REVIEW ARTICLE

Perinatal Problems in Multiple Births

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SUMMARY

Background: Multiple pregnancies have become more common in the industrialized world because of rising maternal ages and advances in reproductive medicine.

Methods: Selective literature review.

Results: Multiple pregnancy carries a higher risk of prematurity, intrauterine growth restriction, and prenatal death, as well as elevated risks to the mother including preeclampsia, diabetes, and hemorrhage during delivery. Genetic tests and ultrasonography are the most important tests for monitoring during pregnancy. Ultrasound aids in the detection of the feto-fetal transfusion syndrome and in the determination of zygosity.

Conclusions: The care of women with multiple pregnancies requires the collaboration of specialists in prenatal medicine, obstetrics, and neonatology as well as a properly functioning integration of outpatient and inpatient care.

Cite this as: Dtsch Arztebl Int 2010; 107(38): 663–8
DOI: 10.3238/arztebl.2010.0663

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Multiple pregnancies have become more common in the industrialized world due to advances in reproductive medicine. As a result, obstetric care for women with multiple pregnancies and neonatal care for multiple babies have become more intense and challenging. Specialists in prenatal medicine, obstetricians, and neonatologists in hospitals and in private practice are faced with a whole array of challenges.

In order to facilitate competent collaboration at these interfaces, the authors compiled key messages in this review article on the basis of scientific and clinical insights and a selective literature search including established national (1) and international (2) guidelines.

Frequency

Worldwide, the frequency of multiple births is subject to vast variations. Hellin's rule of 1895 for predicting the rates of multiple births has more or less retained its validity to this day. If the rate for twins is 1 : 85, the rate for triplets is $1 : 85 \times 85$, and for quadruplets, $1 : 85 \times 85 \times 85$. In early pregnancy, these rates are much higher. Boklage described the development of 325 twin pregnancies; 19% of these resulted in twin births at term, 39% in singleton births, and 43% in stillbirths. He calculated a probable conception rate for twins of 1 : 8 (3).

In most European countries, the rate of twins fell in the 1960s from about 12/1000 pregnancies to 9.5/1000 pregnancies. From the early 1980s, numbers rose again, to 12/1000 and, by about 1990, to 13 to 14/1000 pregnancies. While the trend in the 1960s and 1970s was primarily a function of the changed age structure of pregnant women (mostly an increase in pregnancies in younger women, later an increase in pregnancies in women older than 35), the rise after 1990 is regarded mainly as a consequence of developments in reproductive medicine (assisted reproductive technologies) (4). Induced ovulation and in vitro fertilization (IVF) are considered to be the main causes underlying the increase.

The occurrence of multiple births in the mother's family is more important for the frequency of dizygous twins than such an occurrence in the father's family. Women who themselves were one of a pair of dizygous twins had twins in about 2% of cases. By contrast, only 1% of women whose husbands were dizygous twins gave birth to twins themselves (e1).

Duration of pregnancy

The average term of pregnancy is notably shorter in multiple pregnancies *(Table)* (e2). In 1987, the rate of

TABLE

Average duration of multiple pregnancies

Type of pregnancy	Weeks
Singleton	39
Twins	36
Triplets	32
Quadruplets	30

premature births for twins (<37+0 weeks' gestation) in the US was 44.5% compared with 9.4% for singletons (5). Presumed reasons for the shorter pregnancies include the mechanical stress on the cervix, the fact that uterine circulation is reduced relative to the weight of fetus and placenta, and the relatively reduced placental function. Further, the maturation of the gap junctions—owing to raised estrogen activity and prostaglandin synthesis—and the relative drop in progesterone activity in multiple pregnancies seemed to be relevant for the shortened term.

Prenatal ultrasonography

Perinatal mortality has fallen thanks to the increased detection rate of multiple fetuses. In Germany, ultrasonographic investigations in all pregnant women, according to maternity guidelines, have resulted in a situation where almost all multiple pregnancies are detected. Early detection is important for management of the pregnancy, for monitoring mother and babies, as well as for intrapartum management and to prepare the parents.

