The validity of Weinberg's rule has been questioned on various grounds, as extensively reviewed by Derom et al.[37]. Considering the incidences of multiple births it should be realized that the majority of conceptions, multiple as well as single, fail before clinical recognition and will not result in the birth of a live infant. Boklage[10] analyzed a number of data sets to derive a mathematical estimate of twinning. He postulated that the true rate of twin conception is approximately 12%. Based on his mathematical analysis he further estimated that for every liveborn twin pair 10-12 twin pregnancies result in single births, and that 12-15% of all live single births would be products of twin embryogenesis. Indeed, recent advances in early detection of pregnancies by ultrasound have shown that the disappearance rate of one fetus in twin gestation may vary between 10%[8] and 30%[111]; gestational sacs observed early in gestation disappear more frequently than do well-defined fetuses demonstrated by ultrasound at 6-7 weeks gestation. The "vanishing twin syndrome", a term coined by Keith in 1980, may be considered a physiological incident rather than a pathophysiological accident[73].

The rate of natural dizygotic, but not that of monozygotic, twinning is

influenced by heredity, race, maternal age and parity, seasonality, nutrition and environment, as extensively reviewed by Derom et al.[37]. There is evidence that all of these factors predispose to polyovulation by causing a relatively high level of endogenous FSH secretion[84,119]. Some of the highest twinning rates in the world are found among the women of the Yoruba tribe in Nigeria, approximately 5% of all maternities[97]. Hardman[56] found that the staple food of the Yoruba, a particular species of yam, contains steroid substances that may stimulate FSH secretion. No firm evidence exists for a genetic or other influence on monozygotic twinning. A recent analysis of the large Swedish twin registry showed that the incidence of twin births in monozygotic twin mothers was not significantly increased compared with non-twin controls, but monozygotic mothers had significantly more monozygotic twins[75].

From approximately 1960 until the middle of the 1970s a decline in the rate of multiple births occurred in most European countries as well as in the U.S.[37,126]. Following the nadir of this decline in the mid 1970s the rate of twin births increased and by the mid of 1980s exceeded the pre-1960 figures[37]. There is evidence that the decline in the twinning rate between 1960 and the mid 1970s can be explained by a drop in mean maternal age during pregnancy, and the rise thereafter by a continuing increase in the mean age of pregnant women[38]. The additional increase from the mid 1980s onwards must be most likely attributed to the increasing use of ovulation induction and of assisted reproductive technology procedures in the treatment of female infertility, as shown clearly in the results of the East Flanders Prospective Twin Survey[38]. Not only do these procedures themselves carry a relatively high risk of inducing multiple pregnancy, also the number of previously infertile women undergoing such treatment has increased tremendously. The steep increase since the mid 1970s in the number of dizygotic twins and higher order multiple births in Japan, where the natural rate of multifetal pregnancy is among the lowest in the world, is a case in point[61]. Also the rate of triplet births has shown a steep increase in many developed countries since the mid 1970s, e.g. 300% in The Netherlands[37]. There is no doubt that this change is mainly due to ovulation induction and advanced reproductive technology.

Multiple pregnancies are associated with various antenatal and perinatal

complications, which justifies their characterization as high risk. Some of these complications are specific of multiple pregnancy, others also occur in singleton pregnancies but are encountered more often in multifetal gestations. Specific complications of multiple pregnancy include antenatal demise of one fetus in the second or third trimester of pregnancy, with continuing development of the co-twin. The frequency of occurrence of single fetal death in twin pregnancies based on hospital populations varies between 0.5% and 7%[17,43]. This complication confronts the obstetrician with a difficult problem with regard to the management of pregnancy. A decision whether or not to terminate the pregnancy must depend on the balance between the risk of leaving the surviving fetus in an intrauterine environment that may have caused the death of its co-twin and exposing the mother to an associated risk of coagulopathy[72,109,117] on the one hand, and preterm delivery on the other. Published reports deal with small numbers of patients, and the risks involved in expectant management are not well established.

Many studies deal with the incidence of structural anomalies in twins compared with singleton pregnancies[15]. Monozygotic twinning in itself may be considered a structural anomaly, because the separation of a human blastomere into two separate zygotes does not represent the normal course of embryologic development. Some anomalies are unique to monozygotic twinning, such as incomplete separation leading to conjoined twins, fetus-in-fetu, and acardiac malformation. Monochorial placentation may provide a less favorable environment for the developing fetus and it has been suggested that this could be the explanation for the increased incidence of other, nonspecific, fetal anomalies in monozygotic twins[59,92]. However, caution must be used in interpreting results of studies on the incidence of fetal anomalies in mono- and dizygotic twins because determination of zygosity is usually based on Weinberg's rule. In two studies[18,91] in which zygosity was determined by direct methods no significant difference could be established in the overall rate of fetal malformations by type of placentation. No information is available in the literature concerning perinatal outcome in multifetal pregnancies in which one fetus has a structural anomaly. At present access to antenatal diagnosis and high resolution ultrasonography is widely available, and it is of practical clinical importance to be able to estimate the risk to a twin fetus when an anomaly has been

demonstrated in its co-twin.

Vascular communications are almost universal in monochorionic placentation and may be associated with what is generally known as the twin-to-twin transfusion syndrome. Because this condition may also occur in higher order multiple monochorionic pregnancies, the term feto-fetal transfusions syndrome is to be preferred. The incidence of the feto-fetal transfusion syndrome quoted in the literature based on hospital populations varies between 7.5% and 17.5%[7,115,123,128], and accounts for 15-17% of the perinatal mortality in twins[7,123]. Part of the variation in incidence may be attributed to the fact that there is no agreement with regard to the criteria of the diagnosis of feto-fetal transfusion. Detection of discordant fetal growth by ultrasound early in pregnancy suggests feto-fetal transfusion[95] although not all discordant growth in monochorial twins is due to twin transfusion[4]. Placental vascular anastomoses with reversal of blood flow early in embryonic development may lead to the development of an acardiac twin[132]. Other complications of the feto-fetal transfusion syndrome include poly- and oligohydramnios, hydrops of the recipient twin, preterm labor, rupture of membranes and delivery. Management with bedrest, tocolysis, serial amniocentesis[45], selective feticide[141], digoxine treatment[35], and laser techniques for ablating vascular anastomoses[36] have been reported to benefit neonatal survival, but controlled studies are not available.

Several studies indicate that multifetal gestations impose greater demands on maternal physiological systems than do singleton pregnancies. It is generally believed that the increase in the occurrence of maternal complications of pregnancy, such as preterm labor, hypertensive disorders, and gestational diabetes is to be considered a consequence of an increased burden on maternal adaptive capacity[21]. The maternal complications may in turn contribute to a higher incidence of an unfavorable outcome of twin and triplet pregnancies. However, it should be emphasized that the majority of the studies on maternal complications of multifetal pregnancy lack appropriate control groups and are based on hospital populations with a potential selection bias because of a tendency to include patients with complicated multiple pregnancies.

The incidence of preterm labor and delivery in multifetal gestation appears to be significantly increased compared to that in singleton pregnancies, and contributes

substantially to the elevated perinatal morbidity and mortality[11,12,19,68,95]. Rates of preterm delivery, that is delivery before 37 completed weeks, reported in the literature range between 40 and 50%[20,129]. Hospitalization for bedrest and various other interventions to reduce the occurrence of preterm labor and delivery have been and still are used, including prophylactic cervical cerclage and administration of betamimetic agents. Several controlled, randomized trials have failed to provide evidence of beneficial effects of any of these prophylactic measures[2,26,31,32,53,54,57,81,83,85,98,113,118].

The majority of published reports on complications of hypertensive disorders in twin and triplet pregnancy show an incidence that is 3-5 times higher than that in singleton pregnancies[6,77,79]. However, the definition of hypertensive disorders in pregnancy varies greatly in those reports[1,71,77,87,110,136], in particular with regard to the presence or absence of proteinuria, an important determinant of the disease[1,71,87,110,136].

MacGillivray et al.[80] and Dwyer et al.[40] state that two placentas impose a greater diabetogenic effect on carbohydrate metabolism than one, and therefore account for the increased incidence of gestational diabetes in multiple pregnancies in their studies. In contrast, other investigators found no increase in glucose intolerance in women with twin pregnancies[93,121].

In Europe, most obstetricians still prefer to aim for vaginal delivery in twins, unless there is a standard obstetric indication for cesarean section, such as the development of fetal distress or obstructed labor. A cause of obstructed labor that is unique to multifetal frequency is fetal locking, a rare condition with an incidence of about 1 in 1000 twin deliveries[16]. The optimal management of delivery for triplets is debated. In their review Petrikovsky and Vintzileos[101] show that the vaginal route was primarily chosen as the mode of delivery in most reports between 1978 and 1985, with cesarean section rates in the larger series varying between 7 and 32%. However, more recent reports indicate a dramatic increase in the number of cesarean sections in triplets reaching levels of 80-100%[13,94,112]. Although some authors[94] suggest improved neonatal outcome in association with cesarean delivery, there are no randomized trials to support this view.

Based on the considerations above the objectives of this thesis are:

- to assess antenatal complications in a population-based series of twin and triplet pregnancies.
- to assess the course and outcome of twin pregnancies complicated by single fetal death occurring in the second half of gestation.
- to assess the incidence and severity of hypertensive disorders in twin gestations compared with singleton pregnancies.
- to assess preterm delivery and perinatal mortality rates in uncomplicated twin pregnancies and in twin pregnancies with one twin with a structural anomaly.
- to assess maternal and perinatal complications in triplet and twin pregnancies.

The studies related to these objectives are described in chapters 2 to 6 of this thesis and followed by a general discussion (chapter 7).

Chapter 2

ANTENATAL COMPLICATIONS IN TRIPLET AND TWIN PREGNANCIES: A POPULATION-BASED STUDY.

2.1. Introduction

There is evidence that twin and higher order multiple pregnancies impose greater demands on maternal physiological adaptation than do singleton gestations. It is generally believed that women with multifetal gestations more often than women with singleton pregnancies may be unable to meet these physiological adaptational demands, and that such maladaptation may explain an increased occurrence of maternal complications of pregnancy[21]. Although there is a large body of literature dealing with twin gestations, only few reports have specifically focussed on the frequency of maternal complications as they occur in multifetal pregnancies[22,24,66,78,95]. In addition, the majority of reports are based on selected hospital populations, which may introduce considerable selection bias.

In order to get an insight into the maternal characteristics of multifetal pregnancies and the associated maternal health problems, an analysis was carried out of data contained in a large population-based series of twin and triplet births in The Netherlands in a four year period (1984-1987). The results were compared with those obtained in singleton pregnancies from the same database, matched for gestational age.

2.2. Material and Methods

The material for the study was obtained from data on pregnancies and births in The Netherlands in the years 1984 through 1987, recorded in the Dutch Perinatal Database. The Database was initiated in 1982 by the Dutch Society for Obstetrics and Gynecology (NVOG). In the study period it contained data on approximately 85% of all hospital deliveries in The Netherlands with a duration of gestation of 16

weeks or more under the care of an obstetrician-gynecologist. For each pregnancy and delivery approximately 60 items were recorded. An anonymous copy of each set of data was sent to the Dutch Center for Healthcare Information (SIG) where the validity of the data was assessed using a plausibility program based on obstetric knowledge. Discrepancies were reported back to the obstetrician in charge and corrections were made where needed[130,131].

The registry over the years 1984-1987 contained data on 274.101 pregnancies, of which 6.171 were twin and 108 were triplet gestations. The 6.171 women with twin pregnancies were delivered of 12.342 infants. For the purpose of this study each of the twin pregnancies was matched for gestational age and month of delivery with six different singleton pregnancies and maternal and fetal-neonatal data of 6.171 twin mothers were compared with those of 37.026 singleton mothers. The 108 women with triplet pregnancies were delivered of 324 infants. Each of the triplet pregnancies was matched for gestational age and month of delivery with nine different singleton pregnancies that had not been used for comparison with the twin pregnancies. Therefore, 108 triplet gestations could be compared with 972 singleton pregnancies. Calculation of gestational age was based on the first day of the last menstrual period, on early ultrasound, or on both. Parity was defined as the number of previous births after 16 weeks gestation. Maternal hypertension was defined as the occurrence of a diastolic blood pressure of 90 mm Hg or more. The information in the Perinatal Database did not allow to distinguish between hypertension already existing before pregnancy and pregnancy-induced hypertensive disorders with or without proteinuria. Fetal mortality (stillbirth) was defined as fetal death beyond 16 weeks gestation.

We used Student's t-test to compare means of continuous variables within and between various groups. Discrete data were analyzed with the chi-square (χ^2) test. A two-tailed probability level of 0.05 or less was considered to represent statistical significance.

2.3. Results

Numerical data are presented in Figures 2.1 - 2.6. Small differences between the numbers of twin, triplet, and singleton pregnancies in the figures are caused by

missing values. Figures 2.1a and b show the maternal age distributions in triplet, twin, and singleton pregnancies. The mean maternal age in triplets was 28.8 years, in twins 28.6 years and in singletons 27.9 years, a nonsignificant difference.

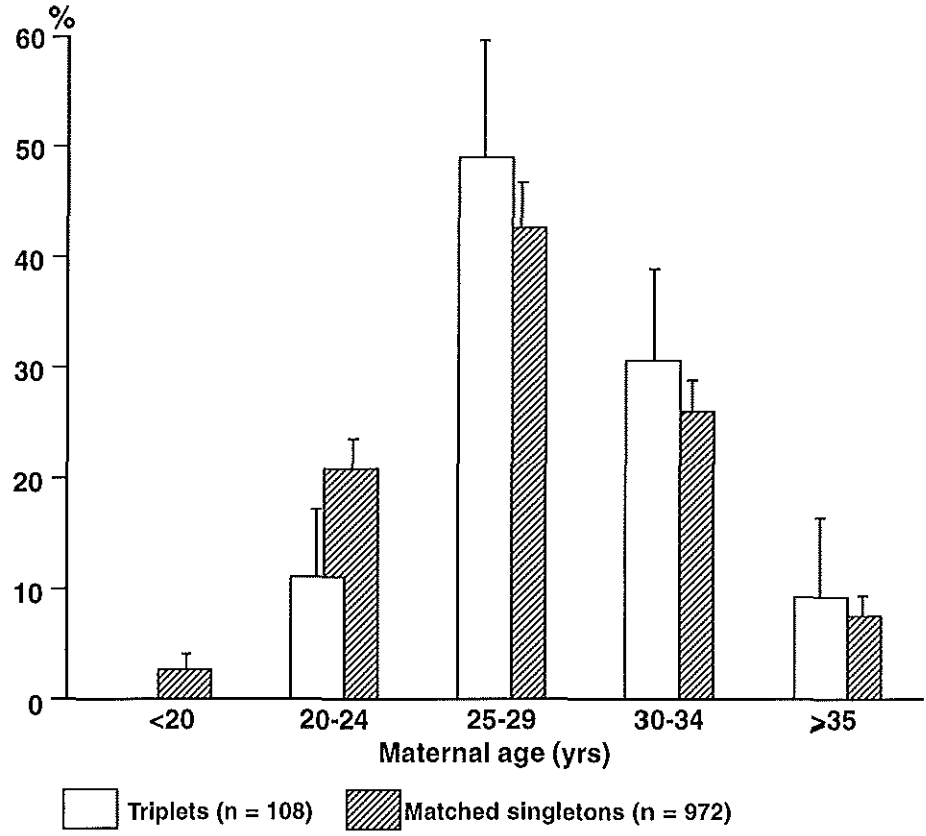

Fig.2.1a *Distribution of maternal age in triplet and matched singleton pregnancies in the study period 1984-1987. The vertical bars indicate 95% confidence intervals.* $\chi^2 = 9.69$; $df = 4$; $p = 0.046$.

A slightly higher proportion of women with triplet pregnancy (39.9%) than with a singleton gestation (33.7%) was 30 years or older, a nonsignificant difference. Also in the case of twin pregnancy the relative number of women over 30 years of age (39.5%) was higher than that in matched singletons (34.6%), a difference that reached statistical significance ($p < 0.05$). Data on parity are presented in Figure 2.2. The proportion of nulliparous women with triplets (44.4%) as well as with

twins (41.1%) was significantly lower than that with singletons (48.0%).

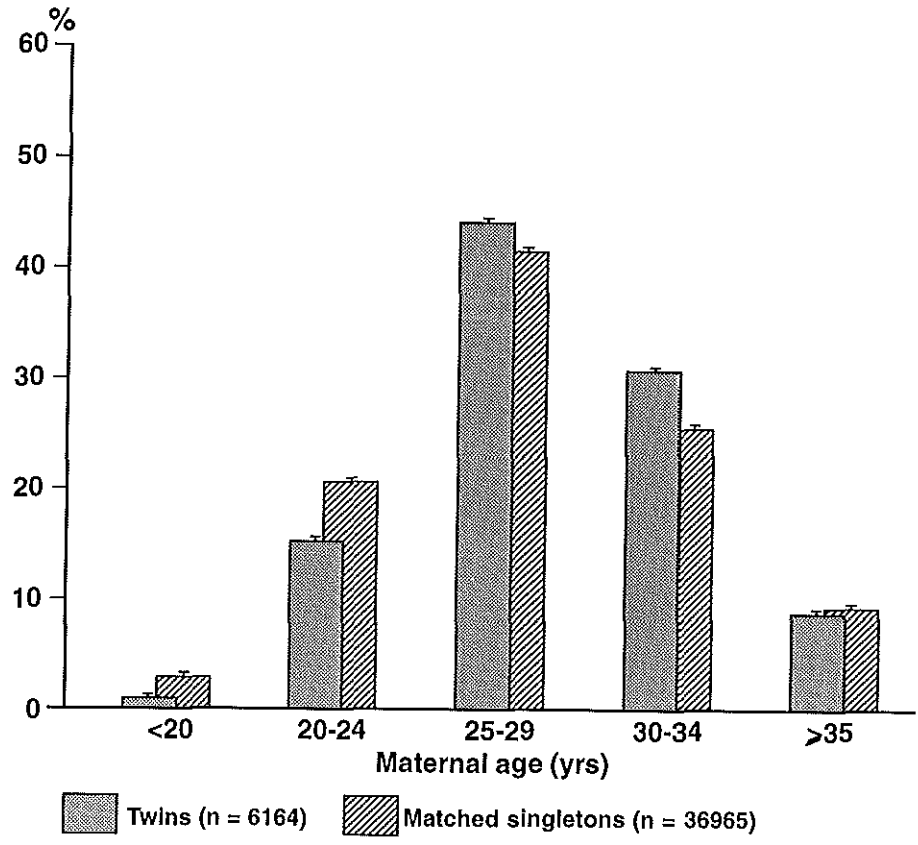

Fig.2.1b *Distribution of maternal age in twin and matched singleton pregnancies in the study period 1984-1987. The vertical bars indicate 95% confidence intervals.* $\chi^2 = 2.20$; $df = 4$; $p < 0.001$.

