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Ph.D. Thesis

CHARACTERIZATION OF TWIN AND MULTIPLE PREGNANCIES IN A TERTIARY CENTER IN HUNGARY

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CONTENTS

1. LIST OF SCIENTIFIC PUBLICATIONS RELATED TO THE SUBJECT OF THE THESIS

1. Nyirati I., Orvos H, Bártfai Gy, Kovács L: Iatrogenic multiple pregnancy: Higher risk than a spontaneous one? J Reprod Med 1997 (42) 695-698
2. Nyirati I, Foroughi E, Hodoniczki L, Bártfai Gy, Kovács L: Számítógéppel vezérelt kardiotokográfia és az arteria umbilicalis véráramlás mérésének egyidejű alkalmazásával szerzett tapasztalataink. Magyar Nőorvosok Lapja 1997 (60) 174-176
3. Tarnai L, Nyirati I, Bánfalvi A, Bártfai Gy, Herczeg J: Antepartum magzati szívhangészlelés során előforduló hibalehetőségek. Magyar Alapellátási Archivum 1999 (4) 254-256
4. Blickstein I, Goldman RD, Kupferminc M, etc., Nyirati I, Bártfai Gy, etc.: Delivery of breech first twins: A multicenter retrospective study. Obstet Gynecol 2000 (95) 37-42

2. ABBREVIATIONS

BA	Biamniotic
BC	Bichorionic
BMI	Body mass index
BPD	Biparietal diameter
bpm	Beat per minute
CTG	Cardiotocography
DZ	Dizygotic
FHR	Fetal heart rate
FMP	Fetal movement profile
FSH	Follicle stimulating hormone
IRDS	Idiopathic respiratory distress syndrome
IUFD	Intrauterine fetal death
IUGR	Intrauterine growth retardation
IUI	Intrauterine insemination
IVF-ET	In vitro fertilization and embryo transfer
LBW	Low birth-weight
LGA	Large for gestational age
LMP	Last menstrual period
MA	Monoamniotic
MC	Monochorionic
MZ	Monozygotic
NBW	Normal birth-weight
NICU	Neonatal intensive-care unit
OI	Ovulation induction
PIH	Pregnancy induced hypertension
SGA	Small for gestational age
US	Ultrasonographic
VLBW	Very low birth-weight

3. INTRODUCTION

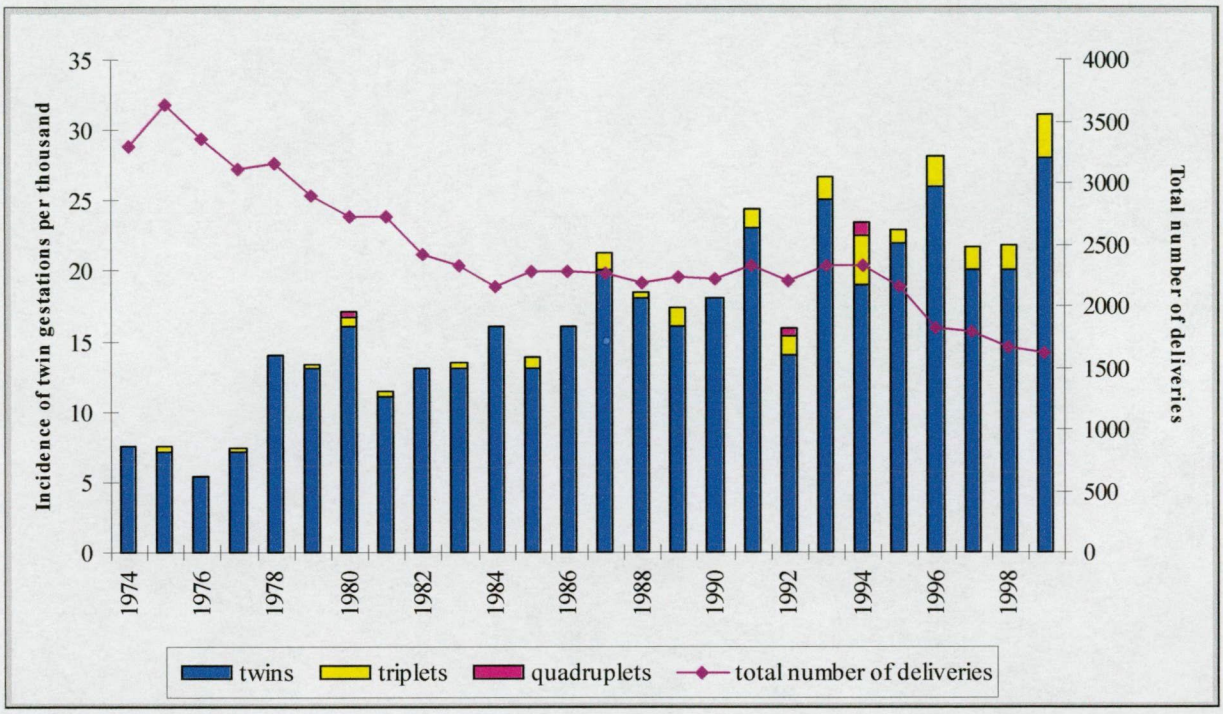
> "... And when her days to be delivered were fulfilled, behold, there were twins in her womb. And the first came out red, all over like an hairy garment; and they called his name Esau. And after that came his brother out, and his hand took hold on Esau's heel; and his name was called Jacob. ..."
>
> The Bible

Scientists and philosophers have always been fascinated by twins. Hippocrates considered that twins were conceived by the division of a sperm into two parts. Interest in obstetrical aspects was kindled in the Renaissance age and anxiety was expressed over the dangers of exsanguination of the second twin after the firstborn's cord had been cut. In the second half of the 19th century, Sir Francis Galton realized that twins could be of value in the study of effects of heredity and environment on human development.[1]

Long before the accurate determination of the zygosity of twins was defined, it was recognized that at least two types existed: identical and fraternal. Identical or monozygotic (MZ) twins develop from the early division of a single fertilized ovum, whereas fraternal or dizygotic (DZ) twins occur as the result of fertilization of two separately released ova by two separate spermatozoa. Twinning rates vary greatly in different parts of the world, mostly because of variations in DZ twinning. It appears that Negroid races have the highest incidence and Mongoloid races the lowest with Caucasians and Asian Indians intermediate.[2] The incidence of MZ twins appears to be relatively and remarkably constant all over the world: between 3 and 4 per 1000 deliveries.[3] There are no factors which have yet been definitely associated with MZ twinning, and no single cause of DZ twinning is known, but some of the associated factors have been recognized. Family studies have shown that the genetic determinant for twinning comes directly through the female line.[2] Lambalk et al.[4] confirmed that an elevated follicle stimulating hormone (FSH) level due to recovery from prolonged hypothalamic amenorrhea increases the risk of DZ twinning. Higher levels of FSH have been described in Nigerian mothers than in mothers in Japan, where there are particularly low rates of twinning.[2,5,6] Nylander[5] found a much lower incidence of twins in Yoruba women living in towns than in rural villages. He suggested that the traditional diet of this tribe may contain some hormone stimulating substance. A positive correlation was found between twinning and the maternal age, parity, menstrual period, maternal height and weight.[2,7-9] For many years,

the Hellin hypothesis (1895) was a common way to estimate the population incidence of multiple gestation. This hypothesis postulates that, if a known rate of twins (n) has been determined in a population, the rate of triplets will be n^2, that of quadruplets n^3, and so forth. Since the early 1970s, however, the incidence of twin and multiple gestations has increased dramatically, due to the growing use of ovulation induction drugs, mainly FSH stimulation and other operative-assisted reproductive techniques.[10,11] ***(Figure 1)***

Figure 1. Incidence of twin gestations at our Department between 1974 and 1999



Newborn twins tend to be smaller than singletons. The twin fetus has to share the maternal supply and nourishment. A fetus of a twin pregnancy usually manages to grow at the same rate as a singleton for the first two trimesters.[12] From gestational week 30-32 onward, the rate of growth decreases relative to that of singletons.[13] However, Crane et al.[14] showed that if discordant twins (a birth-weight difference of over 25%) were excluded, then the biparietal diameter (BPD) and growth of twins were the same as those of appropriately grown singletons throughout the pregnancy. MZ twins are lighter than DZ twins and their intrapair birth-weight difference is greater.[15] There is no obvious reason for this difference, but three possible explanations have been suggested: 1. The lower weight can be related to events in early embryonic development when the cell mass is reduced by its division into two embryos.

2. The antigenic differences between DZ twins can beneficially affect intrauterine growth. 3. Maternal factors such as height, weight and hormonal levels may play a part. In MZ twins a birth-weight discrepancy is described as being mainly due to the feto-fetal transfusion syndrome and the excentric insertion of one of the umbilical cords. Recent studies suggested that a growth discordance may be noted earlier than previously observed.[16,17] According to Isada et al., an inter-fetal size difference may begin in the first trimester and exhibit a trend to increasing variability with increasing gestational age.[17] Rodis et al.[18] found that the smaller sibling displayed a lower rate of growth as early as weeks 23-24 of gestation. The birth-weight of twins appears to be unrelated to birth order. Most recent studies have found no significant differences in weight between the first- and second-born.[19,20]

The greater the number of fetuses, the earlier labor is likely to start. Many studies have shown that the average length of gestation for twin pregnancies is approximately 260 days, i.e. 3 weeks shorter than the 280 days for singletons.[8,21,22]

Mean birth-weights vary to an extraordinary degree between populations.[23-27] The smallest newborns at term were found among the Lumi tribe in New Guinea. The largest reported newborns at term were born in Anguilla and Nevis, West Indies. Pregnancy at high altitude substantially slows intrauterine growth and great variations can therefore be found within a given ethnic group.[25]

A strong relationship between mean birth-weight and socioeconomic status within a community was found in data collected from a number of comparative studies.[28-30] Cigarette smoking by a pregnant woman reduces the growth of the fetus and increases the rate of prematurity.[31,32]

A positive association has been reported between the fetal growth rate and the maternal age and parity.[33,34] A similar finding was presented by Blickstein et al.,[35] who suggested that primiparas may have significantly smaller twins as compared with multiparas. A clearly positive correlation was established between the maternal stature, and especially the maternal height and the neonatal birth-weight.[29] There have been numerous studies on maternal pre-pregnancy weight and weight gain during pregnancy with various results.[36,37]

Mothers of growth retarded-newborns often exhibit chronic ill-health, involving mainly respiratory- or heart- diseases, hypertension and pyelonephritis.[38] On the other hand, maternal diabetes enhances the rate of growth of the fetus.[39] Pregnancy-induced hypertension (PIH) and preeclamptic toxemia also seem to have negative effects on fetal growth.[40,41] The

same holds for pregnancies complicated by drug abuse.[42,43] Intrauterine growth retardation (IUGR) due to uterine factors is thought to be related to insufficient uteroplacental perfusion; this may be a result of a suboptimal implantation site. Structural placental factors including single umbilical artery, velamentous cord insertion, bilobate placenta and placental hemangiomas are commonly noted in pregnancies complicated by IUGR.[38,44] Infections such as rubella, toxoplasmosis, syphilis and cytomegalic inclusion disease may also reduce the fetal growth rate.[45] Varicella-zoster and human immunodeficiency virus have recently been suggested as possible etiologies of IUGR.[46] Major congenital malformations in general are also associated with slow intrauterine growth.[38,47]

The gender of the fetus is related to the rate of its growth. Males grow faster than females. The male : female sex ratio is lower in twins than in singletons.[48] The higher incidence of females in multiple births is not limited to MZ twins. The less favorable conditions of a multiple pregnancy possibly raise the mortality rate of the more vulnerable male still further.

IUGR is mostly defined as a birth-weight < the 10th percentile of the gender-specific birth-weight standard for the given gestational age, but it is defined more recently as reflected by the birth of an infant weighing less than the genetic growth potential. IUGR itself can be divided into symmetrical and asymmetrical types. The latter usually develops in the last 10-12 weeks of pregnancy; it is most likely due to a decreased placental circulation. Symmetrical IUGR results from severe, early nutritional deprivation and from chromosomal abnormalities.

