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Atypical twin-to-twin transfusion syndrome

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BACKGROUND

Monochorionic twins constitute 25-30% of all twin gestations.[1,2] The incidence of multiple gestations has been rising for several years due to increase in maternal age and the wide use of assisted reproductive technology (ART).[2] Extended culture associated with blastocyst transfer is associated with a significant increase in monozygotic twinning with its inherent complications.[3] The complications of monochorionic gestations include twin-twin transfusion syndrome (TTTS, 10-15%), selective fetal growth restriction (sFGR, from 10-15%), twin anemia polycythemia sequence (TAPS, 3-13%), and twin reversed arterial perfusion sequence (TRAP, in around 1%). Most of these are attributed primarily to a single shared placenta with intertwin vascular connections.

TTTS complicates 8-10% of monochorionic gestations and without treatment can lead to significant mortality and morbidity.[4] The diagnosis of TTTS relies on the presence of oligohydramnios-polyhydramnios sequence. The staging of TTTS is traditionally described by the Quintero classification which was developed in 1999 and is based on ultrasonographic findings.[5] According to this classification, the severity of TTTS is assigned according to stringent ultrasound criteria, describing TTTS as a chronologically progressive complication. Traditionally, Stage 1 TTTS has been defined as oligohydramnios (deepest vertical pocket [DVP] <2 cm) in the donor, and polyhydramnios (deepest vertical pocket >8cm or <6cm prior to 18 weeks' gestation) in the recipient. Stage II is failure to visualize the bladder of the donor, suggestive of fetal anuria, along with oligohydramnios-polyhydramnios sequence. Stage III is characterized by the finding of critically abnormal fetal Doppler parameters in either the arterial or the venous system of the donor/recipient. Stage IV is characterized by the finding of fetal hydrops, and Stage V by intrauterine fetal demise of either one or both twins. However, this hypothesis of serial progression in severity with increasing stage has been challenged and refuted by a large clinical series.[6]

A subset of monochorionic diamniotic (MCDA) twin pregnancies exhibit advanced TTTS without any signs of preceding stages, e.g. presence of critical Doppler abnormalities without demonstrable donor anuria. These cases have been grouped into an overarching category called 'atypical TTTS'. Another group referred to as atypical TTTS are those with co-existent pathologies, like TAPS, sFGR, cardiac compromise or complicated by spontaneous septostomy. In a retrospective series by Paek et al[7], the prevalence of 'atypical' TTTS', defined as severe TTTS without meeting amniotic fluid criteria (oligohydramnios-polyhydramnios sequence), was reported as 7.2%, the majority of which were either Quintero stage 3 or 4. Laser photocoagulation is the therapy of choice for TTTS occurring at least up to 26 weeks,[8-10] so it is of paramount importance to differentiate cases of atypical TTTS from other non-

TTTS pathologies to avoid delay or confusion in the diagnosis and allowing optimal outcomes by timely referral for prenatal laser therapy. Table 1 enlists the studies which report on the atypical TTTS cases.

Here we collate different case scenarios which have been described as atypical TTTS and aim to better elucidate the underlying mechanisms.

Scenario 1: TTTS with sFGR

The coexistence of sFGR with TTTS is not uncommon, with a reported prevalence of up to 65%.[11,12] sFGR is explained by unequal placental territory sharing whereas unbalanced placental vascular anastomoses is fundamental to the development of TTTS. The exact mechanism by which these two pathologies are interrelated remains elusive.

There are varying opinions among experts as to whether cases of TTTS complicated by sFGR should be considered as 'atypical' or not. It can be argued that in TTTS cases with concomitant sFGR, the donor twin usually suffers from sFGR due to decreased vascular perfusion and net volume depletion, which is the basic pathology in TTTS itself; therefore, growth discordance is merely a part of the clinical spectrum of the disease. The counter argument is that a number of studies have shown that TTTS donors with sFGR have an increased risk of demise post-laser and poor perinatal survival compared to non-sFGR TTTS donor twins. Therefore, they should be considered as special cases as their outcomes are significantly different to what is generally expected with TTTS twins at similar Quintero stages.[11-14]

In a large series from the Netherlands, Groene et al noted significantly lower perinatal survival for donor twins in the TTTS with sFGR compared to the recipients (72% versus 81%) post laser therapy (Table 1).[12] Similarly, Van Winden et al reported poor post laser donor survival rates in their cohort of 241 TTTS cases with growth restricted donor fetuses.[11] In both series, the risk of adverse outcomes was proportional to the degree of Doppler abnormality in the growth restricted donor fetuses, and not merely to size discordance. Until recently, the survival rates following laser therapy in TTTS have been variably reported depending on the definition of sFGR. According to the ISUOG guidelines, sFGR has now been defined as EFW of either twin as less than 10th centile and inter-twin weight discordance of ≥25%.[15] Donepudi et al described a cohort of 492 TTTS cases (where sFGR was defined according to ISUOG guidelines) to study the predictors of donor demise after laser therapy.[16] An inter-twin weight discordance of 37% with EFW of donor less than the first percentile was found to be most predictive of donor demise at 30 days of birth. As size discordance appears quite prevalent in TTTS fetuses, it may be reasonable to define only those cases as 'atypical' which have

associated umbilical artery Doppler abnormalities, which has a significant bearing on the outcomes, independent of TTTS itself (Figure 1).

Unlike growth restricted singletons or dichorionic diamniotic (DCDA) twins, MCDA twins with sFGR demonstrate a long latency period from the time of diagnosis to deterioration or need for delivery (up to 10 weeks versus 3–4 weeks from diagnosis of FGR in singletons or DCDA twins).[17-20] This is attributed to rescue transfusion to the smaller fetus from the arterio-arterial anastomoses with an increase in its functional placental territory. On the other hand, these large arterio-arterial channels can lead to acute unpredictable transfusion events with adverse perinatal outcomes. It has been postulated that laser therapy results in the loss of protective anastomoses to the donor twin, which may be reliant on these channels for its supply of nutrients, culminating in increased adverse outcomes.[11-14] However, if the donor twin is growth restricted not due to a small placental share, but as a result of fluid imbalance causing siphoning away of nutrients, they would benefit from the laser photocoagulation of anastomoses. Currently, there are no objective criteria or ultrasound features to differentiate between these two groups.