Figures 2.3a and 2.3b summarize data with regard to maximum diastolic blood pressures during pregnancy. Information on diastolic blood pressure appeared to be missing in 1.5% of the twin pregnancies and in 3.9% of the singleton controls. The proportion of women with triplets who had hypertension in pregnancy was higher (32.5%) than that in women with a singleton pregnancy (24.7%), but the difference did not reach statistical significance. Also in women with a twin gestation hypertension occurred more often (29.7%) than in their singleton controls (24.2%),

and in this case the difference was significant at $p < 0.001$.

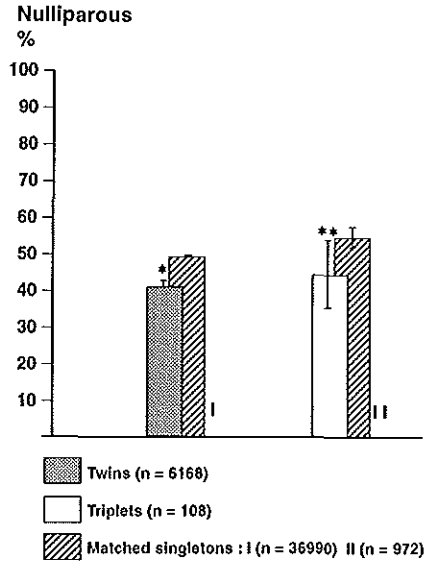

*Fig.2.2 Distribution of nulliparity in twin, triplet, and matched singleton (I: matched with twins; II: matched with triplets) pregnancies in the study period 1984-1987. The vertical bars indicate 95% confidence intervals * $p < 0.001$ ** $p = 0.044$.*

Gestational age at delivery in twin and triplet pregnancies is presented in Figure 2.4. Since the singleton births were matched for gestational age at delivery they are omitted from the figure. Preterm delivery at 32 weeks or less, leading to severe prematurity, occurred almost four times more often in triplets (37.1%) than in twins (10.3%), a highly significant difference ($p < 0.001$). Of the 108 women with triplet pregnancies 98 (90.7%) were delivered before a gestational age of 37 weeks (median 36.4 weeks). This is significantly different from the 2.819 of 6.171 women with twin pregnancies that were delivered before 37 weeks' gestation (45.7%, $p < 0.05$). No data are available on the cause of preterm delivery, i.e. spontaneous preterm labor or planned delivery because of pregnancy complications.

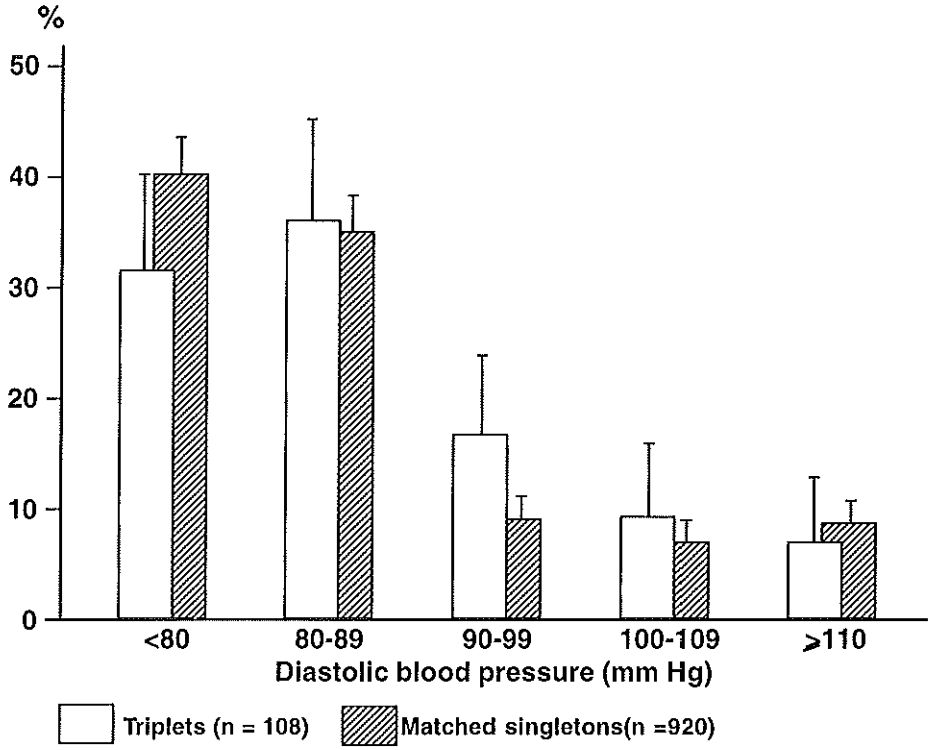

Fig. 2.3a *Distribution of maximum diastolic blood pressure in triplet and matched singleton pregnancies in the study period 1984-1987. The vertical bars indicate 95% confidence intervals.* $\chi^2 = 8.93$; $df = 4$; $p = 0.06$.

Figure 2.5 shows the cesarean section rate among the groups. The proportion of women with triplet pregnancy delivered by cesarean section (58%) was more than twofold that in women with matched singleton pregnancies (25%), a significant difference ($p < 0.001$). The proportion of twin mothers delivered by cesarean section (18%) was significantly different from that in singletons (16%) albeit clinically irrelevant.

Figure 2.6 presents data on fetal death in multifetal pregnancies and their singleton controls. Fetal death in triplet pregnancies was found to be 4.6%, not significantly different from the 5.0% recorded in singleton controls. On the other hand, the proportion of twin pregnancies with fetal death (2.5%) was only half of that in singleton controls ($p < 0.001$).

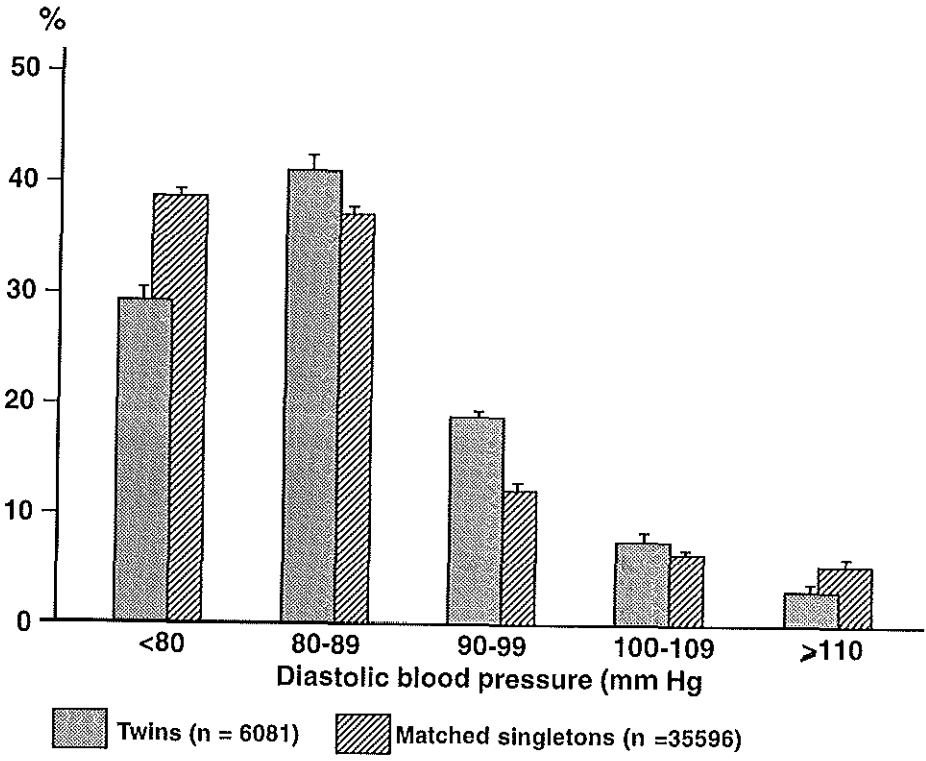

Fig.2.3b *Distribution of maximum diastolic blood pressure in twin and matched singleton pregnancies in the study period 1984-1987. The vertical bars indicate 95% confidence intervals. $\chi^2 = 385.0$; $df = 4$; $p < 0.001$.*

4. Discussion

Textbooks and large reviews[21,22,50,58,66,67,68,70,78,95,122] discuss maternal, fetal and neonatal problems associated with multifetal pregnancy. However, there is considerable doubt and disagreement with regard to the frequency of occurrence of many of these problems. In addition, several of the studies fail to include a control group of women with a singleton pregnancy, and are based on hospital populations. In a hospital-based study there is a potential selection bias because of a tendency to include patients with complicated multiple pregnancies, in particular when higher

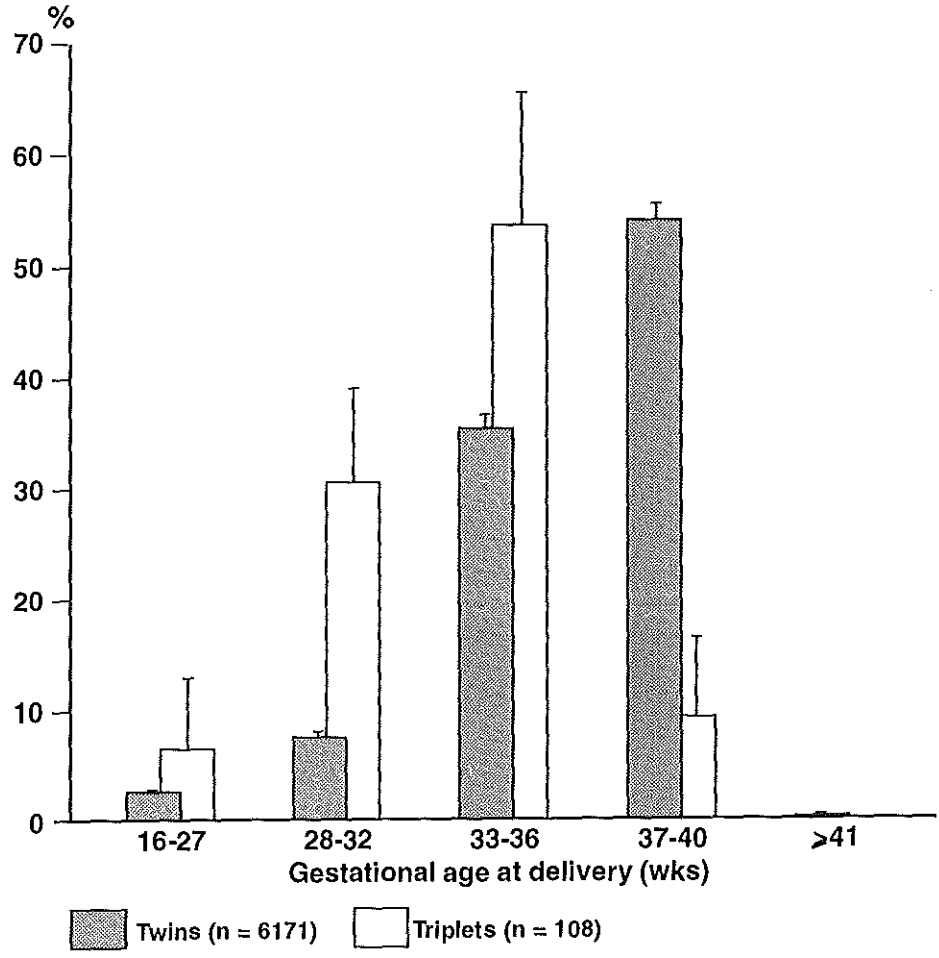

Fig. 2.4 Gestational age at delivery in triplet and twin pregnancies in the study period 1984-1987. $\chi^2 = 125.7$; $df = 4$; $p < 0.001$. *The vertical bars indicate* 95% confidence intervals.

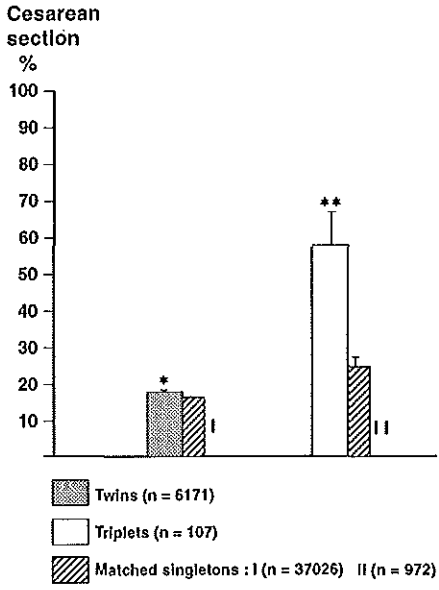

Fig.2.5 Cesarean section rate in twin, triplet and matched singleton (I: matched with twins; II: matched with triplets) pregnancies in the study period 1984-1987. The vertical bars indicate confidence 95% confidence intervals.
** p = 0.0017 ** p < 0.001.*

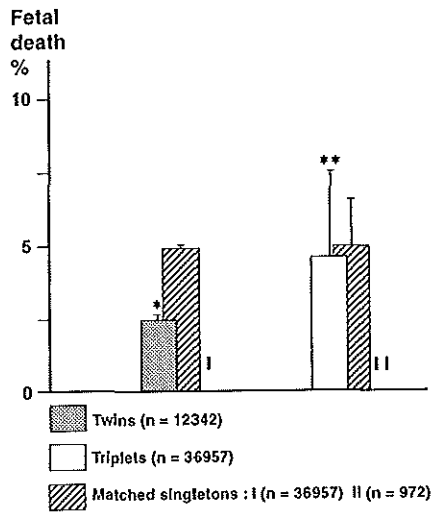

Fig.2.6 Distribution of fetal deaths in twin, triplet and matched singleton (I: matched with twins; II: matched with triplets) pregnancies in the study period 1984-1987. The vertical bars indicate 95% intervals.
** p < 0.001 ** p = 0.76.*

level specialized perinatal centers are involved.

It has been documented in studies of perinatal outcome in multiple pregnancies that the high incidence of antenatal complications is responsible for the elevated perinatal morbidity en mortality[50,67,86]. This seems to be largely due to the increased rate of low birthweight deliveries from preterm births and delivery of small-for-gestational age infants[50,67]. However, there is doubt as to whether multifetal pregnancies are at increased risk of perinatal mortality and morbidity compared with singleton pregnancies of similar gestational age at delivery[68]. In an effort to address that issue we analyzed data on pregnancy, delivery, and perinatal

outcome in The Dutch Perinatal Database, made available by the Dutch Center for Healthcare Information (SIG) over the years 1984-1987. The population-based database contains relevant, reliable, but limited medical and obstetric information on approximately 85% of all hospital deliveries in The Netherlands and made it possible to match multifetal pregnancies with singleton gestations for gestational age at delivery. The singleton pregnancies were also matched by month of delivery, to prevent differences in outcome due to progress in perinatal care.

The relative number of women over 30 years of age who delivered triplets and twins was somewhat higher than that of women who had single births, in general agreement with other reports[37]. Also parity showed a positive association with multifetal pregnancy, but in this study we could not separate the effect of age from that of parity. Other studies[51,127] have indicated that increased maternal age and increasing parity exert an independent positive influence on twinning rates. Based on data from the U.S.A. in 1987 Taffel[127] reports that in first births the twinning rate increases with maternal age; in higher order live-births, the twinning rate shows a steady rise, but independent of maternal age.

Maximum diastolic blood pressure levels were significantly higher in women with twin pregnancies compared with women with singleton pregnancies. The majority of published reports[6,77,79] on complications of hypertensive disorders in twin pregnancies show a frequency 3-5 times higher than that in singleton pregnancies. The definition of hypertensive disorders in pregnancy varies greatly in those reports[1,71,77,87,110,136], in particular with regard to the presence or absence of proteinuria, an important determinant of the severity of the disease[33,137]. In the Dutch Perinatal Database no distinction is made between hypertension already existing before pregnancy and pregnancy-induced hypertensive disorders. In the study period no data on proteinuria were included and it was not possible to distinguish between proteinuric preeclampsia with its increased maternal and fetal risks and non-proteinuric pregnancy-induced hypertension.

Preterm birth is the most frequent complication in triplet and twin pregnancies. In this study the frequency of delivery before 37 weeks' gestation was 45.7% among women with twin pregnancy, in agreement with findings from other series[20,50,67,129]. The mean gestational age at delivery in the triplet pregnancy group

was 33.3 weeks, compared with 32-34 weeks in other reports[13,34,52,62,74,90,94,112,125].

The optimal management of delivery in multifetal pregnancies is debated. In their review Petrikovsky and Vintzileos[101] show that in triplets the vaginal route was primarily chosen as the mode of delivery in most reports between 1978 and 1985 with cesarean section rates in the larger series varying between 7% and 32%. However, more recent reports indicate a dramatic increase in the number of cesarean sections in triplet as well as in twin gestations, reaching levels of 80-100%[13,94,112]. This tendency is reflected in the 50% cesarean section rate in triplets found in the present study. Dommergues et al[39] and Wildschut et al[140] report, however, that vaginal delivery in triplets does not compromise maternal and neonatal outcome and that in trained hands the vaginal route of delivery is at least as safe as cesarean section for triplets.

