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Twin-to-twin transfusion syndrome (TTTS) pathogenesis, diagnostics, classification and treatment options

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ABSTRACT

Twin to twin transfusion syndrome (TTTS) belongs to the group of multiple monochorionic pregnancies complications. The pathogenesis of this syndrome is not entirely clear, however there is a correlation between the location of the placentas trailers of umbilical cord, and the tendency to its occurrence. Moreover it is characterized by the existence of vascular connections in common placenta. It results in hemodynamic disorders, which consist in full leakage from one fetus called a "donor" to another fetus called the "recipient". Hypotony, hypotrophy, hypovolemia, anemia and oliguria are being developed in donor's as the result. Whereas the second fetus is under the risk of hypertrophy, hypertension, hypervolaemia, polycythemia and polyhydramnios. TTTS is a complication occurring in 10-15% of all monochorionic pregnancies. If no treatment is performed the fetal mortality occurs in 60-100% of cases. Diagnosis of twin-to-twin transfusion syndrome is based on ultrasound assessment of amniotic fluid volume. The conditions of diagnose are: the occurrence of common chorioid for both twins in the first trimester and measurement of the maximum fluid pocket. The main and preferred therapeutic method is fetoscopic laser coagulation of vascular connections. Treatment depends on the age of the fetus. The most important factor affecting prognosis is early diagnosis of TTTS and consultation at the reference center of fetal therapy.

Keywords: Perinatology, multiple pregnancy, prenatal diagnosis, twin-to-twin transfusion syndrome

1. INTRODUCTION

Due to statistics the incidence of twin pregnancies is increasing worldwide. This increase is related to many factors. These include advanced maternal age and more frequent use of assisted reproductive technology (ART). Moreover increasing popularity of ART enhances the possibility of an incident of multiple pregnancies too. All this is associated with greater demand on the transfer of 2 or 3 embryos in order to achieve higher pregnancy rate. The others factors which increase the risk of multiple pregnancy are: mother's ethnicity, previous history of pluriparity (>3 births), previous history of twinning, maternal height and weight, breast-feeding, season of the year, a large number of sexual relations and period after discontinuation of oral contraception [1-3]. Interestingly, the genetic predisposition to dizygotic twin pregnancies has also been confirmed. Probably this tendency is inherited by female fetuses as an autosomal recessive trait associated with chromosome 3. The paternal factor is also significant in the familial occurrence of twins and is most likely associated with a greater number of spermatozoa in the ejaculate and prolonged fertilizing capacity of the sperm. [4]

In a multiple pregnancy the same complications as in a single pregnancies may occur, however their prevalence is much higher, therefore multiple pregnancies are a group at a higher risk of complications for both mother and fetuses. The risk is higher in case of the monochorionic twin pregnancies than in dichorionic pregnancies and of course singletons. The most frequent and the most important complication of a multiple gestation is its premature termination. According to statistics, more than 50% of twins are born before the 37th week of intrauterine life. Furthermore these complications can be divided into maternal and fetal and neonatal. The first ones are: anemia (Hb <10 %), hypertension, gravidarum, intrahepatic cholestasis, premature rupture of the membranes, premature separation of the placenta and placenta previa. Fetal and neonatal complications are premature delivery intrauterine growth restriction (IUGR), breathing disorders, polyhydramnios, central nervous system bleeding, umbilical cord prolapse and umbilical cord collisions by monoamniotic twins. [5-7]

2. TYPES OF TWINNING

One of the types of multiple pregnancy is a twin pregnancy in which two fetuses develop in the uterus. For this pregnancy type, we can distinguish dizygotic (DZ) so called fraternal twins, which are created as a result of fertilization of separate eggs by two separate sperm. It is being created from the very beginning by two separate and genetically different embryos.

Born newborns are not similar to each other. Factors leading to such a type of pregnancy are: polyovulation, superfecundation and superfetation. Another type of twin pregnancy is pregnancy with monozygotic (MZ) or identical twins. It is a result of the fertilization of a single egg by the sperm. The zygote, created through the process of fertilization, is divided into two genetically identical embryonic structures. This process usually takes place between 14th to 16th day of fertilization. [4, 8] (Figure 1)

The division time of the primarily single zygote in the case of monozygotic twins determined whether, we can distinguish dichorionic diamniotic, monochorionic diamniotic and monochorionic monoamniotic pregnancies. Dichorionic diamniotic pregnancy affects approximately 25-30% of monozygotic twins, in which the division of a single zygote initially took place in a period shorter than 4 days after fertilization.

