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ORIGINAL ARTICLE

M. Hohlagschwandtner · P. Husslein · K. Klebermass
M. Weninger · A. Nardi · M. Langer

Perinatal mortality and morbidity

Comparison between maternal transport, neonatal transport and inpatient antenatal treatment

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Abstract The purpose was to assess differences in neonatal morbidity and mortality between maternally transferred, neonatally transferred and inborn neonates. We evaluated a continuous series of all antenatal transported infants (ATI, n=247) and postnatal transported infants (PTI, n=34) to the NICU and all preterm inborns (NTI, n=120) delivered at the University Hospital of Vienna. Data collected included sociodemographic, obstetrical and neonatal data. Mild neonatal morbidity was defined as RDS, BPD, ROP, PDA, NEC or IVH I–II, whereas severe neonatal morbidity was defined as the presence of PVL or IVH III–IV. Data were analyzed statistically using the Spearman correlation Coefficient, the Kruskal-Wallis test, and a multivariate model. There was a substantial gain in gestational age from transfer to delivery in the ATI group and from admission to delivery in the NTI group (2.1 and 5.6 weeks, respectively). The neonatal survival rate was 88.7% in the ATI and 97.5% in the NTI group. No neonate died in the PTI group; there was a significantly higher percentage of severe neonatal morbidity than in the ATI group (11.8% vs. 4.9%). We could not observe a significant difference with respect to the risk of death among the three study groups. There was a strong trend towards higher probability of severe neonatal morbidity in the NTI group. The risk of severe neonatal morbidity is much higher in the PTI-group (rel. risk 0.19, 0.06). Antenatal transfer guaranteed a significantly better neonatal outcome concerning severe neonatal morbidity than postnatal transport, and compared favorably with inborn admissions, even given the higher gestational age and birth weight in the NTI-group.

M. Hohlagschwandtner (✉) · P. Husslein · M. Langer
Department of Obstetrics and Gynecology,
University Hospital of Vienna, Waehringer Guertel 18–20,
A-1090 Vienna, Austria
Tel.: ++43-1-404002822, Fax: ++43-1-404002861

K. Klebermass · M. Weninger
Department of Neonatology and Intensive Care,
University of Vienna, Austria

A. Nardi
Institute for Statistics, University of Vienna, Austria

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Introduction

The rapid advances in neonatal intensive care of the past two decades have been accompanied by a decrease in neonatal mortality, particularly in settings with expertise in neonatal intensive care [4, 7, 16, 17, 23]. Neonatal mortality and morbidity rates depend not only on technological progress, but also on the way in which perinatal care is organized [5, 25]. When the needs of the mother or the unborn are beyond the scope of the current facility, antepartum maternal referral to a tertiary care center may become necessary. Perinatal regionalization integrates primary obstetric hospitals with perinatal centers containing a technologically well-equipped neonatal intensive care unit (NICU), where high risk pregnant women and critically ill newborns can receive appropriate levels of intensive care within a designated perinatal region. Several studies [1, 6, 9, 10, 13, 14, 19, 27, 29] demonstrated a significant reduction in neonatal mortality when the fetus was transferred in utero rather than after delivery. Others have failed to show significant differences between survival of antenatal and neonatal transports [2, 20, 21]. Moreover, evaluations of neonatal morbidity have shown that neonates after maternal transfer in most cases suffered less morbidity than neonatal transfers [9, 14, 20, 21]. However, the association between outcome and the mode of transport may be biased by numerous obstetric and neonatal factors if these are not properly analyzed [2, 18]. From an obstetrical point of view a prospective study is nearly impossible to design. Direct comparison of maternal and neonatal transport presents methodological problems because of potential selection bias, with decisions regarding maternal transport being made at an earlier stage and based on different factors than decisions for neonatal transport [12]. Another bias is the uneven distribution of risk factors in the groups with different modes of transport.