Since the recognition of newborns who are small for gestational age (SGA) or large for gestational age (LGA) depends on the birth-weight in relation to the gestational age, an accurate assessment of gestation is essential. Although more than 50% of pregnant women may be certain of their menstrual age, more than 10% may have a difference of at least a week from the ultrasonographic (US)-calculated gestational age.[49] The US dating of pregnancy before week 20 of gestation is a better predictor of the expected date of delivery than in combination with the last menstrual period (LMP), within even a 7-day margin of error.[50]

The neonatal problems resulting from slow intrauterine growth are different from those associated with short gestation. This observation reinforces the importance of using growth curves that are appropriate for the population being examined when assessing rate of the fetal growth of any individual newborn. It is also obvious that twin and higher-order pregnancies must be treated as a quite separate issue, in terms of fetal growth rate. Since the

lowest perinatal mortality rate occurs 3 weeks earlier in twin pregnancies than in singletons, further support of the definition of preterm birth in twins is needed.

Despite improvements of both obstetric and neonatal care, the risks to twin fetuses and newborns remain at least 3 times those for singletons. The main factors responsible for the increased perinatal morbidity and mortality rates of twins are prematurity, IUGR of one or both fetuses, and their complications.[52-55] According to the accepted definition of preterm birth (less than 37 weeks of gestation), 8.5% of singletons and 50% of twins are born preterm.[22,55]

In recent decades the incidence of perinatal mortality has decreased due to the improvements in obstetrical management; nevertheless, the perinatal mortality is still about 5 times higher in twin pregnancies than in singletons.[56] According to Lumme and Saarikoski,[57] in spite of the decreased rate of perinatal mortality, no significant changes in stillbirth rate in multiple pregnancies were found in a 22-year period. US examinations have shown that the death of one or more fetuses in the first trimester, i.e. the "vanishing twin syndrome", is quite common and the complication rate is not higher when the pregnancy continues.[58] Intrauterine fetal death (IUFD) of one twin in the second or third trimester could be complicated by serious adverse effects on the mother and the surviving fetuses.[59] Reported monofetal intrauterine death occurs in 0.5-7.0% of all multiple pregnancies, and the most appropriate explanations of death are placental insufficiency, cord entanglement, IUGR, discordant growth, twin-to-twin transfusion syndrome, and fetal malformation.[59-63]

In Hungary, the perinatal morbidity and mortality rates are higher than in the developed industrial countries. The early diagnosis of fetal jeopardy is therefore an essential question for obstetricians. In the past 25 years, the perinatal mortality has decreased significantly in Hungary;[56] the rate at our Department has fallen from 27.5‰ to 10.2‰. Besides the neonatal intensive care, the use of electronic fetal heart rate monitoring has played a major role in this dramatic decrease. The intra- and inter-observer variances resulting from the visual interpretation of the traces have led to the development of computerized antepartum cardiotocographic (CTG analysis).[64-68] However, an adequate computerized analysis program is not yet available for intrapartum monitoring.[69-71]

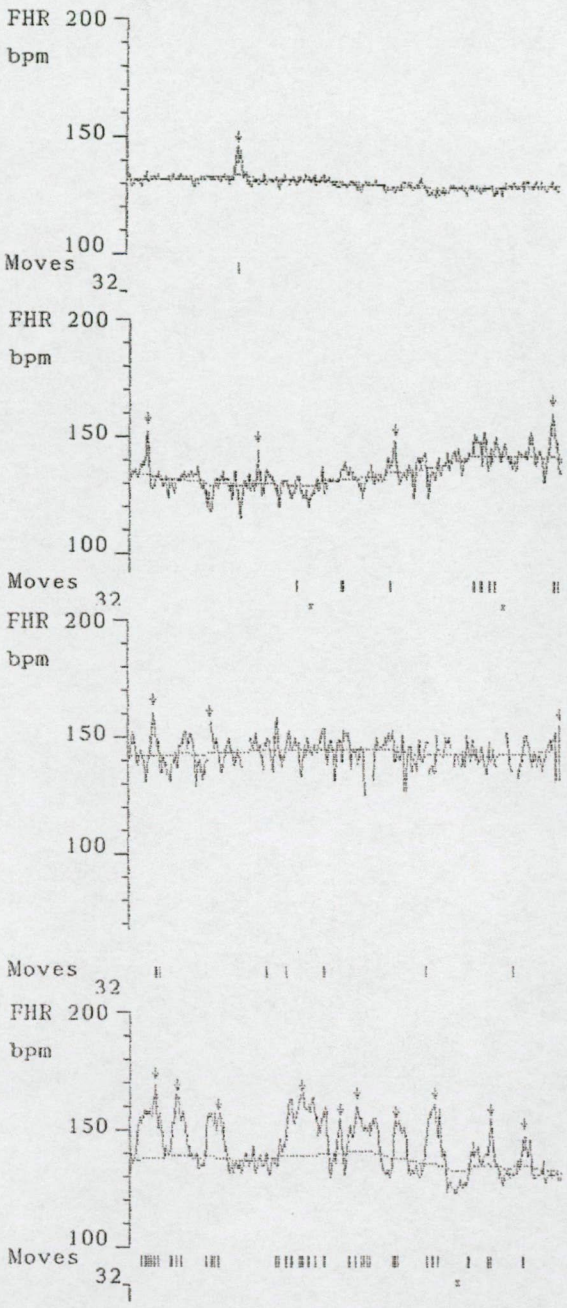
CTG is a noninvasive diagnostic method that is used most frequently for the intrapartum monitoring of fetal well-being. It records fetal heart rate, fetal movements and

uterine activity simultaneously.[72] The great advantage of CTG is that it can be repeated unrestrictedly, allows an immediate assessment and provides continuous registration in contrast with periodic auscultation, which informs the physician on the fetal condition in only a tenth of the labor period.[73] It is important to point out that the evaluation of cardiotocograms depends on the stage of labor. Certain changes detected in the first stage of labor should be interpreted differently than in the second stage. It should also be emphasized that fetal heart rate and frequency, and the mean duration and the strength of contractions change dynamically during labor. In clinical practice, we can distinct three stages as concerns the instrumental monitoring of labor:

1. the start of pains (the latent phase of the first stage of labor),
2. the active phase of the first stage of labor,
3. the second stage of labor.

Intrapatum monitoring gives information on the placental reserve capacity. In cases of signs indicating fetal hypoxia, safe labor management can be established only by close and conscientious monitoring, including the application of fetal pH control. When normal dilatation pains are present, with an optimal frequency of 3 contractions per 10 min, each uterine contraction induces a change in fetal heart rate.[72] During contractions, the oxygenization of the fetus decreases temporarily. When the placental function is normal, the decrease in oxygen supply is accompanied by accelerations that are indicative of sympathetic excitement. Clinical experience suggests that reflex accelerations proceed with an increase in fetal heart rate variability. This phenomenon is also called an arousal reaction. On the basis of the fetal movements, four sleep-awake states can be distinguished, according to which Nijhuis identified four specific CTG traces ***(Figure 2).***[74] A permanent decrease in placental reserve capacity triggers signs of hypoxia that can be observed in the CTG trace. Gradually developing late decelerations are indicative of a cumulative effect. If the rhythm of the subsequent contractions is too fast to permit the elimination of accumulating acidotic metabolites, the vagal tone increases as a result of the excitement of chemoreceptors. The mode of delivery must be determined on the basis of a the joint assessment of the clinical picture and the CTG trace. Blood-gas analysis may help in the attainment of the best decision.

Figure 2. "Fetal movement profile" criteria achieved by Nijhuis



F1 period

F2 period

F3 period

F4 period

FHR: fetal heart rate
Bpm: beat per minute
F1: quiet sleep period - stable, narrow oscillation bandwidth; isolated accelerations
F2: active sleep period - wider oscillation bandwidth; more accelerations
F3: REM (rapid eye movements) period - stable, wide oscillation bandwidth; no accelerations
F4: awake period - unstable, wide oscillation bandwidth large and long-lasting accelerations

Twinning is a unique challenge for both the medical staff and the parents during pregnancy, delivery and the child-bearing age. In the early postpartum period the mothers of twins have to contend with the difficulties and disappointments of breast-feeding. Twins are at higher risk of neonatal complications and of maternal-infant separation in the postpartum period. Thus, mothers of twins who must produce milk for two babies are particularly at risk of an insufficient milk supply.

During pregnancy the breast, the body and the psyche are prepared for lactation, and a healthy newborn is able to suckle the breast at birth. Successful lactation is a result of neuro-endocrine reflex interactions between the mother and her infant. Lactation consists in two physiological mechanisms: *milk secretion*, which is controlled by the prolactin released from the anterior pituitary in response to the suckling stimulus of the infant, and *milk ejection,* a reflex in which the oxytocin released from the posterior pituitary in response to suckling causes contractions of the alveoli of the breast. This results in the ejection of the milk from the mammary ducts and nipple.[75]

A steady decline in breast-feeding began in industrialized societies in the early 1900s, and then spread to developing countries.[76-77] The feeding practices for infants in the USA between 1900 and 1980 have been described.[77] The authors observed the lowest rate of breast-feeding in 1970, when only 1 in 4 mothers breast-fed her newborn in the hospital. Within recent decades, the rate of breast-feeding in hospitals has increased dramatically. The return to breast-feeding began among the upper socio-economic classes and spread through society in a similar way as the earlier abandonment of breast-feeding. Differences in the compositions of human milk and unmodified cow's milk have been known for many years. Recent studies of the nutritional needs of infants and advances in technology have led to the evelopment of more adequate infant formulas, but all experts agree that human milk is the best infant nutrition.[78]

4. AIMS OF THE STUDY

1. Characterization of multiple pregnancies, deliveries and newborns in a tertiary center in Hungary.
2. Study of the occurrence of intrauterine fetal death in multiple pregnancies.
3. a) To examine the sleep-awake periods for singleton and twin fetuses during the last three hours of the second stage of labor (active phase), using continuous CTG traces.
   b) To compare the number of fetal sleep-awake periods, F4 periods and decelerations with the neonatal outcome.
4. Study of the effects of early and simultaneous breast-feeding of twin newborns.

5. MATERIALS AND METHODS

At the Department of Obstetrics and Gynecology of the University of Szeged, a retrospective analysis was made of all multiple births of more than 24 weeks of gestation between 1 January, 1991 and 31 December, 1999. During this 9-year period, the total number of deliveries was 18173, of which 431 were multiple gestations, i.e. an the incidence of 2.37%. 402 twin, 26 triplet and 3 quadruplet pregnancies were recorded. Gestational age was calculated on the basis of the first day of the LMP and was confirmed by the results of early US examination. If the difference was more than 7 days, the US result was considered valid.

Birth-weight discordance was defined as the percentage difference between the multiple siblings, calculated as [A-B]/A*100 (A = birth-weight of the largest twin, B = birth-weight of the smallest twin).

Since there were only 3 quadruplet pregnancies, these were excluded from the study.

6. CHARACTERIZATION OF TWIN PREGNANCIES, DELIVERIES AND NEWBORNS IN A TERTIARY CENTER IN HUNGARY

Table 1 reveals that the mean maternal age and primiparity were similar in the twin and triplet pregnancies. There was no difference in pre-pregnant maternal body mass index (BMI), but the mean maternal weight gain was higher in triplet gestations.

