

Twenty-six triplet pregnancies: a retrospective analysis

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Abstract

Methods Twenty-six triplet pregnancies were delivered over 6 years.

Results Over 80% of pregnancies resulted after infertility treatment (21/26). Mean maternal age was 32. On average, the infants were delivered after 32 + 0 weeks; in 4 cases delivery was at <28 weeks. In 1 case, the leading triplet was delivered spontaneously, the remaining babies by Caesarean. Main indications for Caesarean were: premature membrane rupture, premature contractions, maternal hospitalisation for foetal lung maturation/tocolysis/antibiotics. Mean birth weights were (triplet I–III): 1,730, 1,630 and 1,550 g. Hydrops fetalis and renal agenesis resulted in IUFD of the leading triplet in two cases. All newborns were cared for by neonatology.

Conclusions Triplet pregnancies are challenging for all specialities involved. They should be managed from an early stage in cooperation with an experienced centre, allowing outpatient care for as long as possible if there are no complications. This also has a cost-reducing impact.

Keywords Triplet pregnancy · Hospitalisation · Statistical data · Multifoetal pregnancy

Introduction

There has been an increase in multiple pregnancies over the last 15–20 years as a result of the option of assisted reproductive techniques. This applies to twin as well as triplet and higher-order multiple pregnancies. According to American data, the number of triplet pregnancies increased four-fold in a survey period between 1980 and 1997 [1]. According to data from the German IVF register [2], the mean clinical pregnancy rate is 25% (per embryo transfer). The frequency of multiple pregnancies is 25%, of which 22.5% are twin pregnancies and 2.5% triplets. With the increase in multiple pregnancies, mounting challenges exist for obstetrics and neonatology in the ante- and post-natal period, as higher-order multiple pregnancies are associated with increased perinatal morbidity and mortality, even though both are on the decline [3], and higher maternal morbidity compared to twin pregnancies [4]. Not only the medical time and effort, but also the expense factor will play an increasing role in the future in view of the background of the diagnosis related groups (DRGs), from the decision to go ahead with assisted reproduction to the partly intensive medical care required during hospitalisation of the mother and babies.

This publication aims to describe the perinatal and neonatal data of triplet pregnancies which were under our care, and also outlines the costs of reproductive procedures and hospitalisation.

Methods

Twenty-six triplet pregnancies were cared for and delivered at the University Hospital for Women in Tuebingen, Germany, over a 6-year period.

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The median maternal age was 33 years (22 min–37 years max), 20 (77%) of the 26 women were nulliparous. Conception occurred spontaneously in five cases (19%), the remaining 21 (81%) triplet pregnancies resulted after infertility treatment. The results of the different methods (in vitro fertilisation/embryo transfer, intracytoplasmic sperm injection, hormone treatment and intrauterine insemination) are shown in Table 1.

The mothers were treated as outpatients for as long as possible, i.e., they received individual prepartal management, and no predetermined gestational age was given for hospitalisation. A complete 32 weeks gestation was aimed for at delivery, the minimal target was 28 completed weeks of pregnancy. Hospitalisation was recommended in the 32nd week where the pregnancy had been uncomplicated up to that point.

Biometry and precision diagnostics with Doppler sonography (Arteria umbilicalis and A. cerebri media, and where necessary additionally ductus venosus in the case of suspected artery perfusion disturbance; and uterine Doppler flow measurements in the case of hypertension problems) were performed between 20 and 22 weeks gestation and then every 4 weeks, and in some cases, in-between by the mother's local practice obstetrician and gynaecologist. If the chorionicity could not be positively determined sonographically, this was carried out postpartally, as all placentas from triplet pregnancies are examined by the Pathology Department. Cervical length measurement was performed using transvaginal ultrasound if manual palpation showed cervical shortening or the patient reported contractions. As a result of persistent contractions the measurement was repeated accordingly. During the inpatient stay, CTGs (cardiotocography) were performed two to three times daily, according to noticeable problems.