These cases of TTTS with concomitant sFGR are still candidates for laser therapy; however, parents should be made aware of the potentially worse prognosis. In presence of factors which are associated with risk of donor demise, the option of selective reduction should be discussed in order to improve long term outcomes for the surviving twin.

Scenario 2: Cases of TTTS with evidence of cardiac compromise without notable amniotic fluid discordance

Occasionally cases of TTTS are encountered where there is evidence of cardiac compromise (fetal hydrops, cardiomegaly, pulmonary stenosis, etc) on fetal echocardiography without significant amniotic fluid discordance (AFD) (Figure 2; Supplementary video 1).

Although the Quintero classification of TTTS is simple, aids communication with patients and allows comparison of different treatment modalities, it does not correlate well with perinatal outcomes, and progression/regression may not always be related to the assigned stage.[6] This may be due to the fact that it does not take into account the component of cardiovascular compromise as a contributory mechanism to the pathophysiology of TTTS. Quintero staging was proposed in 1999 when the prevalence and spectrum of fetal cardiovascular effects in TTTS had not been fully appreciated. However, over the following two decades, it has been established that subtle cardiac dysfunction is present, especially in the recipient twin, even in the earliest stages of TTTS, which increases in severity with disease progression.[21]

Although the primary pathology of TTTS is unbalanced vascular anastomoses, cardiovascular compromise occurs due to the endocrine cascade and inter-twin fluid imbalance. Volume depletion in the donor twin activates the renin angiotensin aldosterone system (RAAS) leading to compensatory release of vasoactive mediators like endothelin-1, renin and angiotensin-2. These enter the shared circulation causing deleterious effects on the recipient, which is already compromised due to the volume overload. The recipient exhibits a constellation of features of cardiac compromise manifested by cardiomegaly, atrioventricular regurgitation, increased flow velocity across pulmonary valve, ventricular dilation and subsequent progression to ventricular hypertrophy and functional right outflow tract obstruction.

Therefore, the cardiovascular system of the recipient twin bears the brunt of both direct (fluid overload) and indirect (endocrine) mechanisms, which is not acknowledged in the traditional Quintero classification, especially in the early stages.

Therefore, a number of scoring systems have been proposed to effectively characterize cardiovascular functional status in TTTS fetuses: the Cincinnati modification of the Quintero staging, Cardiovascular Profile Score (CVPS), and Children's Hospital of Philadelphia (CHOP) score.[22,23] Unfortunately, there is only modest correlation among these systems, and none correlates well with the therapeutic response and outcomes. This may be due to discrepancy in reporting of outcomes and wide variation in treatment protocols at different fetal therapy centers. The functional cardiovascular changes in the early stage of TTTS show an acute response to laser therapy and generally resolve unless they have already caused irreversible structural lesions. Cardiac changes may persist or even progress, necessitating continued cardiac monitoring, even in the postnatal period.[24,25] However, the current recommendations would limit the fetal therapy specialists from offering laser therapy in these atypical cases. Unlike TTTS cases with sFGR, selective reduction does not appear to be very reasonable as majority of these functional lesions disappear after laser therapy without any sequelae. It has been proposed that the role of inter-twin pair discordance of cardiovascular parameters as early markers of cardiovascular dysfunction needs to be explored to inform management decisions.[26]

Scenario 3: TTTS with concomitant pre-operative TAPS

The monochorionic twin-specific complication of TAPS was first described in 2007 by Lopriore et al where the investigators first reported two pairs of MCDA twins with hemoglobin discordance but without any fluid discordance.[27] The reported incidence of spontaneous TAPS is 1-5%.[15,28] TAPS is defined as a chronic form of feto-feto transfusion through small vascular channels which allow slow passage of red blood cells to cause hemoglobin discordance, without causing a significant volume shift to trigger a compensatory RAAS activation.

Traditionally, TTTS and TAPS have been defined by mutually exclusive definitions of fluid and hemoglobin discordance, respectively. TTTS generally develops at pre-viable gestations while the incidence and severity of TAPS increases with advancing gestation. As more sonographers now routinely examine the middle cerebral artery (MCA) Dopplers in line with recommendations from professional bodies for fortnightly surveillance of MCDA twins,[15] there is an increasing subset of TTTS fetuses in which hemoglobin discordance is also being identified. This preoperative occurrence of concomitant TAPS is different to that seen after laser therapy for TTTS, the latter largely attributed to residual missed small anastomosis at the periphery of the placenta. Thus, TTTS with spontaneous TAPS can be suspected by the presence of oligohydramnios-polyhydramnios together with inter-twin MCA peak systolic velocity (PSV) discordance (Figures 3 and 4).

There is scarce literature regarding the occurrence of preoperative spontaneous TAPS in TTTS cases, although there are sporadic case reports and series. In 1998 Denbow *et al* first described a series of 36 twin pregnancies with TTTS, also demonstrated to have intertwin hemoglobin discordance of varying degrees on fetal blood sampling, with progressive increase with gestational age.[29] The authors suggested assessment of hemoglobin discordance (>15%) to time elective delivery and not as a diagnostic criterion for TTTS.

Since then, two large series of TTTS with preoperative TAPS have been described comprised of 134 and 369 MCDA twin pregnancies, respectively.[30,31] In the first series by Vanwinden *et al*,[30] published in 2015, the prevalence of TAPS in TTTS fetuses was 2.4%. They further described the cases as 'typical' or 'atypical' based on the number and size of the placental anastomoses. Typical cases of TAPS had smaller and few communications with striking color difference of the fetal skin visualized at the time of fetoscopy, whereas cases were labeled as atypical if the placental communications were extensive, large caliber and predominantly superficial. There was no difference in the Quintero staging of the typical and atypical TTTS-TAPS cases. In the second series by Donepudi et al published in 2016,[31] the prevalence of preoperative TAPS was 8.3% of TTTS cases, and the authors reported fewer and smaller intraplacental anastomosis compared to the cases of TTTS without TAPS.

Tollenaar et al applied the new antenatal diagnostic criteria for TAPS i.e. Delta MCA PSV >0.5MoM to report a higher prevalence of 15.2% TTTS-TAPS in their cohort of 461 fetuses with TTTS.[32] Although both Donepudi et al and Tollenaar et al report similar or favourable perinatal outcomes and later onset of the disease in TTTS cases with TAPS compared to isolated TTTS, caution should be exercised before drawing conclusions owing to the retrospective nature of the series.