Table 1. Maternal characteristics

	Twins (n=402)	Triplets (n=26)
Mean maternal age (years)	28.5 ± 5.2	28.2 ± 4.9
Primiparas	162 (40.3%)	11 (42.3%)
Mean pre-pregnant maternal BMI	23.7 ± 4.9	23.5 ± 4.1
Mean maternal weight gain (kg)	14.8 ± 5.3	17.9 ± 5.4

The frequency of preeclampsia was very high in both groups. Gestational diabetes was found in 19.2% of the triplet pregnancies, in contrast with 3.5% in the twin pregnancies. Due to cervical incompetence, operation with cervical cerclage was needed in 14.9% of the twin and 73.6% of the triplet pregnancies. Intravenous tocolysis was administered in 36.1% of the twins and 42.3% of the triplets ***(Table 2).***

Table 2. Maternal complications associated with pregnancy

	Twins (n=402)	Triplets (n=26)
Preeclampsia	67 (16.7%)	7 (26.9%)
Gestational diabetes	14 (3.5%)	5 (19.2)%
Cervical incompetence	60 (14.9%)	296 (73.6%)
Threatened preterm delivery	145 (36.1%)	11 (42.3%)

Among the twin gestations 20.9% resulted from assisted reproduction, as compared with 73.0% among the triplets ***(Table 3).***

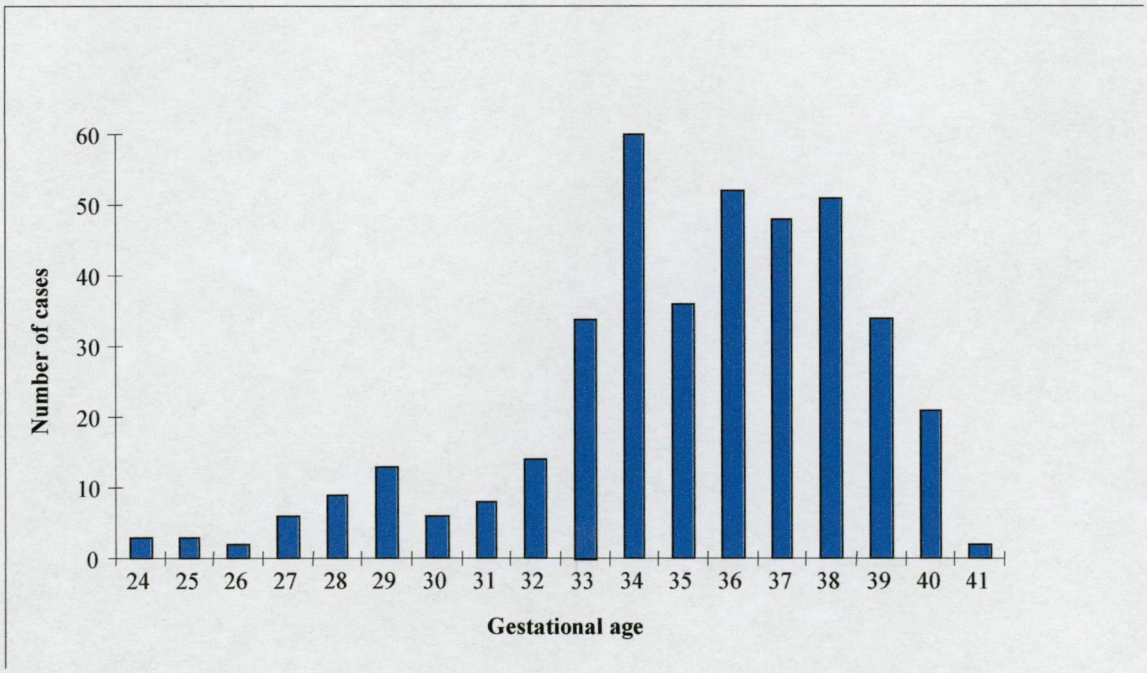
Table 3. Type of gestation

	Twins (n=402)	Triplets (n=26)
Spontaneous	318 (79.1%)	7 (27.0%)
OI	53 (13.2%)	9 (34.6%)
OI + IUI	7 (1.7%)	4 (15.4%)
OI + IVF-ET	24 (6.0%)	6 (23.0%)

OI: ovulation induction
IUI: intrauterine insemination
IVF-ET: in vitro fertilization and embryo transfer

Most of the twin babies was delivered in the 34th weeks of gestation, and 60.7% of the twins were delivered before 37 completed weeks ***(Figure 3).*** Preterm delivery (< 37 weeks) was registered in 84.2% of triplet pregnancies. The mean gestational age was 247.7 days (35.4 weeks) in the twin pregnancies and 236.4 days (33.9 weeks) in the triplet pregnancies ***(Table 6).***

Figure 3. Distribution of cases by gestational age



The mean birth-weight of the triplet newborns was considerably lower than that of the twin babies, and the mean birth-weight of the consecutive newborns was much lower ***(Table 6).*** The mean birth-weight of the first twin was 2226.2 g and that of the second twin 2209.9 g. The birth-weight of the boys was higher than of the girls (2263.4 vs 2173.7g), but the difference was not significant. In 62.7% of the twin newborns the birth-weight was below 2500 g; in 5.7% of the cases the neonatal birth-weight did not reach 1000 g ***(Figures 4 and 5).***

Figure 4. Birth-weight for gestational age, I

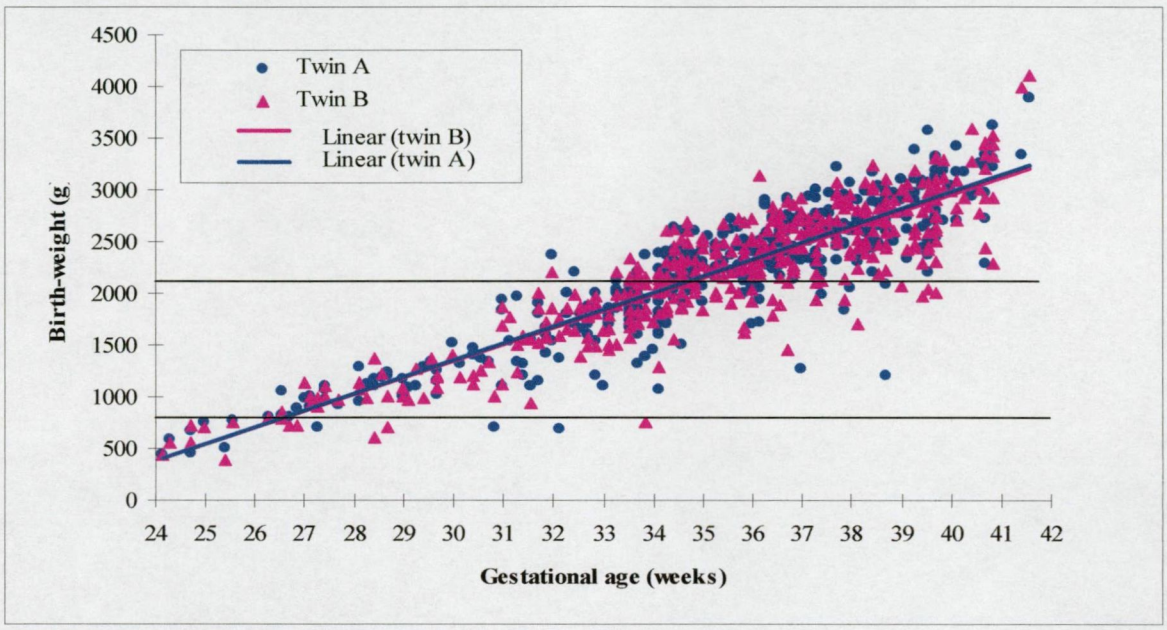
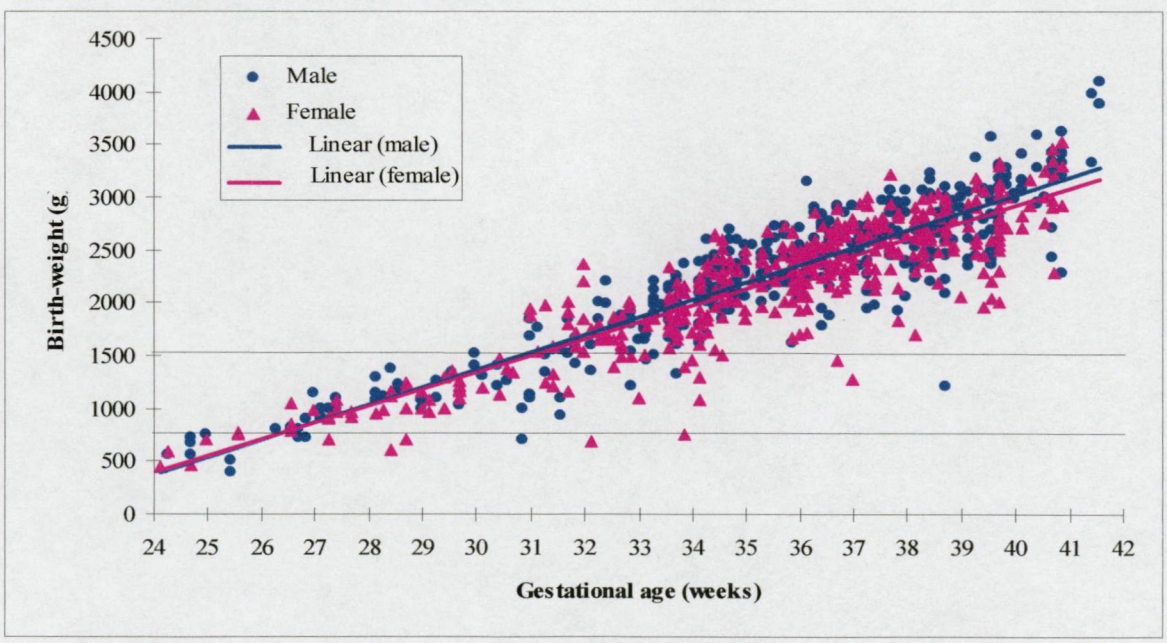


Figure 5. Birth-weight for gestational age, II



Most of the twin pregnancies demonstrated a low birth-weight for both neonates. Both newborns were delivered with a normal birth-weight in only 26.2% of the cases, and in 4.0% both babies had a very low birth-weight ***(Table 4).***

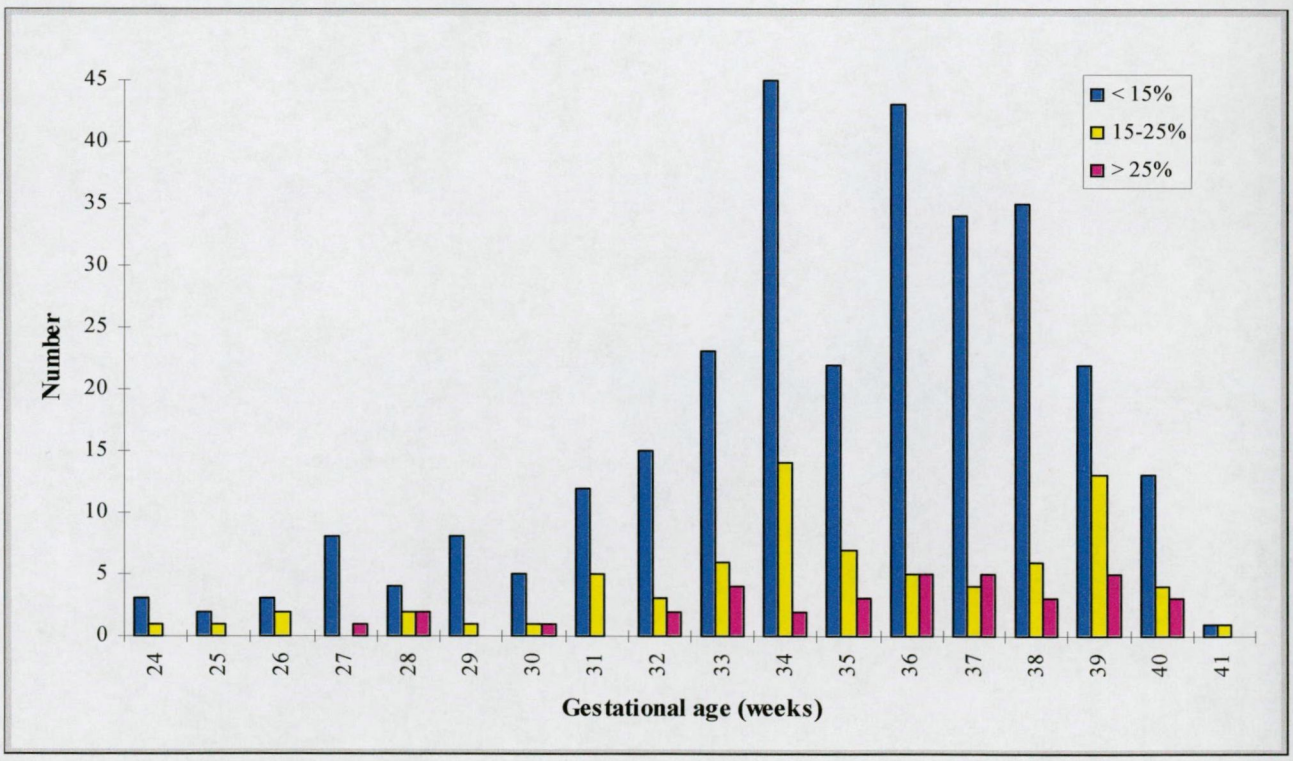
Table 4. Birth-weight of twins

Twin B \ Twin A	VLBW	LBW	NBW
VLBW	16 (4.0%)	8 (2.0%)	0
LBW	6 (1.5%)	177 (44.0%)	48 (11.9%)
NBW	0	42 (10.4%)	105 (26.2%)

NBW (normal birth-weigh): ≥ 2500 g
LBW (low birth-weight): 1000-2499 g
VLBW (very low birth-weight): < 1000 g

Discordant growth, when the difference between the largest and the smallest newborn was more than 15%, was found in 27.6% of the twins and 60.8% of the triplets. The difference exceeded 25% in 8.9% of the twins and 42.3% of the triplets (***Table 6*** and ***Figure 6***).

