Diplomarbeit

Maternal complications and hemodynamic effects following intrauterine interventions for complicated monochorionic pregnancies – a retrospective study

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Graz, am 26.03.2018 *Angela Valentina Zenz eh.*

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Zusammenfassung

Fragestellung:

Das feto-fetale Transfusionssyndrom (twin-to-twin transfusion syndrome = TTTS) ist eine Komplikation monochorialer Zwillingsschwangerschaften, deren Grundlage oberflächliche Gefäßanastomosen an der Plazenta zwischen den beiden Feten sind. Über diese Anastomosen kann es zu signifikanten Volumenverschiebungen zwischen den fetalen Kreisläufen kommen, welche zu stark unterschiedlichen Fruchtwassermengen, schweren hämodynamischen Komplikationen und letztlich zum intrauterinen Fruchttod eines oder beider Kinder führen können. Die einzige kausale Behandlung eines fortgeschrittenen TTTS ist die intrauterine Laserkoagulation der plazentaren Gefäßanastomosen. Bei sehr ungünstiger Prognose kann auch ein Nabelschnurverschluss (cord occlusion) durchgeführt werden.

Einen wesentlichen Bestandteil der Therapie stellt die Fruchtwasserentlastung (Amniondrainage) am Ende der Eingriffe dar. Bei größeren Drainagevolumina wurden allerdings auch mütterliche hämodynamische Veränderungen beobachtet. Betroffene Schwangere wiesen klinische Zeichen der Hämodilution, Hypovolämie sowie beeinträchtigter Nierenfunktion auf. Die zugrundeliegende Pathophysiologie ist noch nicht abschließend geklärt.

Im Rahmen der vorliegenden Arbeit sollten diese Phänomene untersucht werden und mütterliche Kreislaufparameter sowie allgemeine maternale Komplikationen nach intrauterinen Eingriffen analysiert werden.

Methodik:

Es handelt sich um eine retrospektive Datenanalyse von 80 intrauterinen Eingriffen bei komplizierten monochorialen Zwillingschwangerschaften an der Universitätsklinik für Frauenheilkunde und Geburtshilfe Graz zwischen 2010 und 2016. Hauptzielgrößen waren Drainagevolumen, maternales Hämoglobin, Hämatokrit, Albumin, Blutdruck, Herzfrequenz, Diuresevolumen, die prä- sowie postoperativ untersucht wurden. Zusätzlich wurden interventionsbezogene Komplikationen erfasst.

Ergebnisse:

Das mittlere Drainagevolumen betrug rund 1400 ml (0 - 4040 ml). Es konnte ein signifikanter Abfall der maternalen Hämoglobin-, Hämatokrit und Albumin-Werte zwischen der prä- und postoperativen Messung dargestellt werden. Weiter zeigten sich auch mütterliche Kreislaufparameter wie Blutdruck und Herzfrequenz im postoperativen Verlauf signifikant verändert. Ein Zusammenhang zwischen Drainagevolumen und den Veränderungen von Hämoglobin, Hämatokrit und Albumin wurde nachgewiesen. Die maternale Diureseleistung zeigte ebenfalls einen signifikanten Abfall zwischen sechs bis zwölf Stunden postoperativ. Der mütterliche Body-Mass-Index zeigte eine signifikante negative Korrelation zur postoperativen Blutdruckveränderung. Ein signifikanter Zusammenhang zwischen der Höhe des Drainagevolumens und dem Auftreten von pPROM als eine der wichtigsten Komplikation bei intrauterinen Eingriffen war darstellbar. Die mütterliche Gesamtkomplikationsrate bei intrauterinen Zwillingseingriffen lag an unserem Zentrum bei rund 4%.

Schlussfolgerung:

Schwere mütterliche Komplikationen bei intrauterinen Zwillingseingriffen sind sehr selten. Weit häufiger erscheinen hämodynamische Veränderungen aufzutreten, die derzeit noch Fragen nach den exakten pathophysiologischen Grundlagen offen lassen.

Abstract

Purpose:

Twin-to-twin transfusion syndrome (= TTTS) is a complication of monochorionic twin pregnancies on the basis of placental anastomoses between the two fetuses. Through these anastomoses significant volume shifts may arise leading to discordant amniotic fluid levels, hemodynamic changes, stepwise deterioration and eventually intrauterine death (IUFD) of one or both fetuses. The only causative treatment of TTTS consists of intrauterine laser photocoagulation of the placental anastomoses or selective feticide by cord occlusion in the case of unfavorable prognosis to save at least one child.

An important part of intrauterine interventions is the amniodrainage at the end of the procedure. Following large-volume drainage maternal hemodynamic changes have been reported. These included signs of hemodilution and hypovolemia as well as impaired kidney function. The underlying pathophysiology is currently not entirely clear.

Methods:

This study is a retrospective data analysis of 80 intrauterine interventions in complicated monochorionic twin pregnancies performed at the Department of Obstetrics and Gynecology at the Medical University of Graz between 2010 and 2016. Maternal parameters such as drained volume of amniotic fluid, hemoglobin, hematocrit, albumin, blood pressure, heart rate and volume of diuresis pre- and postoperative and intervention-related complications were analyzed.

Results:

The average drainage volume was 1400 ml (range 0 - 4040 ml). A significant decrease of maternal hemoglobin, hematocrit and albumin between pre- and postoperative could be described. Maternal systolic and diastolic arterial blood pressure and heart rate showed a significant change postoperatively. A correlation between volume of amnioreduction and change of hemoglobin, hematocrit and albumin could be demonstrated. The maternal diuresis showed a significant decrease between six and twelve hours postoperatively. There was a significant negative correlation between maternal BMI (Body-Mass-Index) and postoperative

arterial blood pressure changes. A significant correlation between amount of drained amniotic fluid and pPROM (preterm premature rupture of membrane) as one of the most important complications of intrauterine interventions could be illustrated. The total rate of maternal complications following intrauterine interventions was 4% (n=3).

Conclusion:

Severe maternal complications due to intrauterine interventions are extremely rare. Hemodynamic changes occur far more frequently, which still keep the exact pathophysiological background open at present.

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Glossary

AA anastomosis	artery-to-artery anastomosis
AD	amniodrainage
Alb	albumin
AT-2	angiotensin II
AV anastomosis	arteriovenous anastomosis
BMI	Body-Mass-Index
BPdia	diastolic arterial blood pressure
BPsys	systolic arterial blood pressure
CI	confidence interval
CO	cardiac output
DCTA	dichorionic triamniotic (triplets)
GA	gestational age
Hb	hemoglobin
Hkt	hematocrit
HR	heart rate
IUTx	intrauterine transfusion
MCDA	monochorionic diamniotic twins
MVP	maximum vertical pocket
Na	sodium
NT	nuchal translucency
pPROM	preterm premature rupture of the membranes
RAS	renin-angiotensin system
SD	standard deviation
SEM	standard error of the mean
TAPS	twin anemia-polycythemia sequence
TPR chart	temperature, pulse and respiration chart
TRAP sequence	twin reversed arterial perfusion
TTTS	twin-to-twin transfusion syndrome
VCI	velamentous cord insertion
VV anastomosis	vein-to-vein anastomosis

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1 Introduction

1.1 Twin-to-twin transfusion syndrome (TTTS)

Twin-to-twin transfusion syndrome is a complication of monochorionic diamniotic (MCDA) twin pregnancies that occurs in 10-15% (1). The syndrome shows an imbalance in blood shift between the twins based on angioarchitecture of the single placenta. Without treatment TTTS has a mortality rate of about 90% (2), which demonstrates that TTTS can progress to a highly severe complication.

1.1.1 Pathophysiology of TTTS

MCDA twins share a common placenta. In virtually all cases, intertwin anastomoses are present on the placental surface, thus connecting the two fetal circulations. There are three main types of anastomoses: arteriovenous anastomoses (A-V) enabling exclusively unidirectional flow from artery to vein, and artery-to-artery (A-A) as well as vein-to-vein (V-V) anastomoses, allowing bidirectional blood flow. TTTS arises as a result of unbalanced blood volume shifting through these anastomoses. The likelihood of unequal volume sharing is increased if there are several A-V anastomoses in the absence A-A or V-V anastomoses which usually are protective, acting in a compensating way (1, 3-5). The hypovolemic twin is defined as donor twin, while the recipient twin suffers from volume-overload. The resulting imbalance of blood flow leads to a discordance of amniotic fluid, usually between 16 and 26 weeks of gestation (5, 6), which becomes apparent as an oliguria and oligohydramnios in the donor and polyuria and polyhydramnios in the recipient (7). As a consequence of the decreased blood flow, the renin-angiotensin system (RAS) is activated in the donor twin, thus increasing tubular reabsorption and releasing angiotensin II (AT-2) to raise arterial blood pressure. However, elevated AT-2 may worsen oliguria and oligohydramnios by decreasing renal and placental perfusion, which may additionally contribute to growth restriction (2). Additionally, renal tubular hypoplasia and atrophy may occur as a result of inadequate renal

perfusion. Persistent oliguria subsequently leads to oligo-/anhydramnios and the typical appearance of a "stuck twin" (1, 4).

In the recipient twin the production of cardiac atrial natriuretic peptide is increased because of volume overload. This leads to a raised glomerular filtration rate, a lowered tubular reabsorption and suppression of antidiuretic hormone. All these aspects together increase the urine production of the recipient twin leading to a polyhydramnios (2). In the recipient twin, RAS is not downregulated but rather elevated, an effect potentially caused by transfer of RAS effectors via placental anastomoses from donor to recipient twin. As a result of the volume overload the recipient has a high risk of cardiovascular anomalies, such as "ventricular hypertrophy, atrioventricular (8) valve regurgitation and increased pulmonary outflow and aortic outflow velocities" (2).