Premature contractions, even without confirmation of cervical shortening, were treated with intravenous β_2 -sympathomimetics (Partusisten®) over at least 24 h. This was accompanied by intravenous magnesium sulphate 50% for

persistently severe symptoms in one case and pathological uterine Doppler measurements with gestosis in two cases. Vaginal smears were taken on admission and where contractions were present, and subsequently treated locally (vaginally) after verification of the causative organism without raised infection parameters, otherwise a resistance-checked systemic antibiotic treatment followed. In all but one case (emergency section due to footling presentation), induction of foetal lung maturation was commenced with 2×12 -mg betamethasone (Celestan®) within 24 h in the 32nd week of pregnancy at the latest. In the case of threatened premature delivery (rupture of the membranes, bleeding, increasing contractions), induction was repeated. So-called maximum therapy was performed in relevant cases from 23 + 5 weeks gestation in agreement with the neonatology team and the parents.

The leading triplet was delivered spontaneously in one case; all other babies were delivered by Caesarean section. Two emergency sections were performed as a result of rupture of the membranes with footling presentation.

Complications and diagnoses occurring in the neonatal period which required appropriate treatment and hospitalisation of the neonate are categorised in Table 2 with the corresponding number of cases. There was one case of intrauterine foetal death (IUFD), and another infant died peripartally during Caesarean section as a result of renal agenesis. The total number of infants born alive was 76. One case of sepsis was diagnosed by haemoculture. Cardiopulmonary adaptation disorders improved relatively quickly, mostly after a few hours or days and are classified separately here under apnoea/bradycardia syndrome and respiratory distress syndrome (RDS).

Eight infants were categorised as eutrophic. Two of these infants were the only eutrophic siblings in their triplet set and in both of the remaining triplet sets, all three newborns were eutrophic. Hypotrophy was confirmed with a weight <10th percentile.

Foetofoetal transfusion syndrome (FFTS) occurred in one triplet pregnancy, with one donor and two acceptors.

Table 1 Method of conception, maternal age and perinatal results in relation to chorionicity

	Monochorionic (<i>n</i> = 3) (12%)	Dichorionic (<i>n</i> = 5) (19%)	Trichorionic (<i>n</i> = 18) (69%)
Maternal age (median) (years)	35	29	33
Gestational age (median) (weeks)	32	30	33
Birth weight (median) (g)	1,610	1,455	1,750
Conception (<i>n</i> = 26)			
Spont. (<i>n</i> = 5) (19%)	1	1	3
IVF/ET (<i>n</i> = 9) (35%)	1	3	5
ICSI (<i>n</i> = 3) (12%)	–	–	3
IUI (<i>n</i> = 5) (19%)	1	1	3
OS ^a (<i>n</i> = 4) (15%)	–	–	4

^a OS = only ovarian stimulation

Table 2 Complications and diagnoses in the neonatal period requiring treatment and hospitalisation (total $n = 76$)

Problem	Diagnosis with number of cases (n) and (%)
Infection	Unspecified infection (9) (11.8%) Rota enteritis (4) (5.3%) <i>E. faecalis</i> (3) (3.9%) Amnion infection syndrome (2) (2.6%) Sepsis (2) (2.6%) Necrotising enterocolitis (1) (1.3%)
Metabolism/ acid/base	Hypoglycaemia (8) (10.5%) Hyperbilirubinaemia (23) (30.3%) Acidosis (2) (2.6%) Anaemia (13) (17.1%)
Cranium	Posthaemorrhagic hydrocephalus (1) (1.3%) Subependymal bleeding (6) (7.9%) Retinopathy I–II (7) (9.2%) Retinopathy III (2) (2.6%)
Lungs	Apnoea/bradycardia syndrome (28) (36.8%) Tachypnoea (4) (5.3%) Fluid in the lung (11) (14.5%) RDS (21) (27.6%) Isolated apnoea (3) (3.9%) Cardiopulmonary adaptation disorder (10) (13%) Emphysema (1) (1.3%)
Intestine	Intestinal perforation (2) (2.6%) Adhesion ileus (1) (1.3%)
Heart/circulation	Stenosis of the aortic isthmus (1) (1.3%) Ductus arteriosus persistens (3) (3.9%) Hypotension (7) (9.2%) Atrial septal defect (1) (1.3%) Pulmonary artery stenosis (2) (2.6%)
Other	Inguinal hernia (2) (2.6%) Deafness (1) (1.3%) Umbilical hernia (1) (1.3%)