Figure 6. Birth-weight discordance in twin pregnancies



A vertex position of the first newborn was recorded in 67.4% of the twins and 69.2% of the triplets ***(Tables 5 and 6).*** In 63.6% of the twin pregnancies, vaginal (or operative vaginal) delivery was available. The pregnancy was terminated by Cesarean section in 36.5% of the twins and in 89.5% of the triplets. Unfortunately there was a very high rate of missing data as concerns placentation (25.1%). We found bichorionic-biamniotic placentation in 53.7% of the twin gestations and monochorionic-monoamniotic placentation in 2.3% of the cases ***(Table 6).***

Table 5. Mode of delivery according to the fetal position

	Vaginal	Operative vaginal	Cesarean section
Vertex-vertex	142	11	31
Vertex-breech	50	3	9
Vertex-transverse	11	1	13
Breech-vertex	4	0	18
Breech-breech	1	0	25
Breech-transverse	5	0	26
Transverse-breech	0	0	3
Transverse-transverse	0	0	49

Table 6. Perinatal outcome, I

	Twins (n=402)	Triplets (n=26)
Mean gestational age at delivery (days)	247.73 ± 25.3	236.4 ± 21.8
Mode of delivery		
vaginal	237 (59.0%)	3 (11.5%)
operative vaginal	18 (4.5%)	0
Cesarean section	147 (36.5%)	23 (89.5%)
Mean birth-weight (g)		
first newborn	2226.2 ± 658.7	1829.0 ± 527.1
second newborn	2209.9 ± 660.6	1796.8 ± 509.9
third newborn		1677.9 ± 431.5
Birth-weight discordance		
< 15%	291 (72.4%)	10 (38.5%)
15-25%	75 (18.7%)	5 (19.2%)
> 25%	36 (8.9%)	11 (42.3%)
M:F sex ratio		
first newborn	0.89	1.37
second newborn	1.05	0.90
third newborn		0.58
Placentation		
BC-BA	216 (53.7%)	
MC-BA	76 (18.9%)	
MC-MA	9 (2.3%)	
unknown	101 (25.1%)	
Position of first fetus		
vertex	271 (67.4%)	58 (69.2%)
breech	79 (19.7%)	7 (26.9%)
transverse	52 (12.9%)	1 (3.9%)

BC: bichorionic, BA: biamniotic
MC: monochorionic, MA: monoamniotic

The frequency of an Apgar score < 7 at 5 min was similar for the first and second twins and it was twice as high as for the first and second triplet newborns and three times as high as for the third triplets. The umbilical cord blood pH was not measured in all newborns, but the pH level of the consecutive newborns was much lower. In consequence of prematurity or immaturity, more than one-fifth of the twin newborns and 42.3% of the triplet newborns

newborns were transferred to the NICU. Intrauterine death occurred in 1.6% of the twins and 5.1% of the triplets. Early neonatal death (within 168 h) was very high for both twin and triplet newborns ***(Table 7)***.

Table 7. Perinatal outcome, II

	Twins (n=402)	Triplets (n=26)
Apgar score at 5 min < 7		
first newborn	42 (10.4%)	5 (19.2%)
second newborn	45 (11.2%)	7 26.9%)
third newborn		8 (30.8%)
Umbilical cord blood pH < 7.2 #		
first newborn	27/359	2/24
second newborn	58/359	2/24
third newborn		4/24
Newborn transferred to NICU		
first newborn	95 (23.6%)	11 (42.3%)
second newborn	94 (23.4%)	11 (42.3%)
third newborn		12 (46.2%)
Perinatal mortality		
stillbirth	13/804	4/78
death within 168 h	23/804	4/78

#Measurement was not performed in all cases
NICU: neonatal intensive care unit

There were significant differences between spontaneous versus induced multiples in the rates of maternal complications during pregnancy ***(Table 8)***.

Table 8. Maternal complications associated with pregnancy in spontaneous and induced multiples

	Twins		Triplets	
	Spontaneous (n=314)	Induced (n=88)	Spontaneous (n=9)	Induced (n=17)
Gestational diabetes	4 (1.3%)	4 (4.5%)	0	1 (5.95%)
Preeclampsia	31 (9.9%)	13 (14.8%)*	3 (33.3%)	3 (17.6%)
Cervical incompetence	43 (13.7%)	18 (20.5%)*	3 (33.3%)	12 (70.6%)
Threatened preterm delivery	84 (26.8%)	20 (22.7%)	4 (44.4%)	8 (47.1%)

*Significant difference between spontaneous and induced groups ($p<0.05$)
Statistical analysis could not be performed in all groups

Gestational diabetes and incompetent cervix requiring treatment by cerclage were more frequent in the induced twin group than in the spontaneous one. Interestingly, the rate of preeclampsia was significantly lower in the induced triplet pregnancies (17.6%) as compared with the spontaneous triplets (33.3%). The numbers of patients with threatened preterm delivery were similar among the induced and the spontaneous twins and triplets. The perinatal outcome is indicated in ***Table 9.*** The gestational ages at delivery were similar in the spontaneous and induced groups. Operative vaginal delivery and Cesarean section were more common in the induced than in the spontaneous twin group. Cesarean delivery was performed in all the spontaneous triplet pregnancies, in contrast with the induced group, where rapid vaginal delivery occurred in 2 cases. There was no statistical difference between the induced and spontaneous twins as concerns the mean neonatal birth-weights of twin A and twin B. Among the induced triplets, the birth-weights of the first and second newborns were significantly lower than those of their spontaneous counterparts. The Apgar score and the umbilical cord blood pH were much worse in both induced groups. Transfer to the NICU was significantly more common in the induced newborns. We defined growth discordance as a birth-weight difference of at least 25%. On this basis, 14.7% of the induced twin newborn pairs showed discordant growth, in contrast with 7.3% of the spontaneous twins. The difference between the triplet groups was not significant in respect of a birth-weight discordance. The perinatal mortality rates were similar in the twin groups, but the rates of IUFD and early neonatal death (within 168 h) differed significantly. In the triplets, early neonatal death was extremely high (19.6%) in the induced group, and intrauterine death also occurred more frequently than in the spontaneous triplet group.

Table 9. Perinatal outcome in spontaneous and induced multiples

	Twins		Triplets	
	spontaneous (n=314)	induced (n=88)	spontaneous (n=9)	induced (n=17)
Mean gestational age at delivery (days)	251.2 ± 31.8	239.0 ± 33.8	232.8 ± 28.0	231.1 ± 28.2
Mode of delivery				
vaginal	207 (65.9%)	30 (34.1%)*	0	2 (11.8%)
operative vaginal	12 (3.8%)	6 (6.8%)*	0	0
Cesarean section	95 (30.3%)	52 (59.1%)*	100%	15 (88.2%)
Mean birth-weight (g)				
first newborn	2267.7 ±628.7	2208.4 ±648.1	2193.0 ±351.1	1641.3 ±412.2*
second newborn	2251.0 ±634.6	2180.1 ±671.6	1919.3 ±411.4	1536.5 ±472.7*
third newborn			1858.3 ±298.8	1525.0 ±398.3
Growth discordance	23 (7.3%)	13 (14.7%)	3 (33.3%)	8 (47.1%)
Apgar score at 5 min < 7				
first newborn	34 (10.8%)	15 (17.0)*	2 22.2%)	3 (17.6%)
second newborn	38 (12.1%)	16 (18.1%)*	2 (22.2%)	5 (29.4%)
third newborn			2 (22.2%)	6 (35.3%)
Newborn transferred to NICU				
first newborn	68 (21.7%)	27 (30,7%)*	4 (44.4%)	6 (35.3%)
second newborn	69 (22,0%)	27 (30,7%)*	5 (55.6%)	6 (35.3%)
third newborn			5 (55.6%)	7 (41.2%)
Perinatal mortality				
stillbirth	9/628	4/176	1/27	3/51
death within 168 h	37/628	8/176	3/27	10/51

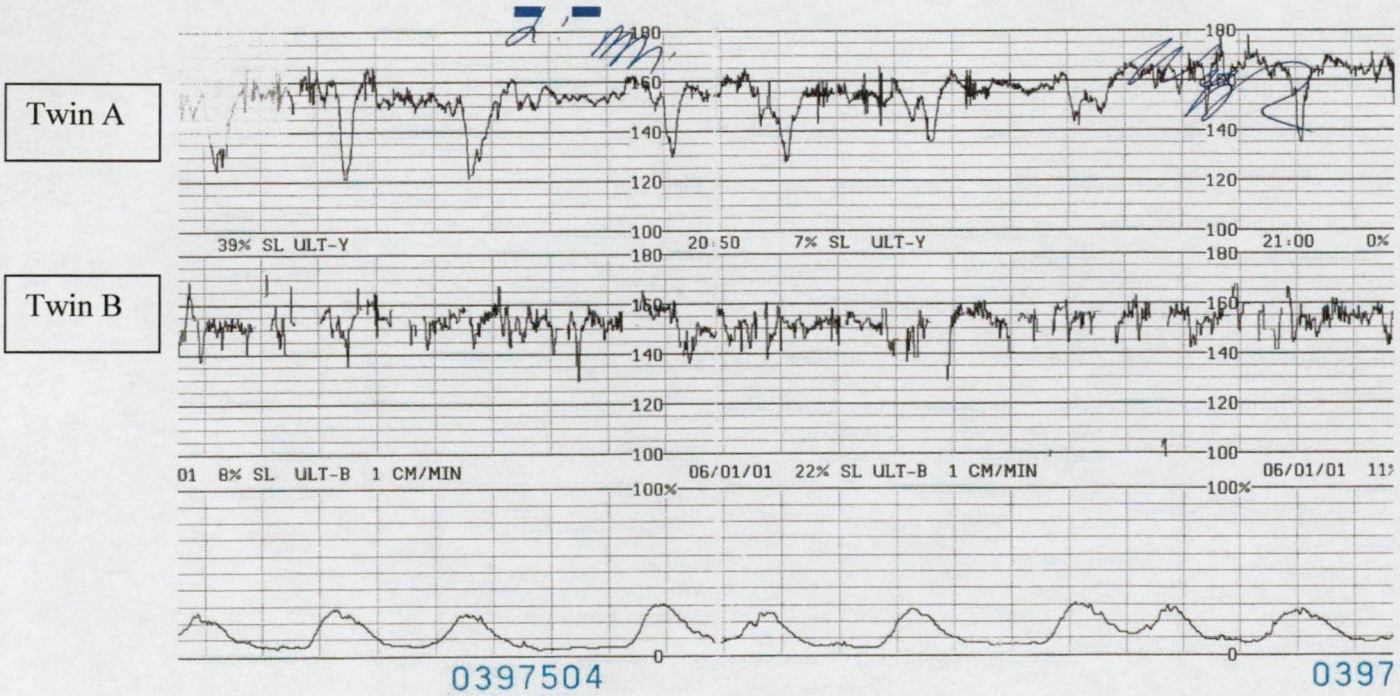
*Significant difference between spontaneous and induced groups ($p<0.05$)
Statistical analysis could not be performed in all groups

7. STUDY OF SURVIVAL PROBABILITIES OF TWIN FETUSES: INTRAUTERINE FETAL DEATH IN TWIN PREGNANCIES

In the multiple pregnancies the intrauterine fetal death of 1 fetus occurred in 13 cases (3.1%) and both fetuses died in another 2 cases (0.5%). Nine gestations were conceived spontaneously, and 6 resulted from assisted reproductive techniques. All but 2 pregnancies in the studied group were complicated by threatened preterm delivery and 3 of the 15 were terminated at term. In 2 triplets and 1 twin pregnancies, cervical cerclage according to McDonald was performed due to cervical incompetence. Pregnancy-induced hypertension, gestational diabetes mellitus and severe preeclamptic toxemia with an episode of antepartum eclampsia were noted ***(Table 10).***

The fetal surveillance assessment was achieved by CTG ***(Figure 7)*** and blood flow velocity waveform analysis. Both methods were applied in 8 pregnancies, and only the non-stress test in 1 pregnancy. With the exception of 3 triplet pregnancies, non-reassuring tests of CTG or/and flowmetry of the umbilical artery were performed before the diagnosis of intrapartum fetal death. In 6 cases, neither CTG nor flowmetry was carried out and fetal death occurred before admission to our Department ***(Table 10).***

Figure 7. Simultaneous CTG recording of twin fetuses.
(Twin A has hypoxic signs, while twin B has reactive fetal heart rate patterns.)



