Controlled Amnioreduction for Twin-to-Twin Transfusion Syndrome: Perinatal and Long-Term Neurodevelopmental Outcome

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Abstract

Objectives: Twin-to-twin transfusion syndrome (TTTS) is a severe condition causing preterm delivery, fetal death, and neurodevelopmental disorders. The aim of this study was to develop a simple procedure for amnioreduction that would be controlled by the amniotic pressure and volume removed. Design: Prospective study of cases diagnosed with TTTS. Setting: Lis Maternity and Women's Hospital, Israel. Population: Eleven patients with severe TTTS at stages II and III of Quintero classification were enrolled in the study. Methods: The amniotic pressure was measured along with the removed volume of the amniotic pressure between 17-34 weeks of gestation. The umbilical artery systolic/diastolic ratio for each twin was measured at the beginning and after every 500cc of removed amniotic fluid. Long-term neurodevelopmental outcome of infants with TTTS was performed. Main Outcome Measures: The survival rate was 86.4% although 91% of all twins were Quintero stage III. Results: 18 procedures were performed in this study without any maternal complications. The pattern of amniotic pressure versus the volume removed demonstrated an exponential relationship with a plateau. No tendency in the systolic/diastolic ratio variations was observed during the procedure. Of the 19 surviving twins, 13(59.1%) were considered neurologically normal, 5 (22.73%) neurologically subnormal and 1 (4.55%) abnormal. Results were compared to classical amnioreduction and laser technique procedures. Conclusions: The procedure resulted in a high rate of twin survival. The amniotic pressure was reduced towards normal values. The new procedure seems to be more efficient in terms of twin survival and positive long-term outcomes. Clinical trial ID: NCT04148

'Tweetable abstract'

The efficiency of the controlled amnioreduction procedure has the potential to increase survival rates and wellness of both TTTS fetuses.

Introduction

Monochorionic diamniotic twins are high risk pregnancies that can be complicated (9-15% of all cases) by twin-to-twin transfusion syndrome (TTTS) [1-3]. This severe condition can lead to polyhydramnios in the recipient twin, premature delivery and poor perinatal outcome [4, 5]. Currently, TTTS remains a challenge in modern fetal medicine and in the absence of treatment perinatal mortality is extremely high (>80%)[6, 7].

Management of TTTS has evolved considerably over the last decades[1-7]. Presently, the fetoscopic laser ablation (FLA) of the superficial placental anastomoses is the most common treatment strategy. Many studies compared between amnioreduction (AR) of excess amniotic fluid with FLA strategies and most concluded that FLA is the optimal TTTS treatment, since it resulted in higher survival rate and less neurological complications at six months of age[8-11]. However, the FLA procedure is limited to weeks 16-26 of gestation [12] and is heavily hindered by anatomical restrictions such as anterior placenta. Moreover, the incidence of neurodevelopmental impairment in TTTS survivors treated with FLA is still high [8]. Thus, no single treatment seems to be associated with a clearly improved survival[13].

The amniotic fluid volume increases progressively throughout a normal singleton pregnancy; from 200 to 300 mL in week 16 to 1400 mL in week 40 [14, 15], while maintaining a linear relationship between amniotic pressure and gestational age [16-18]. A similar tendency exists in normal twin pregnancy. However, it has been noted that amniotic pressure in most cases of polyhydramnios and TTTS is higher than in case of an uncomplicated gestations and it significantly falls with the amniotic fluid drainage [19-23]. A comprehensive literature search did not reveal a consensus regarding the volume and rate of amniotic fluid removal, as well as the intrauterine pressure during the procedure. As a result there is neither a commonly accepted treatment protocol, nor indicators for interruption of amniotic fluid drainage. The clinical threshold to terminate the procedure is subjective and based on the clinical experience.

In the present study we implemented a controlled AR procedure and measured the relationship between amniotic pressure, volume removed and blood flow of each twin during the procedure. We also analyzed the long-term neurodevelopmental outcome of children born following a pregnancy complicated by TTTS whose mothers underwent the controlled AR.