Standardized curves can be used to diagnose multiple pregnancies, determine gestational age, and monitor fetal growth. It is important to point out that fetal growth curves for head diameter and femur length do not differ statistically for singletons and twins (e3, e4). A differentiated examination for malformations is indicated.

Further, investigations specific to multiple pregnancies are important, to determine zygosity and placentation.

Determination of zygosity: the basics

Monozygous twins

Monozygous twins originate from the division of a single embryo. The estimated rate is 4 monozygous twins in 1000 births. Embryo-fetal mortality in monozygous twins is higher than in dizygous twins and singletons. The rate of serious malformations in monozygous twins is reported at 2.3%, compared with 1% in singletons. The rate of slight malformations is 4.1% for monozygous twins, compared with 2.5% in singletons. Statistically less favorable results have been noted for monochorionic, monoamniotic twins; pregnancies of 2 girls have yielded better results in this context (e5). If embryo splitting occurs within 5 days after fertilization, dichorionic-diamniotic twins will result (30% of cases of monocygotic twin pregnancies). Embryo splitting between the 5th and 7th days of fertilization will result in monochorionic-diamniotic twins (70% of cases). In 1% of cases, embryo splitting occurs after day 8, resulting in monochorionic-monoamniotic twins. Conjoined twins are the consequence of incomplete division on days 15 or 17 after fertilization. In Europe, about 1 in 33 000 births results in conjoined twins (e6).

Dizygous twins

Fertilization of 2 different ova from 2 different follicles results in dizygous twins. Follicular growth is regulated by the gonadotropins. It has been stated that higher concentrations of follicle stimulating hormone (FSH) result in higher numbers of dizygous twins. The production of FSH is influenced by periods of light and darkness. In Scandinavia, a larger number of dizygous twins is said to be conceived in July, and a lower number in January. The probability of having dizygous twins rises with a maternal age up to about 39 years and drops afterwards. It also falls in periods of malnutrition (e7).

Higher multiples

Multiple pregnancies with higher numbers of fetuses can arise from the fertilization of 1, 2, or more ova and division of 1 or more fertilized ova, with the result of a multiple pregnancy that is simultaneously dizygous and monozygous.

Knowing the zygosity is important to correctly assess risk factors during the pregnancy. One possible consequence, for example, is a difference in growth in a scenario of deficient intrauterine development of one twin, or in the feto-fetal transfusion syndrome; the latter, however, affects exclusively monozygous twins.

Ultrasonography is the indispensable diagnostic tool for detecting zygosity. At 10 to 15 weeks of pregnancy, in dichorionic pregnancies, the lambda shape ("twin peak") of the ovum's separating membrane is visible at the placental insertion *(Figure 1)*. Separate placentas or a (fused) placenta, as well as membrane thickness (monozygous twins have a thin membrane, dizygous twins have a thick membrane) are important findings.

The physiological disappearance of an embryo or early fetus from a multiple pregnancy (vanishing twin) leads to resorption, an empty amniotic sac, or a fetus papyraceus. Clinically, this process is usually noticed only as a hemorrhage from the uterus.

Prenatal genetic diagnostic testing

Since the 1970s, women have been offered genetic diagnostic tests; this obviously also applies to multiple pregnancies.

Amniocentesis in the second trimester and chorionic villus sampling are the methods of choice. The

complication rate for amniocentesis in multiple pregnancies has been reported to be 5 times higher than for singleton pregnancies (0.6% to 1%) (e8).

Selective feticide

The most common and most important risks for multiple pregnancies are the shortened pregnancy term and the increased risks for the mother: for triplets, 20% pre-eclampsia, 30% anemia, 35% postpartum hemorrhage; for quadruplets, 32% pre-eclampsia, 25% anemia, 21% postpartum hemorrhage (6, e9, e10).

Selective reduction of higher multiple pregnancies to twins is undertaken with the aim of reducing the risks to the mother's or fetuses' lives. Several methods are in common use—hysterotomy, cardiac puncture, intracardiac air injection, or injection of cardiotoxic substances—on the basis of experiences with indicated feticide in a scenario of malformations of one of the fetuses (7).