The gestational age ranged between 24 and 38 weeks. Three mothers with triplets underwent Cesarean section and 2 twin pregnancies were terminated by Cesarean section due to the breech presentation of the first fetuses, and in 1 induced twin pregnancy Cesarean section was performed because of the onset of labor at 25 weeks of gestation and the pregnancy was complicated by severe toxemia and eclampsia ***(Table 11).***

The estimated time that elapsed between fetal death and delivery varied from a few hours to 14 days; in 2 cases the time was not identifiable. Discordant growth was registered in 9 cases out of 15. Intrauterine fetal death in the twin pregnancies occurred more often in monochorionic (60%) than in bichorionic (40%) placentation. In the triplet pregnancies, 2 placentas were trichorionic, 1 was bichorionic-triamniotic and the fourth one was monochorionic-triamniotic ***(Table 11)***. The causes of intrauterine death were established by autopsy. Placental insufficiency/infarction of the placenta was registered in 7, infection in 2, severe IUGR and placental abruption in 1 case. Two stillborn neonates had omphalocele with congenital cardiac malformations with various minor abnormalities. Both fetuses in the monochorionic-monoamniotic twin gestations died intrauterine. The fetuses in one of the monoamniotic pregnancies displayed manifest signs of the twin-to-twin transfusion syndrome. No obvious cause of intrauterine death could be found in the other monoamniotic pregnancy and in one of the triplet pregnancies ***(Table 11).*** The pregnancy was prolonged in 5 cases, without any coagulation disorders in the maternal coagulation profile.

Two live-born neonates died within a few hours because of extreme immaturity, with birth-weights of 580 and 550 g. Late neonatal death was registered in 1 immature newborn weighing 1100 g at delivery, and another 7 infants were treated in the NICU; they were discharged after 10-25 days. One of the surviving twins had minor congenital anomalies ***(Table 12).*** In our registry, there was no trace of any early sequel of IUFD.

Table 10. Intrauterine death in twin pregnancies, I

Case	Age (years)	Conception	Pregnancy	Complications	Fetus	NST	flowmetry
1	31	ovulation induction	twin	-	✞A	-	-
		+ IUI		-	✞B	-	-
2	30	spontaneous	twin	-	A	R	-
				-	✞B	*S*	-
3	35	ovulation induction	twin	PIH	A	-	-
				-	✞B	-	-
4	33	spontaneous	twin	-	A	R	normal
				-	✞B	*S*	normal
5	27	spontaneous	twin	-	A	R	normal
				-	✞B	*S*	***increased S/D***
6	32	ovulation induction	triplet	-	A	R	normal
		+		-	✞B	R	normal
		IVF-ET		-	C	R	normal
7	28	spontaneous	triplet	cervical	A	R	normal
				incompetence	B	*S*	normal
				-	✞C	*S*	***reverse flow***
8	23	spontaneous	twin	-	A	R	normal
				-	✞B	*S*	normal
9	23	ovulation induction	triplet	cervical	✞A	R	normal
				incompetence	B	R	normal
				-	C	R	normal
10	28	ovulation induction	twin	toxemia, eclampsia	✞A	-	-
				-	B	-	-
11	29	spontaneous	twin	-	A	-	-
				-	✞B	-	-
12	23	spontaneous	twin	cervical incompetence	A	-	-
				-	✞B	-	-
13	31	spontaneous	twin	gestational diabetes	✞A	-	-
				-	✞B	-	-
14	26	spontaneous	twin	-	✞A	-	-
				-	B	R	normal
15	29	ovulation induction	triplet	-	A	R	-
		+		-	B	R	-
		IVF-ET		-	✞C	R	-

IUI: intrauterine insemination, IVF-ET: in vitro fertilization and embryo-transfer,
PIH: pregnancy-induced hypertension , R: reactive, S: questionable, suspicious, NST: non-stress test

Table 11. Intrauterine death in twin pregnancies, II

Case number	GA	Birth-weight A	Birth-weight B	Birth-weight C	Placentation	ETDD	Type of delivery	Etiology of death
1	29	✞1240 F	✞1000 F		MC-MA	< 24 h	vaginal	unknown
2	35	1820 F	✞2100 M		MC-BA	< 48 h	vaginal	placental insufficiency
3	24	580 F	✞ 550 M		BC-BA	?	vaginal	PIH, infection
4	37	2320 F	✞2500 F		BC-BA	< 24 h	vaginal	placental insufficiency
5*	36	2390 M	✞750 F		BC-BA	< 10 days	CS	IUGR
6*	34	2020 F	✞1050 M	2320 M	TC-TA	< 12 h	CS	placental insufficiency
7*	34	1820 M	1770 M	✞2400 M	MC-TA	< 48 h	CS	placental abruption
8*	38	3010 M	✞2000 M		MC-BA	< 2 h	CS	multiple anomalies
9*	29	✞850 M	1320 F	1330 F	BC-TA	<14 days	vaginal	unknown
10	25	✞450 F	550 M		BC-BA	< 14 days	CS	toxemia, placental infarction
11*	31	1750 F	✞680F		MC-BA	?	vaginal	placental infarction
12	28	1100 F	✞800 F		MC-BA	< 14 days	vaginal	infection
13*	27	✞1200 F	✞700F		MC-MA	< 3 days	vaginal	twin-to-twin transfusion
14*	37	✞1560 M	2840 M		BC-BA	17 days	vaginal	placental infarction
15*	34	1760 M	1000 F	1500[#]	TC-TA	< 12 h	CS	placental infarction, multiple anomalies

✞: intrauterine death, M: male, F: female, *: discordant growth, GA: gestational age
MC: monochorionic, BC: bichorionic, MA: monoamniotic, BA: biamniotic, TC: trichorionic, TA: triamniotic, ETDD: estimated time between intrauterine death and delivery, CS: Cesarean section, IUGR: intrauterine growth retardation, PIH: pregnancy-induced hypertension
[#] Abnormality of sexual differentiation

Table 12. Intrauterine death in twin pregnancies, III

Case number	Live co-twin	Birth-weight (g)	Apgar score at 1, 5 and 10	Complications	Transfer
2	A	1820	4, 8, 8	prematurity, minor congenital anomalies	NICU, home
3	A	580	1, 4, 4	immaturity, IRDS III, early neonatal death	NICU,✞
4	A	2320	10, 10, 10	prematurity	home
5	A	2390	6, 8, 8	prematurity	home
6	A	2020	8, 9, 9	prematurity, IRDS I-II	NICU, home
	C	2320	8, 9, 10	prematurity	home
7	A	1820	2, 6, 7	pre- and dysmaturity, IRDS I	NICU, home
	B	1770	3, 6, 7	pre- and dysmaturity, IRDS I	NICU, home
8	A	3010	10, 10, 10	-	home
9	B	1320	10, 10, 10	prematurity, IRDS I, intrauterine infection	NICU, home
	C	1330	8, 10, 10	prematurity, IRDS I-II intrauterine infection	NICU, home
10	B	550	2, 2, 6	immaturity, IRDS III, early neonatal death	NICU,✞
11	A	1750	8, 9, 10	prematurity, IRDS I	NICU, home
12	A	1100	1, 3, 3	immaturity, IRDS II, late neonatal death	NICU,✞
14	B	2840	10, 10, 10	-	home
15	A	1760	7, 8, 9	prematurity	NICU, home
	B	1000	3, 5, 9	prematurity, IUGR	NICU, home

NICU: neonatal intensive care unit
✞: early or late neonatal death
IRDS: idiopathic respiratory distress syndrome

8. EXAMINATION OF INTRAPARTUM CARDIOTOCOGRAMS AND SLEEP-AWAKE PERIODS IN SINGLETON AND TWIN FETUSES DURING THE SECOND STAGE OF LABOR

The intrapartum cardiotocograms of 300 singleton and 42 twin pregnancies between weeks 28 and 42 of gestation were subjected to retrospective analysis. The recordings were made with Kranzbühler, Hewlett Packard and Oxford Sonicaid Team cardiotocographs. The advantage of the latter two cardiotocographs is that they have the ability to record twin fetuses simultaneously. The continuous intrapartum cardiotocograms ***(Figure 8)*** of the last 3 h of the first stage of labor in vaginal deliveries, and of the last 3 h before resorting to Cesarean section, were selected into the study. Good trace-quality and low sign-loss were important criteria. In addition to the above-mentioned criteria, in twin pregnancies, only traces simultaneously recorded with the same cardiotocograph were accepted ***(Figures 7 and 9).*** Visual analysis was made separately by two CTG experts to eliminate intra-observer variance in the interpretation of traces. Fetal movements were evaluated in accordance with the "Fetal Movement Profile" (FMP) criteria (F1-F4) of Nijhuis[13] Decelerations were defined as periods with an amplitude > 20 beats per min below the baseline and duration > 30 s. In 62% of the traces, FMP was assessed cardiotocographically, and the number of fetal movements was given by the device as a percentage every tenth minute. This was of great help in the analysis especially as concerns differentiation of the F2 and F4 periods.

Figure 8. Intrapartum CTG monitoring. (A change in awake-sleep periods can be seen.)

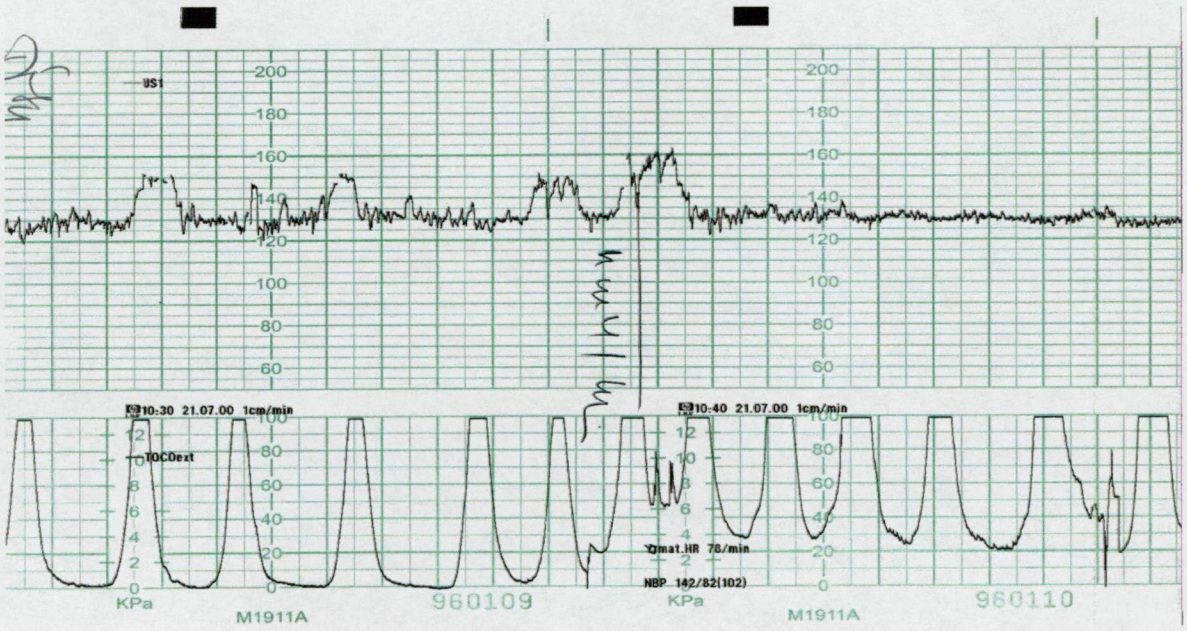


Figure 9. Simultaneous intrapartum CTG monitoring of twin fetuses.
(Twin A and twin B are in different sleep-awake periods.)