Results

Over 80% of the triplet pregnancies investigated resulted after infertility treatment (21 out of 26 cases) with a mean maternal age of 32 years (median, 33 years; min, 22 years; max, 37 years). The duration of hospitalisation before Caesarean section was 20 days on average, median 17 days (min 7 days not including the two emergency section cases, max 47 days). The maternal duration of stay in hospital after delivery was a mean of 8 days, median 8 days (3–13 days) (Table 3). Cerclage according to McDonald was performed on one patient at 20 + 4 weeks gestation due to cervical insufficiency. The infants were delivered after a mean of 32 + 0 weeks gestation (median, 32 + 6 weeks; min, 24 + 6; max, 35 + 6 weeks). In 4/26 (15.4%) cases, delivery was performed before 28 weeks, in 18/26 cases (69%), the 32nd week could be completed. In one case, the leading triplet was born spontaneously after unremitting contractions at 25 + 1 weeks (♀, 745 g), and 2 days later at 25 + 3 weeks gestation, the siblings were delivered by

Table 3 Duration of hospitalisation of mother and newborn

	Mean	Median	Min–max
Mother			
Hospitalisation before section ($n =$ days)	20	17	7–47
Hospitalisation after section ($n =$ days)	8	8	3–13
Newborn			
Hospitalisation ($n =$ days)	37	27	Max, 163

Caesarean section after bleeding and the start of amniotic infection syndrome (AIS). An emergency section had to be performed in two cases as a result of footling presentation of the leading triplet after premature rupture of the foetal membranes.

Eighteen of the triplet pregnancies investigated were trichorial (69%), three monochorial (12%) and five dichorial (19%).

Also listed in Table 3 is the duration of hospital stay of the newborns on the neonatal intensive care unit. This was a mean of 37 days (median 27 days, max 163 days). As the infants were immediately transferred to another hospital in some cases, no minimum length of stay is given.

The main indication for admission to the obstetric ward with consecutive Caesarean section was premature labour or premature rupture of the foetal membranes with threatened AIS. Intrauterine growth restriction (IUGR) of one triplet was diagnosed by ultrasound in two cases at 31 + 5 weeks and 32 + 0 weeks, respectively, and symptoms of pre-eclampsia were present in three patients (29 + 5 to 30 + 0 weeks). FFTS with pathological Doppler measurements, an oligohydramnios also with pathological Doppler measurements, placenta praevia totalis as well as increased vaginal bleeding were diagnosed in one pregnancy, respectively. A summary is shown in Table 4. Two deliveries were performed as planned at 35 + 6 and 34 + 2 weeks gestation, respectively, and the patients could be monitored as outpatients up to the date of surgery.

Premature contractions [15/26 women (58%)] occurred at a mean gestational age of 29 + 3 weeks (median, 30 + 2; min, 23 + 0; max, 32 + 1), premature rupture of the membranes occurred on average after 30 + 0 weeks (median, 29 + 3; min, 27 + 0; max, 34 + 4).