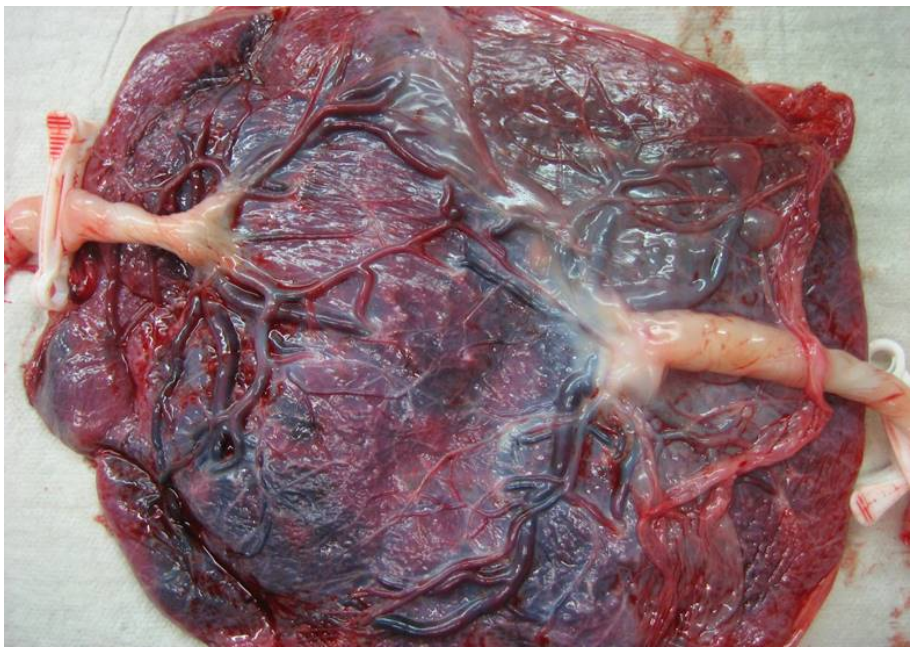

Fig. 1: Intertwin anastomoses on the placental surface.

1.1.2 Staging of TTTS

In clinical practice the staging system by Quintero et al is the most widely used and accepted. This staging system contains 5 stages, which are assessed by ultrasound examination. Stage I presents with oligohydramnios in the donor twin and polyhydramnios in the recipient twin, defined by a maximum vertical pocket (MVP) of < 2 cm in the sac of the donor > 8 cm in the sac of the recipient twin. In stage II the bladder of the donor twin is empty and cannot be visualized. Stage III is defined as abnormal Doppler wave forms appearing in the donor's and/or recipient's umbilical artery/vein and ductus venosus. Stage IV represents fetal hydrops, stage V intrauterine fetal death in one or both twins (7, 9, 10).

However, stages do not necessarily progress in a chronological manner. Sometimes not all stages are successive and, for example, fetal demise can also occur in stage I or II. TTTS can thus progress extremely fast. Therefore, close surveillance is mandatory and usually follow-up scans are recommended at least fortnightly (7).

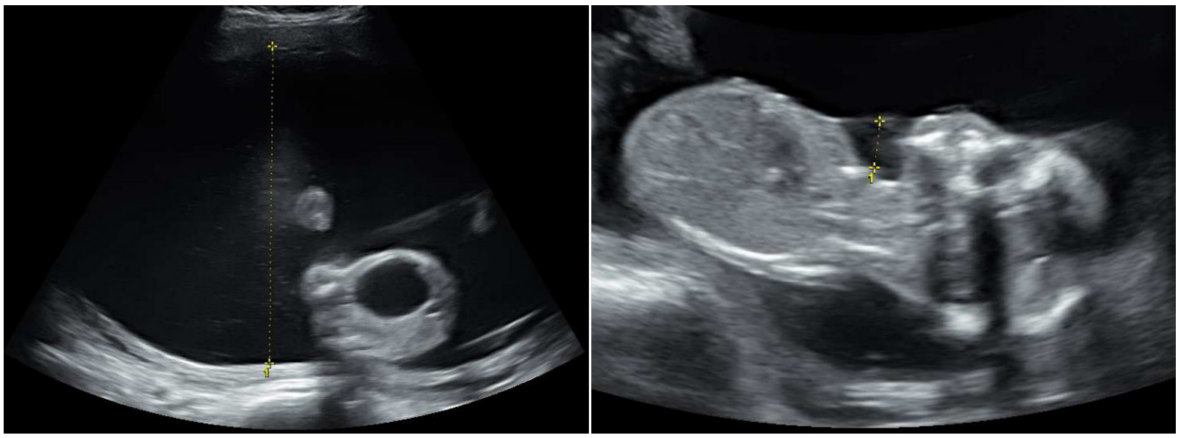

Fig. 2: Stage I: Polyhydramnios (MVP >8 cm) in recipient's sac and oligohydramnios in donor's sac ("stuck twin").

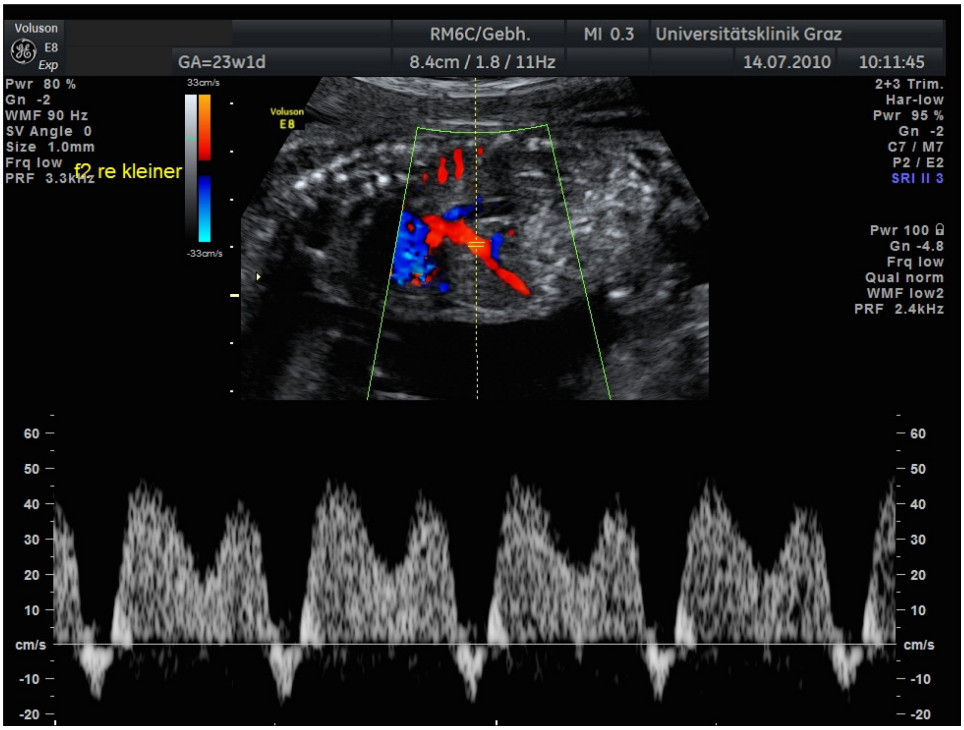

Fig. 3: Stage III: Reversed a-wave in the ductus venosus of a recipient twin.

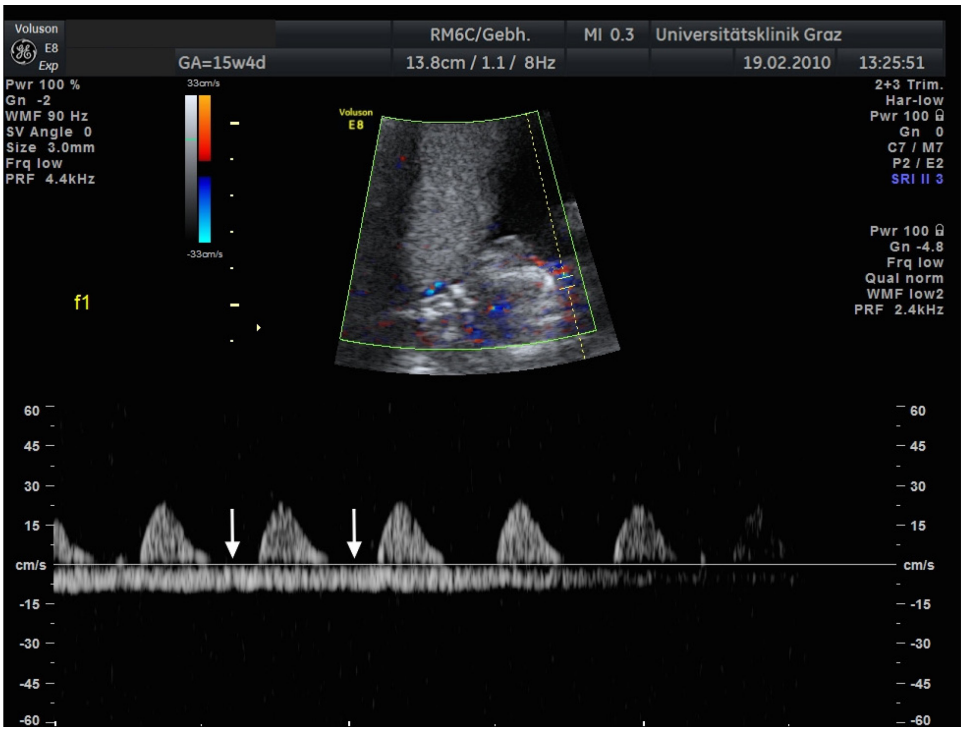

Fig. 4: Stage III: Absent end-diastolic flow (arrows) in the umbilical artery of a donor twin.