Twin A

Twin B

Data concerning the pregnancies and the condition of the neonates were obtained from the case histories. The venous umbilical cord blood pH was registered in the database. The pH measurements were performed with a Gem Premier Plus device. The neonate was not considered healthy if signs of growth retardation were present, the venous cord blood pH was less than 7.20, the 5-min Apgar score was less than 7, the neonate was referred to the NICU and the reason for the referral was not a low birth weight.

The average age of the mothers in the singleton pregnancies was 26.7 ± 4.5 years, while in the twin pregnancies it was 29.8 ± 4.1 years. The proportion of premature rupture of membranes was high in both groups (33.7% in the singleton pregnancies and 40.5% in the twin pregnancies). The administration of oxytocin infusion during labor was necessary in 68.7% and 66.7% in the two groups. In our study, the average gestational age was 39 weeks in the singleton and 35 weeks in the twin pregnancies. The proportion of premature births was 10 times higher in the twin pregnancies than in the singletons. The rates of spontaneous vaginal delivery were 71.7% and 65.7% in the two groups ***(Table 13)***.

Table 13. Characterization of the pregnancy and the delivery in singletons and twins

	Singletons (n =300)	Twins (n =42)
Mean maternal age (yeasr)	26.7 ± 4.5	29.8 ± 4.1
Premature rupture of membranes	101 (33.7%)	17 (40.5%)
Oxytocin infusion	206 (68.7%)	28 (66.7%)
First stage of labor (min)	478.3 ± 221.1	350.8 ± 217.5
Second stage of labor (min)	16.2 ± 11.5	25.3 ± 28.5
Gestational age at delivery	39.0 ± 1.5	35.1 ± 3.5
Grav.s. < 37	19 (6.3%)	27 (64.3%)
Mode of delivery		
vaginal	215 (71.7 %)	15 (35.7%)
operative vaginal	70 (23.3%)	3 (7.1%)
Cesarean section	45 (15.0%)	24 (57.3%)

A majority of the neonates were born in good general condition, with a normal cord blood pH and Apgar score. In 1.3% of the singletons and in 9.5% each of twins A and B, we found low 5-min Apgar scores (<7). The venous cord blood pH was lower than 7.20 in 22% of the singleton neonates, in 7.1% of the A siblings and in 14.2% of the B siblings. 1.7% of the singletons, 11.9% of twins A and 19% of twins B were referred to the NICU for reasons other than low birth-weight ***(Table 14).***

Table 14. Condition of the neonates in singleton and twin pregnancies

	Singletons (n =300)	Twins A (n =42)	Twins B (n =42)
Mean birth-weight at delivery (g)	3405.4 ± 532.1	2283.7 ± 623.2	2205.9 ± 639.3
Apgar score at 5 min <7	4 (1.3%)	4 (9.5%)	4 (9.5%)
Mean pH of umbilical cord	7.27 ± 0.09	7.28 ± 0.05	7.25 ± 0.05
<7.20	66 (22.0%)	3 (7.1%)	6 (14.2%)
Acute intrapartum distress	51 (17.0%)	2 (4.8%)	3 (7.1%)
Treatment in the NICU (all)	19 (6.3%)	19 (45.2%)	24 (57.1%)
without prematurity	5 (1.7%)	5 (11.9%)	8 (19.0%)

In the final evaluation of the intrapartum CTG traces, we did not find a significant ($p<0.05$) difference between the fetal heart rates of twins A and B or between those of the twins and the singletons. The average of the changes in the sleep-awake periods was between 4.3 and 4.8. In the last 3 h of the first stage of labor, the fetuses exhibited the characteristic picture of the awake period (F4) 2.1-2.5 times on average. We found an F3 period in only 7 traces (2.3%). The average number of decelerations in the above-mentioned 3 h section of the CTG traces was between 4.7 and 4.9 ***(Table 15).***

Table 15. Parameters of intrapartum cardiotocograms in singletons and twins

	Singletons (n =300)	Twins A (n =42)	Twins B (n =42)
Mean number of periodic changes	4.3 ± 1.7	4.8 ± 1.0	4.5 ±0.9
Mean number of F4 periods	2.1 ± 1.0	2.5 ± 0.9	2.4 ± 0.8
Mean number of decelerations	4.7 ± 6.0	4.9 ± 4.1	4.8 ± 4.0

We did not find a case among the twins where there was no change in the sleep-awake periods. Among the singletons, we found 1 case where there was no period change in the 3 h section of the trace. The fetus, born with 2470 g in week 35 of gestation by vaginal delivery was in the F1 state throughout, and we observed 6 deep variable decelerations, too. The neonate was born with 1, 5 and 10-min Apgar scores of 3, 6 and 10, and with a venous cord blood pH of 6.96. The condition improved quickly, and the early neonatal period was untroubled.

On the basis of the venous cord blood pH values, three subgroups were created: 1) <7.20, 2) 7.20 - 7.25 and 3) >7.25. Significant differences were found ($p<0.05$) as concerns the number of periodic changes, and the occurrence of F4 periods and decelerations in the different pH subgroups in the singleton pregnancies. Similar differences could be observed for the twin A and B fetuses, but, because of the low number of cases, significance could not be calculated. ***(Figures 10-12).***

Figure 10. Periodic changes according to the pH level

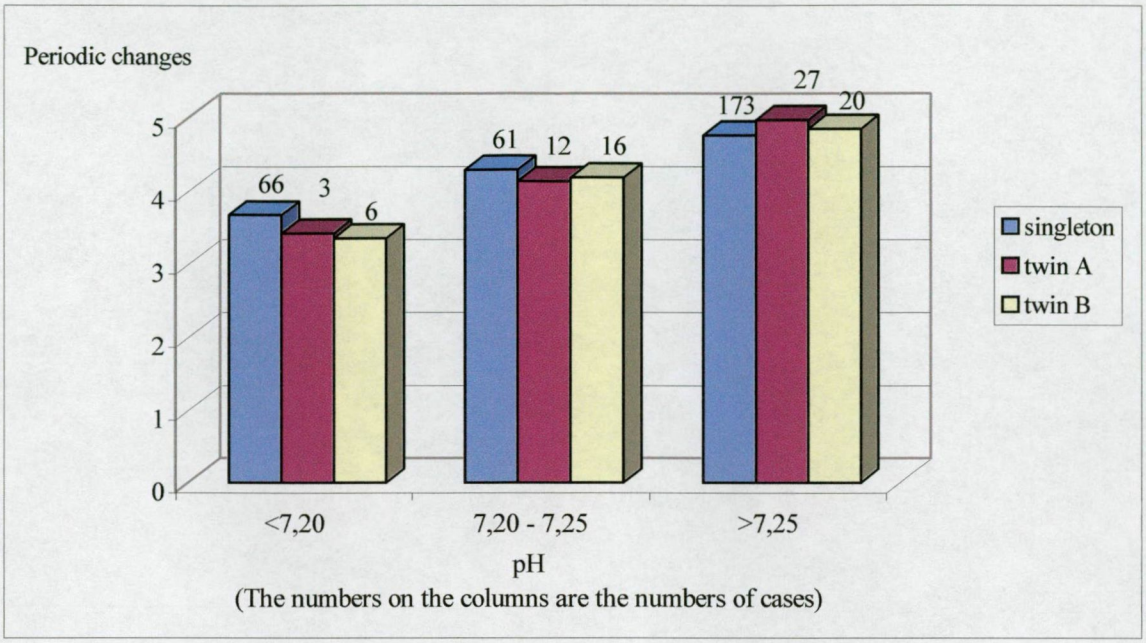


Figure 11. Number of F4 periods according to the pH level

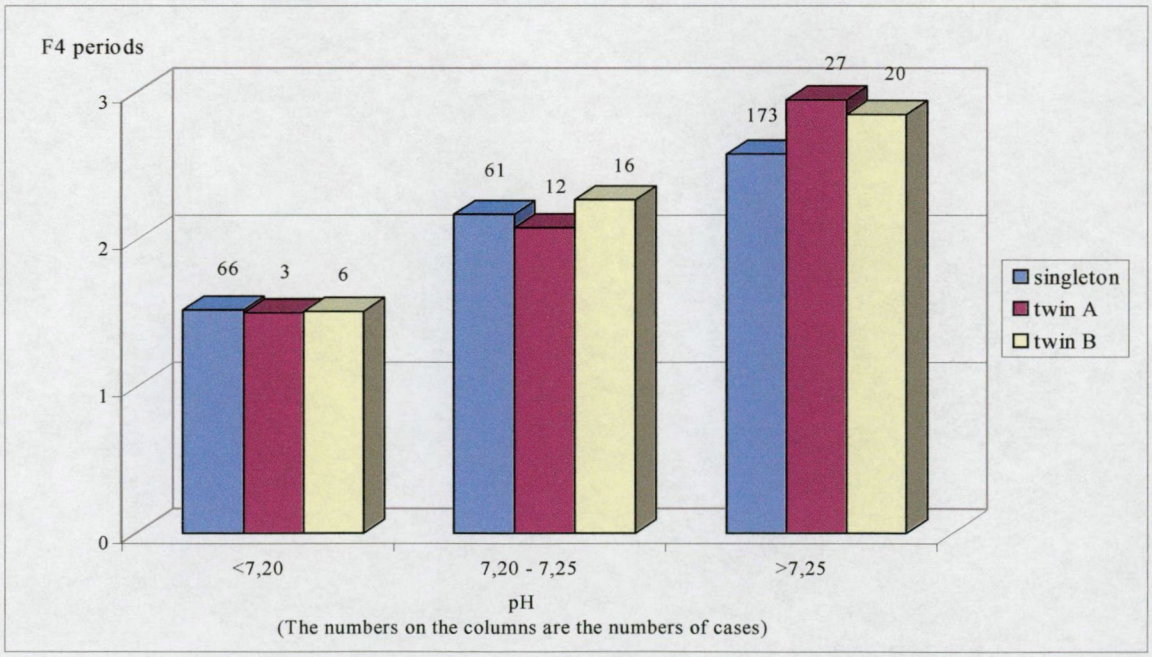
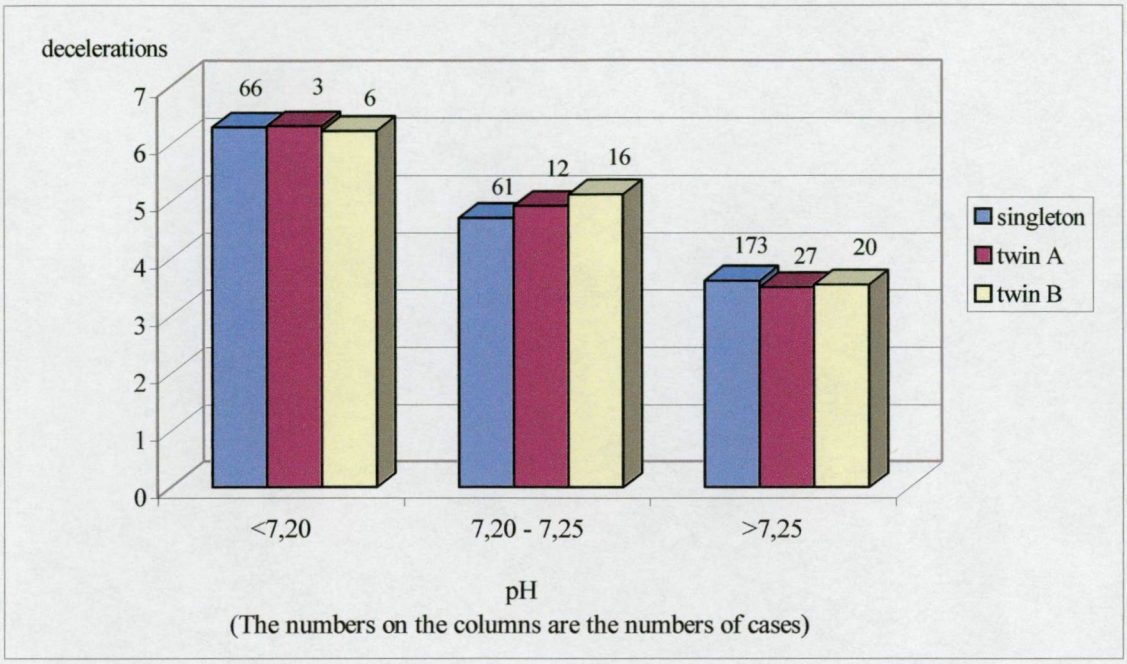