Methods

Population

The study group consisted of 11 patients with monochorionic-diamniotic twins that were diagnosed with severe TTTS at stages II or III according to the Quintero classification [24] between 2004 and 2015. We collected the following maternal and perinatal data: maternal age, parity, stage of TTTS at diagnosis, gestational age at the first controlled AR procedure, number of controlled AR procedures, volume removed per one AR session, gestational age at delivery and birth weight for each twin (see Table 1). All the surviving twins were recruited for a long-term neurodevelopmental follow up. The study was approved by the ethics committee of the Tel Aviv Sourasky Medical Center (No. 04-220) and informed consents were signed by the participants.

Controlled amnioreduction procedure

AR was done while simultaneously recording the removed amniotic volume, the amniotic pressure and the flow velocity waveform (FVW) at the umbilical cord. The controlled AR was performed via epidural 18G hypodermic needle under continuous transabdominal ultrasound guidance and local maternal anesthesia. The excess amniotic fluid was drained into a sterile bag through a plastic tube and a 3-way stopcock attached to the hub of the needle. The removed volume of fluid was recorded every 500 ml and followed by measurement of the amniotic pressure and FVW.

The amniotic pressure in the polyhydramniotic sac was measured by a water manometer at the level of the needle tip. The stopcock was opened to the atmosphere to allow for the amniotic fluid to flow from the uterus into the manometer tube. After stabilization within a few seconds, the pressure was acquired in cmH_2O and converted to mmHg by a factor of 0.74. Immediately after reading the pressure, the tap was closed and the fluid re-directed into the sterile bag. The twins FVW was measured with a Doppler ultrasound machine (Sonoline Elegra, Siemens and GE Voluson E6) at the free loop of the umbilical cord. At least five sequential normally shaped FVWs were acquired and the umbilical artery systole/diastole (SD) ratio was calculated.

In case of uterine contractions prior to the procedure, the patients were treated by Indomethacin (PR, 100 mg). In case of repeated uterine contractions, the amniotic pressure was recorded immediately after complete relaxation. The procedure was terminated when the amniotic pressure did not change after two sequential drainages of 500 mL each or in case of maternal discomfort. The duration of the controlled AR was about 80 minutes per procedure. The procedure was repeated only if TTTS occurred again.

Long-term neurodevelopmental follow-up

The long-term neurodevelopmental outcomes of twins born following a pregnancy with TTTS complication were evaluated using a parental questionnaire in Hebrew. The parents completed the questionnaire when the children's age ranged between 2 and 13.5 years. The questionnaire on the overall health status of the twins

included 10 subscales that describe distinctive neurodevelopmental and functioning areas: vision, hearing, speech, gross motor, fine motor, self-care, emotions expression, memory/learning, cognitive and problem-solving, and feeling discomfort or pain. The responses were rated according to a 3-point scale: optimal (i.e., normal evaluation results), suboptimal (i.e., mild anomalies without functional deficits) or abnormal (i.e., neurological and/or functional impairment or deficits).

Statistical analysis

Descriptive statistics was used for the demographic, clinical, obstetrical and perinatal parameters. The survival rate was compared to that reported in the literature. Neurodevelopmental outcomes in surviving twins were compared to those previously reported by using the frequency of abnormal score across the 10 subscales.

Results

The 11 patients recruited for this study underwent 18 controlled AR procedures due to severe TTTS. The choice of AR treatment instead of FLA was done by the mother. There were no cases of maternal infection or complications as well as premature delivery in the upcoming 48 hours passed the procedure. Clinical and perinatal outcome characteristics of the study population are presented in Table 1.

Ten of 11 TTTS cases were categorized as Quintero stage III (91%). The gestational age at the first AR treatment ranged from 17 to 32 weeks, with a mean age of 26.8 weeks. The amniotic fluid volume removed during a single session varied between 700-4500 ml. The time required to perform the procedure ranged from 20 minutes to more than two hours, in accordance with the drained volume. Five patients (45.5%) were treated with the serial controlled AR. Thus, the number of amniocenteses ranges from one to four per pregnancy (mean 1.6), in a median interval of 14.5 days. In all cases births were premature with delivery at 28 to 35 gestational weeks. The mean donor weight was 1185±470g and the mean recipient weight was 1566±547g. Nine out of 11 twin pairs were born alive. The outcomes in the other 2 pregnancies were as follows: a spontaneous delivery at week 35 with one surviving twin and the other macerated stillbirth, and a late abortion in week 22 with intrauterine death of one fetus and the co-twin died soon after birth. Therefore, the total survival rate was 19 out of 22 twins (86.4%).