1.1.3 Diagnosis of TTTS

Determination of chorionicity in the first trimester is of great importance, since in later gestation this becomes more difficult or even impossible because the amnion and chorion are not separated from each other and therefore not distinguishable. In monochorionic twin pregnancies only two layers of amniotic membranes can be found on ultrasound examination. Dichorionic twins have an additional chorionic layer in between forming the so called 'lambda sign'. This must not be confused with the 'false' or 'open' lambda sign which is formed by the attachment of amniotic membranes in monochorionic twins in early pregnancy (6).

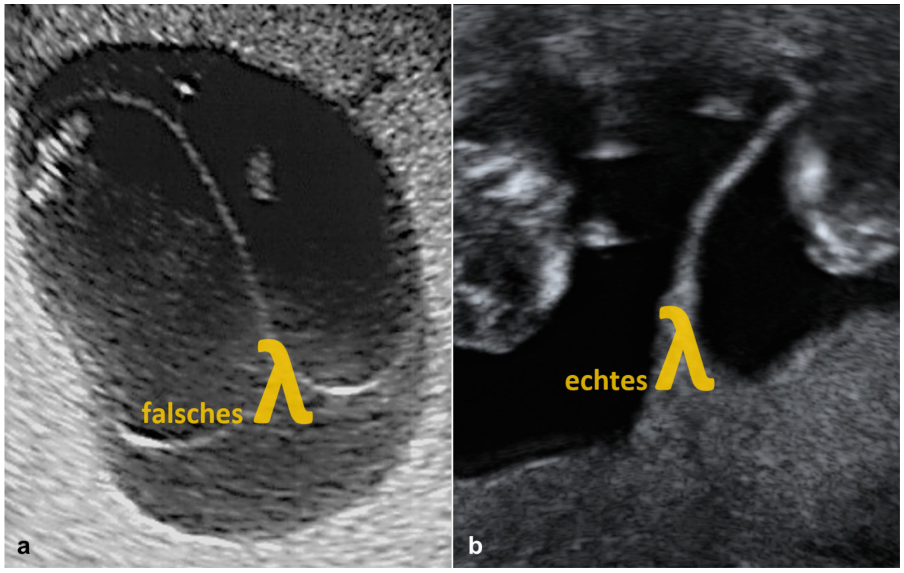

Fig. 5: Two thin layers of amniotic membrane (‘false’ or ’open’ lambda sign) of a monochorionic twin pregnancy (a). ‘Lambda sign’ with an additional chorionic layer can be found in dichorionic twin pregnancies (b).

The diagnosis of TTTS is made by ultrasound in the presence of oligohydramnios and polyhydramnios in MCDA twins according to the criteria described above.

1.1.4 Prediction of TTTS

Specific sonographic findings may be used in the prediction of TTTS and other complications (selective growth discordance and intrauterine demise) in MCDA twin pregnancies (table 1). In the first trimester these include discordance in crown-rump length or nuchal translucency (NT). Increased NT in the recipient may be a first sign for hemodynamic changes. Another first-trimester predictor can be changes in ductus venosus a-wave. If any of these findings are detected by sonography, closer monitoring, e.g. every week, is recommended.

An important predictor for complications in the second-trimester is velamentous cord insertion (VCI), which affects about one third of MCDA twins with TTTS, and can lead, together with unequal placental sharing, to growth discordance of the twins. Another second-trimester finding associated with TTTS is intertwin membrane folding. This can arise if only a small amount of amniotic fluid is left and it leads in more than a third of cases to TTTS (2, 6, 7).

First- and second-trimester sonographic findings associated with TTTS
First-trimester
Crown-rump length discordance
Nuchal translucency discordance
Reversed or absent a-wave in the ductus venosus
Second-trimester
Abdominal circumference discordance
Membrane folding
Velamentous placental cord insertion

Table 1: Predictors of TTTS/IUGR/IUFD in first and second trimester (7).

1.1.5 Treatment of TTTS

If left untreated TTTS is associated with perinatal mortality in 90% (1), which emphasizes the importance of adequate management of the disease. Historically, several treatment options have been suggested in case of severe TTTS: amnioreduction (amniodrainage; AD), selective laser photocoagulation (laser therapy), selective reduction (cord occlusion) and termination of pregnancy (1).

Amnioreduction was one of the first therapy options of TTTS. It may prolong the pregnancy but it is not a causative solution for TTTS and also entails various complications, such as rupture of the membranes or intra-amniotic bleeding and impaired neurodevelopmental outcome. However, amnioreduction may be a suitable management option in early-stage TTTS (stage 1) or in advanced gestational age (>26 weeks of gestation). By reducing the amniotic fluid the intra-amniotic pressure decreases, thus improving placental perfusion (2, 11, 12).

At present, the best outcome in severe TTTS (stage II and higher) is provided by intrauterine laser therapy. For this purpose, an endoscope is inserted in the recipient's sac to map the angioarchitecture of the placenta. Arteries can be distinguished from veins, since they have a dark color and cross over veins. All anastomoses are selectively ablated with laser energy, ideally leading to complete separation of the placental territories (1, 13). At the end of the laser therapy an amnioreduction is carried out.

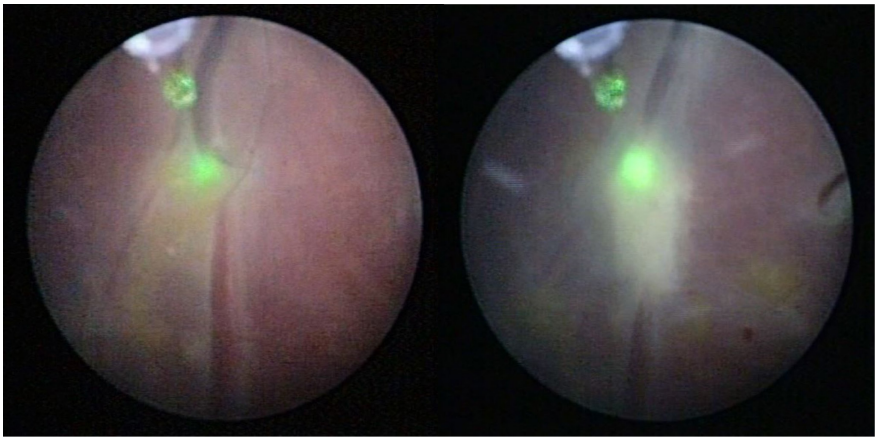

Fig. 6: Fetoscopic laser ablation of placental anastomoses.

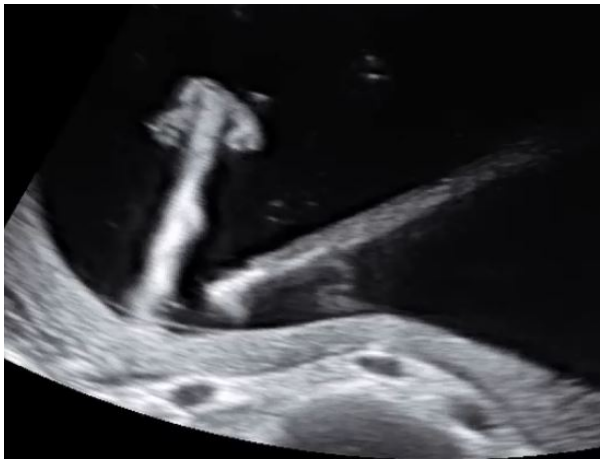

Fig. 7: Ultrasound image of fetoscopic laser ablation.

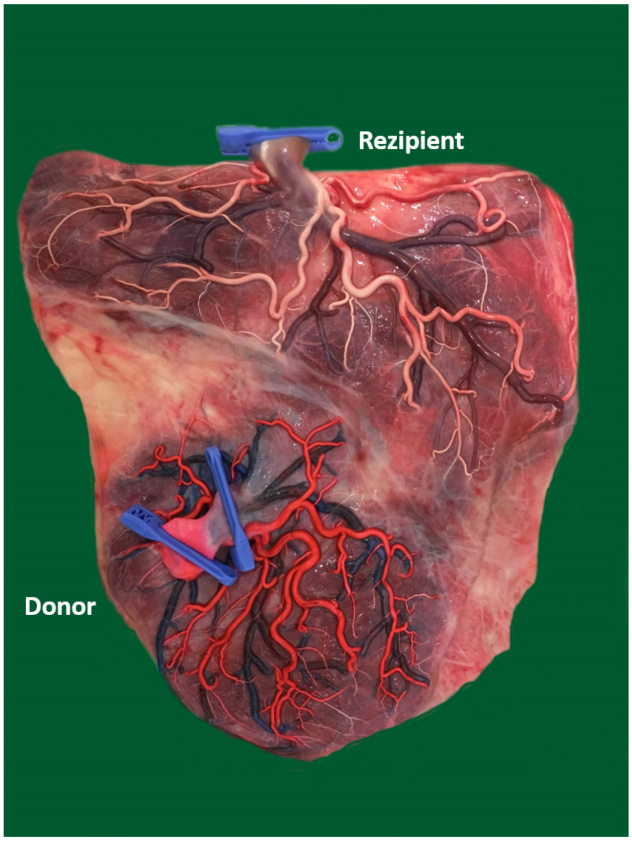

Fig. 8: Monochorionic placenta after fetoscopic laser ablation (this picture is provided with the kind permission of Prof. Liesbeth Lewi, UZ Leuven, Belgium).

Selective feticide is an alternative management option in case of technical or anatomical issues, fetal malformations or imminent demise of one twin with the aim of protecting the other one. Here, bipolar cord coagulation or interstitial laser is performed to stop the blood flow leading to death of this twin, while the other is protected (1, 2, 7, 14).
Pregnancy termination should be considered in the case of poor perinatal outcome or severe brain injury (14) and should only be offered as a last treatment option and not as an alternative treatment (15).