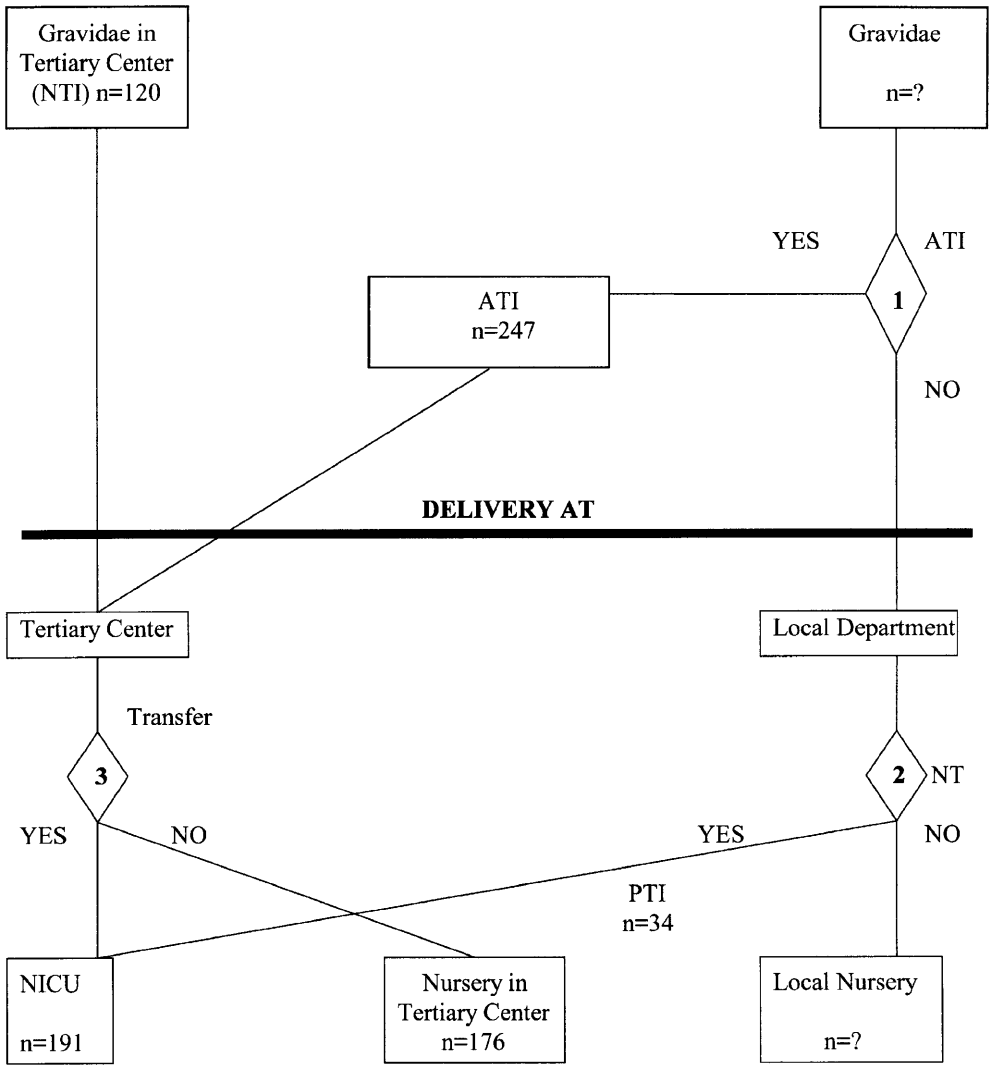

Fig. 1 Flow chart of referral decisions concerning ATI, NTI and PTI

Regarding these facts a study was performed to assess differences in mortality and morbidity between fetuses transferred antenatally for delivery at a tertiary center, infants transported to a tertiary center after delivery and infants born to mothers treated as inpatients in a tertiary center.

Material and methods

During the 2-year period from April 1, 1996 through March 31, 1998, we evaluated a continuos series of all antenatal referrals to the Department of obstetrics and Gynecology and postnatal referrals to the NICU at the University Hospital as well as all preterm inborns delivered at the University Hospital of Vienna. Antenatally transported infants (ATI, *n*=247) were defined as a referral of a pregnant women at an gestational age >24 weeks by ambulance with a paramedic from the Department of Obstetrics of a community or regional hospital to the Department of Obstetrics and Gynecology, University of Vienna. Decisions for ATI (Fig. 1, Decision 1) were made by senior consultants of 25 different departments of ObGyn with an average distance of 58.6 km to the tertiary center. Thus, the catchment area is Eastern Austria, including rural and metropolitan areas with hospitals run by different public and private organizations. Postnatally transported infants to the NICU (PTI, *n*=34) were performed within 1 week post partum after decision 2 (Fig. 1) by pediatric consultants. Non transported infants (NTI, *n*=120) were defined as all infants with a gestational age more than 24 weeks born in our perinatal center after the gravida has received inpatient antenatal treatment at the university obstetrics department.