The fetal mortality in the twin group was significantly lower than that in the singleton group with the same gestational age at delivery. This supports the findings reported by Kilpatrick et al.[68] that, when matched for gestational age at delivery, the perinatal mortality in twins is not higher than that in singleton pregnancies. The finding that the fetal mortality in triplets (4.6%) was about twice that in twins (2.5%), but not significantly different from that in singleton pregnancies matched for gestational age at delivery, must be interpreted with care. The fetal mortality rate in the singleton group is high, and may be subject to selection bias caused by hospital referrals of maternal and fetal complications in singleton pregnancies. National statistics, which include all births, give an overall fetal mortality rate of 0.5-0.6% for The Netherlands. Because data on neonatal deaths were incomplete in the Dutch Perinatal Database they were omitted from the study. With regard to the Dutch Perinatal Database Elferink et al.[42] reported that about 30% of the first week mortality of preterm newborns is not recorded by the obstetrician. This is due to the fact that obstetricians fail to adjust data when changes occur many days after birth, during the stay of a newborn in a Neonatal Intensive Care Unit or after discharge. This problem of underreporting will be solved when the Dutch Neonatal Registry will be linked to the Perinatal Database.

In conclusion, the information obtained in the present study by means of analysis of data of a population-based registry supports observations reported in the

literature with regard to the distributions of maternal age and parity, the incidence of preterm delivery, and the mode of delivery in twin and triplet gestations. Due to the limitations of the registry more detailed questions concerning maternal and perinatal outcome in multifetal pregnancies, in particular with regard to severe maternal hypertensive disorders and to fetal structural anomalies and single fetal deaths could not be answered in this study. In an attempt to find answers to these questions we analyzed data from the Department of Obstetrics of the University Hospital Rotterdam, which will be reported in the following chapters.

Chapter 3

EXPECTANT MANAGEMENT OF TWIN PREGNANCY WITH SINGLE FETAL DEATH*

3.1. Introduction

Antenatal demise of one fetus in the late second or third trimester of twin pregnancy confronts the obstetrician with an unusual and difficult problem with regard to the management of pregnancy. A decision whether or not to terminate the pregnancy must depend on the balance between the risks of leaving the surviving fetus in an intrauterine environment that may have caused the death of its co-twin and perhaps exposing the mother to an associated risk of coagulopathy[72,109,117], and the neonatal problems associated with preterm delivery of the surviving fetus. Because of the relative rarity of the condition, published reports deal with small numbers of patients and the risks involved in expectant management are not well established. At our institution, patients with multiple gestation and antenatal death of one fetus have been managed expectantly according to the same protocol for 20 years. In an attempt to contribute to the development of rational guidelines for management, we reviewed a consecutive series of 29 twin pregnancies with an antenatal diagnosis of single fetal death after 20 weeks gestation. In order to evaluate the contribution of various complications to the outcome of pregnancy, twin pregnancies with single fetal death were matched with twin pregnancies without fetal death.

* *The main substance of this chapter was published in: Santema JG, Swaak AM, Wallenburg HCS. Expectant management of twin pregnancy with single fetal death. Br J Obstet Gynaecol 1995; 102: 26-30.*

3.2. Material and Methods

The study population consisted of all twin pregnancies delivered at the University Hospital Rotterdam, The Netherlands, from 1973 through 1993, with ultrasonographic evidence of a viable twin pregnancy at 20 weeks' gestation or more and an antenatal diagnosis of fetal demise later in pregnancy, with a period of time of 12 hours or more between fetal death and delivery. The time at which the ultrasonographic diagnosis of fetal demise was made was taken as the time of fetal death. After single fetal death had been diagnosed, the pregnancy was allowed to continue in all cases under close maternal and fetal surveillance until the spontaneous onset of labor after 34 weeks or the development of a complication with a standard obstetric indication for termination of pregnancy. Threatened preterm labor before 34 weeks' gestation was treated with intravenous tocolysis. The parents were carefully counselled with regard to the difficult emotional experience of having lost one baby and facing the risk of prematurity and neonatal intensive care of the second infant.

Maternal surveillance included serial platelet counts, but coagulation profiles were only determined in case of retention of the dead fetus for more than five weeks. A careful ultrasonographic examination was done to exclude major congenital abnormalities of the surviving fetus. Fetal growth and condition were assessed by serial ultrasound and regular cardiotocograms. After delivery, the placenta was examined macroscopically and histologically, and the type of placentation was determined. An autopsy was performed unless this was against the parents' wish. The condition of the surviving twin was assessed by the pediatrician and data were reviewed from the charts. Follow-up data of the surviving infants were obtained by means of a questionnaire sent to the parents and from attending physicians.

Each twin pregnancy with single fetal death was matched for maternal parity with two twin pregnancies under antenatal care and delivered at the University Hospital Rotterdam in the same year as the index case. The matching was performed without knowledge of the course of pregnancy in the control cases, except for the fact that both infants were born alive. Outcome measures were the incidence of complications of pregnancy, gestational age and mode of delivery, birthweight, placentation, and perinatal outcome.

Variables are presented as median and range throughout. The chi-square (χ^2)

test was used to assess discrete data and differences between continuous variables in both groups were analyzed with Wilcoxon's rank sum test. A p-value of less than 0.05 (two-sided) was taken to represent significance.

3.3. Results

During the period studied there were 531 twin pregnancies with a duration of gestation of 20 weeks or more. In 33 of these pregnancies one twin died before birth and in 29 of these cases an ultrasonographic diagnosis of single fetal death was made twelve hours or more before delivery. These 29 pregnancies constitute the study group. Delivery following spontaneous labor occurred within 24 hours after the diagnosis of fetal death in six cases; between 1 and 7 days in 14 cases; between 8 and 35 days in five cases, and between 35 and 56 days in the remaining four cases. The matched control group consists of 58 twin pregnancies. Data on the clinical characteristics and outcome of pregnancies in both groups are summarized in Table 3.1.

Maternal age was not different between groups. Eleven pregnancies in the study group (38%) and four in the control group (7%) were complicated by a pregnancy-induced hypertensive disorder ($p < 0.001$). Pregnancy-induced hypertension (PIH) was defined as the development of a diastolic blood pressure of 90 mm Hg or more after the 20th week of pregnancy in a previously normotensive woman. PIH with proteinuria of 0.3 g/L or more in a 24 urine collection period without evidence of urinary infection or contamination was termed preeclampsia[33]. In the study group nine patients (31%) had preeclampsia, six of them severe with proteinuria of more than 5 g/24 h. In five women preeclampsia was present at the time of diagnosis of single fetal death; in four patients it developed later in pregnancy. Three of the nine patients were referred from other hospitals before the diagnosis of single fetal death because of the severity of the preeclampsia. Severe preeclampsia did not occur in the control group.

The occurrence of gestational diabetes was not different between groups. The only other maternal complication concerned a patient in the study group who had a low platelet count and anemia caused by folic acid deficiency. In the four cases of retention of a dead fetus during 5 to 8 weeks, all maternal coagulation variables

remained normal. In two pregnancies (24 and 26 weeks gestation), the fetal co-twin died 5 and 10 days, respectively, after the demise of the first twin.

Table 3.1. *Clinical characteristics and outcome in a study group of twin pregnancies with single fetal death and a control group of twin pregnancies without fetal death. Values are given as median (range) or number, as appropriate.*

	Study group (n=29)	Control group (n=58)
Maternal age (yrs)	30 (19-44)	28 (19-41)
Parity (n)		
0	13	26
≥ 1	16	32
Pregnancy complications		
pregnancy-induced hypertension	2	2
preeclampsia	9	2
gestational diabetes	2	1
Gestational age at delivery (wks)	33 (24-40)	34 (23-39)
≤ 28	5	3
> 28 ≤ 37	21	37
> 37	3	18
Mode of delivery		
vaginal	23	51
cesarean section	6	7
Birthweight (g)		
stillborn	975 (315-2817)	
liveborn	1880 (540-3370)	2160 (550-3640)
Placenta		
monochorionic	13	13*
dichorionic	16	45
Perinatal mortality		
stillborn	31	0
liveborn	27	116
neonatal death	5	11

*$p < 0.01$

Cardiotocography showed signs of fetal distress, but both fetuses were not considered salvageable and it was decided to abstain. Fetal weights were 350 g and 620 g, and 750 and 880 g, respectively. Placentation was monochorionic in both cases with extensive vascular communications and evidence of feto-fetal transfusion in one case.

Median gestational age at delivery was not different between groups, but delivery before 28 weeks occurred somewhat more often in the study group (17.2%) than in controls (5.2%). Two of the five births before 28 weeks in the study group were due to induction of labor following the intrauterine demise of both fetuses; all other preterm deliveries in both groups were due to spontaneous preterm labor. Six patients in the study group were delivered by cesarean section because of severe preeclampsia and fetal distress. In the control group cesarean section was performed because of fetal distress in four patients and malposition of the presenting fetus in three. The median weight of the liveborn twins in the study group (1880 g) was not significantly different from that in controls (2160 g).

The neonatal mortality in the study group (18.5%) was twice that of the controls (9.5%), but the difference was not significant. The neonatal mortality in the study group was mainly due to four infants born between 25 and 28 weeks' gestational age, one with a monochorionic and three with a dichorionic placenta, who died between 1 and 96 hours after birth because of problems related to extreme prematurity. One apparently healthy newborn in the study group died suddenly and unexpectedly 2 weeks after birth. Because autopsy was refused no diagnosis could be made but no neurological or developmental abnormalities had been apparent; there were no signs of infection or coagulopathy, and the placenta was monochorionic. The 11 neonatal deaths in the control group occurred 1 to 144 hours after birth and were all related to extreme prematurity (23-29 weeks).

None of the liveborn infants in the study or control groups showed congenital malformations. At autopsy no malformations were apparent in any of the stillborn twins, but extensive autolysis precluded reliable histologic examination in most cases. The incidence of 45% of monochorionic placentation in the study group was twice that of 23% in controls ($p < 0.01$); mono-amniotic pregnancy was not observed. In five cases of monochorionic placentation in the study group feto-fetal

vascular communications were observed; one monochorionic placenta showed evidence of partial placental abruption.

In the study group three infants were lost to follow-up, so data of 19 infants were available. The median age at follow-up was 4 years and 2 months, with a range of 2 months - 18 years. Seventeen children showed no evidence of abnormality on developmental assessment. One infant, 11 years of age at follow-up, had had epileptic seizures until the age of 3 years and showed a mild delay in gross motor development. One infant, 9 years old at follow-up, had spastic quadriplegia. Both infants were born preterm at gestational ages of 32 and 35 weeks, respectively, and had a monochorionic placenta. Repeat ultrasonograms had not revealed evidence of multicystic encephalomalacia.

3.4. Discussion

A reliable estimate of the incidence and period of gestation of the post-conceptional loss of one fetus in twin pregnancy is hampered by the lack of prospective data. Ultrasound examination indicates that the "vanishing twin" phenomenon is relatively common in the first trimester with a good prognosis for the surviving fetus[73], but single fetal demise diagnosed in the later part of multiple pregnancy is generally considered an uncommon event[5,25,27,46,55,72,104,120,130]. In their comprehensive review of the literature, Landy & Weingold[72] collected 94 case reports, but they point out that data are often erroneously grouped together, including early fetal loss, fetus papyraceus and late intrapartum fetal death. These authors identified 15 cases with an antenatal diagnosis of single fetal death in the course of the second or third trimester of twin pregnancy managed expectantly. With an earlier publication[55] and seven later reports[5,25,27,46,104,120,133] we found 144 cases published in the accessible literature until 1995. To the best of our knowledge the 29 cases described in the present report constitute the largest single series reported as yet.

The incidence of single fetal death of 5.4%, found in the present series of 531 twin pregnancies after 20 weeks gestation, cannot be applied to the population at large as many of the patients were referred to our hospital from other units after the diagnosis had been made. Incidences quoted in the literature, based on hospital

populations, vary between 0.5% and 7% in twin pregnancies[43]. In the only prospective study published so far, based on data from the Collaborative Perinatal Project, single antepartum fetal death was reported in seven of 188 monozygotic twin pregnancies, an incidence of 3.7%[89]. Assessment of fetal and maternal risks involved in the expectant management of advanced twin pregnancy with single fetal death must be based on a rather limited number of published cases.

We observed a high incidence of pregnancy-induced hypertensive disorders, in particular preeclampsia, in twin gestation complicated by single fetal death compared with control twin pregnancies matched for parity. Again, this observation cannot be generalized because in some patients preeclampsia was the primary reason for referral from another hospital. In four of nine cases preeclampsia may have contributed to fetal death. The occurrence of pregnancy-induced hypertensive disorders is not mentioned in the majority of published cases. In one report four of 16 pregnancies were complicated by preeclampsia and two of them improved temporarily after the death of one fetus[46].

An important maternal hazard in association with retention of a dead fetus in singleton pregnancy is consumptive coagulopathy, caused by the release of thromboplastins from the tissues of the dead fetus into the maternal circulation; it is reported to occur in approximately 25% of cases of retention for 5 weeks or longer[103]. The possibility of development of this complication is also emphasized by most authors reporting cases of single fetal death in multiple gestation[72]. In their review Landy & Weingold[73] discuss three patients who developed disseminated intravascular coagulopathy (DIC) at an unspecified time after the occurrence of single fetal death in twin pregnancy. In later publications maternal DIC was reported in only one case 12 weeks after the first twin had died[120]. In our four patients in whom the dead fetus was retained for more than 5 weeks, no changes in maternal coagulation variables were observed. The available evidence, derived from a small number of cases, suggests that the risk of maternal DIC due to prolonged retention of a dead fetus in twin gestation may be low and may not be different from that in singleton pregnancy.

The etiology of single fetal death in our cases remains obscure, as in the majority of published cases. It has been suggested that fetal growth retardation due

to competition for uteroplacental circulation and nourishment could be an important factor[27]. However, uncertainty about the exact date of fetal death and autolysis and loss of weight during intrauterine retention prohibit a reliable diagnosis of low birthweight in the dead fetuses. In most cases autolysis of the dead fetus precluded a histologic diagnosis of the underlying cause of fetal death. Except for making a diagnosis of monochorionic or dichorionic placentation, histologic examination of the placenta was not found to be helpful, because of the often extensive secondary placental changes caused by the retention of the dead fetus. Our study shows monochorionic placentation in 45% of twin pregnancies with single fetal death as compared with 23% in twin gestation with live fetuses. A prevalence of monochorionic placentation has been reported by most authors, varying between 50 and 70% of cases. Vascular communications are almost universal in monochorionic placentation[107] and may be associated with feto-fetal transfusion with hyperperfusion of one twin and underperfusion of its co-twin, leading to growth retardation and later fetal death. The fact that we found evidence of feto-fetal vascular anastomoses in only five of 13 monochorionic placentas, associated in all cases with death of the smaller fetus, may be explained by the collapse of chorionic vessels in the part of the placenta that belongs to the dead fetus, which makes recognition of vascular communications difficult.

In our series the main cause of neonatal death was prematurity. Cerebral abnormalities caused by fetal coagulopathy and cerebral infarction due to transfer of thromboplastic material from the dead twin to the live fetus, which may occur in case of a monochorionic placenta with a shared circulation[72], were not observed. Although ultrasound after fetal death of one twin has demonstrated the intrauterine development of cystic cerebral cavities, intraventricular hemorrhage and microcephaly in the surviving co-twin[60,116], our study does not confirm reports that multicystic encephalomalacia is a frequent finding in the survivor or that only half the number of surviving twins is "normal" on follow-up[43]. It seems likely that prematurity and low birthweight constitute the main cause of the elevated incidence of neurologic complications observed in surviving infants after single fetal death in twin pregnancy.

The obstetric and neonatal results of our study support an expectant

management of twin pregnancy with single fetal death under close maternal and fetal surveillance. An important aspect of such an approach that requires further investigation is the complex parental emotional response caused by grieving the death of one baby while anxiously awaiting the birth of the survivor.

Chapter 4

HYPERTENSIVE DISORDERS IN TWIN PREGNANCY*

4.1. Introduction

The majority of published reports on complications of twin pregnancy show an elevated incidence of hypertensive disorders, which tend to occur earlier and to run a more severe course than in singleton gestation. Incidences of 20-30 per cent are reported, 3-5 times higher than in singleton pregnancies[6,77,79]. Unfortunately, in particular the older studies lack adequate control groups and the criteria used to define hypertensive disease vary markedly[1,71,77,87,110,136]. In some cases no distinction is made between pregnancy associated with hypertension already existing before pregnancy and pregnancy-induced hypertensive disorders, with or without proteinuria[1,71,87,110,136]. In addition, many reports do not distinguish between proteinuric preeclampsia, with its increased maternal and fetal risks, and nonproteinuric pregnancy-induced hypertension, the main risk of which is the development of preeclampsia[30]. A reliable assessment of the risk of pregnancy-induced hypertensive disease in twin pregnancy has become even more relevant since evidence has become available that a low dose of aspirin may prevent the development of early-onset preeclampsia with preterm delivery in pregnancies at high risk[14,29], which could include multiple pregnancy.

The present study was designed to assess the incidence and severity of hypertensive disorders in twin pregnancy in a consecutive series of 187 patients attending the antenatal clinic of the University Hospital Rotterdam from early in pregnancy. Strict definitions were applied and the results were compared with those in a control group of an equal number of women with singleton pregnancies, matched for maternal age, parity and gestational age at delivery.