1.1.6 Expected outcome after in utero therapy

The Eurofetus trial carried out investigations on outcome after in utero therapy and reported a significantly higher median gestational age at delivery for the laser group (33.3 weeks) than for the amnioreduction group (29.0 weeks). The survival of at least one twin at the age of 6 months was also higher (76%) in the laser group than in the amnioreduction group (56%). A significant difference could be also found regarding neurological complications at the age of 6 months: in the laser group 52% of the children were free from neurological complications, whereas in the amnioreduction group only 31% had no neurological complications (7).

Roberts et al performed a Cochrane review comparing the outcome after laser therapy and amnioreduction (13): Laser therapy showed better results for overall death (48% vs. 59%) of the fetuses as well as perinatal (26% vs. 44%) and neonatal (8% vs. 26%) death than amnioreduction. Additionally the number of children without neurological abnormalities was significantly higher when treated with laser therapy (52%) than with amnioreduction (31%). These results may emphasize the importance of fetoscopic laser therapy for treatment of TTTS.

Summarizing several studies including more than 1000 cases of TTTS treated using laser therapy, the overall perinatal survival was 64.8%, which may be the best available data currently. Following table should give a general overview of the results (7).

Perinatal outcome of TTTS pregnancies treated using fetoscopic laser ablation	
n	1008
Stage I	6.7% (68/1008)
Stage II	51.1% (515/1008)
Stage III	34.8% (351/1008)
Stage IV	7.3% (74/1008)
2 survivors	48.7% (491/1008)
1 survivor	32.2% (352/1008)
0 survivor	19.1% (192/1008)
Neonatal death	5.8% (117/2016)
Overall perinatal survival	64.8% (1306/2016)

Table 2: Perinatal outcome after fetoscopic laser ablation (7).

In summary, the expected overall survival rate after fetoscopic laser ablation is about 50-70%. These rates are highly dependent on the stage of TTTS and therefore decrease with higher stage.

1.1.7 Possible fetal and maternal complications due to TTTS therapy

Although laser therapy is the best treatment option for severe TTTS at present, complications may arise nevertheless. Rustico et al. reported about the fetal and maternal complications at their department. The main fetal complications were recurrence of TTTS (11.3%), TAPS (twin anemia polycythemia sequence; 3.3%), reversal of TTTS (1.3%) and cerebral lesions of one twin (2.0%) (8).
Recurrence of TTTS arises as a result of missed inter-twin anastomoses at laser therapy or revascularization of these anastomoses.
Post-laser TAPS is another specific complication of selective laser coagulation and occurs in 2-16% (16). TAPS has the same underlying pathophysiology as TTTS but differs in the manifestation and in morphology of the inter-twin anastomoses. TAPS is characterized by significant inter-twin hemoglobin differences due to chronic blood loss through inter-twin anastomoses, which are usually significantly smaller than those in placentas with TTTS. Slow transfusion has been found to result in hemodynamic changes but not in shifts of amniotic fluid. Thus, the typical oligohydramnios-polyhydramnios sequence is not found in cases with TAPS (5, 17). The post-laser TAPS is the result of missed small-sized anastomoses at laser therapy, therefore slow transfusion through small residual anastomoses is still active (16).

Reversal of TTTS following laser therapy is a result of missed V-A anastomoses. In recent years, coagulation of the whole chorionic plate aiming to ablate all inter-twin vessels by using the so-called ‘Solomon technique’ has widely been implemented to prevent TAPS and recurrence or reversal of TTTS (14). Cerebral lesions were due to hemorrhagic or ischemic lesions in the study of Rustico et al. Rates regarding survival were also recorded: sIUFD occurred in about 26.0%, dIUFD in 6.6% (8).
Benoit et al reported overall survival rates for at least one twin ranging from 76 to 88%, for both twins from 36 to 68% after laser therapy (1), whereas the impressive variability of results may be due to the grade of experience of the surgeon.
The median gestational age at delivery ranges from about 32 to 33 weeks after laser therapy (1). Fisk et al showed that patients delivered at >32 weeks of gestation after laser therapy in 58% of cases, whereas patients treated only with serial amnioreduction delivered at this gestational age only in 31% of cases(14).

One of the most frequent complications after TTTS treatment is pPROM (preterm premature rupture of membrane) leading to preterm delivery. Rustico et al. reported that 28.7% of patients were affected by pPROM within one week after laser therapy. But nevertheless also without pPROM the risk for preterm delivery was higher after laser therapy than without. Thus, prematurity and low birth weight are often responsible for neonatal death, which accounts for 7% of the treated population. Moreover pPROM may entail a risk for miscarriage (8).
Beside fetal complications, maternal complications can play a considerable role as well. Possible maternal complications can range from mild forms, such as amniotic fluid leakage or vaginal bleeding, to severe manifestations like placental abruption or mirror syndrome (18). Rustico et al reported a 10.7% overall rate of maternal complications, from which 6.0% were severe and 4.7% mild (8).

Another rare but severe complication is the ‘mirror syndrome’, which is also named the "Ballantyne syndrome"(19). Mirror syndrome describes a serious disease where fetal symptoms are "mirrored" by the mother. Thus, in the case of TTTS stage IV, fetal hydrops and placental edema lead to maternal edema, which can affect skin or lungs. The underlying pathophysiology is still unclear (20). Probably antiangionetic factors are increased in MCDA twins with TTTS and are suspected to be responsible for endothelial dysfunction. Chai et al. speculate that amnioreduction and the consequently decreasing maternal abdominal pressure contribute to the manifestation of the disease as well. The main symptoms of mirror syndrome were summarized as "edema, anemia, hemodilution, hypoproteinemia, and proteinuria" (20).

1.1.8 Possible maternal hemodynamic effects after amnioreduction

Maternal effects after amnioreduction are quite common and their pathophysiology is still not completely understood (20). Nizard et al. evaluated maternal hemodynamic changes after fetoscopic laser ablation followed by amnioreduction (21): The study population was classified into two groups depending on the drainage volume of amniotic fluid. Group A included all patients with a drained volume of > 1000 ml while group B included those with < 1000 ml. They recorded hemodynamic parameters such as hemoglobin (Hb), hematocrit (Hkt), mean arterial pressure, heart rate and echocardiographic parameters. They found a decrease in Hb, Hkt and mean arterial pressure but an increase in cardiac output. The fall of the Hb and Hkt were interpreted as signs for hemodilution after high-volume drainage (21).
Huber et al. described this phenomenon of hemodilution caused by increased fluid volume in the maternal circulation and not as a result of blood loss. They speculate that a decreased shift of volume from the mother to the recipient and an increase of re-absorption from the amniotic cavity are responsible for this mechanism. They could also find a significant correlation between the drained amniotic volume and the fall of Hb and Hkt (22).
Nizard et. al additionally demonstrated that the mean arterial pressure decreased whereas the CO increased. The latter is probably due to two reasons: on the one hand amnioreduction leads to a decreased uterine pressure resulting in improved uterine and placental perfusion. This possibly decreases the cardiac afterload. On the other hand, declined maternal abdominal pressure may contribute to an enhancement of venous return to the heart leading to a greater cardiac preload. The combination of these mechanisms could be responsible for an increase of CO despite decreased mean arterial pressure (21).

1.2 Aim of the study

In this study, maternal hemodynamic parameters were recorded and analyzed in relation to the volume of amniodrainage. Furthermore, we report on maternal surgery-related complications.

2 Materials und Methods

2.1 Inclusion criteria

All monochorionic pregnancies with TTTS that were treated at the Department of Obstetrics and Gynecology at the Medical University of Graz between August 2010 and August 2016.
Intrauterine interventions included laser therapy, cord occlusion, amnioreduction and laser therapy combined with cord occlusion.

2.2 Exclusion criteria

Patients who underwent fetoscopic intervention for any other indication than TTTS.

2.3 Data collection

Data was collected retrospectively from electronic databases (Open Medocs and PIA View Point) and from the medical records. Furthermore, the existing local registry on monochorionic twin pregnancies was used. These sources provide a large number of various documents and information from where the required data was extracted.

Maternal parameters were mainly recorded from medical reports, medical history, fever charts, nursing documentations and laboratory values as well as surgery reports, anesthesia records and documentations of the recovery room.

The required data was inserted into a Microsoft Excel file which was password-protected. Moreover, all data was used in a pseudonymised form and marked with a unique research number. Only authorized persons had access to the data.

2.4 Measured parameters

2.4.1 Maternal parameters

The following table illustrates all maternal parameters.

Maternal parameters
Date of birth
Research number
Gestational age (GA)
Body-Mass-Index (BMI)
Chorionicity
Kind of intervention
Drained volume of amniotic fluid
Systolic arterial blood pressure (BPsys)
Diastolic arterial blood pressure (BPdia)
Heart rate (HR)
Volume of diuresis
Volume of infusion
Hemoglobin (Hb)
Hematocrit (Hkt)
Albumin (Alb)
Osmolality
Sodium (Na)
Severe maternal complications: – Severe hemodilution – Severe anemia – Placental abruption – Retroplacental hematoma – Respiratory insufficiency
Perioperative complications within 14 days post-surgery

Table 3: Maternal parameters.

A number of general characteristics were investigated initially. The date of birth was taken from Medocs and was used to determine the age of the patient. If the person was already noted in the pre-existent registry, the research number was further used. If not, a new research number was given. GA was taken out of the surgery report to obtain it at the time when the intervention was carried out. The BMI was either directly taken from the preoperative assessment or calculated by using the parameters mass and height ($BMI = \frac{mass_{kg}}{height_m^2}$). Chorionicity was collected from medical reports, particularly from ultrasound examinations.

The surgery report provided data about the kind of intervention and the volume of the drained amniotic fluid.