Figure 12. Number of decelerations according to the pH level



In the second part of the study, we created subgroups on the basis of the occurrence of sleep-awake period changes and F4 periods and examined the condition of the neonate (based on the venous pH) according to the occurrence of these factors. More period changes and more F4 periods were related to a better neonatal condition (higher venous pH values) both in the singletons and in the twins. This phenomenon revealed a statistically significant deviation when the subgroups of singleton pregnancies were compared ($p<0.05$). In the twin pregnancies, however, we could not perform a statistical test because of the low number of cases ***(Figures 13 and 14).***

Figure 13. Cord blood pH levels according to the number of periodic changes

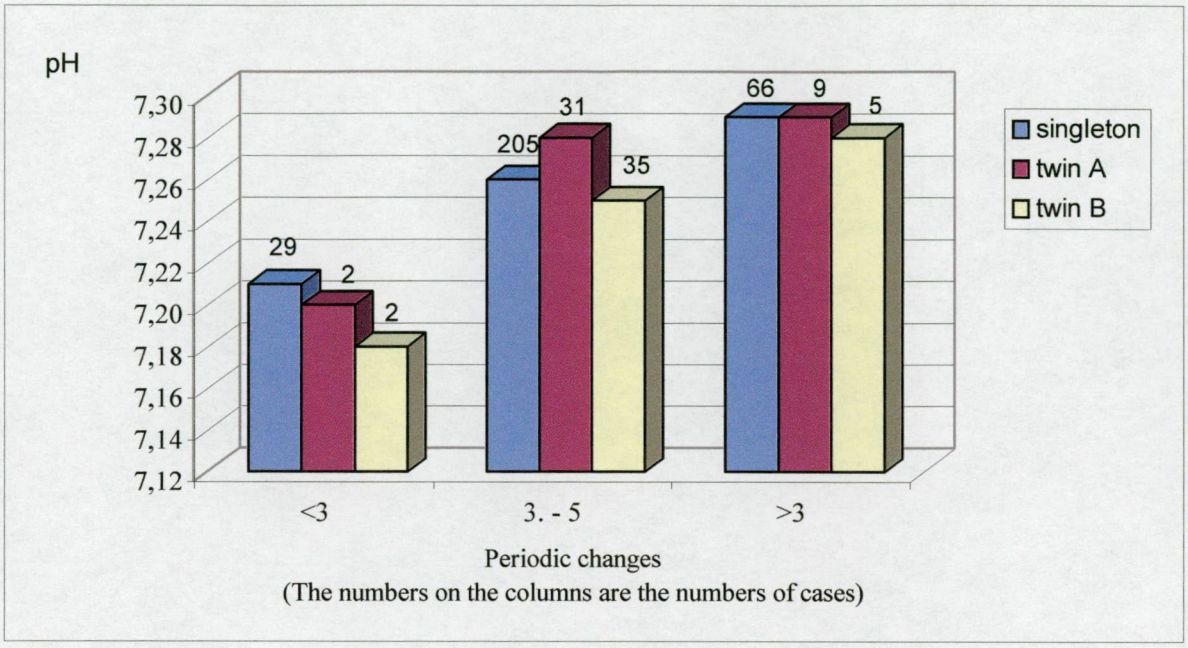
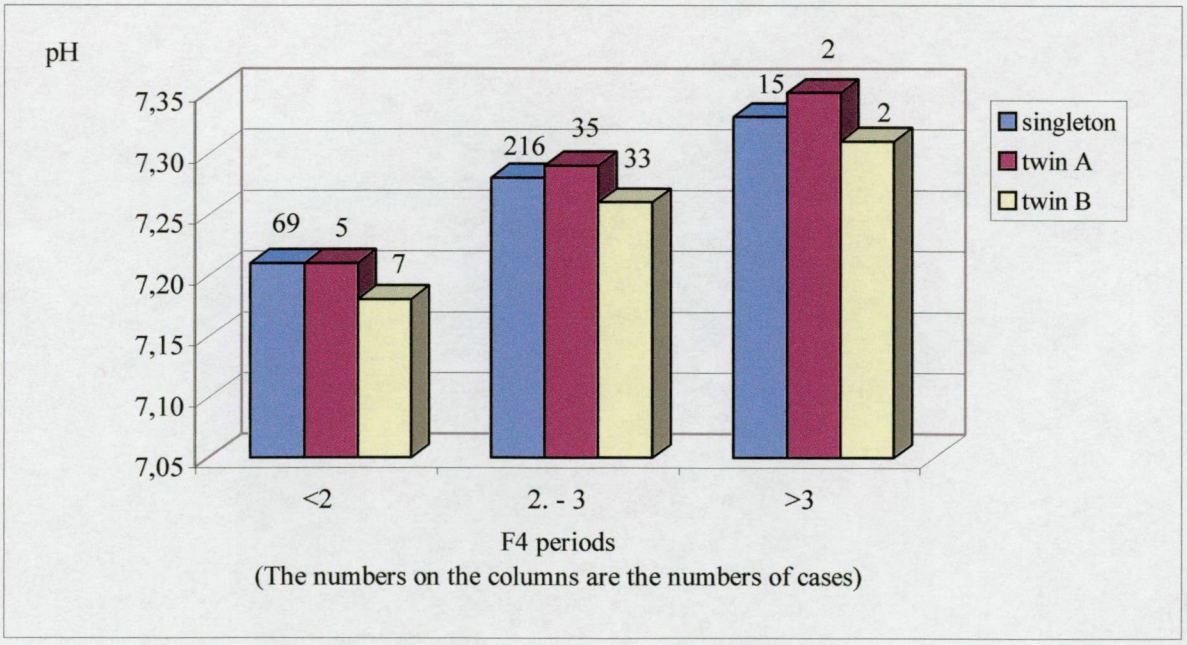


Figure 14. Cord blood pH levels according to the number of F4 periods



9. STUDY OF THE EFFECTS OF EARLY AND SIMULTANEOUS BREAST-FEEDING OF TWIN NEWBORNS.

A retrospective analysis was made of all twin pregnancies with at least 24 weeks of gestation at our Department between 1 January, 1994 and 31 December, 1998. During this period, 232 were multiple pregnancies (215 twins, 15 triplets and 2 quadruplets). The pregnancies with IUFD or major congenital malformations were excluded as were the pregnancies in which the birth-weight of each newborn was less than 2000 g. On the basis of the birth-weight, three groups were created: (1) each newborn had a birth-weight of 2000-2500 g, (2) the largest newborn had a birth-weight of at least 2500 g and (3) each newborns had a birth-weight of at least 2500 g. Early breast-feeding was considered as breast-feeding of the newborn immediately after vaginal delivery or 1.5-2 hours after Cesarean section with epidural analgesia or 6 hours after in cases with general anaesthesia.

Of the 15 triplet pregnancies, two met the criteria of the group 1 and 4 met the criteria of the group 2. The mean maternal age, primiparity and pre-pregnant maternal BMI did not yield significant differences. In the pregnancies where each newborn had a birth-weight of > 2500 g, the mean maternal weight gain was significantly higher than in the other groups ***(Table 16).***

Table 16. Breastfeeding in twin pregnancies, I

	Group 1	Group 2	Group 3
Total	34	55	60
twin pregnancies	32	51	60
triplet pregnancies	2	4	0
Mean maternal age (years)	28.4 ± 5.9	28.6 ± 5.3	28.4 ± 4.1
Primiparous mothers	17 (50%)	22 (40%)	24 (40%)
Pre-pregnant mean maternal BMI	23.1 ± 3.8	24.9 ± 6.31	23.6 ± 4.9
Mean maternal weight gain (kg)	14.8 ± 5.3	14.3 ± 5.8	17.1 ± 4.5*

*Significant difference among groups ($p<0.05$)

Since the groups were created on the basis of the newborns' birth-weight, the mean birth-weights were automatically significantly different in each group. As expected, the mean gestational ages were also different in the groups. Two-thirds of the newborns in group 1 were transferred from our Department during the first 2 days, while 8.3% of the twins in group 3 were a transferred to the NICU ***(Table 17).***

Table 17. Breastfeeding in twin pregnancies, II

	Group 1	Group 2	Group 3
Mean gestational age at delivery (weeks)	36.2 ± 1.8	37.8 ± 6.3	38.6 ± 2.8*
Mode of delivery			
vaginal	21 (61.8%)	28 (50.9%)	24 (40%)*
operative vaginal	1 (2.9%)	5 (9.1%)	3 (5%)
cesarean section	12 (35.3%)	22 (40.0%)	33 (55%)*
Mean birth-weight (g)			
first newborn	2252.6 ± 132.9	2509.8 ± 265.7	2901.0 ± 285.8*
second newborn	2211.1 ± 117.2	2492.0 ± 305.0	2885.5 ±302.4*
third newborn	2190.0 ± 183.8	2015.0 ± 403.2	-----
Newborn transferred to NICU			
first newborn	24 (70.6%)	8 (14.5%)	5 (8.3%)*
second newborn	23 (67.6%)	9 (16.4%)	5 (8.3%)*
third newborn	1 (50.0%)	2 (50.0%)	-----

*Significant difference among groups ($p<0.05$)
Statistical analysis could not be performed in all groups

Early breast-feeding could be carried out in only 10 pregnancies (29.4%) in group 1, 89.1% in group 2 and 95.0% in group 3. In the cases involving early breast-feeding, all of the mothers required rooming-in accommodation.

There were no significant differences according to the duration of neonatal jaundice and the duration of stay at our Department. More than 80% of the newborns with early breast-feeding in each group were exclusively breast-fed at discharge. In the 3 triplet pregnancies, where the newborns were early breast-fed, each baby suckled well and the mothers had enough milk for their 3 newborns at discharge ***(Table 18).***

Table 18. Breastfeeding in twin pregnancies, III

	Group 1	Group 2	Group 3
Early breast-feeding#			
total	10 (29.4%)	49 (89.1%)	57 (95.0%)*
twins	9	47	57*
triplets	1	2	0
Rooming-in accommodation	100%	100%	100%
Mean duration of jaundice (days)**			
first newborn	4.6 ± 2.6	5.4 ± 3.2	3.6 ± 1.7
second newborn	4.6 ± 2.0	4.5 ± 2.6	3.1 ± 1.9
third newborn	5.0 ± 0.0	0.0 ± 0.0	-----
Mean duration of stay at our Department (days)**	9.7 ± 2.2	10.5 ± 3.5	7.8 ± 1.9*
Exclusively breast-fed at discharge			
first newborn	9/10	40/49	53/57
second newborn	10/10	39/49	52/57*
third newborn	1/1	2/2	-----

*Significant difference among groups ($p<0.05$)
Statistical analysis could not be performed in all groups
#At least one of the newborns
**In cases of early breast-feeding

10. DISCUSSION:

1. Characterization of multiple pregnancies, deliveries and newborns in a tertiary center in Hungary.

The perinatal morbidity and mortality rates in multiple gestations are 4 to 10 times higher than in singletons. The high perinatal morbidity and mortality in multiples are associated with increased rates of prematurity, low birth-weight and IUGR.[52,54] Intrauterine fetal growth depends on several factors. Vetter[79] divided these factors into stable and functional factors and evaluated the latter factors, the placental supply and growth factors.