* *The main substance of this chapter was published in: Santema JG, Koppelaar I, Wallenburg HCS. Hypertensive disorders in twin pregnancy. Eur J Obstet Gynecol Reprod Biol 1995; 58: 9-13.*

4.2. Material and Methods

All charts of patients with a twin pregnancy delivered in the University Hospital Rotterdam during the 10 year period between 1983-1992 were reviewed. Of the 447 patients, 187 were booked in the antenatal clinic before a gestational age of 24 weeks and remained under our care until after delivery. The remaining 260 patients were referred to our hospital after 24 weeks gestation for various maternal or fetal complications, including hypertensive disorders, and were not included in the study. Each twin pregnancy was matched for parity, maternal age (to within 2 years), and gestational age at delivery (within 1 week) with a singleton pregnancy, under our antenatal care before 24 weeks' gestation and delivered in the same year as the index case. The matching was done by determining in a blinded fashion without knowledge of the course and outcome of pregnancy the first singleton delivery that was registered before or after the birth of a pair of twins and that met all matching criteria.

Primary end points of the analysis of course and outcome of pregnancy in both groups were the occurrence of pregnancy-induced hypertension (PIH) and preeclampsia. Based on the recommendations of the International Society for the Study of Hypertension in Pregnancy[33], PIH was defined as the occurrence after 20 weeks gestation in a previously normotensive woman of a diastolic blood pressure of 90 mm Hg or more, determined in sitting position at Korotkoff 4 on two occasions at least 4 hours apart. PIH with proteinuria of 0.3 g/L or more in a 24 h urine collection period exclusive of urinary infection or contamination was considered preeclampsia. A diagnosis of the syndrome of hemolysis, elevated liver enzymes, and a low platelet count (HELLP) was made in preeclamptic patients with the simultaneous occurrence of hemolysis in a peripheral smear, serum levels of aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) greater than 30 U/L, and a platelet count of less than 100×10^9/L. Superimposed preeclampsia was defined as proteinuria developing for the first time during pregnancy in a woman with chronic hypertension.

Perinatal mortality was used as a subsidiary end point, and defined as the sum of all fetal deaths with a birthweight of 500 g or more and neonatal deaths of 500 g or more within 28 days after birth per 1000 births. We defined the birthweight

ratio as the quotient of the actual birthweight of the infant and the expected birthweight on the 50th percentile of the Dutch intrauterine growth curve for singleton pregnancies corrected for gestational age, sex and parity[69]. All twin placentae were macroscopically and histologically examined, but investigations to establish zygosity such as blood group determination or HLA tissue typing were not routinely done. Twin pairs with a monochorionic placenta were classified as certainly monozygotic, and all unlike-sex twin pairs were classified as certainly dizygotic. Based on Weinberg's[139] hypothesis that for every pair of unlike-sex dizygotic twins there will be one like-sex pair, the estimated number of monozygotic twins was calculated by substracting the total number of unlike-sex twin pairs from the number of like-sex pairs.

Data are presented as median and range throughout. Differences in continuous variables were assessed with Wilcoxon's rank sum test for comparison between groups, and discrete data were analysed with the chi-square (χ^2) test. A two-tailed probability level of 0.05 or less was considered to represent statistical significance.

4.3. Results

Clinical characteristics and outcome of the 187 predominantly white women with twin and singleton pregnancies are summarized in Table 4.1.

Because of the matching criteria used there are no differences with respect to maternal age, parity and gestational age at delivery. We observed no significant difference between twin pregnancies and singleton controls in gestational age at the first antenatal visit, and in cesarean section rate. There are no significant differences between the birthweights of first and second twins; the birthweight ratios of twins are significantly lower than those of singletons ($p < 0.05$).

The incidence of hypertensive disorders in twin and singleton pregnancies is summarized in Table 4.2. In the twin group 21% met the criteria for diagnosis of a pregnancy-induced hypertensive disorder, as compared with 13% in the singleton group ($p < 0.05$). The difference is due to a significantly higher incidence of PIH in twin than in singleton pregnancies, in particular in nulliparous women, whereas the incidence of preeclampsia is not different between twin pregnancies and singleton controls. Severe preeclampsia (proteinuria > 5 g/L, or HELLP) occurred in 8 of

Table 4.1. *Clinical characteristics and outcome of pregnancy in twin and singleton pregnancies. Values are given as median (range) or number, as appropriate.*

	Twin pregnancy (n=187)		Singleton pregnancy (n=187)	
Maternal age (yrs)	30	(17-47)	30	(17-45)
Parity				
0	103		103	
≥ 1	84		84	
Gestational age at first antenatal visit (wks)	14	(6-23)	13	(6-23)
Gestational age at delivery (wks)	37	(21-41)	37	(21-41)
Mode of delivery				
vaginal	150		158	
LSCS*	37		29	
Birthweights (g)				
first born	2375	(140-3715)	2840**	(150-4130)
second born	2338	(130-3660)	-	-
Birthweight ratio				
first born	0.87	(0.23-1.58)	0.97**	(0.44-1.60)
second born	0.84	(0.12-1.23)	-	-
Perinatal mortality (‰)	58.8		26.7**	
fetal deaths	2		1	
neonatal deaths	20		4	
Zygosity				
certain monozygotic	39			
certain dizygotic	134			
estimated monozygotic	49			

* Lower segment cesarean section, ** $p < 0.05$

187 women with a twin pregnancy compared with 10 of 187 controls, a non-significant difference. Eclampsia was not observed in either group. The median highest diastolic blood pressure before delivery in the twin pregnancies was 80 mm Hg (range 55-130 mm Hg), not different from the median highest diastolic blood pressure in the singleton pregnancy group of 80 mm Hg (range 55-150 mm Hg).

The incidence of pregnancy-induced hypertensive disorders in certainly dizygotic twin pregnancies (31/134) was not different from that in certain or estimated monozygotic twin pregnancies (11/49). The median interval between the diagnosis of PIH and delivery in twin pregnancy (14 days) was twice that in singleton pregnancy (7 days), but the difference is not statistically different; the same is true for the

Table 4.2. *Incidence of hypertensive disorders in twin and singleton pregnancies.*

	Twin pregnancy						Singleton pregnancy					
	Nulliparous (n=103)		Parous (n=84)		Total (n=187)		Nulliparous (n=103)		Parous (n=84)		Total (n=187)	
	n	%	n	%	n	%	n	%	n	%	n	%
Normotensive	73	71	72	86	145	77.6	85	82	73	87	158	84.5
Hypertensive	30	29	12	14	42	22.4*	18	18	11	13	29	15.5
PIH	20	19	8	10	28	15.0*	5	5	7	8	12	6.4
Pre-eclampsia	7	7	1	1	8	4.2	8	8	0		8	4.2
Pre-eclampsia + HELLP	2	2	0		2	1.1	2	2	0		2	1.1
Chronic hypertension	1	1	2	2	3	1.6	1	1	4	5	5	2.7
Chronic hypertension with superimposed pre-eclampsia	0		1	1	1	0.5	2	2	0		2	1.1

* $p < 0.05$ compared with singleton pregnancy

interval between the diagnosis of preeclampsia and delivery in twin (12 days) and singleton (18 days) gestation. The hypertensive disorder was the main indication for termination of pregnancy by induction of labor or cesarean section in 10 twin pregnancies (5 PIH, 5 preeclampsia) compared with 11 singleton pregnancies (5 PIH, 6 preeclampsia). The median gestational age at termination of pregnancy for this indication was 37 (32-40) weeks in twin pregnancies and 34 (28-36) weeks in singletons ($p < 0.05$). Birthweight ratios in twin pregnancies complicated by PIH (median 0.86, range 0.70-1.02) were not different from those in normotensive twin pregnancies (median 0.88, range 0.23-1.58), but somewhat higher than those in twin pregnancies with preeclampsia (median 0.84, range 0.68-0.98), although the difference was not significant.

The perinatal mortality rate in twins was twice that in singletons ($p < 0.05$) due to a higher number of neonatal deaths associated with lethal congenital abnormalities (n=2) and complications of feto-fetal transfusion (n=6). In the twin group two of the perinatal deaths occurred in the 11 patients with preeclampsia, whereas one perinatal death occurred in the 12 preeclamptic singleton pregnancies.

4.4. Discussion

The results of our matched-pair comparative study on the incidence of all pregnancy-induced hypertensive disorders in twin and singleton pregnancies are in general agreement with those obtained in other large series of twin pregnancies and singleton controls[77,79,87]. However, the definition of hypertensive disease in pregnancy varies greatly in those reports, in particular with regard to the presence or absence of proteinuria, an important determinant of the severity of the disease and of pregnancy outcome[137]. In our series the higher proportion of hypertensive disease in twin pregnancies is due to pregnancy-induced hypertension, whereas the incidence of proteinuric preeclampsia is not different from that in singleton pregnancy. In a population study in Aberdeen MacGillivray[79] found that the incidence of preeclampsia in the first pregnancy was five times greater in twin than in singleton pregnancies. Nylander et al.[96] examined the incidence of preeclampsia in twin pregnancies in Ibadan and found only 4.5% in all parities compared with 6% in singletons. However, when they considered first pregnancies only, the rates were 5.9% and 1.1% for twin and singleton pregnancies, respectively. An extremely high incidence of 30% of proteinuric preeclampsia was observed in black African women with twin pregnancy[88]. Part of the differences may be explained by geographical variation in the prevalence of hypertensive disorders, but the majority of reports in the literature cannot be used for international comparison. The elevated incidence of preeclampsia in twin pregnancy in hospital-based studies[77,87] could be due, at least in part, to selection bias, because patients with preeclampsia may be more easily referred to a tertiary care center than women with PIH alone. For that reason we included in our study only women who were under our antenatal care before 24 weeks' gestation.

Some studies have found a higher incidence of preeclampsia in unlike-sex than in like-sex twin pregnancies, which would suggest an immunological cause due to maternal-fetal antigenic differences in dizygotic twin pregnancy[124]. Other studies found higher rates of preeclampsia associated with monozygotic as compared with dizygotic twins[88] or no differences[23]. It should be pointed out that in many studies the fraction of monozygotic twins is estimated by means of Weinberg's rule, based on the assumption that for every dizygotic unlike-sex twin ther must be a like-sex

twin pair[139]. Several authors have challenged that assumption[63,64,105], although results of the large East Flanders Prospective Twin Survey including over 2500 twin pairs in which zygosity was accurately determined, tend to support Weinberg's hypothesis[135]. In our study no influence of zygosity on the incidence of pregnancy-induced hypertensive disorders was apparent, but the numbers are relatively small.

A greater proportion of singleton than of twin pregnancies may be expected to continue until term, and so more singleton than twin pregnancies will be at risk of developing a pregnancy-induced hypertensive disorder later in pregnancy. For that reason we matched for gestational age at delivery. However, in twins preterm delivery is often caused by the condition of multiple pregnancy itself, whereas in singleton pregnancies a higher proportion of preterm deliveries may be attributable to induction of labor for a hypertensive disorder. This was indeed observed in our study and would tend to introduce a bias towards a higher incidence of preeclampsia in singleton pregnancy with a smaller difference in hypertensive disorders between twins and singletons.

The increased incidence of nonproteinuric PIH in twin pregnancies in our study could be due to the higher cardiac output and circulating plasma volume[108,134] in multiple pregnancies compared with singleton gestation. If we accept that in twin compared with singleton pregnancy cardiac output is increased by heart rate[108] as well as by stroke volume, in particular in the third trimester[134], the occurrence of PIH may be explained by failure to decrease peripheral vascular resistance any further when the physiological limit for singleton pregnancy has been reached. In that case normal organ perfusion would be maintained, and the endothelial damage associated with reduced perfusion in preeclampsia[106] would not be expected to occur. The finding that birthweight ratios in twin pregnancies with PIH were equal to those in normotensive twin pregnancies support this hypothesis.

In conclusion, there is no doubt that multiple pregnancy is associated with greater risks for both mother and fetuses compared with singleton pregnancy, but our study failed to substantiate an increased risk of proteinuric preeclampsia in a cohort of predominantly white women with twin pregnancies.

Chapter 5

PRETERM DELIVERY RATE AND FETAL OUTCOME IN STRUCTURALLY AFFECTED TWIN PREGNANCIES: A RETROSPECTIVE MATCHED CONTROL STUDY*

5.1. Introduction

Present day high resolution ultrasound equipment allows early detection of fetal structural anomalies. In singleton pregnancies, obstetric management will be determined by the severity and progression of the anomaly. In twin pregnancies, the complicating factor may be the presence of a normal co-twin. Twin pregnancy is associated with raised preterm delivery and perinatal mortality rates[95]. In most studies, a higher prevalence of anomalies has been found amongst multiple births than amongst singletons[15].

No information is available on the risk of preterm delivery and perinatal mortality in twin pregnancies with one infant being structurally affected. This is of clinical importance, since under these conditions obstetric management will be determined not only by the nature of the structural defect in one twin, but also by the presence of an unaffected co-twin. The aim of this study was to determine whether there is a difference in the preterm delivery and perinatal mortality rates between pregnancies with one affected twin and unaffected twin pregnancies.

* *The main substance of this chapter was published in: Heydanus R, Santema JG, Stewart PA, Mulder PGH, Wladimiroff JW. Preterm delivery rate and fetal outcome in structurally affected pregnancies: a retrospective matched control study. Prenat Diagn 1993; 13: 155-162.*

5.2. Material and Methods

During the period 1982-1990, a total of 71 twin pregnancies were referred to the Department of Obstetrics of the University Hospital Rotterdam, Division of Prenatal Diagnosis, for an anomaly scan because of suspected structural anomalies in one or both fetuses.

In 23 pregnancies, a structural anomaly was identified in one twin fetus, justifying continuation of the pregnancy. Maternal age varied between 20 and 44 years (median 31 years), maternal parity ranged between 0 and 5 (median 1), and gestational age varied between 19 and 37 weeks of gestation (median 26 weeks).

All fetal scans were performed using a Diasonics CV 100 (carrier frequency 3-5 and 5.0 MHz) or a Toshiba SSA 270 (carrier frequency 3.75 MHz). In cases of fetal karyotyping, amniocentesis was performed[102]. Confirmation of the structural anomaly was obtained from autopsy or from clinical records in all 23 cases.

Twenty-three twin pregnancies with proven absence of fetal structural anomalies and delivered in our Obstetric Department served as historical controls. They were matched one-to-one for maternal age and parity, and year of delivery.

Statistical analysis of matched pairs consisted of McNemar's test (two-sided) for determining differences in preterm delivery, mode of delivery, differences in fetal sex, perinatal mortality, and placental structure between the affected and control groups. Perinatal mortality was defined as intrauterine or neonatal death of one or both fetuses in a particular twin pregnancy.

The Wilcoxon matched-pairs signed rank test was applied for comparing birthweight between the affected twin and unaffected co-twin, and between the two unaffected twins in the control group. This test was also used to assess differences in gestational age at delivery between the affected and matched control group. A two-tailed probability level of 0.05 or less was considered to represent statistical significance.

5.3. Results

Tables 5.1 and 5.2 present data on the affected sets of twins; Tables 5.3 and 5.4 depict data on the control twins.

Table 5.1. *Data on affected twin pregnancies (patients 1-11)*

Patient no.	Ultrasound (weeks)	Abnormality	Karyotype	Delivery (weeks)		Perinatal outcome	Postnatal karyotype	Placenta
1	21	-	n	38	♂ 2910	Alive	-	MC DA
		MCA	n		♂ 2000	IUD		
2	25	MCA	-	27	♂ 850	IUD	tri 13	MC DA
					♂ 1060	NND	n	
3	24	MCA	n	34	♂ 1340	NND	-	DC DA
		-	n		♀ 1680	Alive	-	
4	19	-	ref	32	♂ 2300	Alive	-	DC DA
		MCA			♂ 1430	NND	-	
5	28	-	n	37	♀ 2550	Alive	-	DC DA
		MCA	n		♀ 1990	NND	-	
6	26	-	-	26	♂ 820	IUD	-	DC DA
		MCA	-		♂ 1070	IUD	-	
7	24	-	n	24	♂ 510	IUD	-	MC DA
		NTD	n		♂ 220	IUD	-	
8	23	-	n	34	♂ 2800	Alive	-	DC DA
		NTD	n		♀ 1940	NND	-	
9	27	-	-	37	♂ 2110	Alive	-	MC MA
		NTD	-		♂ 2080	IUD	-	
10	30	NTD	-	33	♀ 1320	NND	-	DA
		-	-		♀ 1860	Alive	-	
11	37	NTD	-	40	♂ 2690	Alive	n	DC DA
		-	-		♂ 3210	Alive	n	

MCA = Multiple congenital anomalies; NTD = neural tube defect; n = normal; ref = refused by the couple; IUD = intrauterine death; NND = neonatal death; MC = monochorionic; DC = dichorionic; MA = monoamniotic; DA = diamniotic.

Table 5.2. *Data on affected twin pregnancies (patients 12-23)*

Patient no.	Ultrasound (weeks)	Abnormality	Karyotype	Delivery (weeks)		Perinatal outcome	Postnatal karyotype	Placenta
12	21	-	-	36	♂ 2335	Alive	-	DC DA
		R	-		♂ 2480	NND	-	
13	33	-	-	39	♂ 3120	Alive	n	DA
		R	-		♂ 2760	NND	n	
14	33	R	-	39	♂ 2840	Alive	-	MC DA
		-	-		♂ 2640	Alive	-	
15	35	-	n	35	♂ 2400	Alive	-	?
		R	n		♂ 2460	Alive	-	
16	27	R	n	36	♂ 2670	Alive	-	DC DA
		-	n		♀ 2600	Alive	-	
17	24	R	-	37	♀ 2440	Alive	-	DC DA
		-	-		♂ 2385	Alive	-	
18	21	R	n	22	♀ ?	NND	-	MC DA
		-	n		♀ 190	NND	-	
19	27	-	-	36	♀ 2500	Alive	-	DC DA
		omph	-		♀ 2550	Alive	-	
20	27	omph	ref	33	♂ 1280	NND	-	MC DA
		-			♂ 1785	Alive	-	
21	33	omph	n	37	♀ 1870	Alive	-	DA
		-	n		♀ 2380	Alive	-	
22	20	hygroma	ref	37	♀ 2160	Alive	XO	MC DA
		-	-		♀ 2780	Alive	XO	
23	35	-	ref	37	♀ 2290	Alive	-	MC MA
		CHD			♀ 1820	IUD -		

R = Renal and/or urinary tract anomaly; omph = omphalocele; CHD = congenital heart defect; n = normal; ref = refused by the couple; IUD = intrauterine death; NND = neonatal death; MC = monochorionic; DC = dichorionic; MA = monoamniotic; DA = diamniotic.