Controlled amnioreduction outcome

Amniotic pressures were measured prior, during and at the end of the AR procedure. The pattern of the decreasing amniotic pressure during removal of the excess volume of fluid is depicted in Figure 1. The pressures reached a plateau at the end of the completed procedures except the 5 patients in which AR was interrupted due to the patient discomfort. There was no correlation between the amount of drained amniotic volume, duration of AR procedure and the reached pressure plateau. The obtained amniotic pressures were compared with the normal pressures as reported by Fisk*et al* [16]. The pressure drop at each AR procedure is shown in Figure 2 along with the reference range for singleton pregnancies. The initial pressures for all patients were higher than the normal range. As expected, the post-procedure pressures were lowered to be in the reference range in 61.1% of cases while slightly higher than the norm in 38.9%.

The umbilical artery S/D values that were measured for each fetus pre- and post-procedure are compared with the reference range for singleton pregnancies [25]. The initial S/D ratio of recipient was higher (mean percent difference is 29.3%) in 3 cases, while in the rest cases the donor twin had the higher S/D ratio. Absence of end diastolic flow (AEDF) occurred in 3 donors, and thus, an arbitrary value of 9 was given as the initial one for graphic representation. All these donors showed some hemodynamic improvement after the AR. In general, most (23 of 36, i.e., 63.8%) of the post-procedure S/D ratio became within the normal range according to the given weeks of gestation. Comparison of inter-twin differences of S/D ratio values in pre- and post-procedure did not show some tendency: inter-pair differences were significantly decreased after the procedure in 7 twins, increased in 5 twins and were unchanged in 6 cases.

Long-term neurodevelopmental outcome

We followed up all 19 living twins born between 2004 and 2015. The mean age of the twins at the time of the survey was 7 years (range 2-13 years). Of the 19 tested children, 13 (68.4%) were reportedly normal, 5 children (26.3%) were scored as subnormal and one (5.3%) was rated abnormal due to cerebral palsy. Examples of mild neurologic anomalies included the following functioning areas: vision, speech, dexterity, learning and remembering. The results of the survival rate and long-term neurodevelopmental outcomes were compared with the AR and FLA procedures' results published by other authors [10, 11, 13, 26-28] and are presented in Tables 2.

Discussion

Main Findings

The controlled AR procedure resulted in a relatively high rate of twin survival independently of the gestation week. Moreover, it is objectively more efficient since it revealed positive short and long-term outcomes. The pattern of the amniotic pressure versus the removed fluid demonstrated an apparent exponential relationship with a plateau and represented a logical reason for procedure duration and termination.

The controlled AR procedure was applied to 11 pregnant women with twins diagnosed with TTTS, including severe cases at Quintero stages II and III. In this study group, the procedure was terminated based on amniotic pressure measurements, rather than the removed fluid volume. There were no cases of maternal infection or complications, as well as premature delivery in the 48 hours post procedure.

The overall survival rate was 19/22 (86.4%), which is higher than published outcomes of serial AR interventions [8, 10, 11, 13, 27, 28]. It should be noted that the controlled AR procedure was also successful in cases of severe TTTS in patients who were firstly treated at the gestational ages of 17 to 32 weeks, while in published reports AR was recommended only in cases of mild disease or when FLS interventions were unsuccessful [9].

In the present study the amniotic fluid volume removed during the session varied between 700-4500 ml (Figure 1). Presently, there is no consensus regarding the amount removed per session. The published data revealed a wide variety of values from 400 to 7500 mL, which are within 50% to 435% of the mean volume for any given gestational age[2, 5, 6, 29, 30]. It has been suggested that drainage of a large quantity of amniotic fluid may result in unpredictable changes in blood flow across the vessel connections [31]and 1100 ml should be the weekly maximal removed amniotic fluid ensure survival [32]. The present study demonstrated that there is no definite volume drainage that predicts the procedure efficiency.