The pathophysiology of TAPS with TTTS is still speculative; perhaps a dynamic complex interplay of the anastomotic channels with changes in perfusion pressures may be the driving force. More insight can be obtained into this entity if all such cases had a systematic post-delivery examination and injection of the placenta. Nonetheless, these cases also provide a strong argument that TTTS and TAPS are not two distinct entities but are continuum of a spectrum. The evidence to guide therapy in these complicated pregnancies remains limited. Moreover, the choice of therapy for TTTS and TAPS may be different depending on the severity and the gestational age at presentation.

Scenario 4: Monoamniotic twin pregnancies with TTTS

Monochorionic monoamniotic (MCMA) twins, that share an amniotic sac, are a rare type of monozygotic twins, with a reported incidence of one in 10,000 pregnancies overall or 5% of monochorionic pregnancies.[33] TTTS in MCMA twins is 2.5-2.7 times less common than in MCDA twins.[33] This has been mainly attributed to almost universal presence of protective arterio-arterial anastomoses in the monoamniotic placenta in contiguous cords. Paradoxically, these large anastomoses can also result in episodes of acute transfusion leading to increased perinatal morbidity and mortality. TTTS is particularly challenging to diagnose in MCMA twins, especially in the earliest stages, as the classical oligohydramnios-polyhydramnios feature cannot be demonstrated in the absence of an inter-twin membrane. (Figure 5) Studies report that around 50% of TTTS cases in MCDA twins remain stable in stage 1.[34-36] As the diagnosis of TTTS in MCMA pregnancies tends to rely on an absent bladder in one twin with polyhydramnios, stage 1 cases would remain obscure or unrecognized.

There is paucity of evidence on the optimal therapy for TTTS in monoamniotic twin pregnancies which is comprised of small retrospective series with non-uniform management algorithms.[37] While some centers advocate strict vigilance by in-patient monitoring with daily CTGs, some centers monitor women as outpatients. In the largest review of the outcome of MCMA twins with TTTS, the pooled data demonstrated lower perinatal survival following laser therapy (47% versus 65% in MCMA twins compared to MCDA twins with TTTS, respectively).[38] It has been postulated that proximal cord insertions in MCMA twins with overlapping vascular territories makes identification of the vascular equator difficult with ensuing technical challenges during the laser surgery. The difference in survival rates following laser has also been attributed to delay in the diagnosis of TTTS, hence selection of more advanced cases with cardiovascular compromise. The caveat to this argument is that laser therapy would not be offered to cases, whether MCMA or MCDA, in stage 1 where expectant treatment is the usual norm and therapy is reserved for certain fetal and maternal indications.[36]

Scenario 5: TTTS with spontaneous septostomy / moderate fluid discordance

Infrequently, cases of TTTS have been described in the absence of amniotic fluid discordance, i.e., without oligohydramnios-polyhydramnios sequence, but where there is a distended recipient bladder and the bladder of the suspected donor twin cannot be visualized (Figures 6 and 7; Supplementary video 2). Such sporadic cases may be explained by spontaneous septostomy due to the increased amniotic fluid pressure in the recipient sac.[39-41] Other possible mechanisms include infections or developmental disturbances. The first case of TTTS with spontaneous septostomy confirmed on fetoscopy was described by Yoshimura et al in 2009.[42] Sonographic findings suggestive of spontaneous septostomy are absent/disrupted inter-twin membrane, both fetuses occupying the same side of the membrane and evidence of umbilical cord entanglement in twins previously reported as MCDA.[39] Table 2 lists the assessment tools and findings necessary to diagnose spontaneous septostomy. On the other hand, infrequently a 'stuck twin' can be a pitfall where there may be failure to visualize membranes, especially by an inexperienced operator. To avoid under-diagnosis of such cases, a good practice point is to always assess the integrity and presence of the inter-twin membrane at multiple segments at each scan, even in cases previously documented as MCDA. In cases where septostomy of the inter-twin dividing membrane could not be identified with ultrasound or postnatal placental examination, microseptostomies were demonstrated when indigo carmine was transferred between the amniotic sacs at amniocentesis.[41]

Laser therapy in these cases is technically challenging as the free-floating membranes may obscure visualization of the vascular equator and anastomoses, and therefore, necessitates passage of fetoscope through the defect into the inter-twin membrane to trace the anastomoses. Compared to TTTS with an intact inter-twin membrane, TTTS with spontaneous septostomy is associated with an increased risk of adverse perinatal outcomes such as preterm prelabour rupture of the membranes (PPROM), preterm labor, umbilical cord entanglement and overall lower survival rates.[40]

TTTS generally presents after 16 weeks of gestation, when the implicated inter-twin placental vascular anastomoses have developed, resulting in unbalanced vascular exchange resulting in hemodynamic imbalance and endocrine cascade. However, if the vascular anastomoses are large, TTTS may present in early gestation when the amniotic fluid discordance may appear moderate if stringent criteria are applied (DVP less than 2cm and DVP more than 8cm (6cm before 18 weeks)). In two case series, early gestation moderate amniotic fluid discordance (AFD), variably defined as >3cm or >4cm, had limited predictive value for the development of TTTS, once adjusted for gestational age.[43,44] However, both series are subject

to referral bias so the MCDA twin pregnancies with stable moderate AFD without progression to TTTS may be underrepresented in these study populations. In a series of 84 consecutive MCDA twin pregnancies with AFD not meeting the criteria for TTTS, presence of either concomitant sFGR or absent/reversed umbilical artery end-diastolic blood flow in one twin was associated with high risk for adverse perinatal outcomes.[45]

It cannot be over-emphasized that timely diagnosis is essential as untreated TTTS can result in severe perinatal morbidity and mortality. In future, there may be scope for treating these early cases of atypical TTTS before 16-18 weeks' gestation with non-invasive technology like high-intensity focused ultrasound (HIFU); this technology is in its nascent stage and results from clinical research are still awaited. It is likely that a lower DVP cut off of 6cm in MCDA twins presenting before 18 weeks' gestation will make the diagnosis unambiguous; this would have important implications for research decisions around appropriate timely fetal therapy.[46]

Conclusions

It is important to identify atypical cases of TTTS as their treatment, survival rates, morbidity, and hence counselling may differ from the typical cases. The stringent criteria of Quintero staging appear over-simplistic in light of the current robust evidence on the pathophysiology of TTTS. Contrary to the traditional school of thought with over reliance on AFD for diagnosing TTTS, a holistic approach should be adopted and where necessary, other modalities such as fetal echocardiography should be employed, to better characterize the pathology. Focused efforts are needed to create awareness among healthcare professionals caring for MCDA twin pregnancies and to reach a consensus on the definition of 'atypical' or 'non-isolated' TTTS cases which has clinical and research implications. Owing to the rarity of the condition and heterogeneity in definition, it appears unlikely that randomized controlled trials would be conducted to synthesize robust evidence on how to best manage these pregnancies. Nevertheless, pooling of data and collaboration among centers would help to formulate a uniform protocol for both surveillance and treatment.