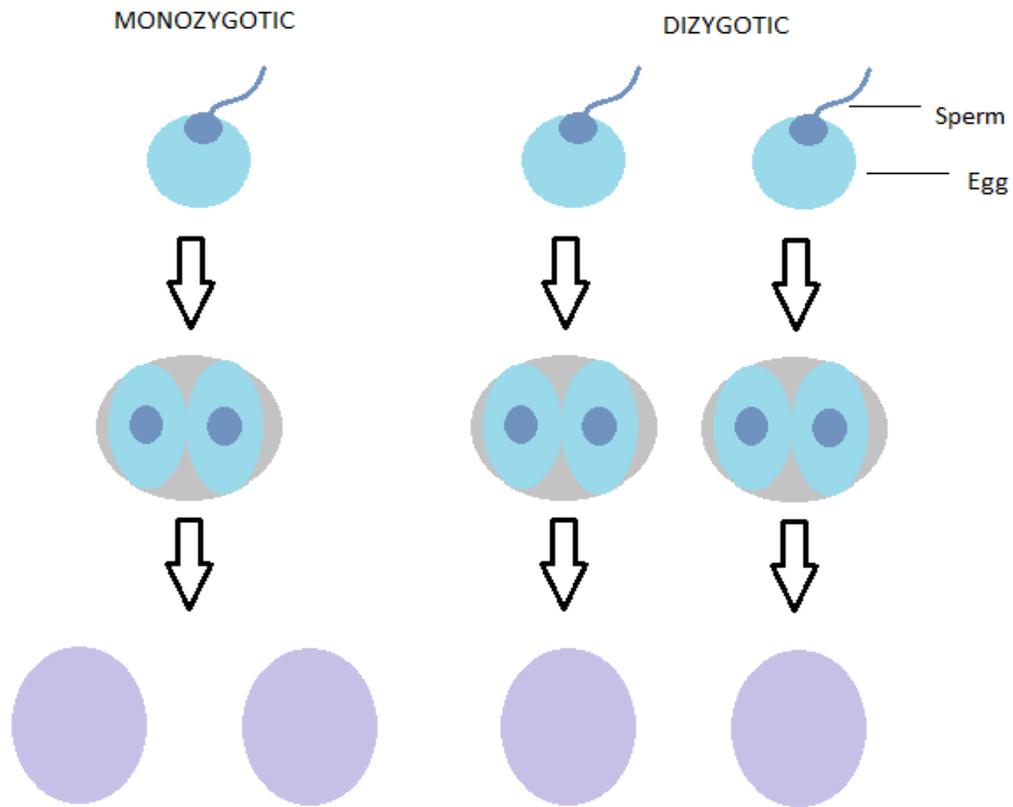


Figure 1. Zygote development in monozygotic and dizygotic twins.

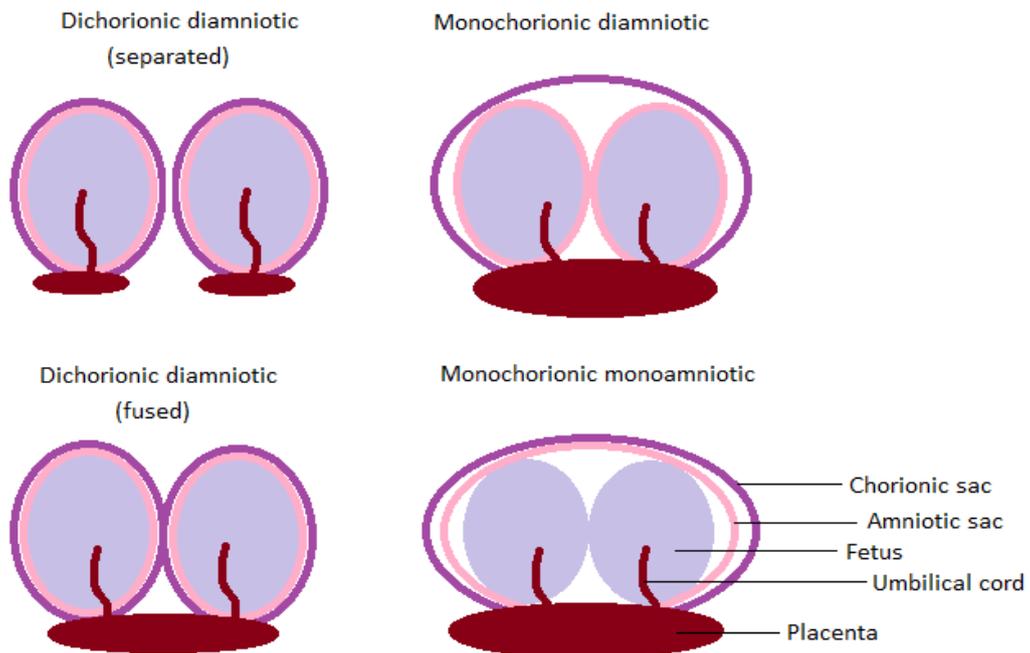


Figure 2. Various types of chorionicity and amniocity in twins.