Data collected include the referring and receiving hospitals, mothers' age and parity, indication for transfer, maternal condition, obstetric treatment, mode of delivery, and neonatal characteristics. Gestational age was based on last menstrual period, HCG testing and early ultrasound. Completed antenatal corticosteroid administration was defined as delivery after 24 h of application of 2× 12 mg of intramuscular betamethasone given at an interval of 24 h. Patients who did not meet these conditions were defined as having undergone partial antenatal corticosteroid administration. In case of gestational age >34 weeks antenatal corticosteroid administration not indicated was considered not indicated. Infants' clinical condition, length of hospital stay, and diagnosis at discharge NICU were analyzed. Weight ranges were classified according to WHO criteria [27]. In addition to mortality, complications analyzed included application of surfactant, days of oxygen therapy (infant flow), days of mechanical ventilatory therapy, Respiratory Distress Syndrome (RDS), Bronchopulmonal Disease (BPD; definition according to [24], Retinopathia of Prematurity (ROP, diagnosed by ophthalmologic examination), Intraventricular Hemorrhage (IVH) by grade (graded from ultrasound according to Papile [22], Periventricular Leucomalacia (PVL), Persistent Duc-

Table 1 Overall data: Study population, obstetrical and neonatal data. Values are given as mean (±SD) and range or percent (n)

	ATI (*n*=247)	NTI (*n*=120)	PTI (*n*=34)
Maternal age [years]	28.1 (±5.3)	29.2 (±5.7)	27.9 (±6.0)
Parity	1.8 (±1.0)	2.0 (±0.9)	1.7 (±1.1)
Gestational age at transfer [weeks]	28.5 (±4.5) (24–41)	29.7 (±5.1) (24–39)	/
Gestational age at birth [weeks]	30.6 (±5.3) (24–42)	35.3 (±4.6) (24–41)	32.2 (±2.98) (25–36)
Birth weight [g]	1502 (±929) (322–3890)	2567 (±917.4) (548–4240)	1853 (±632.4) (884–2994)
Caesarean section	74.5 (184)	50.8 (61)	81.8 (27)
Indication of transfer			
PROM	28.3 (70)	12.5 (15)	32.4 (11)
Preterm labor	22.3 (55)	32.5 (39)	20.6 (7)
Preeclampsia	9.3 (23)	15.8 (19)	5.9 (2)
Other	40.1 (99)	39.2 (47)	41.1 (14)
Antenat. corticosteroids			
Not indicated*	20.3 (50)	72.3 (86)	24.0 (6)
Indicated**	79.7 (196)	27.7 (34)	76 (28)
Completed	64.3 (126)	66.7 (22)	68.4 (13)
Partial	31.6 (62)	18.2 (6)	5.3(1)
None	4.1 (8)	15.1 (5)	26.3 (5)

* Not considered necessary because of a gestational age >34 weeks
** ATI. *n*=246, NTI *n*=119, PTI *n*=25

Table 2 Overall data: Outcome Parameters in the three study groups. Values are given as percent (n). The incidence of the detailed disability is shown in percent (n) with respect to the total number of patients

	ATI (*n*=247)	NTI (*n*=120)	PTI (*n*=34)
Died	11.3 (28)	2.5 (3)	0 (0)
Survival	88.7 (219)	97.5 (117)	100 (34)
No morbidity	81.3 (178)	97.4 (114)	82.4 (28)
Mild neonatal morbidity	13.2 (29)	2.6 (3)	5.9 (2)
Severe neonatal morbidity	5.5 (12)	0 (0)	11.8 (4)
BPD**	13.8 (34)	3.4 (4)	8.8 (3)
NEC***	4.9 (12)	0 (0)	0 (0)
ROP****	5.3 (13)	0 (0)	0 (0)
IVH******I+II	11.0 (27)	4.2 (5)	8.8 (3)
IVH III+IV	8.6 (21)	0.9 (1)	11.8 (4)
PVL*******	5.3 (13)	1.7 (2)	0 (0)