REFERENCES

1. Royal College of Obstetricians and Gynaecologists. Management of Monochorionic Twin Pregnancy. BJOG 2017;124: e1–45.

2. Collins J. Global epidemiology of multiple birth. Reprod Biomed Online 2007;15 Suppl 3:45–52.

3. Dziadosz M, Evans MI. Re-Thinking Elective Single Embryo Transfer: Increased Risk of Monochorionic Twinning - A Systematic Review. Fetal Diagn Ther 2017;42: 81–91.

4. Lewi L, Jani J, Blickstein I, Huber A, Gucciardo L, Van Mieghem T, Doné E, Boes AS, Hecher K, Gratacós E, Lewi P, Deprest P. The outcome of monochorionic diamniotic twin gestations in the era of invasive fetal therapy: a prospective cohort study. Am J Obstet Gynecol 2008;199: 514.e1-8.

5. Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M. Staging of twin-twin transfusion syndrome. J Perinatol 1999; 19(8 Pt 1): 550–5.

6. Luks FI, Carr SR, Plevyak M, Craigo SD, Athanassiou A, Ralston SJ, Tracy TF Jr. Limited Prognostic Value of a Staging System for Twin-to-Twin Transfusion Syndrome. Fetal Diagn Ther 2004;19: 301–4.

7. Paek B, Dorn M, Walker M. Atypical twin-to-twin transfusion syndrome: prevalence in a population undergoing fetoscopic laser ablation of communicating placental vessels. Am J Obstet Gynecol 2016;215: 115.e1-115.e5.

8. Roberts D, Neilson JP, Kilby MD, Gates S. Interventions for the treatment of twin-twin transfusion syndrome. Cochrane Database Syst Rev. 2014;1:CD002073.

9. Baschat AA, Barber J, Pedersen N, Turan OM, Harman CR. Outcome after fetoscopic selective laser ablation of placental anastomoses vs equatorial laser dichorionization for the treatment of twin-to-twin transfusion syndrome. Am J Obstet Gynecol 2013; 209: 234.e1-8.

10. Slaghekke F, Lopriore E, Lewi L, Middeldorp JM, van Zwet EW, Weingertner AS, Klumper FJ, DeKoninck P, Devlieger R, Kilby MD, Rustico MA, Deprest J, Favre R, Oepkes D. Fetoscopic laser coagulation of the vascular equator versus selective coagulation for twin-to-twin transfusion syndrome: an open-label randomised controlled trial. Lancet 2014; 383: 2144-2151.

11. Van Winden KR, Quintero RA, Kontopoulos EV, Korst LM, Llanes A, Chmait RH. Perinatal survival in cases of twin-twin transfusion syndrome complicated by selective intrauterine growth restriction. J Matern-Fetal Neonatal Med 2015;28: 1549–53.

12. Groene SG, Tollenaar LSA, van Klink JMM, Haak MC, Klumper FJCM, Middeldorp JM, Oepkes D, Slaghekke F, Lopriore E. Twin-Twin Transfusion Syndrome with and without Selective Fetal Growth Restriction Prior to Fetoscopic Laser Surgery: Short and Long-Term Outcome. J Clin Med [Internet] 2019;8(7). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6679158/

13. Finneran MM, Templin MA, Stephenson CD. Risk of donor demise after laser therapy for twin-twin transfusion when complicated by growth discordance and abnormal umbilical artery Doppler findings. J Matern-Fetal Neonatal Med 2019;32: 1332–6.

14. Habli M, Livingston J, Harmon J, Lim FY, Plozin W, Crombleholme T. The outcome of twin–twin transfusion syndrome complicated with placental insufficiency. Am J Obstet Gynecol 2008;199:424.e1-424.e6.

15. Khalil A, Rodgers M, Baschat A, Bhide A, Gratacos E, Hecher K, Kilby MD, Lewi L, Nicolaides KH, Oepkes D, Raine-Fenning N, Reed K, Salomon LJ, Sotiriadis A, Thilaganathan B, Ville Y. ISUOG Practice Guidelines: Role of ultrasound in twin pregnancy. Ultrasound Obstet Gynecol 2016;47: 247-263.

16. Donepudi R, Krispin E, Mustafa H, Espinoza J, Nassr AA, Belfort MA, Sanz Cortes M, Mostafaei S, Harman C, Turan O, Shamshirsaz AA. Twin twin transfusion syndrome with and without selective fetal growth restriction: Predictors of donor demise. Prenatal Diagnosis. 2021;41(12):1524–30.

17. Denbow ML, Cox P, Taylor M, Hammal DM, Fisk NM. Placental angioarchitecture in monochorionic twin pregnancies: relationship to fetal growth, fetofetal transfusion syndrome, and pregnancy outcome. Am J Obstet Gynecol 2000;182:417–26.

18. Curado J, Sileo F, Bhide A, Thilaganathan B, Khalil A. Early and late selective fetal growth restriction in monochorionic diamniotic twin pregnancies: natural history and diagnostic criteria. Ultrasound Obstet Gynecol 2019. 2020;55: 661-666.

19. Nikolaos Antonakopoulos, Petra Pateisky, Becky Liu, Erkan Kalafat, Baskaran Thilaganathan, Asma Khalil. Selective Fetal Growth Restriction in Dichorionic Twin Pregnancies: Diagnosis, Natural History, and Perinatal Outcome. J Clin Med 2020; 9: 1404.