It also occurs in all dizygotic twins pregnancies. If blastocyst implantation occurred in other areas of the uterus, there are two placentas but if the distance between them is not sufficient, there is one placenta. If the division of the zygote is performed between 4 to 7 day after fertilization, we are dealing with a monochorionic diamniotic pregnancy. It is related to 70-75% of monozygotic pregnancies. In the case of dividing the zygote after the 7th day after fertilization, the monochorionic monoamniotic gestation develops. It constitutes about 1-2% of monozygotic pregnancies. Each of the mentioned pregnancies carries various complications that may threaten both the life of the mother and the fetus. [4,8] (Figure 2)

3. TWIN TO TWIN TRANSFUSION SYNDROME

3. 1. Patogenesis

Twin to twin transfusion syndrome is a condition that can occur as a complication of a multiple monochorionic pregnancy. The occurrence probability of the TTTS is estimated at 10% to 15% of monochorionic diamniotic pregnancies. [9]

This syndrome may develop at any stage of pregnancy, however, most cases are diagnosed in the second trimester of pregnancy. The majority of cases are in stage III according to the Quintero scale. TTTS results from hemodynamic disorders that arise from intertwin vascular anastomoses in a common placenta. These anastomoses occur in every monochorionic placentas, however TTTS does not develop in every single case of monochorionic gestation. It can distinguish several kinds of anastomoses: arterio-arterial (A-A), veno-venous (V-V) and arterio-venous (A-V). A-A and V-V anastomoses located on the surface of the placenta, are more superficial and have potential for bidirectional flow. A-V anastomoses are named as deep anastomoses settled via capillaries within the cotyledon deep in the placenta. Furthermore they are more likely to cause an unidirectional blood flow between two fetuses. This condition can lead to hemodynamic unbalance between fetuses and final development of TTTS. Moreover this hemodynamic unbalance can be compensated by both V-V and A-A anastomoses, but TTTS placentas are reported to have more V-V than A-A anastomoses. This difference may contribute to the development of TTTS. The absence of arterioarterial anastomoses is also related with higher mortality (42% vs 15%), but the presence of these connections does not always prevent the occurrence of TTTS. The first effect of unidirectional blood flow between the fetuses is the change of blood circulation volume in both twins. One of them is called a donor because it becomes hypovolaemic and the other which becomes hypervolaemic is the recipient. Disorders like this lead to the progressive development of hypotonia, hypotrophy, anemia and oliguria (caused by oligohydramnios) in the donor's organism. In contrast to the first one, in the second fetus organism, which is the recipient, hypertrophy, hypertension, hypervolemia, polycythemia and polyhydramnios are developing. Some of these characteristics are subsequently used in ultrasonography to determine the stage of TTTS using Quintero scale. [10-12]

3. 2. Diagnostics and classification

According to the recommendations of the Polish Gynecological Society, the purpose of ultrasound examination before 10th week are: visualization and localization of the fetal egg, assessment of the pregnancy bubble presence, evaluation of the embryo presence, evaluation of the yolk sac and the reproductive organ assessment. In this study, you can also determine the

number of embryos, chorionicity and amnion sacs. The symptom helpful in the diagnosis of chorionicity of the placenta is the Lambda sign, which is, the visualization of the placental tissue that is tangent between the fetal membranes, characteristic for a dichorionic pregnancy.

The Tau sign, which determines the direct connection between the membranes and the bearing surface, takes the shape of the letter "T" which means the monochorionic pregnancy. To estimate the number of chorionicity, the increased attention to the presence and thickness of the septum should be also paid. The lack of a membrane separating the fetuses means monochorionic pregnancy. The thin barrier <2 mm determined a monochorionic pregnancy. Septum >2 mm is an evidence of dichorionic pregnancy [4, 13].