BPD bronchopulmonal disease, *NEC* necrotizing enterocolitis, *ROP* retinopathy of prematurity, *IVH* intraventricular hemorrhage, *PVL* periventricular leucomalacia

tus Arteriosus (PDA; diagnosed by pulsed Doppler sonography), Necrotizing Enterecolitis (NEC), and sepsis proven by culture. Severe congenital malformations and inborn errrors of metabolism were excluded from final analysis (*n*=9). Mild neonatal morbidity was defined as RDS, BPD, ROP, NEC or IVH I–II whereas severe neonatal morbidity was defined as the presence of PVL and/or IVH III–IV.

Data were analyzed and evaluated statistically. Means, standard deviations and ranges describe continuous variables, distributions (%) are given for categorical variables. Bivariate association was evaluated by Spearman and Pearson correlation coefficients for ordinal and continuous variables respectively. The fetal outcomes among the three study groups were compared by Kruskal-Wallis test. Multivariate analysis was limited to the babies admitted to the NICU. Two separate logistic models were fitted in order to compare the neonatal outcome among the three study groups, adjusting for gestational age antenatal corticosteroid administration. Birth weight was not included in both the models being highly correlated with gestational age (r=0.87). The probabilities of death and severe neonatal morbidity were considered and corresponding logits were formed. Due to the occurrence of monotone likelihood, Firth's procedure was applied, producing parameter estimates by means of penalized maximum likelihood. Confidence intervals are based on profile penalized likelihood [8].

Results

The three study groups were comparable regarding maternal age and parity but not regarding gestational age at delivery and mode of delivery (Table 1). There was a substantial gain in gestational age from transfer to delivery in the ATI group and from admission to delivery in the NTI group (mean gain 2.1 and 5.6 weeks, respectively). The caesarean section rate was similar in the ATI and PTI group (74.5 and 81.8%), but much lower in the NTI group (50.8%). The most common reasons for antenatal transfer were premature rupture of the membranes (PROM) (*n*=70, 28.3%) and preterm labor (*n*=55, 22.3%) (Table 1). There were other, rare indications like gestational diabetes, vaginal bleeding, fetal distress, intrauterine growth retardation (IUGR), and preexisting disease of the mother.

Overall neonatal and outcome data of the three study groups are shown in Table 2 and II. All antenatal transfers were successful in terms that no deliveries occurred en route. The mean birth weights in the three study groups

Table 3 Neonatal data of the children transferred to NICU. Values are given as mean (±SD) and range or percent (*n*)

	ATI *n*=168 (68.0%)	NTI *n*=23 (19.2%)	PTI *n*=34 (100%)
Birth weight [g]	1089 (±490) (322–2940)	1208 (±420) (548–2055)	1853 (±632) (884–2994)
Gestational age at delivery	28.1 (±3.1) (24–37)	28.3 (±3.1) (24–33)	32.2 (±2.9) (25–36)
Antenatal corticosteroids			
Not indicated*	2.9 (5)	0 (0)	24.0 (6)**
Indicated	97.1 (163)	100 (23)	76 (19)**
Completed	62.6 (102)	65.3 (15)	68.4(13)
Partial	33.7 (55)	13.0 (3)	5.3 (1)
None	3.7 (6)	21.7 (5)	26.3 (5)

* Not considered necessary because of a gestational age >34 weeks
** *n*=25; 9 missing

Table 4 Neonatal data and outcome parameters of the children transferred to the NICU in the three groups. Values are given as mean (±SD) and range or percent (*n*)