Several special parameters were extracted from different documents. On the one hand, certain maternal parameters were taken from the anesthesia protocol, such as BPsys, BPdia, HR and infusion volume during surgery; on the other hand, data concerning the time before and after surgery, were excerpted particularly from the TPR (temperature, pulse and respiration) chart and nursing documentation. At this point it has to be mentioned, that the special hemodynamic parameters (BPsys/dia, HR, infusion/diuresis volume) were evaluated at standardized points in time: preoperative, intraoperative and postoperative. The intraoperative period splits up again into 10 minutes before beginning of the surgery, time of transection and time of suture. The postoperative period is divided into 2, 4, 6, 12 and 24 hours after surgery. At all these points of time the parameters were evaluated.

The laboratory values, such as Hkt, Hb, Alb, Osmolality and Na, were taken from Medocs. We evaluated measurements at three time-points (T): preoperative (T0), postoperative (T1 = the same day) and 24 hours postoperative (T2).

For information about maternal and perioperative complications all medical reports were checked with focus on clinical course.

2.4.2 Fetal parameters

As this study focused on the maternal characteristics, fetal parameters had a subordinate position. For this reason, only a few specifications were investigated, including Quintero-stage (I-V), fetal hydrops, which can also be seen as a part of staging, and further fetal mortality. These characteristics could be obtained from medical reports of ultrasound examinations. Furthermore, fetal complications were recorded mainly from medical records and histories.

2.5 Statistical analysis

For the statistical analysis the "IBM SPSS Statistics 23" software was used. The first descriptive statistic was used to illustrate the study population and the distribution regarding intervention and Quintero stage.

The data was then screened regarding normal distribution by applying the Kolmorgorov-Smirnov and Shapiro-Wilk test.

Finally, correlations between related parameters were demonstrated by using Spearman's rho as the data did not correspond to normal distribution. Correlation between not related parameters was tested using the Wilcoxon test, also because normal distribution was not fulfilled.
The Wilcoxon test was used to compare related but not parametric mean values, too. Otherwise, in the case of normal distribution, the t-test was performed.

Graphs and charts were created using SPSS and Microsoft Excel.

3 Results

3.1 Study population characteristics

80 cases of TTTS were included. Table 3 gives an overview of the characteristics of the patients.

Maternal parameters	
Average Age (years)	30.46 (25.22 - 35.70)
Average GA (weeks + days)	20+2 (17+3 – 23+1)
Average BMI	25.13 (20.68 - 29.58)
Chorionicity	
MCDA	79 (98.8%)
DCTA	1 (1.3%)

Table 4: General characteristics.

Maternal average age at intervention was 30.46 years and average GA was 20 weeks + 2 days. The average BMI of the patients was 25.13.

Among all 80 cases 79 contributed to MCDA twin pregnancies (98.8%), and only one to DCTA triplet pregnancy (1.3%).

Detailed information about Quintero stage, type of intervention and volume of amnioreduction is shown in table 4 and the graphs (Fig. 1, Fig. 2, Fig. 3) below:

Quintero stage	
Stage I	13/80 (16.3%)
Stage II	25/80 (31.3%)
Stage III	38/80 (47.5%)
Stage IV	3/80 (3.8%)
Stage V	1/80 (1.3%)
Intervention	
Laser	56/80 (70%)
CO	18/80 (22.5%)
AD	3/80 (3.8%)
Laser+CO	3/80 (3.8%)
Average volume of amnioreduction (ml)	1315.00 (0 - 4040)

Table 5: Quintero stage, type of intervention and volume of amnioreduction.

In Quintero stage I, 12 interventions (15.2%) were carried out; in stage II, 25 (31.6%); in stage III, 38 (48.1%); in stage IV, 3 (3.8%); and in stage V only one (1.3%). The following graph illustrates this distribution.

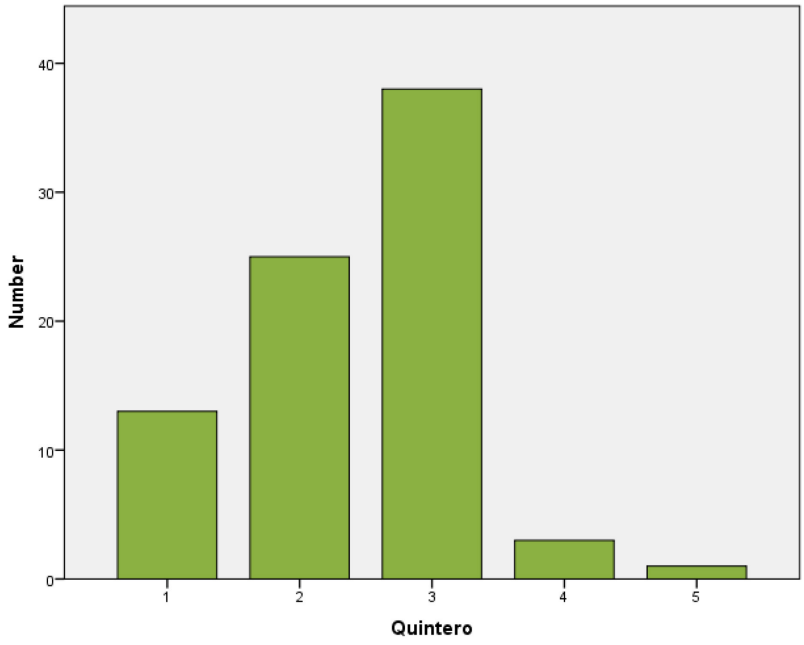

Fig. 9: Distribution among Quintero stages.

The most common intervention performed was laser photocoagulation, which was conducted in 56 cases (70%), followed by CO with 18 cases (22.5%). AD and combination of Laser with CO were each carried out 3 times (3.8%).

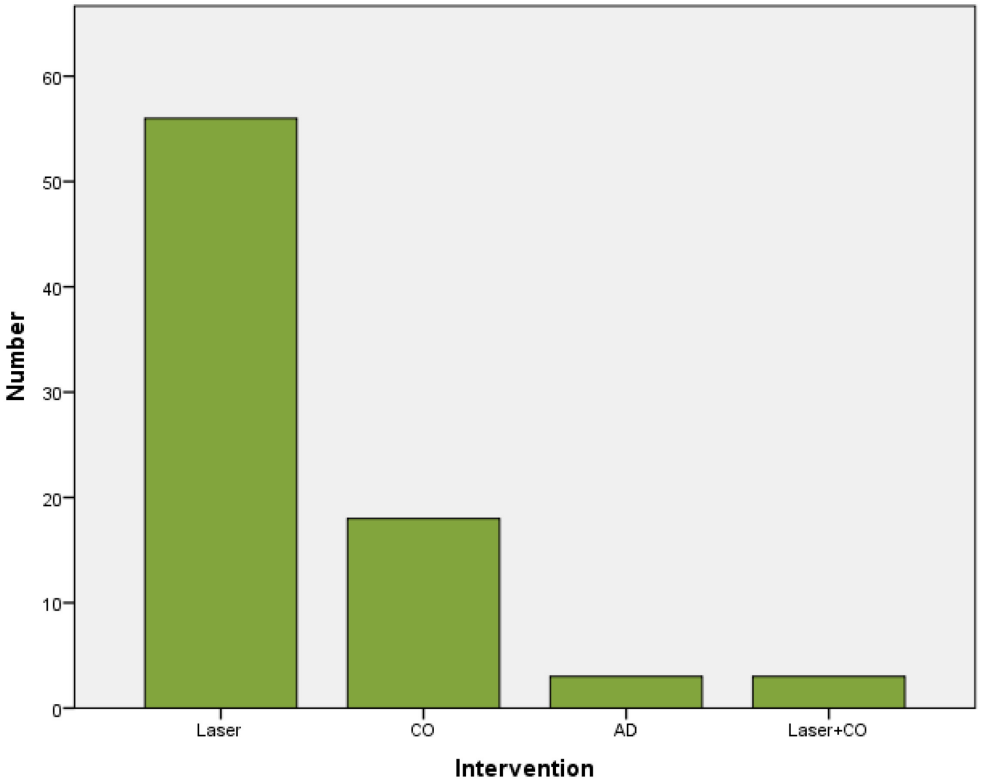

Fig. 10: Distribution of interventions.

The average volume of amnioreduction was 1315 ml with a range of 0 - 4040 ml.

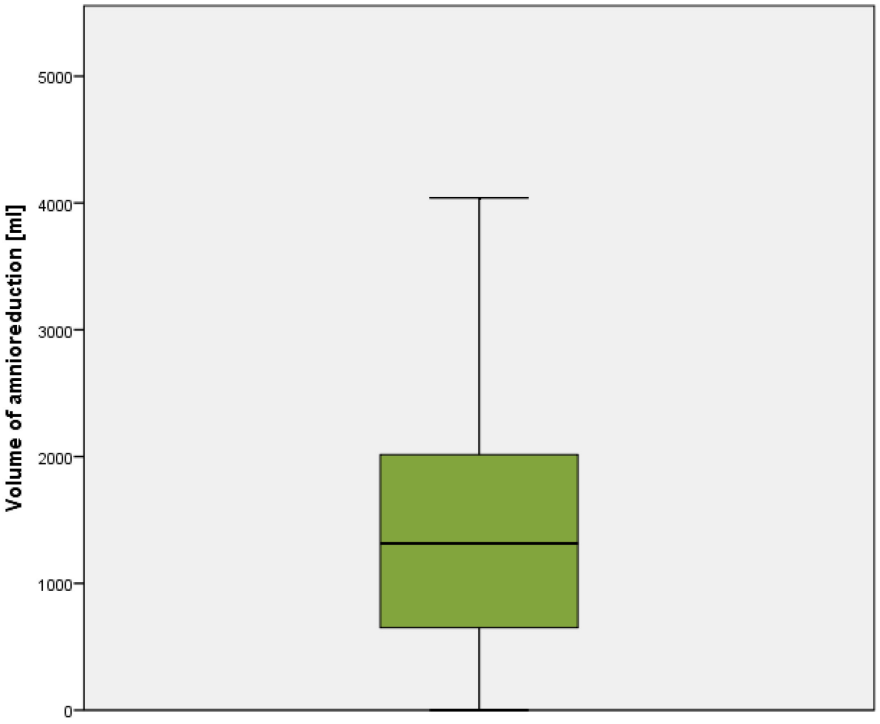

Fig. 11: Distribution of the volume of amnioreduction.