The umbilical artery S/D ratio in uncomplicated twin pregnancy shows close agreement with the normal range for singleton pregnancy[33]. It is obvious that reduction in amniotic fluid volume decreases the pressure associated with polyhydramnios and leads to increased flow from the placenta to the fetus [34]. In the present study, the initial umbilical artery S/D ratio was above the 95th percentile of the normal range in 10 cases and within it in 8 cases**.** The most noticeable positive effect of the procedure on FVW was observed in the 3 cases of severe TTTS with initial AEDF, but the post-procedure S/D ratio did not reach the normal range for the given week of gestation. Nevertheless, this outcome is in agreement with previous reports on higher fetal mortality in cases of AEDF in either the donor or the recipient (i.e., patients 1, 4, 8)[5, 28, 32, 35]. The post-procedure S/D ratio changed to be within the normal range in 63.8% of cases, below it in 4 cases (11.2%) and above it in the remaining 9 cases (25%). We did not observe a tendency in the S/D ratio changes due to the procedure. Thus, we assume that post-procedure changes in S/D ratio are related to the cardiovascular system slow adaptation to gradual changes, but unpredictable.

The present results indicate that the pre-drainage amniotic pressure was higher in comparison to the reference range (Figure 2) and are consistent with some published data [20, 36-38]. As expected, amniotic pressures always decrease with fluid drainage and the mean difference between pre- and post-procedure pressures was 9.1±5.4 mmHg. The pressure drop had an exponential pattern with a final plateau and further volume removal had no effect, as reported by others[20, 22, 39]. While one study observed a linear relationship between the removed amniotic volume and the pressure drop[22], other studies could not find such a relationship[20, 39].

Finally, we also followed for a long-term all surviving twins that their mothers were treated with controlled

AR. Analysis of the data revealed that over 2/3 of the twins were neurologically normal, about 1/4 of them demonstrated minor neurodevelopmental impairment and only one child (about 5%) with a cerebral injury.

Strengths and Limitations

A major limitation of this study is the relatively small sample size. The removed amniotic fluid into a standard urine collecting bag may have up to a 5% measurement error. Meanwhile, an inaccuracy in the amniotic pressure measurement exists that may give an error of up to 10%.

Nevertheless, the results revealed a clear pattern of the amniotic pressure that has not been studied before.

Interpretation

It is apparent that placental communication vessels crossing between the twins may affect hemodynamics of both cardiovascular systems in wide variations. However, to date the pathophysiology of TTTS is still not fully understood and a commonly accepted therapy to treat severe cases of TTTS does not exist. Moreover, there are important unanswered questions related to the AR protocol. How much of the amniotic fluid volume should be removed? What should be the rate of fluid drainage? What are the criteria for amniotic fluid drainage termination? Is the procedure restricted to specific timing during gestation? The research efforts to answer these open questions are still going on.

It has been reported that management of TTTS either with FLA or AR prolongs the pregnancy without guarantee for normal growth of both infants [8, 11]. The present results demonstrated that the controlled AR is safe and can be repeated if needed independent of the gestation week. Therefore, we believe that controlled AR with slow flow rate under gravity is less invasive then FLA. In contrast to suggestions that the fluid should be drained as quickly as possible[28], we have shown that gravity driven fluid drainage at slow rates is more favorable for the fetuses, due to both a gradual pressure drop and increase in the umbilical flow rate from mother to fetus. Furthermore, it seems that gradual reduction of the amniotic volume, as well as decreasing the amniotic pressure on the placental chorionic vessels result in more moderate impact on the cardiovascular system for both fetuses. Nevertheless, the controlled AR procedure resulted in a higher survival rate and positive long-term outcomes compared to other studies[10, 11, 13, 26-28].

Conclusion

The controlled AR procedure based on simultaneous measurement of the amniotic pressure and the removed fluid has been developed. Analysis of the descending amniotic pressure as the removed amniotic fluid volume increases revealed exponential decay with a final plateau for the first time. This asymptotic pattern indicates that removing additional volumes would have a negligible effect on the amniotic pressure. Accordingly, monitoring the amniotic pressure may be more effective for the therapy management rather than estimation of drained fluid volume. Moreover, the final plateau of the amniotic pressure could serve as a diagnostic criterion for procedure termination. The efficiency of this new methodology has the potential to increase survival rates and wellness of both TTTS fetuses. Furthermore, the controlled AR is a simple, non-sophisticated procedure that does not require complicated or expensive equipment and special training.