The fundamental therapeutic measures during maternal hospitalisation were induction of foetal lung maturation (25/26) and antibiotic and tocolytic therapy, alongside monitoring as an inpatient. In 11/24 (46%) (excluding both emergency sections), resistance tested antibiotics were administered intravenously or orally after vaginal swab culture, according to the severity of symptoms and infection parameters. In cases where premature rupture of the

Table 4 Admission/section indications, total ($n = 26$)

Premature contractions ($n = 15$) (58%)	
Gestational age (weeks)	
Mean	29 + 3
Median	30 + 2
Min–max	23 + 0 to 32 + 1
Premature rupture of the membranes ($n = 9$) (35%)	
Gestational age (weeks)	
Mean	30 + 0
Median	29 + 3
Min–max	27 + 0 to 34 + 4
IUGR	$n = 1$
Pre-eclampsia	$n = 3$
FFTS and pathological Doppler measurements	$n = 1$
Oligohydramnios and pathological Doppler measurements	$n = 1$
Placenta praevia totalis	$n = 1$
Uterine bleeding	$n = 1$
Cervical insufficiency: cerclage	$n = 1$

membranes was confirmed, the pregnancy was prolonged in all cases under antibiotic cover and control of infection parameters.

Premature contractions were treated in 14 cases with intravenous β_2 -sympathomimetics (Partusisten®) over a mean of 14 days (median 11 days), and three cases were treated additionally with intravenous magnesium-5-sulphate for 2–9 days. In one case, oral tocolysis was carried out primarily with Partusisten® for 16 days. Tocolysis was consecutively altered to the oral route in four patients (20–40 days) as the contractions ceased under i.v. tocolysis.

The mean weight of the living infants was 1,654 g (median 1,730 g; 600–2,510 g), four babies had an APGAR score of <7, one baby had an arterial umbilical cord pH value of <7.1 (7.05).

Table 5 Duration of selected intensive neonatal treatments in days

	Mean	Median	Min–max
CPAP [triplet pregnancies ($n = 18$), newborns ($n = 43$)]	11	1	1–64
Intubation [triplet pregnancies ($n = 7$), newborns ($n = 14$)]	8	2	1–31
Phototherapy [triplet pregnancies ($n = 12$), newborns ($n = 21$)]	1.4	1	1–3
Antibiotics [triplet pregnancies ($n = 17$), newborns ($n = 31$)]	6.2	5	1–36

Table 6 Hospitalisation costs of the mother and newborns according to DRG-case-list

	Maternal hospitalisation costs (Euros) ($n = 26$)	Triplet hospitalisation costs (Euros)		
		Infant 1	Infant 2	Infant 3
Min	2,832.10	636.46	51.64	671.83
Max	25,835.93	90,982.26	95,828.42	91,811.66
Mean	8,319.75	22,743.46	19,885.26	22,837.38
Median	6,911.33			

Stillborn infants are not accounted for

One IUFD as a result of hydrops fetalis occurred at 25 + 8 weeks gestation before hospital admission. The leading triplet in another pregnancy died during Caesarean section (performed on the grounds of unceasing contractions) as a result of a prenatally diagnosed nonviable renal agenesis.

The main measures taken on the neonatal ward were based on the problems shown in Tables 2 and 5.

Phototherapy was performed in 12 cases, $n = 21$ babies (min 1 day, max 3 days). Ventilation using continual positive pressure (CPAP) was necessary after 18 triplet pregnancies in 43/76 (56.6%) of newborns, and intubation was needed after seven pregnancies in 14/76 (18.4%). The duration of the procedures is shown in Table 5. A total of 31 infants received antibiotics as single or combination treatment, 21 infants were supported with theophylline or caffeine.

An anus praeter had to be created in two cases as a result of intestinal perforation. This was reversed before discharge in the infant with adhesion ileus at 121 days after birth, and the infant with necrotising enterocolitis was discharged with an anus praeter. The infant with post-haemorrhagic hydrocephalus improved after repeated decompression puncture. Laser treatment was performed in the cases with retinopathy degree 3, which led to remission.

The costs of hospitalisation, calculated on the basis of the revenues according to the list of cases for mother and triplets, are listed in Tables 6 and 7. It should be noted that the given costs for infants one to three must be totalled for each set of parents.

Discussion

Spontaneous multiple pregnancies with more than two foetuses are rare [5, 6].