3.2 Maternal and fetal complications

Maternal and fetal complications are presented in the following table:

Maternal complications	
No complications	77/80 (96.3%)
Dyspnea, reduced oxygen saturation, pleural effusion, right-heart overload	1/80 (1.3%)
Severe anemia	1/80 (1.3%)
Retroplacental hematoma	1/80 (1.3%)
Total number of complications	3/80 (3.9%)

Table 6: Maternal complications.

The majority of patients (n=77) did not have any complications. One woman presented dyspnea, reduced oxygen saturation, pleural effusion and right heart overload (1.3%). Severe anemia could be found in one case (1.3%), as well as retroplacental hematoma (1.3%).

In total, 3 cases were affected by complications, which is equivalent to 3.9%.

Fetal Complications	
No complications	61/80 (76.3%)
pPROM	4/80 (5.0%)
sIUFD	9/80 (11.3%)
dIUFD	2/80 (2.5%)
Abortion	2/80 (2.5%)
Intrauterine transfusion (IUTx)	2/80 (2.5%)
Total fetal complications	19/80 (23.8%)

Table 7: Fetal complications.

In 61 cases (76.3%) there were no complications. Preterm PROM occurred in 4 pregnancies (5.0%), sIUFD in 9 cases (11.3%) and dIUFD in 2 cases (2.5%). Two women miscarried (2.5%) and in another 2 patients intrauterine transfusion was required (2.5%).

3.3 Short-term changes in maternal hemodynamic parameters

3.3.1 Hemoglobin, hematocrit, albumin and sodium

Maternal Hb, Hkt, Alb and Na values were evaluated at three time-points as described above. Mean values with standard deviation are presented in the following table.

	T0 ± SD	T1 ± SD	T2 ± SD
Hb (g/dl)	11.4 ± 1.0	9.5 ± 0.7	9.8 ± 1.1
Hkt (%)	32.7 ± 3.0	27.3 ± 1.9	28.7 ± 3.1
Albumin (g/dl)	3.6 ± 0.3	2.8 ± 0.4	3.0 ± 0.3
Sodium (mmol/l)	137.4 ± 1.8	138.9 ± 1.7	138.1 ± 2.1

Table 8: Hb, Hkt, Alb and Na mean values ± standard deviation (SD) at standardized points in time.

There was a significant decrease in Hb, Hkt and Alb levels between the pre- and postoperative periods.

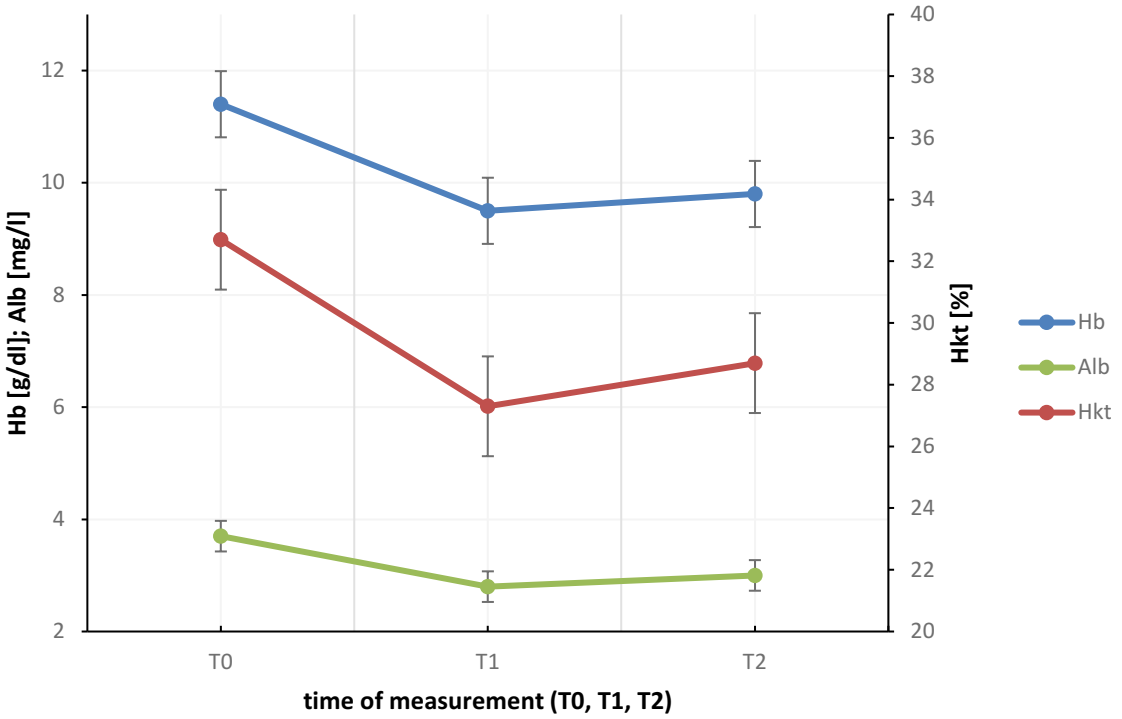

Fig. 12: Hb, Hkt and Alb mean values with standard error of the mean (SEM).

The values between Hkt at T0 and T1 and T2, respectively, showed a significant decline (p=0.000; p=0.000), while there were no differences between T1 and T2.

Albumin presented the same decrease between pre- and postoperative (p=0.000), but also no different values in the postoperative term.

Sodium stayed pre- and postoperatively constant.

3.3.2 Systolic, diastolic arterial blood pressure and heart rate

	Time of suture ± SD	2h postoperative ± SD	24h postoperative ± SD
BPsys (mmHg)	119.5 ± 11.9	108.3 ± 11.4	110.1 ± 11.8
BPdia (mmHg)	68.3 ± 9.1	59.6 ± 9.7	66.3 ± 10.0
HR (bpm)	100.4 ± 19.8	93.0 ± 12.4	91.0 ± 10.9

Table 9: Systolic, diastolic arterial blood pressure and heart rate mean values ± standard deviation (SD) at standardized points in time.

The statistical analysis of systolic and diastolic arterial blood pressure showed both a decrease in the short postoperative term. Between time of suture and 2 hours after surgery the systolic and diastolic arterial blood pressure declined significantly (p=0.000; p=0.000). However, the values of systolic and diastolic arterial blood pressure at 2h postoperative did not differ from 24h postoperative, but remained constant.

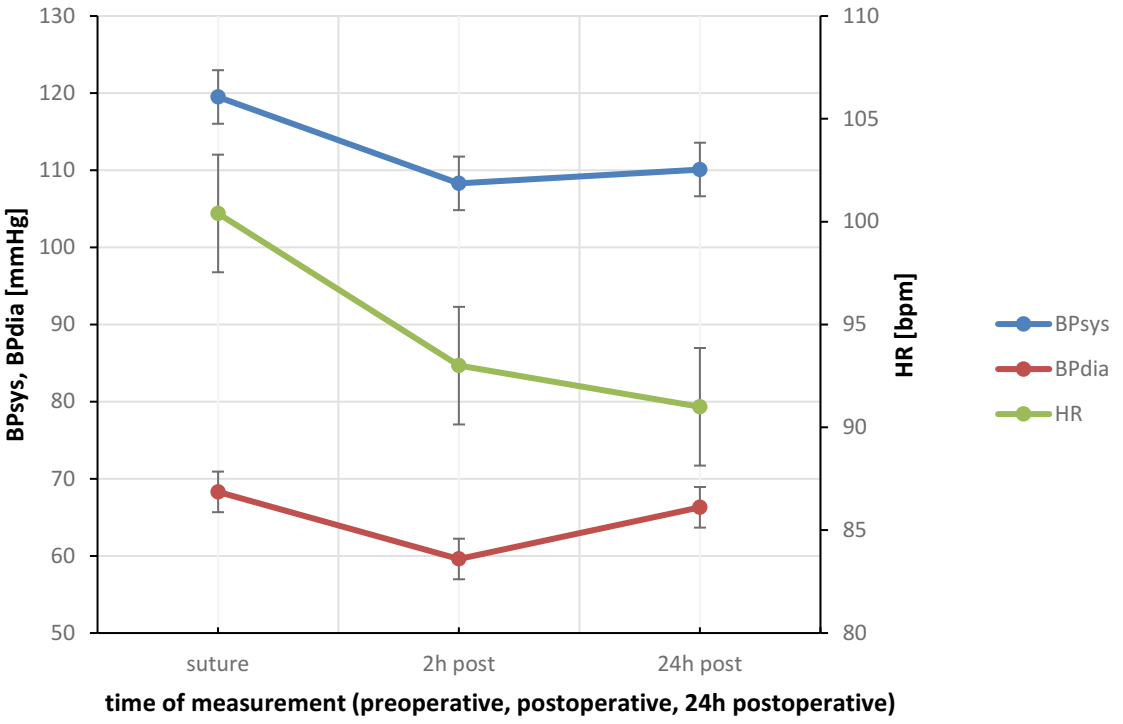

Fig. 13: BPsys, BPdia and HR mean values with standard error of the mean (SEM).

The results for the maternal heart rate were similar: between time of suture and 2 hours postoperative the heart rate decreased significantly (p=0.003). Between 2h and 24h postoperative the values did not change significantly.

3.3.3 Diuresis

Diuresis was recorded in standardized postoperative intervals: 0-2h, 2-4h, 4-6h, 6-12h and 12-24h after surgery. Because of lack of available data only the intervals 0-2h, 6-12h and 12-24h could be included into the statistical analysis. The following table illustrates the diuresis volume per hour.