The purpose of further ultrasound examinations between 11th and 14th week, is preliminary assessment of fetal anatomy and chromosomal aberration markers. In further ultrasound examinations between 18th and 22th and between 28th and 32th week, the fetus is assessed in detail for the fetal organs to exclude congenital malformations and estimate the approximate fetal weight based on biometric parameters [3].

In case of monochorionic diamniotic or monochorionic monoamniotic pregnancy occurrence, it is recommended to monitor it every 2 weeks in the case of complications such as Selective Intrauterine Growth Restriction (sIUGR), Twin for Twin Transfusion Syndrome (TTTS), Twin Anemia Polycythemia Sequence (TAPS) and Twin Reversed Arterial Perfusion (TRAP). Additionally in the case of a monochorionic monoamniotic pregnancy, diagnostics of an umbilical cord collision and incompletely separated fetuses occurrence is performed. [14]

The diagnosis of TTTS in addition to the already confirmed monochorionic gestation is based on the ultrasound measurement of the maximum vertical pocket (MVP). It is used for the diagnosis of oligohydramnios (maximum vertical pocket of < or = 2 cm) in one amniotic sac and polyhydramnios (maximum vertical pocket of > or = 8 cm) in the second amniotic sac. Determination of the stage of advancement of TTTS is also based on hemodynamic measurements using pulsed Doppler in the tricuspid valve, ductus venosus, umbilical vein and in the umbilical artery. The Quintero scale includes 5 stages of clinical severity, ranging from a mild disease to a severe form that results in the death of one or both twins. [15, 16]

The first stage of advancement is characterized by the presence of the oligohydramnios/polyhydramnios sequence. The lack of the possibility to visualize the bladder in the donor fetus qualifies the pregnancy to stage 2. An indispensable element of the third level of advancement is the detection of at least one of the pathologies in the ultrasonography with pulsed Doppler such as umbilical vein pulsation, tricuspid valve or ductus venosus backflow, lack of or diastolic backflow in the umbilical artery. The atypical third stage (3a) defines the coexistence of circulatory disorders with the bladder present in the ultrasound examination of the donor. The next 4th stage of advancement includes pregnancies with generalized swelling of at least one fetus. The last, fifth degree on the Quintero scale is characterized by the intrauterine demise of one or both fetuses. [16]

3. 3. Treatment options

TTTS is a serious complication of multiple monochorionic pregnancy and in the cases of being untreated, is associated with high perinatal mortality of fetuses and newborns (which oscillates between 60-80%). In contrast, twins which have survived are exposed to serious cardiac, neurological and developmental disorders. [17, 18] Moreover cardiac disorders are a major cause of deaths in TTTS recipients in the postnatal period. The most common heart abnormalities of recipients include cardiomegaly, biventricular hypertrophy and

atrioventricular valve regurgitation. In contrast cardiac complications of donors are less impactful, with exception of increased afterload. The necrosis of cerebral white matter may occur as a neurological complication. [19] Regardless of the advancement level, therapeutic options depend (to a large extent) on the age of pregnancy. Therapeutic options include conservative proceedings, amnioreductions, septostomy, fetoscopic laser coagulation of anastomoses and selective fetoreduction. [20]

Amnioreduction is a removal procedure of varying volumes of amniotic fluid by amniocentesis. Amnioreductions can be performed singularly as a first-line procedure, especially in TTTS I and TTTS II, or in series when MVP is greater 8cm. These procedures can be performed starting from the 14th week of pregnancy and also after the 26th week of pregnancy, especially if the mother has a breathing disorder or there is uterine contractile function resulting from polyhydramnios. Amnioreduction can hypothetically relieve intra amniotic pressure and inside placental vessels, which can potentially facilitate blood flow through the placenta and possibly reduce the incidence of pre-term labor associated with polyhydramnios. Serial amnioreductions may result in complications such as premature rupture of membranes (PROM), preterm labour, placental abruption, intrauterine fetal infection or even demise. Amnioreductions as therapeutic methods are related to the average survival rate estimated at about 50%, and in large registers even 60-65%. [11, 15, 20]

Another method of treatment is fetoscopic laser coagulation, which can be performed between 15th and 26th week of pregnancy and in all stages of advancement. In this procedure laser fibre is inserted through a fetoscope into the uterine cavity and next into the recipient's sac with the use of ultrasound guidance. Then a selective or non-selective separation of the placenta into two areas is performed. Such separation is possible thanks to the use of photocoagulation of communicating vessels which connect the two fetuses. The aim of this process is to dichorionize a monochorionic placenta. Initially, all the vessels crossing the separated membranes were coagulated.