20. Vanlieferinghen S, Anselem O, Le Ray C, Shen Y, Marcellin L, Goffinet F. Prognostic Value of Umbilical and Cerebral Doppler in Fetal Growth Restriction: Comparison of Dichorionic Twins and Singletons. PLoS ONE 2015;10: e0123067.

21. Wohlmuth C, Agarwal A, Stevens B, Johnson A, Moise KJ, Papanna R, Donepudi R, Bell CS, Averiss IE, Gardiner HM. Fetal ventricular strain in uncomplicated and selective growth-restricted monochorionic diamniotic twin pregnancies and cardiovascular response in pre-twin–twin transfusion syndrome. Ultrasound Obstet Gynecol 2020;56: 694–704.

22. Shah AD, Border WL, Crombleholme TM, Michelfelder EC. Initial fetal cardiovascular profile score predicts recipient twin outcome in twin-twin transfusion syndrome. J Am Soc Echocardiogr 2008;21: 1105–8.

23. Rychik J, Tian Z, Bebbington M, Xu F, McCann M, Mann S, Wilson RD, Johnson MP. The twin-twin transfusion syndrome: spectrum of cardiovascular abnormality and development of a cardiovascular score to assess severity of disease. Am J Obstet Gynecol 2007;197: 392.e1-392.e8.

24. Mieghem TV, Klaritsch P, Doné E, Gucciardo L, Lewi P, Verhaeghe J, Lewi L, Deprest J. Assessment of fetal cardiac function before and after therapy for twin-to-twin transfusion syndrome. Am J Obstet Gynecol 2009;200: 400.e1-400.e7.

25. Michelfelder E, Tan X, Cnota J, Divanovic A, Statile C, Lim F-Y, Crombleholme T. Prevalence, Spectrum, and Outcome of Right Ventricular Outflow Tract Abnormalities in Twin–twin Transfusion Syndrome: A Large, Single-center Experience. Congenit Heart Dis 2015;10: 209–18.

26. Wohlmuth C, Gardiner HM. Twin–twin transfusion syndrome: don't rely on fluids and bladders to catch it early. Ultrasound in Obstetrics & Gynecology. 2022;59(1):7–10.

27. Lopriore E, Middeldorp, J.M, Oepkes, D, Kanhai H.H, Walther F.J, Vandenbussche F.P.H.A. Twin Anemia–Polycythemia Sequence in Two Monochorionic Twin Pairs Without Oligo-Polyhydramnios Sequence. Placenta 2007, 28, 47–51.

28. Slaghekke F, Kist WJ, Oepkes D, Pasman SA, Middeldorp JM, Klumper FJ, Walther FJ, Vandenbussche FP, Lopriore E. Twin anemia-polycythemia sequence: diagnostic criteria, classification, perinatal management and outcome. Fetal Diagn Ther 2010; 27: 181-190.

29. Denbow M, Fogliani R, Kyle P, Letsky E, Nicolini U, Fisk N. Haematological indices at fetal blood sampling in monochorionic pregnancies complicated by feto-fetal transfusion syndrome. Prenat Diagn 1998;18: 941–6.

30. Van Winden KR, Quintero RA, Kontopoulos EV, Korst LM, Llanes A, Chmait RH. Pre-Operative Twin Anemia/Polycythemia in the Setting of Twin-Twin Transfusion Syndrome (TTTS). Fetal Diagn Ther 2015;37: 274–80.

31. Donepudi R, Papanna R, Snowise S, Johnson A, Bebbington M, Moise KJ. Does anemia-polycythemia complicating twin-twin transfusion syndrome affect outcome after fetoscopic laser surgery? Ultrasound Obstet Gynecol 2016;47: 340–4.

32. Tollenaar LSA, Slaghekke F, van Klink JMM, Groene SG, Middeldorp JM, Haak MC, Klumper FJCM, Oepkes D, Lopriore E. Twin-Twin Transfusion Syndrome with Anemia-Polycythemia: Prevalence, Characteristics, and Outcome. Journal of Clinical Medicine. 2019 Aug;8(8):1129.

33. Shub A, Walker SP. Planned early delivery versus expectant management for monoamniotic twins. Cochrane Database Syst Rev 2015; (4):CD008820.

34. Khalil A, Cooper E, Townsend R, Thilaganathan B. Evolution of Stage 1 Twin-to-Twin Transfusion Syndrome (TTTS): Systematic Review and Meta-Analysis. Twin Res Hum Genet 2016;19: 207-216. doi:10.1017/thg.2016.33

35. Emery SP, Hasley SK, Catov JM, Miller RS, Moon-Grady AJ, Baschat AA, Johnson A, Lim FY, Gagnon AL, O'Shaughnessy RW, Ozcan T, Luks FI; North American Fetal Therapy Network. North American Fetal Therapy Network: intervention vs expectant management for stage I twin-twin transfusion syndrome. Am J Obstet Gynecol 2016;215:346.e1-346.e7. doi:10.1016/j.ajog.2016.04.024

36. Stirnemann J, Slaghekke F, Khalek N, Winer N, Johnson A, Lewi L, Massoud M, Bussieres L, Aegerter P, Hecher K, Senat MV, Ville Y. Intrauterine fetoscopic laser surgery versus expectant management in stage 1 twin-to-twin transfusion syndrome: an international randomized trial. Am J Obstet Gynecol 2021;224:528.e1-528.e12

37. D'Antonio F, Odibo A, Berghella V, Khalil A, Hack K, Saccone G, Prefumo F, Buca D, Liberati M, Pagani G, Acharya G. Perinatal mortality, timing of delivery and prenatal management of monoamniotic twin pregnancy: systematic review and meta-analysis. Ultrasound Obstet Gynecol 2019;53:166–74.

38. Murgano D, Khalil A, Prefumo F, Mieghem TV, Rizzo G, Heyborne KD, Melchiorre K, Peeters S, Lewi L, Familiari A, Lopriore E, Oepkes D, Murata M, Anselem O, Buca D, Liberati M, Hack K, Nappi L, Baxi LV, Scambia G, Acharya G, D'antonio F. Outcome of twin-to-twin transfusion syndrome in monochorionic monoamniotic twin pregnancy: systematic review and meta-analysis. Ultrasound Obstet Gynecol 2020;55: 310–7.