As a result of advancing maternal age at first birth, increased incidence of infertility resulting in the greater use

Table 7 Expected costs of infertility treatment, not including costs of additional services such as serology, etc.

Treatment	Cost (Euros)	Drugs (Euros)
Preliminary examination and counselling of the father	ca. 60	
Insemination	ca. 160	+ca. 70–700
IVF	ca. 1,250	+ca. 1,000–3,000
IVF/ICSI	ca. 2,150	+ca. 1,000–3,000
Anaesthesia	ca. 130	

of assisted reproductive technology (ART) and ovulation inducing hormones has resulted in an increase in the number of higher-order multiple pregnancies in developed countries over the last few years. It has been estimated that in industrialised countries, 75% of triplet pregnancies and higher-order multifoetal pregnancies follow assisted reproductive technologic advances [7]. Our collective had a mean maternal age of 32 years, and 80% of the presented triplet pregnancies resulted after infertility treatment, which is confirmed by the international trend. Imaizumi [8] investigated the twin and triplet rates from 1972 to 1996 in 17 countries and demonstrated a significant increase in all countries, primarily from Scandinavia. The most important factor for the outcome of these pregnancies is premature delivery, which can increase the incidence of neonatal morbidity and mortality and result in a greater risk of permanent disability or early death [9].

The main aim of the care concept of triplet pregnancies is prolongation of the gestation time until as close as possible to the calculated due date (term). An early diagnosis and management plan is therefore important, and is unproblematic in the case of assisted reproduction, as multifoetal pregnancies are expected to occur. However, spontaneous triplet pregnancies can rarely occur, and early diagnosis is essential; usually vaginal ultrasound reveals the correct number of gestational sacs with sufficient accuracy. In previous studies, up to 20% were undiagnosed before delivery, and as a consequence perinatal mortality was 50% among that group [10]. The rate of spontaneous triplet pregnancies in our study was 19% and correlates with published data where a range from 12 [11] to 31% [12] was given.

Studies which investigated the outcomes of triplet pregnancies monitored as inpatients or outpatients have shown that the group monitored as inpatients had outcomes of a higher gestational age and birth weight and less foetal growth retardation [13, 14].

The question of whether hospitalisation or an outpatient care concept should be favoured has been time and again the subject of controversial discussion. According to an early study by McFee [15] patients were hospitalised for the remainder of pregnancy as soon as the diagnosis was

confirmed, whereas others suggested hospitalisation as being essential from the beginning of the third trimester [16]. The argument for a prolonged hospital stay can be seen in the delay of the onset of labour, a better placental blood flow, the relief of discomfort and availability of immediate medical treatment when necessary. Other authors found that prolonged hospitalisation did not significantly increase the length of gestation [5, 17].

In our care concept, the mothers were cared for as outpatients for as long as possible, i.e., individualised prepartal management with no fixed gestational age for hospitalisation. Nevertheless, in our centre we recommend hospitalisation in the 32nd week of gestation. Some centres advocate hospitalisation from the 24th week, after the foetus has reached a viable age in order to be able to therapeutically intervene at any time if necessary [18].

We aim for a gestational age of 32 completed weeks at delivery; the minimum target is 28 complete weeks. The mean gestational age at delivery in our study was 32 + 0 weeks which is similar to the rate reported by others [19]. In our view, prolonged hospitalisation without clear obstetrical problems may lead to poor compliance; however, immediate transfer to hospital is indicated at the onset of complications. Cooperation with the local practice obstetrician enabled nonproblematic pregnancies to be monitored as outpatients where possible, with the advantage of high acceptability from the mothers. It is important to note that this concept is only possible as a result of a network of competence consisting of practice-based colleagues as well as close cooperation with the prenatal/neonatal centre in our region. We recommend prolonged bed rest and appropriate thromboprophylaxis for all mothers who are being monitored as outpatients.