Working groups that have often been faced with the problem of selective feticide believe that transabdominal intrathoracic injection of potassium chloride into embryos aged 11 to 12 weeks is the most effective method (8). In many authors' opinion, the gains for the surviving fetuses justify the procedure (9, e11). When injecting monozygous twins, it needs to be borne in mind that injecting a cardiotoxic substance into one twin may result in the substance transfusing into the other twin, which constitutes a substantial risk. In 10% of pregnant women, complete loss of pregnancy after selective feticide is to be expected.

Selective feticide is extremely problematic and should be avoided by using appropriate artificial reproductive techniques.

The feto-fetal transfusion syndrome (FFTS)

Monozygous, monochorionic twin pregnancies are characterized by interfetal vascularization at the placental level, arterio-arterial and veno-venous anastomoses on the chorionic plate, as well as arterio-venous shunts in the cotyledons (e12). These form the basis for a redistribution of the blood, whose causes have thus far remained unexplained. One possible explanation is that the placental circulation of the donor fetus has increased vascular resistance, owing to placental insufficiency, which causes redistribution of the blood. The acceptor twin will grow larger (9, e13) and develop polyglobulinemia, and/or hypervolemia (acceptor) as well as polyhydramnion, whereas the donor fetus will experience intrauterine growth restriction, anemia, and hypovolemia and develop oligohydramnion. A diagnostic clue is provided by the association of intrauterine weight differences (of more than 20%) and the difference in volume of amniotic fluid seen on ultrasonography (polyhydramnion in the acceptor, oligohydramnion in the donor). The volume of amniotic fluid may decrease to the point where the donor twin, as the small twin, is pressed into the membrane of the ovum (stuck twin) *(Figure 2)*.

Figure 1
Dichorionic twin pregnancy at 15+3 weeks' gestation, with discordant growth; arrow: lambda sign

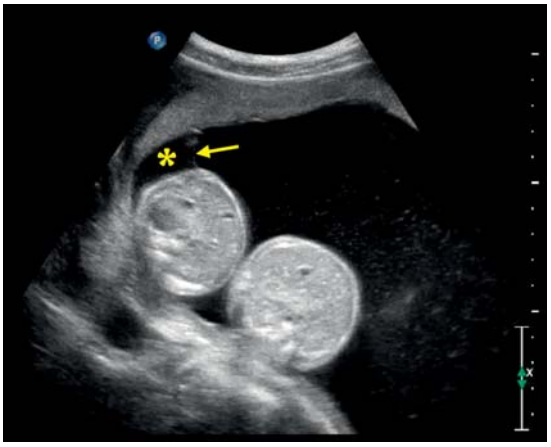

Figure 2
Monochorionic twin pregnancy at 20+2 weeks' gestation and mild feto-fetal transfusion syndrome; arrow: amniotic membrane; star: amniotic cavity of the donor twin

Death rates in FFTS are high (56% to 100%). In 3% to 5% of cases, fetal death occurs in the uterus (10). After the death of one twin, the so called twin embolization syndrome develops in up to 14% of cases (e14). The result is arterial hypotension and embolization of thromboplastic material from the dead fetus into the surviving fetus. The consequences are disseminated intravascular clotting and/or infarction with severe neurological damage, among others (11), so any intervention should take place before an intrauterine fetal death occurs.

Treatment options for FFTS include:

- Repeated amniocentesis and drainage of amniotic fluid; although the pathogenetic mechanism of this treatment is not clear, repeated amniocentesis is an effective method (e15, e16).
- Elective coagulation of the interfetal vascular links is the logical and most stringent therapeutic option (e15, 12, 13).