39. Chmait RH, Aghajanian P, Kontopoulos EV, Quintero RA. Prenatal diagnosis of spontaneous septostomy of the dividing membranes in complicated monochorionic diamniotic multiple gestations. J Ultrasound Med 2009;28: 663–8.

40. Cruz-Martínez R, López-Briones H, Luna-García J, Martínez-Rodriguez M, Gámez-Varela A, Chávez-González E, Villalobos-Gómez R. Incidence and survival outcomes of monochorionic diamniotic twin pregnancies with twin-to-twin transfusion syndrome presenting without amniotic fluid discordance due to spontaneous septostomy and treated with fetoscopy. Ultrasound Obstet Gynecol [Internet]. [cited 2021 Jun 13];n/a(n/a). Available from: https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1002/uog.23129

41. Hackney DN, Khalek N, Moldenhauer J, Ozcan T. Twin-Twin Transfusion Syndrome Presenting as Polyhydramnios in Both Fetuses Secondary to Spontaneous Microseptostomy. AJP Rep 2013;3: 83–6.

42. Yoshimura K, Aiko Y, Inagaki H, Nakata M, Hachisuga T. Prenatal spontaneous disruption of the dividing membrane in monochorionic diamniotic twins detected at the time of fetoscopic laser photocoagulation. J Obstet Gynaecol Res 2009;35: 1129–31.

43. Mieghem TV, Eixarch E, Gucciardo L, Done E, Gonzales I, Schoubroeck DV, Lewi L, Gratacos E, Deprest J. Outcome prediction in monochorionic diamniotic twin pregnancies with moderately discordant amniotic fluid. Ultrasound Obstet Gynecol 2011;37: 15–21.

44. Yamamoto R, Ishii K, Muto H, Kawaguchi H, Murata M, Hayashi S, Matsushita M, Murakoshi T, Mitsuda N. The Use of Amniotic Fluid Discordance in the Early Second Trimester to Predict Severe Twin-Twin Transfusion Syndrome. Fetal Diagn Ther 2013;34: 8–12.

45. Huber A, Diehl W, Zikulnig L, Bregenzer T, Hackelöer BJ, Hecher K. Perinatal outcome in monochorionic twin pregnancies complicated by amniotic fluid discordance without severe twin-twin transfusion syndrome. Ultrasound Obstet Gynecol 2006;27: 48–52.

46. Khalil A. Modified diagnostic criteria for twin-to-twin transfusion syndrome prior to 18 weeks' gestation: time to change? Ultrasound Obstet Gynecol 2017;49: 804–5.

FIGURE LEGENDS

Figure 1. A case of monochorionic diamniotic (MCDA) twin pregnancy at 24 weeks' gestation with twin-twin transfusion syndrome (TTTS) and selective fetal growth restriction (sFGR). An axial view of the fetal abdomen shows a remarkable inter-twin difference in the abdominal circumference; the smaller fetus has oligohydramnios (donor) while the larger twin has polyhydramnios (recipient) (a). Doppler evaluation of the umbilical artery of the smaller twin (donor) shows persistent reversed end-diastolic flow (b).

Figure 2. A case of monochorionic diamniotic (MCDA) twin pregnancy at 23 weeks' gestation with twin-twin transfusion syndrome (TTTS) and cardiac compromise in the recipient twin. The donor twin has reduced amniotic fluid volume (a), but the bladder remains visible. The recipient twin is hydropic (subcutaneous edema and ascites), but no polyhydramnios (b). Doppler evaluation of the ductus venosus in the recipient twin demonstrates reversed "a" flow (c). Four chamber view of the recipient twin shows bivalvular insufficiency (d).

Figure 3. A case of monochorionic diamniotic (MCDA) twin pregnancy at 20 weeks' gestation with twin-twin transfusion syndrome (TTTS) and twin anemia polycythemia sequence (TAPS). There is oligohydramnios-polyhydramnios sequence (the donor twin is stuck to the anterior placenta, while the recipient twin has polyhydramnios) (a). Inspection of the placenta shows discordant placental echogenicity, the polycythemic (TAPS) and donor (TTTS) twin shows an hyperechogenic placenta, while the anemic (TAPS) and recipient (TTTS) twin shows and hypoechogenic placenta (placental dichotomy) (b). Middle Cerebral Artery Doppler evaluation shows diminished peak systolic velocity shown in the polycythemic twin (c) while accelerated flow is shown in the anemic twin (d).

Figure 4. A case of monochorionic diamniotic (MCDA) twin pregnancy at 24 weeks' gestation with twin-twin transfusion syndrome (TTTS) and twin anemia polycythemia sequence (TAPS). There is oligohydramnios-polyhydramnios sequence (the donor twin is stuck to the anterior placenta (a), while the recipient twin has polyhydramnios (b)). The middle cerebral artery (MCA) Doppler has peak systolic velocity (PSV) >1.5MoM in the donor twin (anemic) (c), while the MCA PSV in the recipient twin is <1MoM (polycythemic) (d). After Laser surgery, the MCA PSV gradually returns to normal values in both fetuses (e, f).

Figure 5. A case of monochorionic monoamniotic (MCMA) twin pregnancy at 17 weeks' gestation with twin-twin transfusion syndrome (TTTS). There is polyhydramnios (a), with distended bladder in the recipient twin (b), evidence of umbilical cord entanglement (c) and cardiomegaly in the recipient twin (d).

Figure 6. A case of monochorionic diamniotic (MCDA) twin pregnancy at 21 weeks' gestation with twin-twin transfusion syndrome (TTTS) and spontaneous septostomy. A monochorionic twin pregnancy where a dividing membrane can be seen with both amniotic sacs showing polyhydramnios (a). Placental examination demonstrates a defect in the inter-twin membrane, (septostomy) (b). Axial views at the vesical level in the same case, where a bladder can be seen in the recipient twin (c) but is absent in the donor twin (d) despite being surrounded by amniotic fluid.

Figure 7. A case of monochorionic diamniotic (MCDA) twin pregnancy at 22 weeks' gestation with twin-twin transfusion syndrome (TTTS) and spontaneous septostomy. The figure shows disrupted inter-twin membrane with polyhydramnios on both sides (a), evidence of umbilical cord entanglement in twins previously reported as MCDA (b), distended bladder in the recipient (c) and absent bladder in the donor (d).