Table 5.3. *Data on matched-control twin pregnancies (patients 1-11)*

Patient No.	Delivery (weeks)		Perinatal outcome	Placenta
1	38	♀ 2120	Alive	DC DA
		♂ 2785	Alive	
2	30	♂ 1520	Alive	DC DA
		♂ 1295	Alive	
3	36	♀ 2720	Alive	DC DA
		♀ 2905	Alive	
4	38	♂ 2650	Alive	DC DA
		♀ 3055	Alive	
5	40	♂ 2170	Alive	DC DA
		♀ 2445	Alive	
6	28	♂ 1100	NND	MC DA
		♂ 1100	Alive	
7	37	♂ 1980	IUD	MC DA
		♂ 2505	Alive	
8	39	♂ 2375	Alive	DC DA
		♂ 2540	Alive	
9	38	♂ 3070	Alive	DC DA
		♀ 3070	Alive	
10	34	♂ 2065	Alive	MC DA
		♂ 1865	Alive	
11	36	♀ 2245	Alive	DC DA
		♀ 2230	Alive	

NND = neonatal death; IUD = intrauterine death; MC = monochorionic; DC = dichorionic; MA = monoamniotic; DA = diamniotic.

Structural anomalies included multiple congenital anomalies (MCA) n=6), renal tract (n=7), neural tube (n=5), omphalocele (n=3), cardiac defect (n=1), and cystic hygroma (n=1).

A normal phenotype of the co-twin was confirmed at birth in 22 cases in which no fetal anomaly was diagnosed. In one instance, both infants displayed 45,X,0, although a cystic hygroma was present in only one of these infants.

Table 5.4. *Data on matched-control twin pregnancies (patients 12-23)*

Patient No.	Delivery (weeks)		Perinatal outcome	Placenta
12	34	♀ 1370	Alive	MC DA
		♀ 1550	Alive	
13	35	♂ 2700	Alive	DC DA
		♂ 2450	Alive	
14	27	♀ 760	Alive	DC DA
		♀ 825	Alive	
15	37	♂ 2650	Alive	DC DA
		♂ 2550	Alive	
16	38	♀ 2840	Alive	DC DA
		♂ 3310	Alive	
17	37	♂ 3530	Alive	DC DA
		♀ 3140	Alive	
18	39	♂ 2375	Alive	DC DA
		♂ 2540	Alive	
19	37	♀ 2650	Alive	DC DA
		♂ 3055	Alive	
20	33	♀ 2015	Alive	MC DA
		♀ 1845	Alive	
21	36	♂ 2690	Alive	DC DA
		♀ 3290	Alive	
22	37	♂ 2650	Alive	DC DA
		♂ 2550	Alive	
23	35	♂ 2480	Alive	DC DA
		♀ 2370	Alive	

MC = monochorionic; DC = dichorionic; DA = diamniotic.

Amniocentesis was performed in nine cases: in three out of six cases of MCA, in three out of seven cases of urinary tract anomalies, in two out of five cases of neural tube defects, and in one out of three cases of omphalocele.

In five cases, fetal karyotyping was not carried out because of refusal (n=4) or premature labor (n=1). In the remaining nine cases (in four cases of urinary tract

anomalies, two cases of MCA and three central nervous system abnormalities), fetal karyotyping was not done for unknown reasons. In four cases a postnatal karyotype was obtained, resulting in one case of trisomy 13 (Table 5.1).

The incidence of maternal and fetal pathology, the time and mode of delivery, birth weight, fetal sex, perinatal mortality, and placental structure in affected and control twin pregnancies are presented in Table 5.5.

Table 5.5. Maternal, fetal and placental data from affected and control twin pregnancies

	Affected pregnancy (n=23)		Control pregnancy (n=23)		p-value
Maternal disease	2		3		1.0
Polyhydramnios	4		0		0.1
Preterm delivery (< 37 weeks)	13		11		0.8
Delivery (weeks)	34.2		35.5		0.2
Cesarean section	6		3		0.5
Birthweight (g)	Affected twin	Normal co-twin	twin 1	twin 2	0.003
	1921±697	2228±703	2292±639	2403±698	0.1
Like-sex	19		14		0.2
Perinatal mortality	15		2		< 0.001
Monochorionic placenta	9/19		4		0.2

There was no difference in the incidence of maternal disease (hypertensive disorders, diabetes) between the structurally affected and control twin pregnancies. Polyhydramnios (ultrasonically visualized fluid pocket > 8 cm) was present in four structurally affected pregnancies (cases 1,6,15, and 18) as opposed to none in the control group (p=0.1). Preterm delivery (< 37 weeks) took place in 57% of affected pregnancies to 48% in controls, a nonsignificant difference. There was also no significant difference in the mean gestational age at delivery between affected (34.2±4.9 weeks (SD) and unaffected twin pregnancies (35.5±3.5 weeks (SD)).

No significant difference existed with respect to the mode of delivery between the affected sets of twins and control twins.

Twins were like-sex in 83% of affected pregnancies and in 61% of control twin pregnancies.

Perinatal mortality was significantly higher in the affected than in the control twins.

The birthweight of the affected twin was significantly lower ($p=0.003$) than that of the unaffected co-twin. No significant differences in birthweight were observed within the sets of control twins and between affected and control twin pairs.

A monochorionic placenta was observed in nine out of 19 affected twin pregnancies and in four out of 19 controls. In four affected twin pregnancies information on placental structure was incomplete.

5.4. Discussion

In the presence of a single structurally affected fetus, obstetric management may vary from adjustment of timing, mode, and location of delivery to intrauterine treatment or termination of pregnancy depending on the gestational age. If the affected fetus is one of a set of twins, these options must be reconsidered in the light of the presence of a structurally normal co-twin.

Any intrauterine procedure is associated with an increased risk of preterm labor, which in a multiple pregnancy will also involve the co-twin. Selective feticide is increasingly being practised in early gestation to eliminate a seriously affected fetus in an otherwise normally developing multiple pregnancy[28]. In the present study, the majority of structural anomalies (75 per cent) was first recognized beyond 24 weeks of gestation, rendering selective feticide a highly unattractive procedure.

The preterm delivery rate was high, but not different between the affected (57%) and control twins (48%). Since the incidence of maternal disease was not different between the two study groups, these preterm delivery rates suggest that in twin pregnancy the presence of a structurally abnormal fetus does not significantly alter the rate of preterm delivery when compared with unaffected twin pregnancies. This is in spite of the presence of polyhydramnios in four affected pregnancies. Larger series are, however, needed to substantiate in terms of statistical power the role of prematurity in the outcome of structurally affected twin pregnancies.

The significantly higher perinatal mortality rate in the affected twin pregnancies is predominantly determined by the nature of the anomaly in the

affected co-twin. Neonatal outcome of the unaffected twin was generally good, which is in support of a policy of non-interference during prenatal life in this particular situation.

In affected sets of twins, a significantly lower birthweight of the affected twin compared with its normal co-twin was noted. The presence of a structural anomaly may be associated with reduced cell division and therefore reduced organ growth[65], resulting in a lower birthweight of the affected twin compared with the structurally normal co-twin.

The limitation of this study is that in most instances no information was available on the zygosity of the affected twin pregnancy. It has been demonstrated that the incidence of congenital malformations in monozygotic twins is higher than that in dizygotic twins[114]. Although documentation on the type of placental structure was available in 19 of 23 affected pregnancies, evidence of monozygosity could only be obtained in nine monochorionic cases. Thus, 9/19 (47 per cent) of the affected twin pregnancies were monochorionic against only 5/23 (22 per cent) of the control twins. No information was available on genotyping by blood groups, enzymes of the red cells, or of the placenta[18].

The inconsistency in deciding whether or not to perform fetal karyotyping in this study can be explained in part by the limited knowledge of ultrasonic markers for chromosomal anomalies and the assumed risk of invasive procedures for the unaffected co-twin in the early days of prenatal diagnosis and, in part, by the advanced gestational age at the time at which the anomaly was first recognized.

In conclusion, the findings from this retrospective analysis suggest that the raised perinatal mortality rate in pregnancies with one structurally affected twin is determined by the nature of the anomaly and not by the prematurity rate when compared with structurally unaffected twin pregnancies.

Chapter 6

MATERNAL AND PERINATAL COMPLICATIONS IN TRIPLET COMPARED WITH TWIN PREGNANCY*

6.1. Introduction

Ovulation induction, in vitro fertilization, and related methods of assisted reproductive technology are associated with a considerable risk of triplet and higher order multiple pregnancy[74]. In an attempt to reduce the maternal and perinatal risks of multifetal pregnancy, parents are being offered the option of reduction of the number of fetuses in the first trimester of pregnancy, with the aim to improve the chances of survival and normality of the fetuses that remain[9,41,82,138]. The justification for this recommendation depends on the assessment of the balance of the risks of continuation of the triplet or higher order multiple gestation and those of selective feticide and reduction to twin or singleton pregnancy. Pregnancies with four or more fetuses are clearly associated with an adverse perinatal outcome[9], but assumptions made with regard to the outcome of triplet pregnancy are based on relatively small series, some of which have taken 25 years to collect. Obstetric and neonatal practices have changed considerably over that period of time and may not reflect current standards of obstetric and neonatal care. In addition, very few studies report the course and outcome of triplet gestations in comparison with twin pregnancies as controls[9,76,112]. For that reason, we designed this study to evaluate the triplet pregnancies managed in our perinatal center from 1981-1992 and to compare their course and outcome with those of twin pregnancies in a matched-pair analysis.

* *The main substance of this chapter was published in: Santema JG, Bourdrez P, Wallenburg HCS. Maternal and perinatal complications in triplet compared with twin pregnancy. Eur J Obstet Gynecol Reprod Biol 1995; 60: 143-147.*

6.2. Material and Methods

We reviewed the charts of all triplet pregnancies delivered after a gestational age of 20 weeks or more in the University Hospital Rotterdam (AZR) between January 1 1981 and December 31 1991, an 11 year period in which fetal reductions were not yet performed in our institution. The AZR is a tertiary care perinatal referral center serving a region with 35.000 deliveries per year. Each triplet pregnancy was matched for maternal parity and age (to within 1 year) with the first two sets of twins registered in the AZR before or after the index case that met the matching criteria. The matching was done in a blinded fashion, without knowledge of the course and outcome of pregnancy in the control cases. Antepartum management of uncomplicated multiple pregnancy was on an outpatient basis, with standard obstetric surveillance and regular ultrasound assessment of fetal growth. Antenatal screening for fetal chromosomal abnormalities was offered on the basis of maternal age (≥ 36 yr) or the presence of a known risk factor. No prophylactic measures such as bed rest, cervical cerclage, or oral tocolysis were taken. Patients were admitted only because of obstetric complications.

Outcome measures were analyzed using the following definitions. In pregnancies that were a result of assisted reproduction, the calculated length of gestation was based on the date of embryo transfer or induced ovulation plus two weeks. In spontaneous pregnancies gestational age was based on the date of the last menstrual period and confirmed by early ultrasonography. The criteria recommended by the International Society for the Study of Hypertension in Pregnancy were used to define hypertensive disorders[33]. Anemia was defined as a hemoglobin concentration of 10 g/dl or less. Hospitalization before 37 completed weeks' gestation because of an objective or subjective increase in uterine activity requiring tocolysis, with or without associated cervical change, was considered preterm labor. Demonstrated vaginal loss of amniotic fluid before 37 completed weeks was considered preterm rupture of membranes (PROM). The diagnosis of postpartum hemorrhage was based on clinical assessment, with a blood loss of 1000 ml or more. Birthweight was standardized for gestational age using a birthweight index defined as the quotient of the actual birthweight and the birthweight on the 50th percentile of the Dutch intrauterine growth curve for singleton pregnancies, corrected for gestational age,

sex and parity[69]. Stillbirth was defined as a fetal loss with a weight of 500 g or more. Early neonatal mortality was defined as the number of liveborn infants weighing 500 g or more who died during the first 7 days after birth, and late neonatal mortality as the number of deaths of liveborn infants between 8 and 28 days after birth, per 100 liveborns. The sum of stillbirths and neonatal deaths per 100 births constitutes perinatal mortality.

Variables are presented as median and range throughout. Wilcoxon's rank sum test was used to assess continuous variables, correlations were assessed with the nonparametric Spearman test, and discrete data were analyzed with the chi-square (χ^2) test. In order to adjust for multiple comparisons, a two-tailed probability level of 0.01 or less was considered to represent statistical significance.

6.3. Results

During the 11 year study period 40 triplet pregnancies were delivered after a gestational age of 20 weeks or more, and were matched with 80 twin pregnancies. The majority of the triplets (82%) were a result of assisted reproduction, compared with 36% of the twin pregnancies ($p < 0.001$). The relative number of women referred to our hospital with triplet pregnancies (40%) was twice that with twins (21%). The main indication for referral in both groups was preterm labor.

6.3.1. *Course of pregnancy*

A correct diagnosis of the number of fetuses was made in all patients at 10 (5-29) weeks in triplet pregnancies and at 13 (5-31) weeks gestation in twins. Cervical cerclage was not applied in twin pregnancies, but three women with triplets received a cerclage at the end of the first trimester because of suspected early cervical changes. In the triplet group amniocentesis for antenatal diagnosis of fetal chromosomal abnormalities was performed on the basis of maternal age in four patients, and trisomy 21 was diagnosed in one fetus; the parents decided to accept the fetal abnormality and the pregnancy continued uneventfully. In the triplet group one anencephalic fetus was diagnosed by ultrasound at a gestational age of 16 weeks. In the twin group one fetus with a gastroschisis and, in another patient, a fetus with multicystic kidneys were diagnosed by ultrasound; the parents decided to accept

these abnormalities. Clinical characteristics of pregnancy and delivery in both groups are presented in Table 6.1.

Table 6.1. *Clinical characteristics of pregnancy and delivery in a study group of triplet pregnancies and a control group of twin gestations matched for maternal age and parity. Values are given as median (range) or number (percentage), as appropriate.*

	Triplets (n=40)	Twins (n=80)
Maternal age (yrs)	31 (21-39)	31 (21-39)
Parity		
0	22	44
≥ 1	18	36
Pregnancy complications		
preterm labor	36 (90%)	48 (60%)*
preterm rupture of membranes	5 (12%)	19 (24%)
pregnancy-induced hypertension	9 (22%)	10 (12%)
preeclampsia	1 (2%)	3 (4%)
gestational diabetes	2 (5%)	5 (6%)
anemia	15 (38%)	22 (28%)
antenatal hospitalization	34 (85%)	39 (49%)*
gestational age (wks)	28 (21-36)	31 (23-40)*
duration (days)	16 (1-103)	3 (1-58)*
Gestational age at delivery (wks)	32 (23-37)	35,5 (23-41)*
23-28	11	9
29-32	11	15
33-36	14	24
≥ 37	4	32*
Mode of delivery		
vaginal	15	63*
cesarean section	25	17*
Postpartum hemorrhage	6	5

* $p \leq 0.01$

Most of the women with triplets (85%) but only half the number of mothers with twins (49%) were admitted to the hospital at some time during pregnancy, because of subjective complaints or maternal complications. The difference in antenatal complications was mainly due to the significantly higher incidence of preterm labor requiring intravenous tocolysis in triplets as compared to twins ($p < 0.01$). The median duration of tocolytic treatment was 14 (1-74) days in the triplet group and 5 (1-55) days in twin pregnancies ($p < 0.01$). In the triplet group, 14 patients (35%) and in the twin group 11 patients (14%) received prophylactic steroids to enhance fetal lung maturation. The incidence of pregnancy-induced hypertension and preeclampsia was not different between triplet and twin pregnancies. Of the nine patients with triplets and pregnancy-induced hypertension, three cases were severe with diastolic blood pressures $\geq$ 110 mm Hg, compared with two of 10 cases in twins.

6.3.2. *Labor and delivery*

Of the 40 patients with triplets 36 were delivered before a gestational age of 37 weeks (median 32 weeks), a significant difference ($p < 0.001$) with 48 of 80 patients in the twin group (median 35.5 weeks). There is also a marked difference in very preterm birth before 29 weeks' gestation between triplets (25%) and twins (9%) ($p < 0.01$). The incidence of cesarean section was significantly higher in patients with triplets (62%) than with twins (21%). The indication was elective in 30% of triplets and in 12% of twin pregnancies ($p < 0.001$); the remaining indications were fetal distress and non-vertex presentation of the first twin. All cesarean sections were performed by low transverse incision.

Of the placentae in the triplet group 30 (75%) were triamniotic-trichorionic, five (12.5%) triamniotic-bichorionic and three (7.5%) were triamniotic-monochorionic. One of the three monochorionic placentae was associated with intrauterine death of one fetus. Sixty (75%) of the twin placentae were biamniotic-bichorionic, 12 (15%) were biamniotic-monochorionic and one was monoamniotic. Of two triplet and seven twin placentae no complete data were available.