Diuresis	Mean values [ml] (range)
0-2h post/h	180.00 (25 - 700)
6-12h post/h	204.93 (20 - 483)
12-24h post/h	132.68 (17-283)

Table 10: Mean values and range of diuresis volume.

The first interval (0-2h) showed a mean diuresis volume of 180.00 ml per hour. In the following interval (6-12h) the mean volume per hour is higher at 204.93 ml. In the interval of 12-24h a mean diuresis volume of 132.68 ml was recorded.

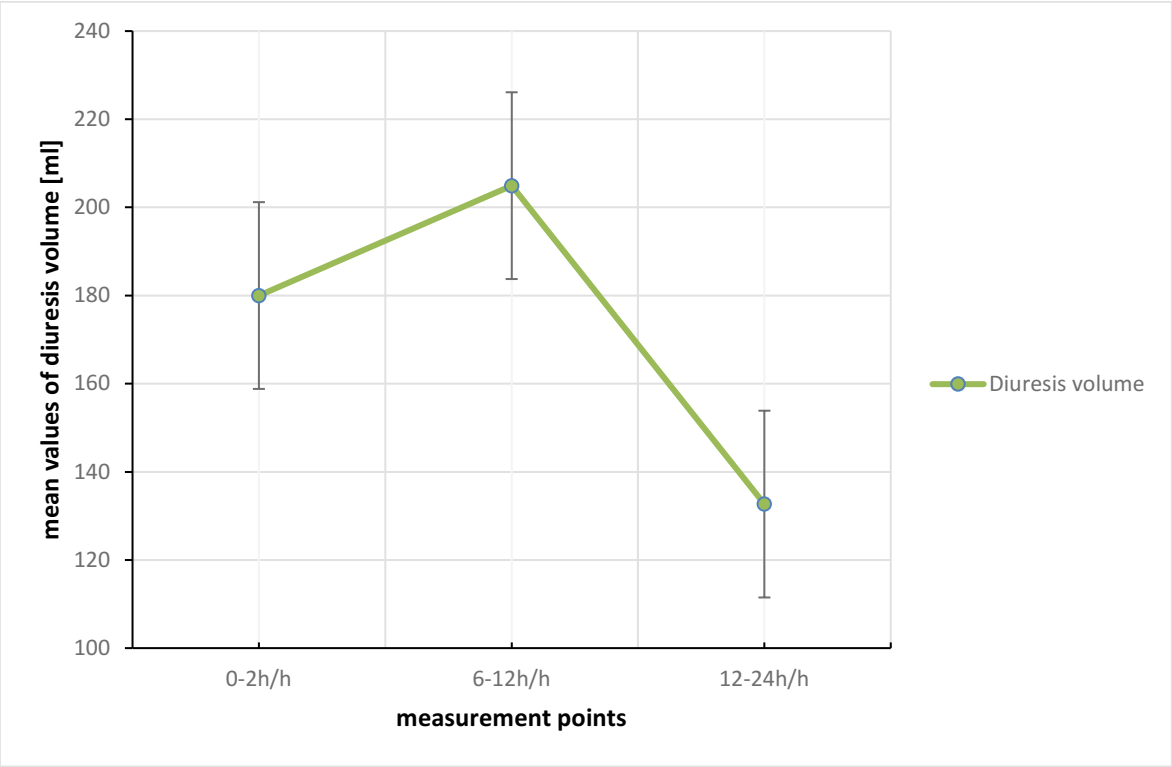

Fig. 14: Mean values of diuresis volume per hour with standard error of the mean (SEM).

Fig. 9 illustrates the course of the diuresis volume during the time period till 24 hours after surgery. Comparing the mean values statistical analysis could not prove the slight increase of the volume per hour between the first two intervals (0-2h/h and 6-12h/h). However, a significant decrease between the intervals 6-12h/h and 12-24h/h could be found (p=0.000).

3.4 Correlation between volume of amnioreduction and maternal hemodynamic parameters

For this study correlations between volume of amnioreduction and maternal hemodynamic parameters, such as Hb, Hkt and Alb, were determined. For this, the change by time of these values was calculated first and then used for statistical analysis. The following table gives an overview of the results.

Volume of amnioreduction	Correlation coefficient	Significance
• **Hb pre - Hb post**	0.491	0.028
• **Hb pre - Hb 24h post**	0.320	0.010
• **Hkt pre - Hkt post**	0.503	0.024
• **Hkt pre - Hkt 24h post**	0.351	0.004
• **Alb pre - Alb post**	-0.359	0.343
• **Alb pre - Alb 24 h post**	0.355	0.46

Table 11: Correlation between volume of amnioreduction and maternal hemodynamic parameters.

Statistical analyses showed a significant correlation, which was positive and weak, between the Hb-change pre- and postoperatively and pre- and 24h postoperatively, respectively. For the parameter Hkt a good positive correlation could be found between Hkt pre- and postoperatively, whereas the correlation between pre- and 24h postoperative was also positive but weak. Albumin had a significant correlation only in the interval of pre- and 24h postoperative, which was positive and weak, too.

3.5 Correlation between volume of amnioreduction and appearance of complications

With the Mann-Whitney-U-Test the correlation between volume of amnioreduction and maternal complications and between volume of amnioreduction and appearance of pPROM, respectively, was calculated. Moreover, the volume of amnioreduction was split up into groups for further statistical analysis: one group including all cases with a volume of amnioreduction between 1500 and 2000 ml, another group with 2000-2500 ml.

Volume of amnioreduction	Significance
• **Maternal complications**	0.349
• **pPROM**	0.028
• **pPROM**	
○ **1500 - 2000 ml**	0.024
○ **2000-2500 ml**	0.059

Table 12: Correlation (significance) between volume of amnioreduction and maternal complications (pPROM).

There was a significant correlation between volume of amnioreduction and appearance of pPROM and 1500-2000 ml volume of amnioreduction and appearance of pPROM, respectively. The following two figures illustrate the correlation.

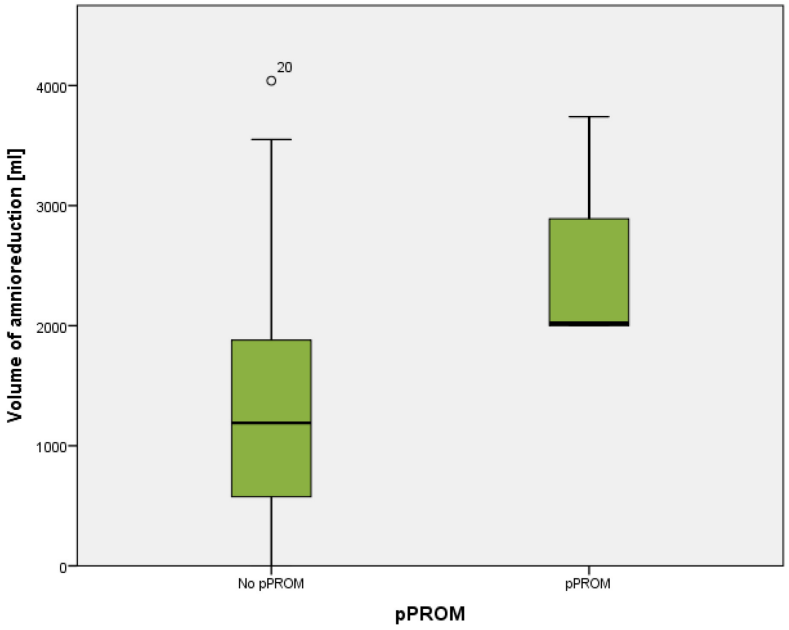

Fig. 15: Correlation between volume of amnioreduction and appearance of pPROM.

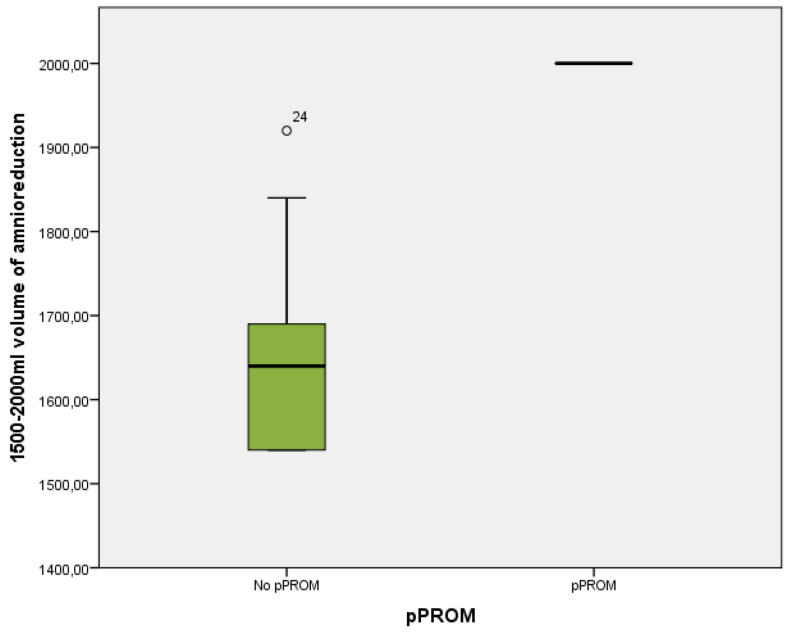

Fig. 16: Correlation between group with 1500-2000 ml volume of amnioreduction and appearance of pPROM.

No significant correlation could be found between the volume of amnioreduction and general maternal complications and between the group of 2000-2500 ml and appearance of pPROM.

3.6 Correlation between Body-Mass-Index and incidence of maternal complications

The BMI of every patient was recorded and correlated with the incidence of maternal complication. Statistical analysis also included correlation between BMI and change of systolic and diastolic arterial blood pressure between the time of suture and 24 hours postoperatively. Table 12 presents the corresponding results.