Table 1. List of studies and their findings which reported cases of atypical twin-twin transfusion syndrome

Study (First author and year) and country	Study design	Period analysed	Definition of cases included	Total TTTS (n)	Atypical TTTS (n)	Prevalence of atypical TTTS	Gestational age at diagnosis (weeks)	Gestational age in weeks at intervention (weeks)	Outcomes reported
Paek et al 2016[7] USA	Retrospective	2003-2015	If the fluid discordance did not meet the criteria for TTTS, in presence of advanced features	345	25	7.2%	Not specified	Not specified	• Gestational age at delivery • At least one survivor • No survivors • One survivor • Two survivors
Van Winden et al 2015[30]	Retrospective	2006-2012	Preoperative TAPS	369	9	2.4%	Not specified	22.9 (17.7–28.6) versus 20.1 (16.3–27.4) in atypical versus typical TTTS, respectively	• Preterm delivery • Gestational age at delivery • Birthweights • 30 days survival Livebirth
Donepudi et al 2016[31] USA	Retrospective	2011-2014	TTTS with preoperative TAPS	122	12	preoperative TAPS 8.3% (11/134)	Not specified	21.4 ±2.3 versus 20.6 ±2.3	• Procedure to delivery interval • PPROM • Livebirth Birthweight
Tollenaar et al 2019[32] The Netherlands	Retrospective	2001-2019	TTTS with anaemia polycythemia (AP)	461	70	15.2%	Not specified	21.0 (18.8–24.0) versus 19.3 (17.3–21.9) in TTTS-AP versus TTTS respectively	• Gestational age at birth • Birth weight discordance • Perinatal survival • Fetal demise • Neonatal mortality

									• Severe neonatal morbidity • Severe NDI
Hackney et al 2013[41] USA	Case report	2013	Double polyhydramnios with collapsed bladder and abnormal umbilical artery Doppler in one of the twins	NA	NA	NA	20+3	22+3	Double demise
Cruz-Martínez et al 2019[40] Mexico	Retrospective	8 Years	TTTS with spontaneous septostomy	248	4	1.6%	Not specified	22+4 for the entire cohort	• Umbilical artery entanglement • PPROM • Preterm labor <32 weeks Overall survival rate
Yoshimura et al 2009[42] Japan	Case report	2009	TTTS with spontaneous septostomy	NA	NA	NA	24	24	NA
Chmait et al 2009[39] USA	Retrospective case series	Not specified	TTTS with septostomy Also reported 2 cases of TRAP and sFGR	213	2	0.94% (TTTS)	18	18	NA
Denbow et al 1998[29] UK	Case series	1988-1997	TTTS with haemoglobin discordance	NA	36	NA	Not specified	Not specified	Overall survival
Groene et al 2019[12]	Retrospective	2001-2019	Presence of sFGR defined as one twin with EFW <10th centile	527	312	59%	Not specified	20.0 (17.9–22.1) versus 19.3 (17.4–22.0) in atypical versus	Primary outcomes • Perinatal survival • Long-term severe NDI Secondary outcomes

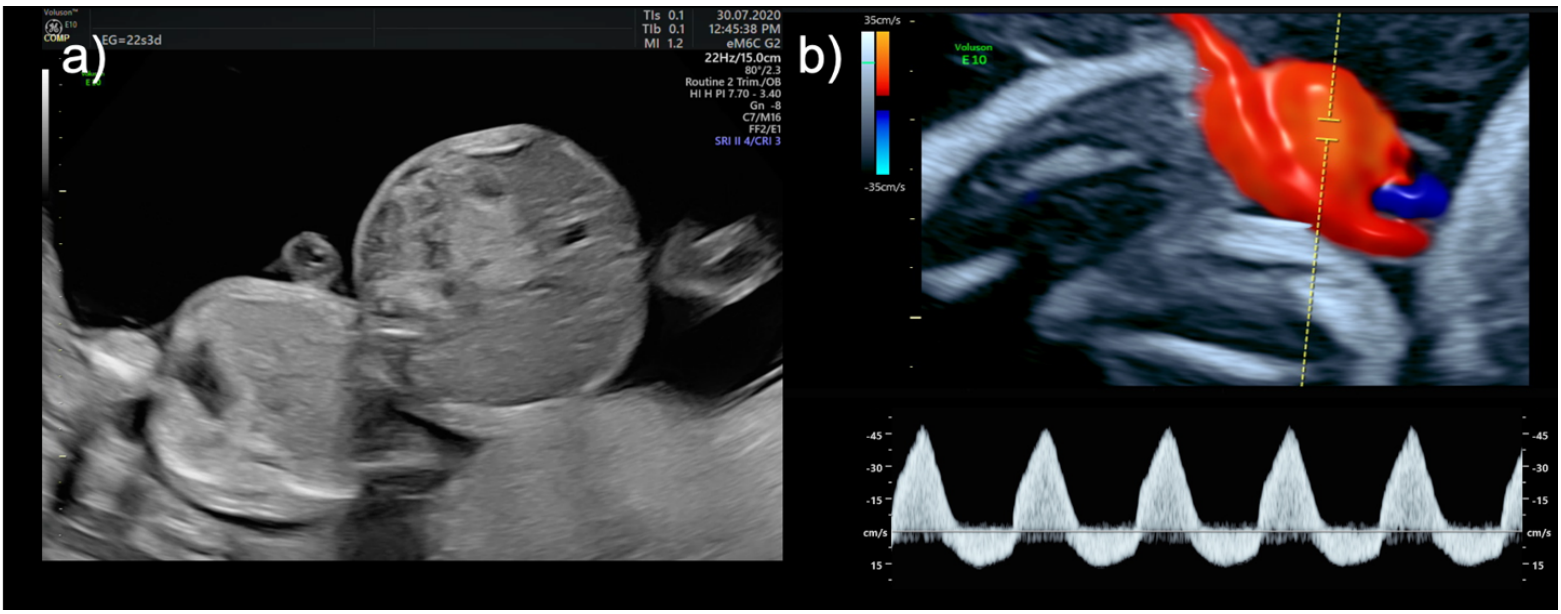
The Netherlands								typical TTTS, respectively	• Fetal death within 24 hours of laser • Neonatal mortality (death within 28 days of birth) • Disease free survival (survival without severe NDI) • Severe neonatal morbidity
Finneran et al 2019[13] USA	Retrospective	2010-2016	AREDF in the Umbilical artery in the donor twin	81	43	53.1%	Not specified	20.8 ± 2.5 for the entire cohort	• Donor demise • Normalization of preoperative umbilical artery Doppler abnormalities
Van Winden et al 2015[11] USA	Retrospective	Not specified	TTTS with donor twin weight <10th centile	369	241	65%	Not specified	20.5±2.3 versus 20.5±2.6 in atypical versus typical TTTS, respectively	• Preterm birth <28 and 32 weeks • Cesarean delivery • Birthweight • 30 days survival
Habli et al 2008[14] USA	Retrospective	Not specified	TTTS complicated by placental insufficiency (EFW <10th centile or Weight discordance >20%)	270	52	19%	20.3 ±2.5 weeks	Not specified	• Donor and recipient survival rates • Echocardiographic parameters
Murgano et al 2020[38] Multicentre	Systematic review and meta-analysis	N/A	MCMA twins with TTTS	888	44	N/A	N/A	N/A	Primary outcome - intrauterine death (IUD) Secondary outcomes