6.3.3. *Neonatal outcome*

Data on neonatal outcome are summarized in Table 6.2. There were 12 fetal losses among the 120 triplets, two with a weight of less than 500 g. Among the 108 liveborn infants there were 18 neonatal deaths. Corrected for three infants delivered

Table 6.2. *Perinatal outcome in triplet pregnancies (n=40) and in twin gestations (n=80) matched for maternal age and parity. Values are given as median (range) or number (percentage), as appropriate*

	Triplet births (n=120)		Twin births (n=160)	
Live births	108	(91.5%)	156	(97.5%)*
birthweight (g)	1478	(300-2980)	2030	(300-3650)*
birthweight index	0.84	(0.10-1.14)	0.86	(0.17-1.32)
Stillbirths**	10	(8.5%)	3	(2.5%)*
birthweight (g)	680	(510-970)	720	(520-900)
5 minute Apgar-score < 7	36	(33%)	17	(11%)*
Early neonatal deaths	10	(10.2%)	7	(4.5%)
birthweight (g)	870	(650-1130)	830	(600-1020)
Late neonatal deaths	4	(4.1%)	4	(2.7%)
birthweight (g)	1120	(970-1555)	900	(780-1030)
Perinatal mortality**	24	(20%)	14	(8.9%)*
Pregnancies with discharge home of ≥ 1 infant	37	(92.5%)	76	(95%)
Neonatal complications				
hospital stay (days)	30	(1-317)	13	(1-143)*
congenital anomalies	6		7	
episodes of bradycardia	35		37	
ventilatory support	37		43	
seizures	2		2	
necrotizing enterocolitis	2		2	
hyperbilirubinemia	54		51*	
intraventricular hemorrhage	2		6	
patent ductus arteriosus	5		5	
bronchopulmonary dysplasia	4		4	

* $p < 0.01$. ** Birthweight > 500 g

at less than 24 weeks gestation with a birthweight range of 400-480 g and one infant with anencephaly, the perinatal mortality of triplet pregnancies was 20%; with 8.9%, the perinatal mortality in twins, corrected for lethal congenital malformations and a birthweight of less than 500 g, was significantly less ($p < 0.01$). The difference is mainly caused by the stillbirth rate of 8.5% in triplets compared with 2.5% in twins ($p < 0.01$). In three triplet pregnancies and in four twin pregnancies all fetuses were lost. Neonatal mortality was associated with very preterm birth (< 29 weeks) in 44% of cases in triplets and in 38% in twins, a nonsignificant difference. Triplets had a significantly lower median birthweight than twins, but there is no significant difference in birthweight index between groups. The median hospital stay was significantly longer in the triplets, mainly related to the lower birthweight. Except for hyperbilirubinemia, which was observed more frequently in triplets, there were no significant differences between triplets and twins in the incidence of major neonatal complications. The number of infants needing ventilatory support was not different between triplets and twins. Triplets received ventilatory support during a median period of 4 (1-52) days compared to 2 (1-59) days in twins, a nonsignificant difference. In the triplet group intraventricular hemorrhage grade II was diagnosed in a 25 weeks' infant, and a grade IV hemorrhage in a 27 weeks' infant; both babies died. In twins intraventricular hemorrhage grade I-II occurred in five infants, grade III in one; the six infants were born between 25 and 30 weeks gestation, and four of them died. Of the triplets four infants had a club foot without other congenital abnormalities; one infant of a 36-year-old mother had Down syndrome and one infant was anencephalic, both diagnoses made antenatally. In the twin group one infant had a prune belly syndrome, one was born with gastroschisis, one infant had an aorta stenosis. Two infants were born with renal dysplasia, one of which was diagnosed antenatally by ultrasound; hypospadia was observed in two neonates.

6.4. Discussion

The majority of the triplet pregnancies in our study were a result of infertility treatment. Consideration of the clinical options of reduction to twins and a policy of expectant management must take into account the risks of maternal, fetal and

neonatal complications and the probability of taking home at least one live and healthy infant associated with both approaches. Our study of triplet and twin pregnancies shows that preterm labor is the most significant antenatal problem, in particular in triplet gestations, with no significant differences between both types of multifetal pregnancy with regard to other major complications. Pregnancy-induced hypertensive disorders are considered a major complication of higher order multifetal pregnancy[101]. Indeed, pregnancy-induced hypertensive disorders occurred in 22% of our triplet pregnancies, in accordance with an incidence of 13-20% reported by others[34,62,90,125]. However, the majority of patients had mild nonproteinuric hypertension, and no difference between the incidence of preeclampsia in triplet and twin gestation could be demonstrated.

Preterm delivery is the most important determinant of neonatal outcome in multifetal gestation. The incidence of delivery before 37 completed weeks in triplet gestation ranges from 64 to almost 100% in various studies[13,34,52,62,74,76,90,94,112,125], compared with 90% in our study. The median gestational age at delivery in triplet pregnancy was 32 weeks in our study, compared with 32 to 34[5] weeks in other reports[13,52,62,74,90,94,112,125]. Our study may be biased towards lower gestational ages at delivery due to the high referral rates because of preterm labor, in particular in the triplet group, but our results are similar to those of a recently reported large study of 198 triplet pregnancies of which 95% were delivered at less than 37 weeks, with an average gestational age at delivery of 34 weeks[94]. In contrast to that study, in which ambulatory perinatal nursing and home uterine contraction monitoring were uniformly used, we applied standard antenatal care on an outpatient basis as long as the course of pregnancy remained uncomplicated. A recent review failed to provide evidence of a significant contribution of the routine use of antepartum hospitalization or prophylactic tocolytic treatment to the prognosis of triplet pregnancies[94].

The optimal management of delivery for triplets is debated. In their review Petrikovsky and Vintzileos[101] show that the vaginal route was primarily chosen as the mode of delivery in most reports between 1978 and 1985, with cesarean section rates in the larger series varying between 7 and 32%. However, more recent reports indicate a dramatic increase in the number of cesarean sections in triplet as well as in twin gestations, reaching levels of 80-100%[13,94,112]. Although some authors

suggest improved neonatal outcome in association with cesarean delivery[94], there are no randomized trials to support this view.

Our study confirms that triplets have a lower median birthweight and gestational age at delivery, and a longer neonatal stay in hospital than twins. However, we found no significant differences in major neonatal complications between triplets and twins.

In our study the stillbirth as well as the total perinatal mortality rates were significantly higher in triplets than in twins. Comparison of perinatal mortality rates between studies may be misleading as the definition varies from report to report. In general, the available recent literature on the outcome of triplet pregnancies indicates a perinatal mortality rate ranging from 13.3-33%[34,62,90,101,125] with some notable exceptions of mortality rates between 4-10%[13,94,112]. Our findings are in close agreement with those in a recent large study showing a 16% perinatal mortality in triplet pregnancies while 15% of the liveborn infants did not survive infancy[11]. For comparison with the results of selective fetal reduction it is more important to consider the relative number of pregnancies terminating in at least one live infant than the overall perinatal mortality. In our study, 92.5 percent of the mothers with triplet gestation had at least one surviving infant, compared with 95% with twin pregnancy. In comparison, discharge home with at least one infant was 88.2 percent in a recent study of 34 triplet pregnancies with reduction to twins[76]. Recent data on reduction of triplets to twins indicate a loss of the entire pregnancy of approximately 8-16% to 24 weeks[44,76] and the experience of the operator rather than the method used appears to be the key determinant of success for an individual patient[44]. Although reduction of triplet to twin pregnancy may be expected to reduce perinatal mortality after 24 weeks, the results of our study do not show significant differences between maternal morbidity and neonatal mortality and morbidity in triplet and twin pregnancies managed expectantly and no marked effect of fetal reduction on these outcomes is to be expected. Also in the only study in which the outcome of triplet gestations managed expectantly was compared with that in triplet pregnancies reduced to twins, no significant effect on neonatal mortality was demonstrated[76].

The data obtained in our study may be used to counsel women with a triplet pregnancy considering selective reduction to twins with regard to the anticipated

perinatal outcome of expectantly managed triplet and twin pregnancy. However, the decision to continue pregnancy or to opt for fetal reduction does not only depend on obstetric considerations but also on the socioeconomic consequences of multiple pregnancy, on the complex ethical problems of fetal reduction, and on the emotional and psychologic problems associated with both policies[48]. Since the majority of triplet and higher order multifetal pregnancies are a result of infertility treatment, we feel that all methods of assisted reproduction should aim at prevention of multifetal gestation. We share the distress expressed by others[44] about the recently advocated extremely agressive application of assisted reproductive techniques with incorporation of multifetal pregnancy reduction as an adjunct of treatment[3].

Chapter 7

GENERAL CONCLUSIONS

In this chapter general conclusions are presented on the basis of the studies reported in this thesis against the background of the objectives formulated in Chapter 1.

In comparison with women with a singleton pregnancy the incidence of antenatal complications in women with multifetal pregnancies even when matched for gestational age at delivery is increased. The increase is mainly due to hypertensive disorders, preterm delivery, and the cesarean section rate. The study reported in Chapter 2, from which these conclusions are derived, is based on a registry in The Netherlands of singleton and multiple pregnancies. The advantages of such a population-based registry are the large numbers and the avoidance of certain selection biases. In practice, however, data are necessarily limited and appear to be not always complete. In The Netherlands about one-third of the deliveries occurs at home under the supervision of a midwife; this data was not included in the registry in the years 1984-1987. This has introduced an important selection bias, because complicated pregnancies and deliveries, including all multifetal pregnancies but only part of the singleton gestations, were referred to hospitals and included in the registry, whereas women with uneventful singleton pregnancies and deliveries were not. This bias explains the high incidence of fetal deaths and other complications in the registry of singleton pregnancies, as reported in Chapter 2.

For these reasons, we decided to analyze in more detail the various complications associated with multiple pregnancy, using data from pregnant women attending the Department of Obstetrics of the University Hospital Rotterdam. From the results reported in Chapters 3-6 the following conclusions can be drawn.

1. Antenatal demise of one fetus in the second half of twin pregnancy is an unusual and difficult problem with regard to the management of pregnancy. Parents are grieving the death of one baby while anxiously awaiting the birth

of the survivor and the obstetrician is confronted with the decision whether or not to terminate the pregnancy. The results of a case-controlled analysis of a consecutive series of 29 twin pregnancies with an antenatal diagnosis of single fetal death after 20 weeks gestation indicate that such a pregnancy can be managed expectantly under close maternal and fetal surveillance until the spontaneous onset of labor after 34 weeks, or until there is an obstetric indication for termination. In this study no association with consumptive coagulopathy was apparent. The main cause of neonatal death was prematurity, multicystic encephalomalacia was not observed.

2. Hypertensive disorders, in particular preeclampsia, constitute a major cause of maternal, fetal and neonatal mortality and morbidity in multiple and in singleton pregnancies. As in the majority of reports also our study of a consecutive series of 187 twin pregnancies showed a significantly higher incidence of pregnancy-induced hypertensive disorders compared with that in an equal number of singleton controls matched for maternal age, parity, and gestational age at delivery. The difference was due, however, to a higher incidence of pregnancy-induced hypertension, whereas the occurrence of proteinuric preeclampsia in twin pregnancies was not different from that in singleton controls. We have put forward the hypothesis that pregnancy-induced hypertension in multifetal pregnancy may be explained by failure to decrease maternal peripheral vascular resistance beyond its physiological limit, resulting in failure to accomodate an increase in cardiac output that is greater than that in singleton gestation.

3. Ultrasonography is currently the principal method for detection of fetal congenital anomalies. In singleton pregnancies obstetric management will be determined by the severity and prognosis of the anomaly, but in twin pregnancies the presence of a normal co-twin constitutes a complicating factor. Assessment of the course and outcome of a consecutive series of 23 twin pregnancies with one fetus affected by a structural anomaly, compared with that in 23 twin control pregnancies without fetal anomalies matched for maternal age and parity, showed a sevenfold higher perinatal mortality rate in affected twin pregnancies. However, the preterm delivery rate and the

incidence of complications of pregnancy were similar in both groups. These findings suggest that the reported elevated perinatal morbidity rate in twin pregnancies with a single structurally affected fetus is determined by the nature of the anomaly.

4. The risk of prematurity is directly proportional to the number of fetuses within the uterus. Selective reduction of the number of fetuses has been proposed as a means to improve perinatal outcome in multifetal pregnancies. The results of the assessment of the course and outcome of a consecutive series of 40 triplet gestations compared with 80 twin pregnancies, matched for maternal age and parity, do not support selective reduction of triplets to twins based on perinatal outcome. The decision to continue a triplet pregnancy or to opt for fetal reduction depends on socio-economic, emotional and psychologic problems associated with both policies. All methods of assisted reproduction should aim at prevention of multifetal gestation.

SUMMARY

CHAPTER ONE presents a general introduction to the thesis. In all industrialized countries, including The Netherlands, the rate of multiple births shows a steady rise, which can be explained in part by the increasing use of assisted reproductive technology. Multiple pregnancies are associated with various antenatal and perinatal complications. Some of these are specific of multiple pregnancy, others are encountered more often than in singleton pregnancies. Based on these considerations, the objectives of the studies reported in the following chapters are outlined. The objectives include an assessment of antenatal complications in a population-based series of twin and triplet pregnancies, assessment of the course and outcome of twin pregnancies complicated by single fetal death occurring in the second half of gestation, assessment of frequency and severity of hypertensive disorders in twin pregnancies, assessment of preterm delivery and perinatal mortality rates in normal twin pregnancy and in twin pregnancies with one twin with a structural anomaly, and assessment of the course and outcome of triplet compared with twin pregnancies.

CHAPTER TWO reports a study designed to compare some maternal characteristics and antenatal complications in a population-based registry of 108 triplet and 6.171 twin pregnancies, with those in a control group of singleton pregnancies matched for gestational age at delivery. Mean maternal age was 28.8 years in women with triplet pregnancy, 28.6 years with a twin pregnancy, and 27.9 years with a singleton pregnancy. The proportion of nulliparous women with triplets and twins was significantly lower than that with singletons (44.4% versus 54.6% and 41.1% versus 49.3%). Hypertensive disorders occurred more often in twin gestation than in singleton controls. The incidence of fetal death in twin gestation (2.5%) was only half that in singleton pregnancies (4.9%), an unexpected finding that may be caused by referral bias. Data on neonatal deaths were incomplete and could not be used. Due to the limitations of the registry more detailed questions concerning maternal and perinatal outcomes in multifetal pregnancy could not be answered.

CHAPTER THREE describes the course and outcome of twin pregnancies with single fetal death in the second half of gestation managed expectantly. A case-controlled study is presented of 29 consecutive pregnancies from 1973 to 1993 with sonographic evidence of a twin gestation at 20 weeks gestation and antenatal demise of a single fetus later in pregnancy, matched for maternal parity with 58 twin pregnancies without fetal death and delivered in the same year as the index case. The frequency and severity of pregnancy-induced hypertensive disorders was significantly higher in the study group than in controls. There were no differences between the study group and controls with regard to median gestational age at delivery (33 weeks vs 34 weeks) and median birthweight of liveborn infants (1880 g vs 2160 g). No maternal coagulopathy was apparent in the 29 patients. The main cause of neonatal death was prematurity; multicystic encephalomalacia was not observed. The results of this study support an expectant management in twin pregnancies complicated by single fetal death.

CHAPTER FOUR describes a case-controlled study to compare the incidence and severity of pregnancy-induced hypertensive disorders in a consecutive series of 187 twin pregnancies matched for maternal age, parity, gestational age at delivery, and year of delivery with 187 singleton pregnancies. In the twin pregnancy group significantly more (21%) patients met the criteria for the diagnosis of a pregnancy-induced hypertensive disorder, than in the singleton group (13%). The difference was due to a significantly higher incidence of pregnancy-induced hypertension in twin (15%) than in singleton (6%) pregnancy, in particular in nulliparous women. The incidence of preeclampsia was similar in twin (6%) and singleton (6.5%) pregnancies without differences in severity and in the occurrence of the HELLP-syndrome. These data show that the incidence of non-proteinuric pregnancy-induced hypertension, but not of proteinuric preeclampsia, is increased in twin pregnancy.

CHAPTER FIVE presents a case-controlled study designed to determine the preterm delivery rate and fetal outcome in 23 twin pregnancies with one structurally affected fetus compared with 23 twin pregnancies without fetal anomalies, matched

for maternal e, parity and year of delivery. The preterm delivery rate was not significantly different (57% vs 48%) between groups. The perinatal mortality was significantly higher in the structurally affected pregnancies (65% vs 9%). The elevated perinatal mortality in the study group was mainly determined by the nature of the anomaly, not by preterm delivery. In the affected twin gestations the birthweight of the anomalous fetus (1920 g) was significantly lower than that of the normal co-twin (2230 g). There was no difference in the incidence of hypertensive disorders or diabetes between both groups. It is concluded that the raised perinatal mortality rate in pregnancies with one structurally affected twin is determined by the nature of the anomaly and not by the rate of preterm delivery.

CHAPTER SIX describes the maternal and perinatal complications of a consecutive series of 40 triplet pregnancies of 20 weeks or more compared with 80 twin pregnancies, matched for parity, maternal age, and year of delivery. Preterm labor occurred significantly more often in triplet (90%) than in twin gestations (48%). Compared with twins, triplets had a significantly lower median birthweight (1478 g vs 2030 g) and gestational age at delivery (32 weeks vs 35.5 weeks). The mean neonatal hospital stay was significantly longer in triplets than in twins, mainly related to the lower birthweight, but there was no significant difference between triplets and twins in the incidence of major neonatal complications. The data of the anticipated perinatal outcome in triplet and twin pregnancies may be used to counsel women with a triplet pregnancy considering reduction to twins.

CHAPTER SEVEN presents general conclusions based on the results of the studies described in this thesis. The results of the analysis of data on multifetal pregnancies in a population-based registry of hospital births in The Netherlands are in general agreement with observations reported in the literature, but due to limitations of the registry detailed questions on maternal and fetal complications and pregnancy outcomes could not be answered. These questions, outlined in the objectives of the thesis, were approached in hospital-based studies, and conclusions were reached as reported in chapters 3 to 6.