	ATI *n*=168 (68.0%)	NTI *n*=23 (19.2%)	PTI *n*=34 (100%)
Time at NICU [d]	24.7 (±35.1) (0–222)	4.6 (±13.44) (0–99)	22.9(±25.1) (1–102)
Ventilation	36.3 (89)	10.1 (12)	52.9(18)
Duration of ventilation [d]	4.5 (±10.1) (0–60)	1.2 (±4.91) (0–30)	4.0 (±5.1) (0–19)
Surfactant	24.1 (59)	3.4 (4)	24.2 (8)
Died	11.9 (20)	2.5 (3)	0 (0)
Survival	88.1 (148)	97.5 (20)	100 (34)
No neonatal morbidity	72.3 (107)	85 (17)	82.3 (28)
Mild neonatal morbidity	19.6 (29)	15 (3)	5.9 (2)
Severe neonatal morbidity	8.1 (12)	0 (0)	11.8 (4)
BPD**	20.4 (34)	17.4 (4)	8.8 (3)
NEC***	7.2 (12)	0 (0)	0 (0)
ROP****	7.8 (13)	0 (0)	0 (0)
IVH******I+II	16.2 (27)	21.7 (5)	8.8 (3)
IVH III+IV	12.6 (21)	4.4(1)	11.8 (4)
PVL*******	7.8 (13)	8.7 (2)	0 (0)

Table 5 Multivariate logistic model adjusting for gestational age and lung maturation with respect to the risk of death and the risk of severe neonatal morbidity

	Odds ratio	Confidenz interval		*p*-value
		lower 95% CL	upper 95% CL	
Outcome death				
ATI vs PTI*	1.787	0.079	40.22	0.8237
NTI vs PTI*	2.404	0.088	65.29	
Gestational age [w]	0.701	0.571	0.86	0.0006
Antenatal corticosteroids 1 vs 0*	3.520	1.395	8.88	0.0076
Outcome severe neonatal morbidity				
ATI vs PTI*	0.19	0.04	0.96	0.0650
NTI vs PTI*	0.06	0.0004	0.75	
Gestational age [w]	0.73	0.56	0.90	0.0022
Antenatal corticosteroids 1 vs 0*	1.67	0.54	4.91	0.3590

* *0* completed lung maturation or not required, *1* partial or no lung maturation

were: 1502 g in the antenatal transfer group, 1853 g in the neonatal transfer group and 2567 g in the inborn group, respectively. Neonatal outcome (survival, mild and severe neonatal morbidity, death) differed significantly (p=0.0001, Kruskal-Wallis test) between the three groups. The neonatal survival rate was 88.7% in the ATI and 97.5% in the NTI group. No neonate died in the PTI group, but the number of neonates who died before neonatal transport is unknown. There was a significantly higher percentage of severe neonatal morbidity in this group than in the ATI group (11.8% vs. 5.5%). There was no neonate with severe neonatal morbidity in the NTI group.

In order to reduce the selection bias we limited the rest of the analyses to babies admitted to the NICU to

evaluate neonatal data for a homogenous group. We only evaluated babies transferred to the NICU after decision 3 (Table 3 and 4). No neonate died in the PTI group, but there was a higher percentage of severe neonatal morbidity in this group than in the ATI group (8.1% vs. 11.8%). There was no neonate with severe neonatal morbidity in the NTI group. In the ATI group 11.9% of the babies transferred to the NICU died.

In order to compare the fetal outcome among the three study groups a multivariate analyses adjusting for gestational age and lung maturation was used. We could not observe a significant difference with respect to the risk of death among the three study groups, whereas there was a significant effect of both antenatal corticosteroid administration and gestational age on the probability of death.

There was a strong trend towards higher probability of severe neonatal morbidity in the NTI group (Table 5). The risk of severe neonatal morbidity is much higher in the PTI group (relative risk 0.19, 0.06). Whereas age is still a significant factor influencing the probability of severe neonatal morbidity, antenatal corticosteroid administration seems not to have a significant influence.

Discussion

The results of the present study show a remarkable trend towards decrease in severe neonatal morbidity when the infant was transferred antenatally rather than after delivery. Whereas several prior studies among inborn and outborn neonates demonstrated similar findings [5, 10, 15, 26, 28], others did not prove a significant difference between survival of antenatal and postnatal transports [2, 20, 21]. In two of the studies [20, 21] the neonatal mortality rate for antenatal transfers was in excess of 20%, which is higher than in the present study. Close cooperation between obstetric and neonatal services and advances in technology in both fields could be the reason for the discrepancies.