Biometry and precision diagnostics with Doppler sonography (Arteria umbilicalis and A. cerebri media, and additionally ductus venosus in the case of suspected arterial perfusion disturbance; and uterine Doppler flow measurements where necessary in the case of hypertension) were performed between 20 and 22 weeks gestation, and every 4 weeks thereafter, then in-between if necessary by the local practice-based specialist.

In the collectives presented here, 8% of the cases had neonatal cerebral haemorrhage, which is comparable with other international work [3, 20]. The feared complication of necrotising enterocolitis was seen in one baby; however, the above-mentioned authors report a higher occurrence of 4% for this serious condition [3]. Fourteen babies required intubation by a neonatologist, which is equivalent to the intubation rate of other groups, (19% in Missfelder-Lobos et al. [18]). The essential factor for adequate lung function is prompt induction of foetal lung maturation, and according to our concept, maximum treatment is applied from 23 + 5 weeks gestational age, in agreement with the neonatology

team and the parents. Induction of foetal lung maturation is always performed under inpatient conditions.

Cervical insufficiency is one of the commonest triggers for premature delivery in higher-order multifoetal pregnancies, and early diagnosis and prophylaxis is therefore of great importance. A triplet pregnancy is not automatically associated with cervical incompetence. Transvaginal cervical length measurement is performed as for single pregnancies, when vaginal palpation shows a shortening of the cervix, or the patient reports contractions. The measurement is repeated according to further progression of the contractions. A cervix length of 25 mm in the 23rd week has a premature delivery risk of 50% before 33 weeks gestation for a triplet pregnancy [21]. A cervix length of less than 25 mm from the 15th up to the 20th week of pregnancy is associated with a premature delivery risk of 100% before 28 weeks gestation [22]. Up to now, there are no standard statements on cerclage indications for triplet pregnancies [23]. The use of prophylactic cerclage without the presence of cervical insufficiency in triplet pregnancies is not clearly proven [23–25] and gestation is not invariably prolonged by cervical cerclage. Routine cerclage in triplet pregnancies has been recommended by some authors [6, 10, 26, 27]. We would like to point out that the studies available in the literature are those where the average duration of gestational age of those who had cerclage was slightly less than those who had none, and the difference is mostly not statistically significant, which is not surprising when taking into consideration the facts mentioned above. Prophylactic cerclage is not favoured in our centre, and its use in one case was as a result of shortening of the cervix to 22 mm in the 23rd week of pregnancy.

It should be noted that despite the uncertain data concerning surgical prophylaxis of premature delivery, a risk-adapted, non-invasive diagnosis of cervical insufficiency can facilitate individualised pregnancy care.

It is a fact that multifoetal pregnancies place an important burden on medical care resources and carry higher social and economic costs than singleton pregnancies. Women with triplet and higher-order multiple pregnancies are associated with higher risks of maternal morbidity and obstetric complications such as diabetes mellitus, gestation hypertension, eclampsia, abruptio placentae and premature rupture of the membranes [4]. Therefore, couples must be provided with objective information before starting an IVF cycle, a treatment that has to be paid privately to a certain extent in some countries. Professional societies should highlight the problem and make suitable recommendations. It could easily be forgotten that the costs do not only include IVF therapies but also the mother's pre- and post-natal hospital stay and treatment, and the post-natal care for the triplets which has to be extensive in most cases, as

shown in this article. An overview of the expected treatments and costs is given in Tables 5 and 6 where we try to highlight not only the costs for different IVF options, but also the figures for post-natal care and hospital stay. The most common treatments for newborn triplets are also presented in this series. It should be pointed out that the data presented are partly based on the various in-house rates of the University hospitals and the respective current DRG-case-lists.

Conclusion

Triplet pregnancies are a challenge for the specialist doctor responsible for monitoring the pregnancy, the maternity and neonatology units, and should be managed with close cooperation between all concerned. They should be monitored from an early stage in cooperation with an experienced centre, thus allowing outpatient care for as long as possible if there are no clinical complications. This also has a cost-reducing impact on the relevant DRGs.

Conflict of interest statement None.

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