SAMENVATTING

HOOFDSTUK EEN geeft een algemene inleiding op het proefschrift. In alle geïndustrialiseerde landen, inclusief Nederland, neemt het aantal meerlinggeboorten geleidelijk toe, wat gedeeltelijk kan worden verklaard door de toenemende toepassing van technieken voor geassisteerde voortplanting. Meerlingzwangerschapppen zijn geassocieerd met verschillende antenatale en perinatale problemen. Sommige van deze problemen zijn specifiek voor meerlingzwangerschappen, andere problemen komen vaker voor bij meerlingzwangerschappen dan bij éénlingzwangerschappen. Op grond van de overwegingen beschreven in dit hoofdstuk worden de doelstellingen geformuleerd van de onderzoeken, die in de volgende hoofdstukken worden beschreven. Deze doelstellingen omvatten een onderzoek naar de antenatale complicaties in tweeling- en drielingzwangerschappen bij de Nederlandse bevolking; een analyse van het beloop en de uitkomst van tweelingzwangerschappen gecompliceerd door intra-uteriene vruchtdood van één foetus in de tweede helft van de zwangerschap; een onderzoek naar het voorkomen van vroeggeboorte en perinatale sterfte bij ongestoorde tweelingzwangerschappen en bij tweelingzwangerschappen met één structureel afwijkende foetus; en tenslotte een analyse van het beloop en de uitkomst van drielingzwangerschappen in vergelijking met tweelingzwangerschappen.

HOOFDSTUK TWEE beschrijft een onderzoek aan de hand van gegevens van de Landelijke Verloskundige Registratie, waarin maternale karakteristieken en antenatale complicaties worden vergeleken van 108 drielingzwangerschappen en 6171 tweelingzwangerschappen met een controlegroep éénlingzwangerschappen, gematched voor zwangerschapsduur bij de bevalling. De gemiddelde leeftijd van de moeder was 28.8 jaar in drielinggroep, 28.6 jaar in de tweelinggroep en 27.9 jaar in de éénlinggroep. Het percentage nulliparae bij de drieling- en tweelingmoeders was significant lager dan dat bij de éénlingmoeders (44.4% versus 54.6% en 41.1% versus 49.3%). Hypertensieve aandoeningen kwamen vaker voor bij tweelingzwangerschappen dan bij éénlingzwangerschappen. Bij tweeling-

zwangerschappen was de foetale sterfte (2.5%) de helft van die bij éénlingzwangerschappen (4.9%). De gegevens over neonatale sterfte waren niet compleet en konden derhalve niet worden gebruikt. Door de beperkingen van de registratie konden meer gedetailleerde vraagstellingen omtrent maternale en perinatale uitkomsten niet worden beantwoord.

HOOFDSTUK DRIE behandelt het beloop en de uitkomst van tweeling-zwangerschappen met een intra-uteriene vruchtdood van één foetus in de tweede helft van de zwangerschap, waarbij een afwachtend beleid werd gevoerd. Een case-controle onderzoek wordt beschreven van 29 opeenvolgende zwangerschappen in de periode 1973 tot 1993 met een echografisch vastgestelde tweelingzwangerschap van 20 weken zwangerschapsduur en een intra-uteriene vruchtdood van één foetus later in de zwangerschap. Deze zwangerschappen werden gematched voor maternale leeftijd met een controlegroep van 58 tweelingzwangerschappen zonder foetale sterfte, bevallen in het Academisch Ziekenhuis Rotterdam in hetzelfde jaar. De frequentie van voorkomen en de ernst van hypertensieve aandoeningen was significant hoger in de studiegroep dan in de controlegroep. Er waren geen verschillen tussen de studiegroep en controlegroep voor wat betreft de gemiddelde zwangerschapsduur bij de bevalling (33 weken versus 34 weken) en het gemiddelde geboortegewicht van de levendgeboren kinderen (1880 gr versus 2160 gr). Er werden geen stollingsstoornissen waargenomen bij de 29 patienten. De hoofdoorzaak van neonatale sterfte was prematuriteit; multicysteuze encephalomalacie werd niet waargenomen. De resultaten van dit onderzoek vormen een steun voor een afwachtend beleid bij tweelingzwangerschappen gecompliceerd door intra-uteriene dood van één foetus.

HOOFDSTUK VIER beschrijft een case-controle onderzoek, waarin het voorkomen en de ernst van hypertensieve aandoeningen bij 187 achtereenvolgende tweelingzwangerschappen worden vergeleken met die bij 187 éénling-zwangerschappen, gematched voor maternale leeftijd, pariteit, zwangerschapsduur bij de bevalling en het jaar waarin de bevalling plaatsvond. In de tweelinggroep voldeed 21% van de zwangeren aan de criteria van hypertensieve aandoeningen, een

significant hoger percentage dan dat in de éénlinggroep (13%). Het verschil was het gevolg van een significant hogere incidentie van zwangerschapshypertensie (15%) in tweelingzwangerschappen dan in éénlingzwangerschappen (6%), vooral bij nulliparae. De incidentie van pre-eclampsie was ongeveer gelijk in de tweelinggroep (6%) en in de éénlinggroep (6.5%). Er was geen verschil in de ernst van de pre-eclampsie en de aanwezigheid van een HELLP-syndroom tussen beide groepen. Deze gegevens tonen aan, dat de incidentie van zwangerschapshypertensie, maar niet van pre-eclampsie, is toegenomen bij tweelingzwangerschappen.

HOOFDSTUK VIJF behandelt een onderzoek naar vroeggeboorte en foetale uitkomst in 23 tweelingzwangerschappen met één foetus met echoscopisch vastgestelde structurele afwijkingen in vergelijking met een controlegroep van 23 tweelingzwangerschappen, waarin echoscopisch geen foetale afwijkingen werden aangetoond. De studie- en controlegroep werden gematched voor maternale leeftijd, pariteit en jaar waarin de partus plaatsvond in het Academisch Ziekenhuis Rotterdam. Er was geen significant verschil in het relatieve aantal vroeggeboorten tussen beide groepen (57% versus 48%). De perinatale sterfte was significant hoger in de groep met echoscopisch vastgestelde structurele afwijkingen (65% versus 9%). De hogere perinatale sterfte in de studiegroep werd hoofdzakelijk veroorzaakt door de afwijking en niet door de vroeggeboorte. Het geboortegewicht van de foetus met de structurele afwijking (1920 gr) was significant lager dan dat van het andere kind (2230 gr). Er was geen verschil in het voorkomen van hypertensieve aandoeningen of diabetes tussen beide groepen. De resultaten van dit onderzoek laten zien dat de hogere perinatale sterfte in tweelingzwangerschappen met één foetus met structurele afwijkingen wordt veroorzaakt door de afwijking en niet door vroeggeboorte.

HOOFDSTUK ZES geeft een beschrijving van de maternale en perinatale complicaties in 40 opeenvolgende drielingzwangerschappen met een zwangerschapsduur van 20 weken of meer, gematched met 80 tweeling-zwangerschappen voor pariteit, maternale leeftijd en jaar waarin de bevalling in het Academisch Ziekenhuis Rotterdam plaatsvond. Vroeggeboorte kwam significant vaker voor bij drielingzwangerschappen (90%) in vergelijking met

tweelingzwangerschappen (58%). In vergelijking met de tweelingkinderen hadden drielingkinderen een significant lager geboortegewicht (1478 gr versus 2030 gr) en was de gemiddelde zwangerschapsduur bij de bevalling significant korter (32.2 weken versus 35.5 weken). De drielingkinderen waren significant langer opgenomen dan de tweelingkinderen, hoofdzakelijk tengevolge van het lagere geboortegewicht. Er was geen significant verschil in neonatale complicaties. Deze gegevens kunnen gebruikt worden bij de voorlichting van vrouwen met een drielingzwangerschap, vooral als reductie tot tweelingzwangerschap wordt overwogen.

HOOFDSTUK ZEVEN geeft de algemene conclusies, gebaseerd op de resultaten van de onderzoeken die worden beschreven in dit proefschrift. De resultaten van de analyse van meerlingzwangerschappen uit de Landelijke Verloskundige Registratie zijn in overeenstemming met gegevens uit de literatuur, maar door beperkingen van de registratie konden gedetailleerde vraagstellingen omtrent maternale en foetale complicaties en uitkomst van de zwangerschap niet worden beantwoord. Deze vraagstellingen, aangegeven in de doelstellingen van dit proefschrift, werden onderzocht in een ziekenhuis populatie en conclusies werden verkregen zoals vermeld in de hoofdstukken drie t.m. zes.

REFERENCES

1. Anderson WJR. Stillbirth and neonatal mortality in twin pregnancy. J Obstet Gynaecol Br Emp 1956; 63: 205-215.

2. Ashworth MF, Spooner SF, Verkuyl DAA, Waterman R, Ashurst HM. Failure to prevent preterm labour and delivery in twin pregnancy using prophylactic oral salbutamol. Br J Obstet Gynaecol 1990; 878-882.

3. Ayers JWT, Petersen EP, Knight L, Peterson S. Incorporation of transvaginal embryo reduction (TVER) with an agressive IVF/GIFT/ZIFT program to optimize pregnancy outcome. Fertil Steril 1991; 36(Suppl): S173.

4. Baldwin VJ, Wittmann BK. Pathology of intragestational intervention in twin-to-twin transfusion syndrome. Pediatr Pathol 1990; 10: 79-93.

5. Ben-Shlomo I, Alcalay M, Lipitz S, Leibowitz K, Mashiach S, Barkai G. Twin pregnancies complicated by the death of one fetus. J Reprod Med 1995; 40: 458-462.

6. Bender S. Twin pregnancy. A review of 472 cases. J Obstet Gynaecol Br Emp 1952; 59: 510-517.

7. Benirschke K. Twin placenta in perinatal mortality. NY State Med J 1961; 61: 1499-1508.

8. Benson CB, Doubilet PM, David V. Prognosis of first trimester twin pregnancies: polychotomous logistic regression analysis. Radiology 1994; 192: 765-768.

9. Berkowitz RL. Lynch L, Chitkara U, Wilkins IA, Mehalek KE, Alvaraz E.. Selective reduction of multifetal pregnancies in the first trimester. N Engl J Med 1988; 318: 1043-1047.

10. Boklage CE. Survival probability of human conceptions from fertilization to term. Int J Fertil 1990; 35: 75, 79-94.

11. Botting BJ, Davies IM, Macfarlane AJ. Recent trends in the incidence of multiple birth and associated mortality. Arch Dis Childh 1987; 62: 941-950.

12. Botting BJ, MacFarlane AJ, Price FV, eds. Three, four and more. A study of triplets and higher order births. London: HMSO, 1990.

13. Boulot P, Hedon B, Pelliccia G et al. Favourable outcome in 23 triplet pregnancies managed between 1985 - 1990. Eur J Obstet Gynecol Reprod Biol 1992; 43: 123-129.

14. Bremer HA, Wallenburg HCS. Aspirin in Pregnancy. Fetal-Maternal Med Rev 1992: 4: 37-57.

15. Bryan E, Little L, Burn J. Congenital anomalies in twins. Ballières Clin Obstet Gynaecol 1987; 1: 697-721.

16. Bryan E. Twins and higher multiple births: a guide to their nature and nurture. London: Edward Arnold 1992.

17. Burke MS. Single fetal demise in twin gestation. Clin Obstet Gynecol 1990; 33: 69-78.

18. Cameron AH, Edwards JH, Derom R, Thiery M, Boelaert T. The value of twin surveys in the study of malformations. Eur J Obstet Gynecol Reprod Biol 1983; 14: 347-356.

19. Campbell DM. Multiple births: too often a disaster. Br Med J 1991; 302: 740-741.

20. Campbell DM, MacGillivray I. Management of labour and delivery. In: MacGillivray I, Campbell DM, Thompson B. Twinning and Twins. John Wiley & Sons Lts, 1988, 143-178.

21. Campbell DM. Maternal adaptation in twin pregnancy. Semin Perinatol 1986; 10: 14-18.

22. Campbell DM, MacGillivray I. Glucose tolerance in twin pregnancy. Acta Genet Med Gemellol 1979; 28: 283-287.

23. Campbell DM, MacGillivray I, Thompson B. Twin zygosity and pre-eclampsia. Lancet 1977; ii: 97.

24. Campbell DM, Campbell AJ. Arterial blood pressure: the pattern of change in twin pregnancy. Acta Genet Med Gemellol 1985; 34: 217-223.

25. Carlson NJ, Towers CV. Multiple gestation complicated by the death of one foetus. Obstet Gynecol 1989; 73 (5PT1): 685-689.

26. Cetrulo CL, Freeman RK. Ritodrine HCl for the prevention of premature labor in twin pregnancies. Acta Genet Med Gemellol 1976; 25: 321-324.

27. Cherouny PH, Hoskins JA, Johnson TR, Niebyl JR. Multiple pregnancy with late death of one fetus. Obstet Gynecol 1989; 74: 318-320.

28. Chitkara U, Berkowitz RL, Wilkins IA, Lynch L, Mehalek KE, Alvarez M. Selective second-trimester termination of the anomalous fetus in twin pregnancies. Obstet Gynecol 1989; 73: 690-694.

29. Clasp Collaborative Group. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. Lancet 1994; 343: 619-628.

30. Collins R, Wallenburg HCS. Pharmacological prevention and treatment of hypertensive disorders in pregnancy. In: Chalmers I, Enkin M, Keirse MJNC eds. Effective Care in Pregnancy and Childbirth. Oxford, Oxford University Press, 1989, Vol I, 512-533.

31. Crowther CA, Verkuyl DAA, Neilson JP, Bannerman C, Ashurst HM. The effects of hospitalization for rest on fetal growth, neonatal morbidity and length of gestation in twin pregnancy. Br J Obstet Gynaecol 1990; 97: 872-877.

32. Crowther CA, Neilson JP, Verkuyl DAA, Bannerman C, Ashurst HM. Preterm labour in twin pregnancies: can it be prevented by hospital admission. Br J Obstet Gynaecol. 1989; 96: 850-853.

33. Davey DA, MacGillivray I. The classification and definition of the hypertensive disorders of pregnancy. Am J Obstet Gynecol 1988; 158: 892-898.

34. Daw E. Triplet pregnancy. Br J Obstet Gynaecol 1978; 85: 505-509.

35. De-Lia JE, Emery MG, Sheafor SA, Jennison TA. Twin transfusion syndrome: successful in utero treatment with digoxin. Int J Gynecol Obstet 1985; 23: 197-201.

36. De-Lia JE, Cruikshank DP, Keye W Jr. Fetoscopic neodymium: YAG laser occlusion of placental vessels in severe twin-twin transfusion syndrome. Obstet Gynecol 1990; 75: 1046-1053.

37. Derom R, Orlebeke J, Eriksson A, Thiery M. The epidemiology of multiple births in Europe. In: Keith LG, Papiernik E, Keith DM, Luke B eds. Multiple Pregnancy: Epidemiology, Gestation & Perinatal Outcome. London, Parthenon Publishing Group, 1995, 145-162.

38. Derom C, Derom R, Vlietinck R et al. Iatrogenic multiple pregnancies in East Flanders Belgium. Fertil Steril 1993; 60: 493-496.

39. Dommergues M, Mahieu-Caputo D, Mandelbrot L, Huon C, Moriette G, Dumez Y. Delivery of uncomplicated triplet pregnancies: Is the vaginal route safer? Am J Obstet Gynecol 1995; 172: 513-517.

40. Dwyer PL, Oats JN, Walstab JE et al. Glucose tolerance in twin pregnancy. Aust NZ J Obstet Gynaecol 1982; 22: 131-134.

41. Editorial. Selective fetal reduction. Lancet 1988; 2: 773-775.

42. Elferink-Stinkens PM, Brand R, Verloove-Vanhorick SP, Van Hemel OJS. Onderrapportage van de eersteweeksterfte bij vroeggeboorte in de Landelijke Verloskundige Registratie. Ned Tijdschr Geneeskd 1993; 137: 298-301.

43. Enbom JA. Twin pregnancy with intrauterine death of one twin. Am J Obstet Gynecol 1985; 152: 424-429.

44. Evans MI, Dommergues M, Timor-Tritsch I, Zador IE, Wapner RJ, Lynch L, Dumez Y, Goldberg JD, Nicolaides KH, Johnson MP, Golbus MS, Boulot P, Aknin AJ, Monteagudo A, Berkowitz RL. Transabdominal versus trans-cervical and transvaginal multifetal pregnancy reduction: international collaborative experience of more than one thousand cases. Am J Obstet Gynecol 1994; 170: 902-909.

45. Feingold M, Cetrulo CL, Newton ER, Weiss J, Shakr C, Shmoys S. Serial amniocentesis in the treatment of twin to twin transfusion complicated with acute polyhydramnios. Acta Genet Med Gemell 1986; 35: 107-113.

46. Fusi L, Gordon H. Twin pregnancy complicated by single intrauterine death. Problems and outcome with conservative management. Br J Obstet Gynaecol 1990; 97: 511-516.

47. Galton F. The history of twins, as a criterion of the relative powers of nature and nurture. Reprinted from Fraser's Magazine (1875) with revisions and additions. J Anthropol Inst 1876; 5: 391-400.

48. Garel M, Blondel B. Assessment at 1 year of the psychological consequences of having triplets. Hum Reprod 1992; 7: 729-732.

49. Gedda L. The role of research in twin medicine. In: Keith LG, Papiernik E, Keith DM, Luke B eds. Multiple Pregnancy: Epidemiology, Gestation & Perinatal Outcome. London, Parthenon Publishing Group, 1995, 3-8.

50. Ghai V, Vidyasagar D. Morbidity and mortality factors in twins: An epidemiologic approach. Clin Perinatol 1988; 15: 123-140.

51. Gittelsohn AM, Milham S Jr. Observations on twinning in New York State. Br J Prev Soc Med 1965; 19: 8-17.

52. Gonen R, Heyman E, Asztalos EV, Ohlsson A, Pitson LC, Shennan AT, Milligan JE. The outcome of triplet, quadruplet and quintuplet pregnancies managed in a perinatal unit: Obstetric, neonatal, and follow-up data. Am J Obstet Gynecol 1990; 162: 454-459.

53. Grant A. Cervical cerclage to prolong pregnancy. In: Chalmers I, Enkin M, Keirse MJNC eds. Effective care in pregnancy and childbirth. Oxford, Oxford University Press, 1989, Vol I, 641-642.