Intrauterine death

Antepartum death of one or more fetuses in multiple pregnancies is common (1% to 5% of all multiple pregnancies) (e17). In addition to the emotional and

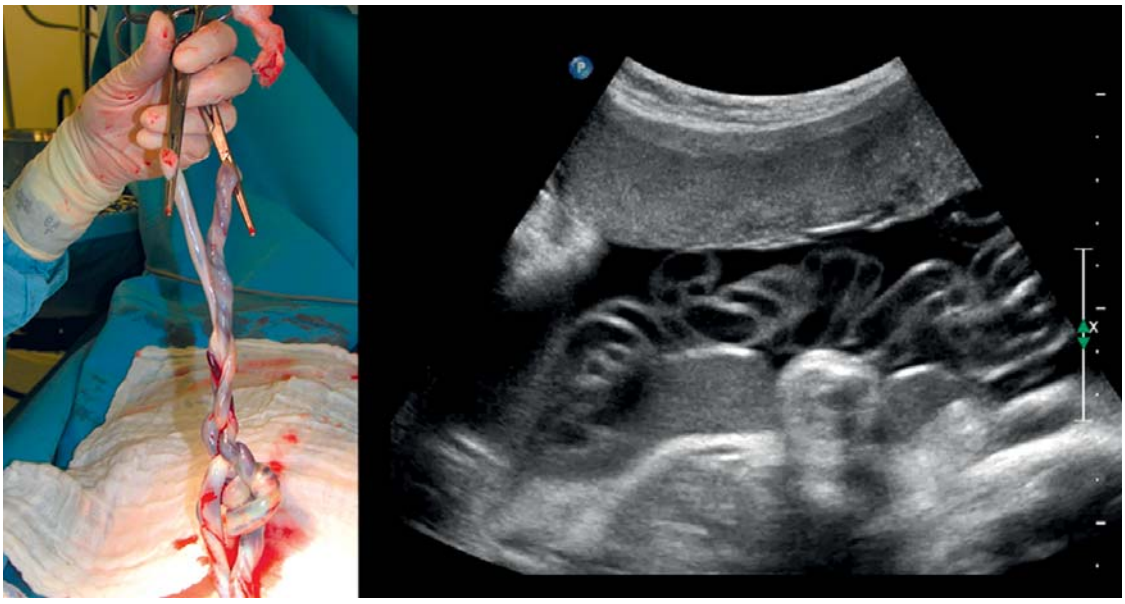

Figure 3:
Umbilical cord problems in a monoamniotic twin pregnancy; antepartum umbilical diagnostic evaluation by ultrasonography and intraoperative situation

* We thank Professor Karim Kalache, Department of Obstetrics, Charité University Hospital, Berlin Mitte, for the images.

psychological burden for the parents, particular attention should be paid to the state of the surviving fetuses (e18).

In monochorionic fetuses with a dead sibling, the surviving fetuses can be expected to have a high rate of neurological impairments. These are thought to be caused by embolization of thrombogenic material from the dead fetus into the surviving one(s).

Reducing the risk of premature birth

The fact that multiple fetuses are at higher perinatal risk than singletons can be explained with the high rate of premature births and the higher rate of babies whose intrauterine growth is restricted. The rate of complications as a result of immaturity and underweight for twins is 40%. The reported rate of premature birth for twins is 30%—3 to 5 times higher than that of comparable cohorts of singleton pregnancies. In addition to early diagnosis of multiple pregnancies, early "unfit to work" notes (at 20 weeks' gestation) and physical rest are recognized as preventive measures (e19, e20); neither inpatient treatment without further risk, nor preventive cerclage (e21), nor prophylactic tocolysis (e22) are any longer among the recommended procedures.

Intrauterine growth restriction

In multiple pregnancies, several factors contribute to intrauterine growth restriction, whose frequency in this setting is reported to be 60% (e23): the mother's nutritional status, reduced uterine blood flow, anomalies of the umbilical cord, placental nutrient transport capacity, position of the placenta, unequal proportions of the placental mass per fetus, and the feto-fetal transfusion syndrome (FFTS).

Determining the gestation of delivery in multiple pregnancy

To avoid intrauterine fetal death near term, a common recommendation these days is that of arranging delivery at 38 weeks' gestation. In women who are planning to have a vaginal birth, the usual procedure is to administer prostaglandin for cervical ripening. The following indications usually mean that at this gestational age, caesarean section as the primary indication is undertaken:

- Triplets or higher multiples
- The preceding sibling is in breech or transverse position
- Estimated weight on ultrasonography of the second twin of more than 500 g above that of the first twin
- Twins with an ultrasound guided estimated weight below 1800 g
- Monoamniotic twins (C-section in 34+0 weeks' gestation) *(Figure 3)*.