Disclosure of interests: the authors have no conflicts of interest

Contribution to Authorship:

A.J.J conceived and supervised the project.

A.J.J planned the experiments.

A.J.J and Z.G. carried out the experiment.

A.F.V developed a questionnaire, contributed to the analyzing and interpretation of the long-term neurodevelopmental results.

Z.G. wrote the manuscript with supervision of A.J.J and D.E.

All authors provided critical feedback and helped shape the research analysis and manuscript.

Details of ethics approval:

The study was approved by the ethics committee of the Tel Aviv Sourasky Medical Center (No. 04-220.

The clinical trial identification number: NCT04148859

URL of the registration site: https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S0009A5A&selectaction=E
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References

1. Blickstein I. The twin-twin transfusion syndrome. *Obstet Gynecol* 1990; **76** : 714-22.
2. Moise KJ Jr, Dorman K, Lamvu G, Saade GR, Fisk NM, Dickinson JE, et al. A randomized trial of amnioreduction versus septostomy in the treatment of twin-twin transfusion syndrome.*Am J Obstet Gynecol* 2005; **193** : 701-7.
3. Yeast JD. Polyhydramnios/Oligohydramnios in twin pregnancy.*NeoReviews* 2006; **7** : 305- 9.
4. van Gemert MJC, Kranenburg-Lakeman P, Milovanovic Z, Vergroesen I, Boer K. Polyhydramnios and arterio-arterial placental anastomoses may beneficially affect monochorionic twin pregnancies. *Phys Med Biol* 2001; **46** : 57-63.
5. Zikulnig K, Bregenzer T, Bäz E, Hackelöer BJ. Prognosis factors in severe twin-twin transfusion syndrome treated by endoscopic laser surgery. *Ultrasound Obstet Gynecol* 1999; **14** : 380-7.
6. Gardiner HM, Taylor MJ, Karatza A, Vanderheyden T, Huber A, Greenwald SE, et al. Twin-Twin Transfusion Syndrome: The Influence of Intrauterine Laser Photocoagulation on Arterial Distensibility in Childhood. *Circulation* 2003; **107** : 1906-11.
7. Fieni S, Gramellini D, Piantelli G, Verrotti C, Cavallotti D. Twin-twin transfusion syndrome: a review of treatment option.*Acta Biomed* 2004; **75** Suppl 1:34-9.
8. Li X, Morokuma S, Fukushima K, Otera Y, Yumoto Y, et al. Prognosis and long-term neurodevelopmental outcome in conservatively treated twin-to-twin transfusion syndrome. *MC Pregnancy and Childbirth*2011; **11** : 32.
9. Wagner S, Repke JT, Ural SH. Overview and Long-term Outcomes of Patients Born With Twin-to-Twin Transfusion Syndrome. *Rev Obstet Gynecol* 2013; **6** :149-54.
10. Senat MV, Deprest J, Boulvain M, Paupe A, Winer N, Ville Y. Endoscopic Laser Surgery versus Serial Amnioreduction for Severe Twin-to-Twin Transfusion syndrome. *N Engl J Med* 2004; **351** :136-44.
11. Crombleholme TM, Shera D, Lee H, Johnson M, D'Alton M, Porter F and ect. A prospective randomized multicenter trial of amnioreduction versus selective fetoscopic laser photocoagulation for the treatment of severe twin–twin transfusion syndrome. *Am J Obstet Gynecol*2007; **197** : 396.e1-9.
12. Sago H, Ishii K, Sugibayashi R, Ozawa K, Sumie M, Wada S. Fetoscopic laser photocoagulation for twin–twin transfusion syndrome. *J Obstet Gynaecol Res* 2018; **44** :831–9.
13. Lopriore E, Nagel HT, Vandenbussche FP, Walther FJ. Long-term neurodevelopmental outcome in twin-to-twin transfusion syndrome.*Am J Obstet Gynecol* 2003; **189** : 1314-9.
14. Beall MH, van den Wijngaard JP, van Gemert MJ, Ross MG. Amniotic fluid water dynamics. *Placenta* 2007; **28** : 816-23.
15. Brace RA & Wolf EJ. Normal amniotic fluid volume changes throughout pregnancy. *Am J Obstet Gynecol* 1989; **161** : 382-8.
16. Fisk NM, Ronderos-Dumit D, Tannirandorn Y, Nicolini U, Talbert D. Normal Amniotic Pressure Throughout Gestation. *British J Obstet Gynecol* 1992; **99** : 18-22.
17. Weiner CP, Heilskov J, Pelzer G, Grant S, Wenstrom K, Williamson RA. Normal values for human umbilical venous and amniotic fluid pressures and their alteration by fetal disease. *Am J Obstet Gynecol*1989; **161** : 714-7.
18. Siders IG, Nicolaides KH. Amniotic fluid pressure during pregnancy.*Fetal Diagn Ther* 1990; **5** : 104-8.