Nowadays in most centers selective coagulation of arterio-arterial, veno-venous and arterio-venous anastomoses is preferred. In the case of non-selective coagulation, at least one fetus survived in 60-65% of pregnancies. In contrast, selective coagulation increased the survival of at least one fetus to 70-75%. Complications that may occur after treatment are: premature rupture of membranes (PROM), spontaneous preterm labor and intrauterine death of one or both twins. According to some research the overall survival rate following laser therapy was notably higher than the amniodrainage (66% vs 57%). Moreover serious neurological complications occur less often after fetoscopic laser therapy than after amnioreduction (5% vs 15%). [10, 20, 22, 23]

Septostomy is an intentional the continuity breakage of membrane, which separate both twins. The aim of the treatment is to eliminate the pressure difference between amniotic sacs, which is caused by occurrence of polyhydramnios and oligohydramnios. This procedure is beneficial for both twins.

The "donor" twin receives circulatory volume which can improve kidney perfusion and thereby urine production. It also prevents the inflow of water from motherly compartment. It is beneficial for the "recipient" twin. Septostomy may also be carried out during amnioreduction, which according to some authors (only in this case) results in a good treatment effect. The discontinuity of the separating membranes exposes the patient to the complications of an iatrogenically monoamniotic pregnancy such as amniotic band syndrome and umbilical cord collisions. [24, 25]

It is possible to consider selective termination of the one twin in selected cases with a very bad prognosis such as severe or lethal anomalies of one twin, contraindications for laser ablation such as maternal nonacceptance of laser or impossible visualisation of the inter-twin membrane on the placenta. There are many selective termination methods such as occlusion of targeted fetal's vessels or the umbilical cord. These procedures can be performed with the use of the sclerosing substances such as ethanol or thrombogenic coils or embucilate gel in embolization techniques. However these methods can indicate threatening complications such as coil migration or return of partial flow within targeted vessels. The second method is mechanical cord occlusion which depends on simple ligation of the selected fetal umbilical cord with the help of the endoscopic technique. [26, 27]

In 2007, a Cochrane study was carried out to estimate which method of the twin-to-twin transfusion syndrome treatment improves fetal, childhood and maternal outcomes. The results were obtained on the basis of the Cochrane Pregnancy and Childbirth Group's Trials Register and the Cochrane Central Register of Controlled Trials in which randomized and quasi-randomized studies of amnioreduction, laser coagulation and septostomy were found. The study also contained the comparison of their outcomes. Additionally three others trials such as the 2004 Eurofetus trail, the 2005 Moise trail and the 2007 NIH trial were included in the study.

The following results of endoscopic laser surgery and amnioreduction comparison were observed. Higher number of terminations of pregnancy were needed in the amnioreduction group than in the laser photocoagulation group (16% vs. none, one trial, 284 fetuses). Moreover the overall death (48% vs. 59%, two trials, 364 fetuses), perinatal death (26% vs. 44%, one trial, 284 fetuses) and neonatal death (7.6% vs. 26%, one trial, 284 fetuses) were lower in the laser photocoagulation group in comparison the amnioreduction group.

The occurrence of the neurological complication such as periventricular leukomalacia was more frequent in the cases of infants treated with amnioreduction than in those treated with laser photocoagulation. The comparison of septostomy to amnioreduction revealed no meaningful variances for fetal death (13% vs. 12.5%), one infant death (40% vs. 50%), both infants death (20% vs. 22%), neonatal death (26% vs. 24%) and overall death (30% vs. 36%). However septostomy was associated with significantly higher need for a combination of therapies, which follow the initial procedure. On this basis, it was suggested that endoscopic laser photocoagulation should be considered in the treatment of all TTTS stages, to improve perinatal and neonatal outcome. Whereas amnioreduction should be considered as a treatment option in those cases of contraindications or other exclusion reasons for laser photocoagulation. [24]

4. CONCLUSIONS

There are many complications that may develop during the course of a multiple pregnancy. One of them which is described in this publication is the twin-to-twin transfusion syndrome which exact mechanism of pathology is unfortunately not fully recognized.

The complications of the syndrome can be dangerous and threaten pregnancy. Therefore women which have been diagnosed with TTTS should be surrounded by advanced prenatal care in specialized centers with the highest degree of referentiality. In highly specialized centers appropriate treatment may be undertaken, depending on the age of pregnancy, the level of advancement and other factors that affect treatment and prognosis.

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