54. Gummerus M, Halonen O. Prophylactic long term oral tocolysis of multiple pregnancies. Br J Obstet Gynaecol 1987; 94: 249-251.

55. Hagay ZJ, Mazor M, Leiberman JR, Biale Y. Management and outcome of multiple pregnancies complicated by the antenatal death of one fetus. J Reprod Med 1986; 31: 717-720.

56. Hardman R. Pharmaceutical products from plant steroids. Trop Sci 1969; 11: 196-198.

57. Hartikainen-Sorri A, Jouppila P. Is routine hospitalization needed in antenatal care of twin pregnancy? J Perinat Med 1984; 12: 31-34.

58. Hawrylyshyn PA, Barkin M, Bernstein A, Papsin FR. Twin pregnancies - a continuing perinatal challenge. Obstet Gynecol 1982; 59: 463-466.

59. Hay S, Wehrung DA. Congenital malformations in twins. Am J Hum Genet 1970; 22: 662-678.

60. Hughes HE, Miskin M. Congenital microcephaly due to vascular disruption: in utero documentation. Pediatr 1986; 78: 85-87.

61. Imaizumi Y. Triplets and higher order multiple births in Japan. Acta Genet Med Gemellol 1990; 39: 295-306.

62. Itzkowic D. A survey of 56 triplet pregnancies. Br J Obstet Gynaecol 1979; 86: 23-28.

63. James WH. Is Weinberg's differential rule valid? Acta Genet Med Gemellol 1979; 28: 69-71.

64. James WH. The current status of Weinberg's differential rule. Acta Genet Med Gemellol 1992; 41: 33-42.

65. Johnson MP, Evans MI. Intrauterine growth retardation: pathophysiology and possibilities for intrauterine treatment. Fetal Ther 1987; 2: 109-122.

66. Kauppila A, Jouppila P, Koivisto M, Moilanen I, Ylikorkala O. Twin pregnancy: A clinical study of 335 cases. Acta Obstet Gynecol Scand Suppl 1975; 44 Suppl: 512.

67. Kiely JL. The epidemiology of perinatal mortality in multiple births. Bull NY Acad Med 1990; 66: 618-637.

68. Kilpatrick SJ, Jackson R, Croughan-Minihane MS. Perinatal mortality in twins and singletons matched for gestational age at delivery at ≥ 30 weeks. Am J Obstet Gynecol 1996; 174: 66-71.

69. Kloosterman GJ. On intrauterine growth. Int J Gynaecol Obstet 1970: 18: 895-912.

70. Kovacs BW, Kirschbaum TH, Paul RH. Twin gestation: I. antenatal care and complications. Obstet Gynecol 1989; 74: 313-317.

71. Kurtz GR, Keating WF, Loftus JB. Twin pregnancy and delivery. Obstet Gynaecol 1955; 2: 35-41.

72. Landy HL, Weingold AB. Management of a multiple gestation complicated by an antepartum fetal demise. Obstet Gynecol Surv 1989; 44: 171-176.

73. Landy HJ, Weiner S, Corson SL, Batzer FR, Bolognese RJ. The "vanishing twin": ultrasonographic assessment of fetal disappearance in the first trimester. Am J Obstet Gynecol 1986; 155: 14-19.

74. Levene MI, Wild J, Steer P. Higher multiple births and the modern management of infertility in Britain. Br J Obstet Gynaecol 1992; 99: 607-613.

75. Lichtenstein P, Otterblad Olausson P, Bengt Källen AJ. Twin births to mothers who are twins: a registry based study. Br Med J 1996; 312: 879-881.

76. Lipitz S, Reichman B, Uval J, Shalev J, Achiron R, Barkai G, Lusky A, Mashiach S. A prospective comparison of the outcome of triplet pregnancies managed expectantly or by multifetal reduction to twins. Am J Obstet Gynecol 1994; 170: 874-879.

77. Long PA, Oats JN. Pre-eclampsia in twin pregnancy - severity and pathogenesis. Aust NZ J Obstet Gynaecol 1987; 27: 1-5.

78. Loucopoulos A, Jewelewitz R. Management of multifetal pregnancies: Sixteen years experience at the Sloan Hospital for Women. Am J Obstet Gynecol 1982; 143: 902-905.

79. MacGillivray I. Some observations on the incidence of preeclampsia. J Obstet Gynaecol Br Emp 1958; 65: 536-539.

80. MacGillivray I, Nylander PPS, Lorney L. In: Human Multiple Reproduction, London, Saunders & Co, 1975, 115.

81. MacLennan AH, Green RC, O'Shea R, Brookes C, Morris D. Routine hospital admission in twin pregnancy between 26 and 30 weeks' gestation. Lancet 1990; 335: 267-269.

82. MacLennan AH. In: Creasy RK, Resnik R (eds). Multiple gestations, Maternal Fetal Medicine: Principles and Practice. Philadelphia, W.B. Saunders 1984, 527-538.

83. Marivate M, de Villiers KQ, Fairbrother P. Effect of prophylactic outpatient administration of fenoterol on the time of onset of spontaneous labor and fetal growth rate in twin pregnancy. Am J Obstet Gynecol 1977; 128: 707-708.

84. Martin NG, Beaini JL, Olsen ME et al. Gonadotropin levels in mothers who have had two sets of dizygotic twins. Acta Genet Med Gemellol 1984; 33: 131-139.

85. Mathews DD, Friend JB, Michael CA. A double-blind trial of oral isoxupurine in the prevention of premature labour. J Obstet Gynaecol Br Commonwlth 1967; 74: 68-70.

86. McCarthy BJ, Sachs BP et al. The epidemiology of neonatal death in twins. Am J Obstet Gynecol 1981; 141: 252-256.

87. McFarlane A, Scott JS. Pre-eclampsia/eclampsia in twin pregnancies. J Med Genet 1976; 13: 208-211.

88. McMullan PF, Norman RJ, Marivate M. Pregnancy-induced hypertension in twin pregnancy. Br J Obstet Gynaecol 1984; 91: 240-243.

89. Melnick M. Brain damage in a survivor after in utero death of monozygous co-twin. Lancet 1977; ii: 1287.

90. Michlewitz H, Kennedy J, Kawada C, Kennison R. Triplet pregnancies. J Reprod Med 1981; 26: 243-246.

91. Myrianthopoulos NC. Congenital malformations. The contribution of twin studies. Birth Defects Original Article Series 1978; 14: 151-165.

92. Myrianthopoulos NC. Congenital malformations in twins. Acta Genet Med Gemellol 1976; 25: 331-335.

93. Naidoo L, Jailal I, Moodley J, Desai R. Intravenous glucose tolerance test in women with twin pregnancies. Obstet Gynecol 1985; 66: 500-502.

94. Newman RB, Hamer C, Miller MC. Outpatient triplet management: a contemporary review. Am J Obstet Gynecol 1989; 161: 547-553.

95. Newton ER. Antepartum care in multiple gestation. Semin Perinat 1986; 10, 1: 19-29.

96. Nylander PP, MacGillivray I. Complication of twin pregnancy. In: Human Multiple Reproduction. WB Saunders, London, 1969, 137-146.

97. Nylander PPS. The frequency of twinning in a rural community in Western Nigeria. Ann Hum Genet 1969; 33: 41-44.

98. O'Connor MC, Murphy H, Dobrymple Y. Double-blind trial of ritodrine and placebo in twin pregnancy. Br J Obstet Gynaecol 1979; 86: 706-709.

99. Orlebeke JF, Eriksson AW, Boomsma DI et al. Changes in the DZ unlike / like sex ratio in The Netherlands. Acta Genet Med Gemellol 1991; 40: 319-325.

100. Parisi P. The twin method. In: Keith LG, Papiernik E, Keith DM, Luke B eds. Multiple Pregnancy: Epidemiology, Gestation & Perinatal Outcome. London, Parthenon Publishing Group, 1995, 9-20.

101. Petrikovsky BM, Vintzileos AM. Management and outcome of multiple pregnancy of high fetal order: Literature Review. Obstet Gynecol Survey 1989; 44: 578-584.

102. Pijpers L, Jahoda MGJ, Vosters RPL, Niermeyer MF, Sachs ES. Genetic amniocentesis in twin pregnancies. Br J Obstet Gynaecol 1988; 95: 323-326.

103. Pritchard JA, Ratnoff OD. Studies of fibrinogen and other hemostatic factors in women with intrauterine death and delayed delivery. Surg Gynecol Obstet 1955; 101:467.

104. Prompeler HJ, Madjar H, Klosa W, Du Bois A, Zahradnik HP, Schillinger H, Breckwoldt M. Twin pregnancies with single fetal death. Acta Obstet Gynecol Scand 1994; 73: 205-208.

105. Renkonen KO. Is Weinberg's differential rule defective? Ann Hum Genet 1967; 30: 277-280.

106. Roberts JM, Redman CWG. Pre-eclampsia: more than pregnancy-induced hypertension. Lancet 1993; 341: 1447-1454.

107. Robertson EG, Neer KJ. Placental injection studies in twin gestation. Am J Obstet Gynecol 1983; 147: 170-174.

108. Robson SC, Hunter S, Boys RJ, Dunlop W. Hemodynamic changes during twin pregnancy. A Doppler and M-mode echocardiographic study. Am J Obstet Gynecol 1989; 161: 1273-1278.

109. Romero R, Duffy TP, Berkowitz RL, Chang E, Hobbins JC. Prolongation of a preterm pregnancy complicated by death of a single twin in utero and disseminated intravascular coagulation. N Engl J Med 1984; 310: 772-774.

110. Russell JK. Maternal and foetal hazards associated with twin pregnancy. J Obstet Gynaecol Br Emp 1952; 59: 208-213.

111. Sampson A, de Crespigny L Ch. Vanishing twins: the frequency of spontaneous fetal reduction of a twin pregnancy. Ultrasound Obstet Gynecol 1992; 2: 107-109.

112. Sassoon DA, Castro C, Davis JL, Hobel CJ. Perinatal outcome in triplet versus twin gestation. Obstet Gynecol 1990; 75: 817-820.

113. Saunders MC, Brouwer DJI, Brown I, McPherson K, Chalmers I. The effect of hospital admission for bed rest on the duration of twin pregnancy: a randomised trial. Lancet 1985; 2: 793-795.

114. Schinzel AAGL, Smith DW, Miller JR. Monozygotic twinning and structural defects. J Pediatr 1979; 95: 921-930.

115. Sekiya S, Hafez ESA. Physiomorphology of twin transfusion syndrome: a study of 86 twin gestations. Obstet Gynecol 1977; 50: 288-292.

116. Sherer MD, Abramowicz JS, Jaffe R, Smith SA, Metlay LA, Woods Jr JR. Twin-twin transfusion with abrupt onset of microcephaly in the surviving recipient following spontaneous death of the donor twin. Am J Obstet Gynecol 1993; 169: 85-88.

117. Skelly H, Marivate M, Norman R, Kenoyer G, Martin R. Consumptive coagulopathy following fetal death in a triplet pregnancy. Am J Obstet Gynecol 1982; 142: 595-597.

118. Skjaerris J, Aberg A. Prevention of prematurity in twin pregnancy by orally administered terbutaline. Acta Obstet Gynaecol Scand Suppl 1982; 108: 39-40.

119. Soma H, Takayama M, Kiyokawa T, Akaeda T, Tokoro K. Serum gonadotropin levels in Japanese women. Obstet Gynecol 1975; 46: 311-312.

120. Sonneveld SW, Correy JF. Antenatal loss of one of twins. Aust NZ J Obstet Gynaecol 1992; 32: 10-13.

121. Spellacy WN, Buhi WC, Birk SA. Carbohydrate metabolism in women with a twin pregnancy. Obstet Gynecol 1980; 55, 6: 688-691.

122. Spellacy WN, Handler A, Ferre CD. A case-control study of 1253 twin pregnancies from a 1982-1987 perinatal database. Obstet Gynecol 1990; 75: 168-171.

123. Steinberg LH, Hurley VA, Desmedt E et al. Acute polyhydramnios in twin pregnancies. Aust NZ J Obstet Gynaecol 1990; 30:196-200.

124. Stevenson AC, Davidson BCC, Say B, Ustuoplu S, Liya D, Abul-Einen M et al. Contribution of fetal/maternal incompatibility to aetiology of pre-eclamptic toxaemia. Lancet 1971; ii: 1286-1289.

125. Syrop CH, Varner MW. Triplet gestation: maternal and neonatal implications. Acta Genet Med Gemellol 1985; 34: 81-88.

126. Taffel SM. Health and demographic characteristics of twin births: United States, 1988. Vital Health Stat 21 1992; 50: 1-17.

127. Taffel SM. Demographic trends in twin births. In: Keith LG, Papiernik E, Keith DM, Luke B eds. Multiple Pregnancy: Epidemiology, Gestation & Perinatal Outcome. London, Parthenon Publishing Group, 1995, 133-143.

128. Tan KL, Tan R, Tan SH, Tan AM. The twin transfusion syndrome. Clinical observations on 35 affected pairs. Clin Pediatr 1979; 18: 111-114.

129. U.S. Department of Health and Human Services. Vital statistics for the United States. Public Health Services National Center of Health Statistics, vol I, 1985.

130. Van Hemel OJS, Schutte F, van Bemmel JH, Chang AMM. Feed-back in an obstetric data base. In: Medical Informatics Amsterdam, 10 years review. Amsterdam: Free University of Amsterdam, 1983; 299-312.

131. Van Hemel OJS. An obstetric database, human factors, design and reliability. PH.D.-thesis, Free University of Amsterdam, 1977.

132. Van Allen MI, Smith DW, Shepard TH. Twin reversed arterial perfusion (TRAP) sequence: a study of 14 twin pregnancies with acardius. Semin Perinatol 1983; 7: 285-293.

133. Van den Veyver IBM, Schatteman E, Vanderheyden JS, Van Wiemeersch J. Meulyzer P. Antenatal fetal death in twin pregnancies: a dangerous condition mainly for the surviving co-twin; a report of four cases. Eur J Obstet Gynecol Reprod Biol 1990; 38: 69-73.

134. Veille JC, Morton MJ, Burry KJ. Maternal cardiovascular adaptations to twin pregnancy. Am J Obstet Gynecol 1985; 153: 261-263.

135. Vlietinck R, Derom C, Derom R et al. The validity of Weinberg's rule in the East Flanders Prospective Twin Survey (EFPTS). Acta Genet Med Gemellol 1988; 37: 137-141.

136. Waddell KE, Hunter JS. Twin pregnancies. Am J Obstet Gynecol 1960; 80: 756-760.

137. Wallenburg HCS. Detecting hypertensive disorders in pregnancy. In: Chalmers I, Enkin M, Keirse MJNC eds. Effective Care in Pregnancy and Childbirth. Oxford, Oxford University Press, 1989, Vol 1, 382-402.

138. Wapner RJ, Davis GH, Johnson A, Weinblatt VJ, Fischer RL, Jackson LG, Chervernak FA, McCullough LB. Selective reduction of multifetal pregnancies. Lancet 1990; 1: 90-93.

139. Weinberg W. Differenzmethode und Geburtenfolge bei Zwillingen. Genetica 1934; 16: 282-288.

140. Wildschut HJ, van Roosmalen J, van Leeuwen E, Keirse MJNC. Planned abdominal compared with planned vaginal birth in triplet pregnancies. Br J Obstet Gynaecol 1995; 102: 292-296.

141. Wittmann BK, Farquaharson DF, Thomas WDS, Baldwin VJ, Wadsworth LD. The role of feticide in the management of severe twin transfusion syndrome. Am J Obstet Gynecol 1986; 155: 1023-1026.

ACKNOWLEDGEMENTS

I wish to express my gratitude to all those who have contributed to the realization of this thesis.

First of all I wish to thank Prof.dr. H.C.S. Wallenburg, my promotor and initiator of this study. His guidance, critical remarks, optimism and encouragement helped me through the sometimes difficult gestation of the study and the birth of the manuscript. I would also like to thank Professors Derom, Birkenhäger and Wladimiroff, for their willingness to assess the manuscript as members of the Thesis Committee.

I am indebted to my colleagues on the 22nd floor of the Hoogbouw for the optimism and support they gave me during the study period. I owe a special debt of gratitude to Piet Struijk, who helped me with the statistical analysis of the data.

Special thanks also to Jos van Blarkom, who typed out the manuscript; without her always cheerful support the manuscript would have never been finished.

I wish to thank M.H. Emanuel and Hayo Wildschut for their willingness to collect the data of the Perinatal Database, and Hayo for his critical approach to the analysis, and his help with the often difficult interpretation.

Many thanks to my colleagues Willem Brouwer and Doaitse Wilbers, who have always supported me in performing this study and, when necessary, took care of my clinical duties in Leeuwarden.

I would like to thank Petra Bourdrez, Ingrid Koppelaar and Astrid Swaak, who so enthousiastically participated in the early beginning of the study.

I wish to thank my family and friends, in and outside Friesland, who stimulated and supported me all along.

Last but not least I wish to thank Marij, Sjoerd, Marius en Edo for their love and understanding without which this thesis could never have been written.

CURRICULUM VITAE

1950	Born in Leeuwarden, The Netherlands
1966 - 1974	Training and employment as laboratory technician in Clinical Chemistry, Groningen, The Netherlands
1975 - 1978	Laboratory technician in Hematology. Laboratorium Volksgezondheid Leeuwarden, The Netherlands
1978 - 1984	Medical School and Internships, University of Groningen
1984 - 1987	Resident in Obstetrics and Gynecology, St. Elisabeth Hospital, Curaçao, Netherlands Antilles
1987 - 1993	Resident in Obstetrics and Gynecology, Zuiderziekenhuis, Rotterdam, (Dr. H.T. Lim, Dr. M. van Lent), University Hospital Rotterdam (Prof.dr. A.C. Drogendijk, Prof.dr. H.C.S. Wallenburg)
1993 - present	Consultant, Department of Obstetrics and Gynecology, Medisch Centrum Leeuwarden, Friesland