19. Fisk NM, Tannirandorn Y, Nicolini U, Talbert DG, Rodeck CH. Amniotic pressure in disorders of amniotic fluid volume. *Obstet Gynecol*1990; **76** :210–4.
20. Garry D, Lysikiewicz A, Mays J, Canterino J, Tejani N. Intra-amniotic pressure reduction in twin-twin transfusion syndrome. *J Perinatol* 1998; **18** : 284-6.
21. Hartung J, Chaoui R, Bollmann R. Amniotic fluid pressure in both cavities of twin-to-twin transfusion syndrome: a vote against septostomy. *Fetal Diagn Ther* 2000; **15** : 79-82.
22. Ville Y, Sideris I, Nicolaides KH. Amniotic fluid pressure in twin-to-twin transfusion syndrome: an objective prognostic factor.*Fetal Diagn Ther* 1996; **11** : 176-80.
23. Meagher S, Tippett C, Renou P, Baker L, Susil B. Twin-twin transfusion syndrome: intraamniotic pressure measurement in the assessment of volume reduction at serial amniocenteses. *Aust N Z J Obstet Gynaecol* 1995; **35** : 22-6.
24. Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M. Staging of twin-twin transfusion syndrome. *J Perinatol* 1999;**19** : 550e5.
25. Maulik D. Doppler Ultrasound in Obstetrics and Gynecology. Berlin: Springer-Verlag Berlin Heidelberg; 2005.
26. Di Mascio D, Khalil A, D'Amico A, Buca D, Panici PB, Flacco ME, et al. Outcome of twin-twin transfusion syndrome according to the Quintero stage of the disease: a systematic review and meta-analysis.*Ultrasound Obstet Gynecol* 2020; doi:10.1002/uog.22054.
27. Lenclen R, Ciarlo G, Paupe A, Bussieres L, Ville Y. Neurodevelopmental outcome at 2 years in children born preterm treated by amnioreduction or fetoscopic laser surgery for twin-to-twin transfusion syndrome: comparison with dichorionic twins. *Am J Obstet Gynecol* 2009;**201** : 291.e1-5.
28. Frusca T, Soregaroli M, Fichera A, Taddei F, Villani P, Accorsi P, et al. Pregnancies complicated by Twin-Twin transfusion syndrome: outcome and long-term neurological follow-up. *Eur J Obstet Gynecol Reprod Biol* 2003; **107** : 145-50.
29. Abdel-Fattah SA, Carroll S, Kyle PM, Soothill PW. Amnioreduction: How Much to Drain? *Fetal Diagnosis and Therapy* 1999; **14** : 279–82.
30. Ville Y, Hyett J, Hecher K, Nicolaides K. Preliminary experience with endoscopic laser surgery for severe twin-twin transfusion syndrome.*N Engl J Med* 1995; **332** : 224-7.
31. Jauniaux E, Holmes A, Hyett J, Yates R, Rodeck C. Rapid and radical amniodrainage in the treatment of severe twin-twin transfusion syndrome. *Prenat Diagn* 2001; **21** : 471-6.
32. Mari G, Roberts A, Detti L, Kovanci E, Stefos T, Bahado-Singh RO, et al. Perinatal morbidity and mortality rates in severe twin-twin transfusion syndrome: results of the International Amnioreduction Registry. *Am J Obstet Gynecol* 2001; **185** :708-15.
33. Giles WB, Trudinger BJ, Cook CM. Fetal umbilical artery flow velocity-time waveforms in twin pregnancies. *Br J Obstet Gynaecol* 1985; **92** : 490–7.
34. Umur A, van Gemert MJ, Ross MG. Fetal urine and amniotic fluid in monochorionic twins with twin-twin transfusion syndrome: simulations of therapy. *Am J Obstet Gynecol* 2001; **185** : 996-1003.
35. Taylor MJ, Denbow ML, Duncan KR, Overton TG, Fisk NM. Antenatal factors at diagnosis that predict outcome in twin-twin transfusion syndrome. *Am J Obstet Gynecol* 2000; **183** : 1023-8.
36. Bruner JP and Crean DM. Equalization of amniotic fluid volumes after decompression amniocentesis for treatment of the twin oligohydramnios-polyhydramnios sequence. *Fetal Diagn Ther* 1999;**14** : 80-5.
37. Bajoria R. Chorionic plate vascular anatomy determines the efficacy of amnioreduction therapy for twin–twin transfusion syndrome.*Human Reproduction* 1998; **13** : 1709–13.
38. Saade GR, Belfort MA, Berry DL, Bui TH, Montgomery LD, Johnson A, et al. Amniotic septostomy for the treatment of twin oligohydramnios-polyhydramnios sequence. *Fetal Diagn Ther* 1998;**13** : 86–93.
39. Bower SJ, Flack NJ, Sepulveda W, Talbert DG, Fisk NM. Uterine artery blood flow response to correction of amniotic fluid volume. *Am J Obstet Gynecol* 1995; **173** : 502-7.