BMI	Significance
• **Maternal complications**	0.918
• **BPsys suture - BPsys 24h post**	0.004
• **BPdia suture - BPdia 24h post**	0.248

Table 13: Correlation (significance) between BMI and maternal complications/change of BP (sys + dia).

No significant correlation was found between BMI and maternal complications and change in diastolic arterial blood pressure. But a significant negative correlation between BMI and systolic arterial blood pressure could be found (correlation coefficient = -0.343). Therefore, the higher the BMI, the smaller the decrease of systolic arterial blood pressure in the period between time of suture and 24 hours postoperative.

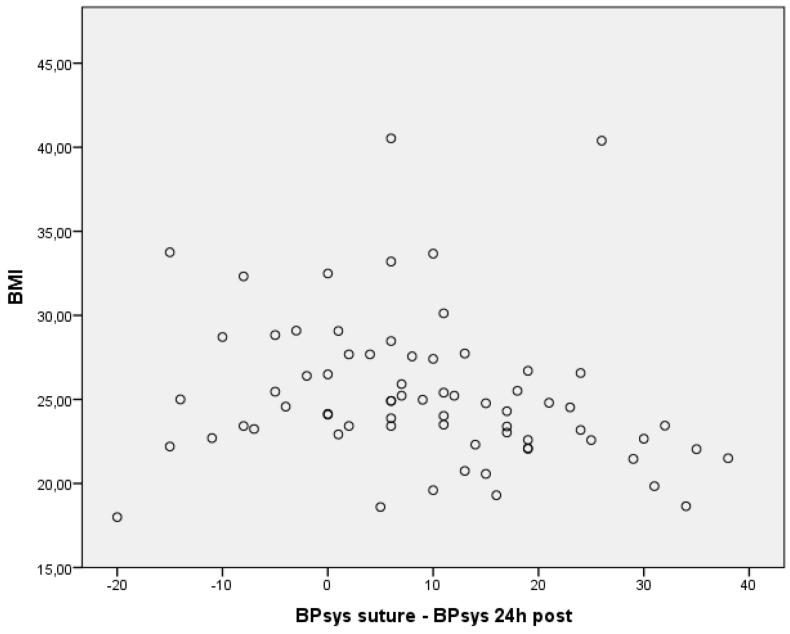

Fig. 17: Correlation between BMI and change of BPsys.

4 Discussion

The aim of this study was to report on maternal hemodynamic changes and complications after intrauterine interventions for TTTS. We retrospectively included 80 patients who underwent intrauterine interventions between August 2010 and August 2016 at our clinic. The size of our study population was comparable or even larger than the ones in similar studies: The study of Nizard et al. included 39 cases, the one of Huber et al. 109 patients and the study of Gussi et al. consisted of 60 cases with hemodilution following treatment of TTTS by laser therapy and subsequent amnioreduction (21, 22, 23).

Interventions in our study were performed at 21 weeks of gestation +/- 20 days, which is comparable to Nizard et al. (21).

In the postoperative period a significant decrease of hemoglobin, hematocrit and albumin was demonstrated, which may be interpreted as a sign of hemodilution.
Furthermore, there was a significant correlation between the volume of amniotic fluid drained at surgery and the alterations of the maternal hemodynamic parameters. Given that no relevant surgical complications were observed in those patients, we hypothesize that observed signs of hemodilution might be a result of amnioreduction during fetoscopic interventions.
Nizard et al. reported a correlation between the volume of amnioreduction and the resulting grade of hemodilution in their work too. Hemodilution was just observed in group A, where patients underwent drainage of at least 1000 ml of amniotic fluid. In group B (drainage volume < 1000 ml) no significant effects were observed (21). Huber et al. found effects of maternal haemodilution following fetoscopic surgery and amniodrainage as well (22).

At present we can only speculate about the exact pathophysiology of this process. Huber et al. suggested that the reduction in intrauterine pressure in the event of amnioreduction may improve placental perfusion, thus leading to a better reabsorption of amniotic fluid which might eventually result in dilution of maternal blood (22).

Another hypothesis was postulated by De Lia et al.: After laser therapy they found not only maternal anemia but also significant hypoproteinemia. They raise the question of inadequate nutrition of the mother and speculate, that insufficient intake of proteins and calories might be causative for maternal hemodilution. Subsequent increased colloid osmotic pressure (COP) in the recipient twin may then lead to passive water influx from maternal circulation leading to polyhydramnios (24). However, recent reviews demonstrate that vascular anastomoses together with endocrine factors are the most likely causes for the onset of TTTS (3, 5). Furthermore, De Lia et al. did not explain observations during the specific post-interventional period and seek to explain maternal hemodilution as a reason for polyhydramnios and not, vice versa, maternal hemodynamic alterations due to the treatment of polyhydramnios (24).

Additionally, we found a postoperative decrease in maternal systolic and diastolic arterial blood pressure and heart rate, a finding which also agrees with hemodilution. Nizard et al. described a decrease of maternal systolic and diastolic arterial blood pressure after amnioreduction as well (21). We hypothesize, that the reason for this phenomenon might be an expansion of maternal blood: The reduced intrauterine pressure after amnioreduction leads to an increased placental perfusion resulting in a volume shift of maternal blood into the placental territory. This might be the reason for the decrease of maternal systolic and diastolic arterial blood pressure. Interestingly, and in contrast to our observations, Nizard et al. did not find a change of maternal heart rate after amnioreduction. They speculate that, in addition to a decreased cardiac output and blood pressure after amnioreduction, cardiac preload is increased because of improved venous return to the heart (21). As in our study no maternal echocardiographic measurements were available, further investigations are necessary to obtain an exact explanation of this mechanism.

Maternal hemodynamic parameters showed changes only between the preoperative measurements and the ones immediately after the intrauterine intervention. However, the parameters remained stable for 24 hours postoperatively. Nizard et al. obtained similar results: In group A (drainage volume > 1000 ml) hemodynamic parameters, including hemoglobin, hematocrit and plasma proteins, showed a significant decrease in the short term interval (period

preoperative and 6 hours postoperative). From 6 to 24 post-interventional hours the values remained stable. In group B (drainage volume < 1000 ml) they could not find any changes (21). Gussi et al. demonstrated the same phenomenon: Between the pre-interventional measures and 6 hours post-interventionally a significant decrease of hemoglobin, hematocrit and plasma proteins could be observed. However, values stayed stable between 6 and 24 hours after surgery (23). Therefore, we can assume, that maternal hemodynamic changes after amnioreduction only happen during the first 6 postoperative hours. In considerations of these observations and available data, it might be beneficial to provide specific surveillance of maternal hemodynamics during this critical period to prevent severe maternal hemodynamic complications.

Maternal diuresis per hour showed a significant decrease postoperatively, which emphasizes again the phenomenon of hemodilution. But the fall of diuresis appeared only in the period of 6-24 hours postoperatively. So, for this parameter a decrease in the short term after surgery was not found in our study. However, to our knowledge we are the first who included maternal diuresis in connection with intrauterine interventions into the study and described a significant alteration. Nevertheless, it would be important to evaluate diuresis according to a standardized protocol in further studies to obtain consistent data for statistical analysis.

Interestingly, there was a correlation between volume of amnioreduction and rate of pPROM, which is one of the most important and relatively frequent complications after intrauterine interventions. This correlation was particularly distinctive in the group with a drained volume of 1500 - 2000 ml. Unfortunately, it was not possible to demonstrate a significant correlation in the group of 2000-2500 ml drained amniotic volume as expected. However, Snowise et al. described in their study an overall incidence of pPROM of 39% after fetoscopic laser surgery (25). They could not demonstrate a correlation between the occurrence of pPROM and the amount of amniotic fluid drained. A correlation between volume of amnioreduction and the rate of pPROM in our data set seems to be possible, although the statistical analysis of our data was weak and limited which principally might be due to lack of available data.

Another interesting and new finding is the significant negative correlation between maternal BMI and change of systolic arterial blood pressure until 24 hours postoperatively. The higher the BMI, the smaller the decrease of systolic arterial blood pressure in the postoperative period. Therefore, maternal BMI may play a role regarding postoperative hemodynamic changes and seems to have a protective function regarding changes in maternal hemodynamics, probably due to consequences for intra-abdominal pressure changes.

The rate of total maternal complications was 3.9% in our study, which corresponds to 3 of 80 cases, and can be compared with the rate of 6.0% in the study of Rustico et al. (8).

Strengths of our study were the systematic approach for data collection and the overlapping availability in written and digital form. However, the limitations of every retrospective study design also applies to our study. Another important limitation was, that data concerning long-term outcome and follow-up was not available for all cases. However, most analyses were performed within the short-term period and long-term results were mostly not within the scope of this study.

The next step for further investigations on this topic should be a prospective study with a standardized protocol to prove and confirm our findings. In the pre- as well as in the post-operative term hemodynamic parameters should be measured at standardized points in time. Additionally, it would be important to measure the maternal blood pressure and heart rate continuously as well as the intraabdominal pressure with a urinary catheter in the intraoperative period. At the same time the amniodrainage should be conducted slowly under continuous surveillance of maternal and fetal parameters. Furthermore, changes in placental thickness can could be measured by ultrasound and serve as a proxy for placental expansion before and after amniodrainage.
The obtained data could provide new knowledge about a possible cut-off for volume of drained amniotic fluid. Within this limit severe complications for the mother as well as the fetuses may be prevented in future.

5 Conclusion

Severe maternal complications following intrauterine interventions for TTTS are rare. However, some typical maternal hemodynamic changes could be observed. They may be clinically relevant, especially in the short postoperative term. Moreover, it was possible to show a correlation of those findings with the volume of amniotic fluid drained. Further investigations are needed to clarify underlying pathophysiology.

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