Neonatal morbidity and mortality

In the literature, the data on whether a multiple pregnancy per se increases neonatal morbidity and mortality are inconsistent. This is partly due to different study populations, different study designs (prospective or retrospective data collection), and different time periods (before or after introduction of surfactant therapy and of intrauterine laser ablation). Neonatal morbidity and mortality rise with the number of fetuses in a pregnancy, but simultaneously the term of the pregnancy decreases so that problems associated with premature birth gain importance. Comparisons between singletons and multiple siblings always need to consider the gestational age, birth weight, and sex (14, e24).

Neonatal mortality

Compared with singletons, twins develop intrauterine growth restriction after about 32 weeks' gestation, and triplets after 29 weeks' gestation (15). In multiple fetuses with a birth weight below the 10th percentile, neonatal mortality is increased. Once gestational age, extent of growth restriction, and sex have been adjusted for, however, neonatal mortality in twins with fetal growth restriction is similar to that of singletons (e25, 15, 16). In this context, twins' discordant weight seems to have an important role. Increased neonatal mortality has been described for a weight difference of more than 25%. Primarily the smaller twin is affected, especially if s/he has a birth weight below the 10th percentile (17–19). If the weight difference is great, however, the larger twin also seems to have a higher mortality risk (e26, 20).

An increase in neonatal mortality has been described for monochorionic twins compared with dichorionic twins, especially if one twin underwent intrauterine death (21, 22).

Data differ with regard to the question whether the sequence of birth has an influence in the prognosis. In very small twins (birth weight below 1500 g), an increased mortality risk has been described for the second twin, independently of the delivery mode (e27). Others have not found any such differences (15).

Neonatal morbidity

Neonatal respiratory distress syndrome

The frequency of neonatal respiratory distress syndrome increases with the number of siblings (23% in triplets, 65% in quadruplets, 75% in quintuplets), however, this is in a scenario of decreasing gestational age (e27, e24). The risk of respiratory problems is higher in boys and in the second twin (23, e28). A complete cycle of prenatally administered steroids reduces the incidence of neonatal respiratory distress syndrome for multiple or singleton births (e27). However, a decreasing effect of prenatal lung maturation has been described for increasing plurality (24).

Cerebral impairments

The frequency of cerebral impairments is strongly influenced by gestational age and birth weight, for singletons as well as for multiple fetuses. But chorionicity and intrauterine fetal death of a sibling also play a large part. A meta-analysis of 28 studies found that the risk of neurological damage in the surviving twin is 4 times higher in monochorionic than in dichorionic twins (22).

Necrotizing enterocolitis

The risk of necrotizing enterocolitis (NEC) in monochorionic twins was found to be increased by a factor of 4 (3.8% versus 0.9%) after gestational age and birth weight had been adjusted for (21).

Long term results

Children from multiple pregnancies have an increased risk of neurological abnormalities. Parents should be informed about this risk, and appropriate regular postnatal examinations should be organized (25).

Conflict of interest statement
The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

Manuscript received on 12 May 2009, revised version accepted on 29 October 2009.

Translated from the original German by Dr Birte Twisselmann.

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KEY MESSAGES

- Multiple pregnancies are on the increase.
- Risks for the baby—such as premature birth, growth restriction, and intrauterine death—are higher, as are risks for the mother (such as pre-eclampsia, gestational diabetes, and hemorrhages).
- Ultrasonography is important to monitor the pregnancy, to detect growth discrepancies, zygosity, and in the feto-fetal transfusion syndrome.
- Neonatal morbidity of multiple fetuses are characterized by neonatal respiratory distress syndrome, necrotizing enterocolitis, and cerebral damage.
- Providing care for women with multiple pregnancies constitutes a challenge for specialists in prenatal medicine, obstetricians, and neonatologists.

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