Potential selection bias must be addressed. Two situations of decision play an important role. First the decision to transfer a woman antenatally, which in our situation is made by an experienced consultant. Judging by the characteristics of the ATI group concerning gestational age, birth weight, and risk factors we can exclude a favorable selection. Second there is the decision to transfer a baby after delivery. A putative bias favoring the PTI group may be that infants born at very early gestational ages at outlying delivery hospitals were regarded as “non viable” and decided not to be transferred. Had these infants and possible perinatal deaths been included in the study, mortality and morbidity in the PTI group would have been expected to be even higher. The comparison of morbidity and mortality in groups with different modes of transport may be of limited validity because of the uneven distribution of pre-existing risk factors [18].

Concerning the three leading maternal conditions-PROM, preterm labor, and preeclampsia no evidence of overrepresentation of risk factor could be found. Prior retrospective comparisons between neonates matched for birth weight and gestational age also neglected other risk factors like preeclampsia, antepartum bleeding, PROM, and amnionitis that may affect outcome [3].

From a methodological perspective, a true prospective trial studying the effect of maternal transport versus neonatal transport would have to randomize for group allocation at the time of decision 1 (Fig. 1). Two factors kept others and us [20] from performing a prospective study meeting these obstetric requirements. First, the heterogeneous technical equipment and staff availability in 25 different departments, and second, the ethical implications of the preliminary evidence of a favorable outcome after MT. Zeitlin et al. [30] discussed the problem of selection bias for evaluation studies of perinatal transfer. They concluded, that all analyses must be adjusted for gestational age and birth weight, the two factors that most strongly influence the direction of bias and the risk of mortality and morbidity.

In our data set we found a much higher gestational age at birth in the inborn than in the maternal transfer group. As a consequence 13.8% of the neonates of the ATI groups suffered from BPD, whereas there were only 3.4% of neonates with this syndrome in the NTI group. The high rate of severe neonatal morbidity in the PTI group remains an unsettled issue. Although none of the babies died in this group, 11.8% had a severe neonatal morbidity and a total of 17.7% suffered from either mild or severe neonatal morbidity. Considering the mean birth weight of 1853 g and the fact that all severe congenital malformations and inborn errors of metabolism were excluded from final analysis, this is a surprisingly disappointing outcome. Either those children suffered from more severe conditions, or this high rate of severe neonatal morbidity would have been reduced by antenatal transport.

The analysis of the babies transferred to the NICU in the three study groups showed the discrepancy between neonatal birth weight and neonatal outcome in the PTI group compared to the other groups even stronger. Whereas the rate of IVH III–IV was similar in the ATI and PTI group (12.6 vs 11.8%), the rate of PVL was significantly higher in the ATI than in the PTI group (7.8 vs 0%). However, 11.8% of the children in the PTI group survived with severe neonatal morbidity, whereas the rate of children surviving with severe neonatal morbidity was only 8.1% in the ATI group. This is due to a higher neonatal mortality rate in the ATI group compared to the PTI group (11.9 vs 0%), where babies survived with severe neonatal morbidity because of a higher birth weight and gestational age.

According to Zeitlin et al. [30] we adjusted for the factors that most strongly influence the direction of bias and the risk of mortality and morbidity. In our data set gestational age and birth weight were highly correlated, preventing us from including both of them in a multivar-

iate model. When we adjusted for gestational age and antenatal corticosteroid administration, the difference concerning severe neonatal morbidity among the three study groups, showed a strong trend towards higher probability of severe neonatal morbidity in the NTI group. There was no significant difference of the probability of death among the three study groups. So we could prove that the risk of severe neonatal morbidity is much higher in the PTI group than in the ATI group, while the risk of death is not signifinatly higher in the ATI group than in the PTI group.

The results of the present study show that antenatal transfer guaranteed a better fetal outcome concerning severe neonatal morbidity than postnatal transport, and compared favorably with inborn admissions, even given the higher gestational age and birth weight in the NTI group. A further reduction in severe neonatal morbidity groups with high birth weight may thus be achieved by avoiding postnatal transport through better selection of patients likely to profit from antenatal transport. Audits between perinatal centers and peripheral obstetrical units could help enhance staff motivation and cooperation and, subsequently, improve perinatal outcome.

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