Figure Captions

Figure 1	The amniotic pressure versus the drained volume of amniotic fluid during the controlled AR procedure.
Figure 2	Amniotic pressure drop after the controlled AR procedure versus the week of gestation as compared with the normal amniotic pressure range. Black dash curves represent the 5% and 95% percentiles of amniotic pressure during the weeks of gestation; arrows represented the pressure drops obtained during the controlled AR procedure.

Table 1. Clinical characteristics of the study population with TTTS

No	**Maternal data**	**Maternal data**	**Maternal data**	**Maternal data**	**Maternal data**	**Maternal data**	**Twins out-come**	**Twins out-come**	**Twins out-come**
	Age [years]	**Quintero stage of TTTS**	**Gestation age at first AR [weeks]**	**Number of AR**	**Volume re-moved per AR [mL]**	**Delivery week & mode**	**Twin 1**	**Twin 1**	**Twin 2**
							Weight [g]	**Apgar Score**	**Weight [g]**
1	41	III	17	1	700	35-SD	2301	9/10	*
2	40	II	30	2	4500 2200	34-CS	1455	8/9	2235
3	48	III	26	2	3000 3000	35-CS	2043	9/10	2075
4	34	III	20	2	1500 1500	22 Late abortion	381	**	555
5	32	III	21	4	3000 2700 4000 3000	28-CS	820	9/10	1151
6	25	III	29	1	4500	32- CS	1115	7/8	1708
7	36	III	29	2	2000 2000	31- CS	1117	7/9	1339
8	33	III	28	1	2300	29- CS	773	4/8	931
9	31	III	29	1	2700	31- CS	1180	6/8	1494
10	29	III	31	1	3000	33- CS	1329	7/8	1727
11	35	III	32	1	3000	32- CS	1637	5/8	1697

* survival one twin (IUFD)

** late abortion, early neonatal death

Table 2. Comparison of perinatal and long-term neurodevelopmental outcome between the study group and literature

Reference	Survival rate, %	Long-term neurodevelopmental outcome	Long-term neurodevelopmental outcome	Long-term neurodevelopmental outcome	Long-term neurodevelopmental outcome
		Normal, %	**Subnormal, %**	**Subnormal, %**	**Abnormal, %**
Frusca at el, 2003	53.4%	58.1%	16.1%	16.1%	25.8%
Lopriore at el, 2003	52.7%	74%	74%	74%	26%
Senat at el, 2004	41%	———-	———-	———-	———-
Crombleholme at el, 2007	60%	———-	———-	———-	———-
Lenclen, at el, 2009	61.1%	81%	81%	9.5%	9.5%
Li at el, 2011	57.1%	70%	70%	10%	20%
Di Mascio at el, 2020 *	85.0% at stage II 80.6% at stage III	———-	———-	———-	———-
The present study	86.4%	68.4%	68.4%	26.3%	5.3%

* The data published by these authors include only FLA procedure results and aggregated from the systematic review.

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