Different types of ovulation induction therapy were introduced into the clinical practice at our Department in the early 1970s. However, due to the rather expensive technique of IVF and other operative- assisted reproductive techniques, these methods did not become widespread until the mid-1980s. In the past 20 years, there has been a marked decreasing trend in the number of births in Hungary and in the Department of Obstetrics and Gynecology in Szeged, while the incidence of multiple pregnancies has been increasing ***(Figure 1)***. A similar trend was described in the early 1980s following the East Flanders Prospective Twin Survey (an analysis from 6 European countries) by Derom et al.[48] Because of the higher perinatal morbidity and mortality rates, mothers with multiple gestations should be provided with extra ante-, intra- and postnatal care.[80] Our study confirms the results of Tan et al.[81] and Gissler and Hemminki,[82] indicating that maternal complications and an unfavorable perinatal outcome are more common in induced than in spontaneous multiple pregnancies. Interestingly, this contrasts with the findings of Olivennes et al.,[83] who observed no difference in perinatal outcome between the twin IVF-ET group, stimulated twin gestations and spontaneous twin pregnancies. Numerous investigators have noted an increased incidence of preeclampsia among multiples compared with singletons.[81-84] We observed a high incidence in all groups, but surprisingly a significantly lower incidence of preeclampsia was found in the induced triplet pregnancies than in the spontaneous group. Skupski et al.[84] reported that the rate of preeclampsia is higher in triplets conceived by IVF than in triplets induced by IVF and reduced to twins. However, in consequence of the small number of triplets, care has to be taken with this finding. They suggest that the number of fetuses, the placental mass and uteroplacental perfusion are very important factors as regards the development of preeclampsia. The rate of premature deliveries was similar in spontaneous and induced pregnancies. The same findings were described by Olivennes et al.[83] High rates

of Cesarean section were reported by other investigators in pregnancies following assisted reproductive techniques[81-83]. Like Tan et al.,[81] we found an increased rate of Cesarean delivery in induced as compared with spontaneous multiple gestations. Discordant growth among multiple fetuses suggests a heightened degree of risk, with a medical and economic consequences of high-level care in a special center for these fetuses and newborns.[80-82] Mordel et al.[86] describe triplet newborns with a rate of discordance double that of twins. In our study, the number of pregnancies with discordant birth-weights was also very high, especially in the induced twin group. One-third of the induced triplet pregnancies were complicated by discordant growth.

2. Study of the occurrence of intrauterine fetal death in multiple pregnancies.

In twin pregnancies, IUFD is 2-4 times more frequent than in singleton pregnancies.[87] This risk is even greater in triplet pregnancies. Maternal diseases, placental insufficiency, cordcomplications and fetal malformations are frequently reported as main causes.[59,87,89] However, it is often impossible to establish the etiology of intrauterine fetal death because of the macerated fetus. A close association has been reported between PIH or preeclampsia and fetal death.[89-90] In our study, 2 of the 13 women (15.4%) suffered from hypertension disease. Placental factors such as placental insufficiency and anemic infarction of the placenta were the most probable causes of fetal death. This is similar to the findings of other authors.[52,87] We confirm that single intrauterine deaths are about 3 times more frequent in monochorionic gestations than in dichorionic ones.[61] There were 2 monoamniotic gestations and both of them were complicated by the death of both fetuses. In one of these monoamniotic gestations one fetus was anemic, while the other was polycytemic, and a severe discordance was found due to twin-to-twin transfusion. It has been reported that a higher rate of discordance is associated with an increased risk of fetal loss.[62] In our study, a severe discordance was diagnosed in 54% of the cases.

The literature indicates that the impact of IUFD on the surviving twin is approximately 46%.[87] Especially poor prognosis was described for the live co-twin in monochorionic gestations. Benirschke[61] suggested that almost 100% of monochorionic placentas have vascular communications. One fetus dies and the other may suffer from vascular injury to the brain, kidney, skin and other organs.[59,91-93] The high incidence of neurological symptoms in survivors could be explained by hypoxia and hypotension at the time of single fetal death.

However, prematurity remains the most frequent complication to live twins.[59] In our series, the incidence of premature deliveries was 85%.

The risk of maternal coagulopathy after intrauterine fetal death in singleton pregnancies was reported by Pritchard.[94] However, disseminated intravascular coagulation the mother after monofetal death in multiple pregnancy is a very rare event.[95] There was no maternal coagulopathy either in our studied group or in a similar group analyzed previously in Hungary.[96]

On the basis of our clinical survey, the recommended clinical policy is as follows: In gestations of more than 36 weeks complicated by IUFD, induced delivery is recommended. Between 24 and 36 weeks, termination of pregnancy is advised if fetal or maternal complications occur.

3. a) Examination of the sleep-awake periods for singleton and twin fetuses during the last three hours of the second stage of labor (active phase), using continuous CTG traces.

Intrapartum monitoring has a significant role in the early recognition of fetal compromise. Labor involvs a significant stress for the fetus. Intrapartum monitoring helps the obstetrician to distinguish physiological stress from distress. Fetal distress is a sign of the inability to cope with intrapartum stress, a condition which may lead to asphyxia. The latter is characterized by hypoxia and acidosis. Frequently, we can determine certain factors which endanger fetal well-being as early as the antepartum period. In such cases, intrapartum monitoring helps prevent the development of hypoxic complications.[97]

In our study, we chose the active phase of the first stage of labor to examine the fetal sleep-awake periods and the changes in fetal heart rate that emerge in response to intrapartum stress. According to van Woerden,[98] the mature and healthy fetus spends 60-70% of its time in the F2 state in the antepartum period (length: 34±6 min) and 25% in the F1 state (length: 17±8 min). In 6% of the time, no fetal movement can be observed and the variability of the baseline is low (7±0.5 bpm). Our study has showed that sleep-awake periods can be observed in healthy fetuses in the intrapartum period too, that awake (F4) states supervened 2 times in the examined 3 h-long period, and that changes in sleep-awake states occurred 4 times. Therefore, we can state that fetuses spend most of their time in the F1 and F2 states in the intrapartum period, similarly as found in antepartum surveys.

3. b) Comparison of the number of fetal sleep-awake periods, F4 periods and decelerations with the neonatal outcome.

Higher venous cord blood pH values accompany a greater number of period changes and a greater number of F4 states, while a higher occurrence of decelerations is associated with a lower venous cord blood pH. In 1 singular pregnancy, the fetus remained in the F1 state throughout the 3 h period, and it was born with a venous cord blood pH of 6.96 and with 1, 5 and 10-min Apgar scores of 3, 6 and 10. Thus, we can conclude that the exclusive presence of a sleep state and few sleep-awake period changes may be ominous signs of fetal hypoxia.

One of the current great challenges for obstetricians is that more and more mothers want 'natural labor' and a thoroughly healthy baby. Although labor is a physiological process, it is well known that 'normal labor' is a retrospective diagnosis. Intrapartum CTG monitoring helps us to recognize not just severe fetal hypoxia: through analysis of fetal sleep-awake periods, it also enables us to realize the risk of intrapartum stress converting into distress. In this way, we can take measures in time to prevent the development of asphyxia.[99,100] The continuous recording of fetal movements together with the fetal heart rate would also provide a significant help to the obstetrician in the first stage of labor.

4. Study of the effects of early and simultaneous breast-feeding of twin newborns.

Until the 20th century, human milk was the only source of nutrients for infants after birth. From the beginning of last century, with the decline of breast-feeding, evaporated milk and infant formulas were gradually applied.[76,77]. After World War II, modified evaporated infant formulas were replaced universally. In the USA, Martinez and Nalazienski[76] analyzed a large nationally representative sample of mothers who were surveyed by mail-questionnaires to determine the trend of breast-feeding in hospital and up to 6 months of age at home. Their data indicated that approximately 14% of infants 2 months of age were breast-fed in 1971. From that year on, they noticed an increasing trend in both the incidence and duration of breast-feeding. This occurred at all ages and in all demographic categories surveyed.

Two main factors influence the initiation of breast-feeding: maternal and family attitudes towards breast-feeding; and the attitudes of the health-care staff who come into contact with the mothers and neonates prenatally, intrapartum and postnatally.[77] Most women know that mother's milk is the best for newborns. The new parents need personal advice from the obstetrician and the health counselor, who discuss with them the option of breast-feeding.

The first few weeks of lactation usually have a critical role as regards the outcome and duration of nursing. The first feeding should be accomplished as soon as possible and whenever the infant is hungry after that. The important factors are the time of nursing, the frequency of feedings, the availability for demand feeding, the positioning during breast-feeding and the total time spent suckling a day. The more frequent the suckling, the quicker the milk production.[75] Any kind of supplementation of a breast-fed newborn is reported to delay the arrival of true milk. According to Schultzmann et al.,[101] in the unsupplemented group the true milk arrival appeared at 55 h after delivery; and in the supplemented group in which the infants received more than 300 ml water or glucose water per day it appeared at 65 h.

Most primiparous mothers require encouragement to promote milk production. The medical staff involved in the care of the new mother should therefore be well informed about the physiologic principles of lactation, the preparation of the breast, and the management of breast-feeding. In recent papers, the importance of early and repeated contacts with a health-counselor has been described, which is associated with a significant increase in breast-feeding exclusivity and duration.[102,103] Riva et al.[102] found that exclusive breast-feeding was practised by 67% of mothers who were visited 6 times, and by 50% of mothers who were visited 3 times by a health-counselor, as compared with only 12% of control mothers at 3 months postpartum.

All mothers at our Department are seen by a lactation consultant. She helps mothers in the initiation of breast-feeding after delivery and follows up frequently until their discharge from the Department. If the newborns are able to nurse, each baby's suckling effectiveness is evaluated by measurement of the infant's weight. Our data confirmed that breast-feeding mothers and their newborns spend a shorter period in the maternity ward.[103]

Neifert and Thorpe[104] reported that mothers of twins were less likely either to initiate breast-feeding in the hospital or to continue nursing at 6 months postpartum as compared with all mothers. They found that exclusive breast-feeding was particularly less common among mothers of twins. Twins can be nursed successfully, but the breasts have to be regularly and effectively emptied. The first postpartum week is an extremely critical period in the establishment of lactation. During this period, inadequate emptying of the breasts is probably the main leading cause of a milk insufficiency. Whenever any doubt exists about either twin's ability to empty the breasts regularly, the mother is advised to use an electric breast pump in order to empty her breasts fully after each nursing.

Numerous positions for the simultaneous nursing of twins have been described.[105] The practice in our hospital is to advise mothers concerning simultaneous breast-feeding, and the lactation consultant helps them find the most convenient position. The simultaneous nursing of twins has the important advantage of being time-efficient and of allowing the more vigorous baby to stimulate the milk-ejection reflex for both of them. It is still controversial whether same-breast nursing minimizes cross-contamination, but allowing the more vigorous infant regularly to suckle both breasts helps to stimulate adequate milk production bilaterally. Simultaneous nursing may generate a higher maternal prolactin response during breast-feeding, which may help to stimulate increased milk production. The main drawback of simultaneous nursing is that it does not permit the mother to give each baby her individual and undivided attention during feedings.

After Cesarean section some modifications of the early breast-feeding routines are necessary. Whenever the mother's condition permits, attempts should be made for the newborn to perform the first suckling. As about 50% of twin pregnancies result in premature delivery, the mothers need to be instructed on appropriate techniques of production, collection, maintenance and storage of her milk as soon as possible following delivery, even though her infant may not be feeding for several days or weeks.[106]

One of the major stresses for parents of twins is infant feeding in the early postpartum period.[107] Breast-feeding is often a disappointing experience because of the almost continual feeding in the first days and the fear of insufficient milk production. The use of an electric breast pump to provide the required milk yield, practical advice about breast-feeding techniques and nursing positions, and the lactation consultant's follow-up during the hospital stay should facilitate successful breast-feeding among mothers of twins.

Our study confirmed that, under optimal circumstances, the breast is capable of producing sufficient milk to nourish two, and even three infants.[108] As milk production is a very important factor in the successful nursing of twins, in the early postpartum period every effort should be made to maximize the milk supply. Once lactation is well established, most of the mothers of twins find breast-feeding more convenient than bottle-feeding.[104]

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13. ANNEX