									miscarriage, single IUD, double IUD, neonatal death perinatal death, survival of at least one twin, survival of both twins and preterm birth <32 weeks' gestation.

MCDA: monochorionic diamniotic; MCMA: monochorionic monoamniotic; TTTS: twin-twin transfusion syndrome; NDI: neurodevelopmental impairment; sFGR: selective fetal growth restriction; AREDF: absent or reversed end-diastolic flow; TAPS: twin anemia polycythemia sequence; PPROM: preterm pre-labor rupture of the membranes; TRAP: twin reversed arterial perfusion

Table 2. Diagnosis of spontaneous septostomy

Assessment tools	**Features**
History	• Previously recorded monochorionic diamniotic (MCDA) twin pregnancy with disproportionate increase in amniotic fluid in one of the twin sacs
Ultrasound	• Disrupted intertwin membrane with irregular margins • Both fetuses lying on the same side of the membrane • Umbilical cord entanglement in previously documented MCDA twins
Fetoscopy	• Direct visualisation of the membrane defect
Ancillary techniques	• Instillation of indigo carmine dye in one of the sacs (especially useful to detect microseptostomies)
Postnatal examination of placenta	• Direct visualisation of the defect in the intertwin membrane



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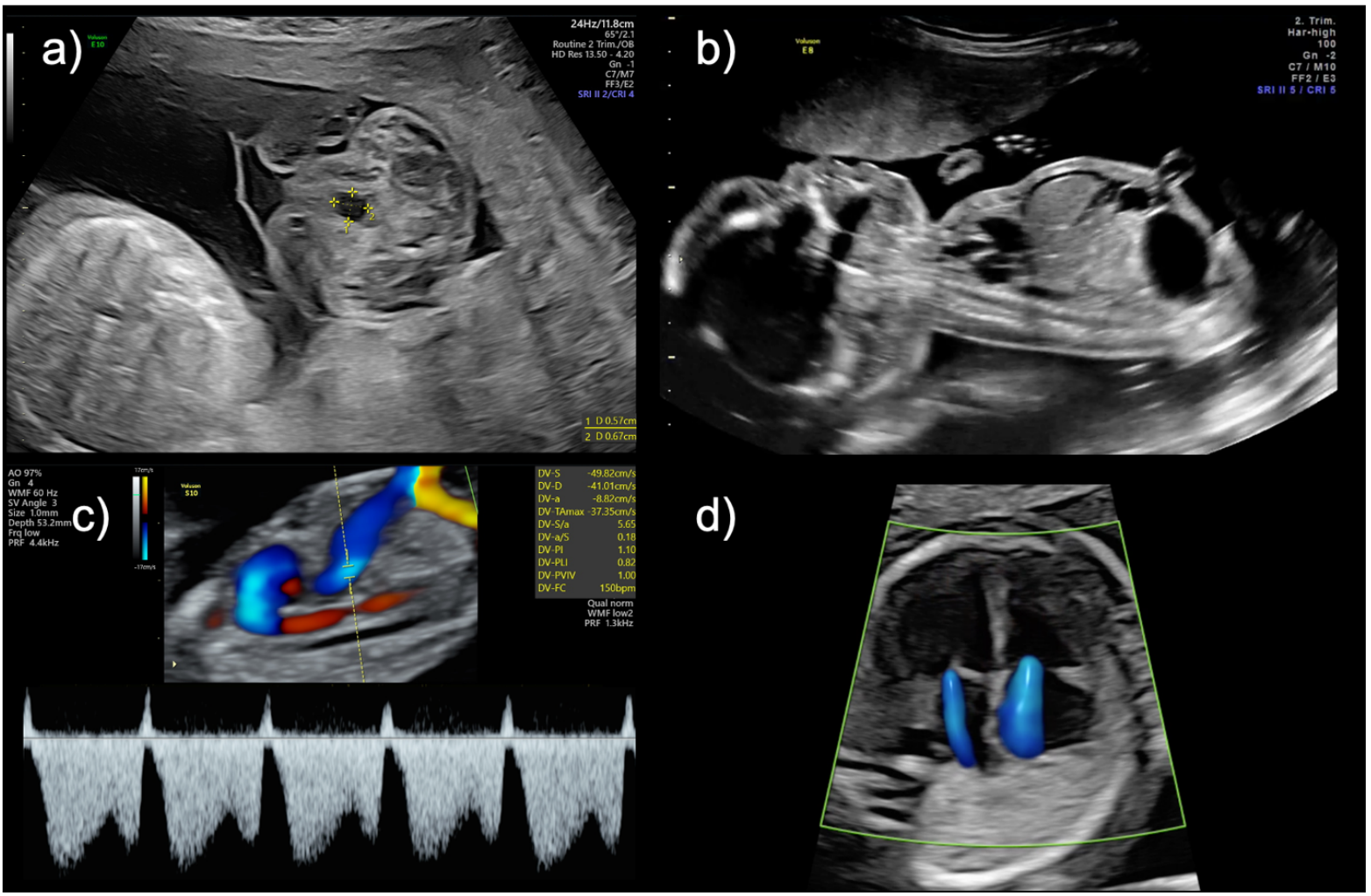

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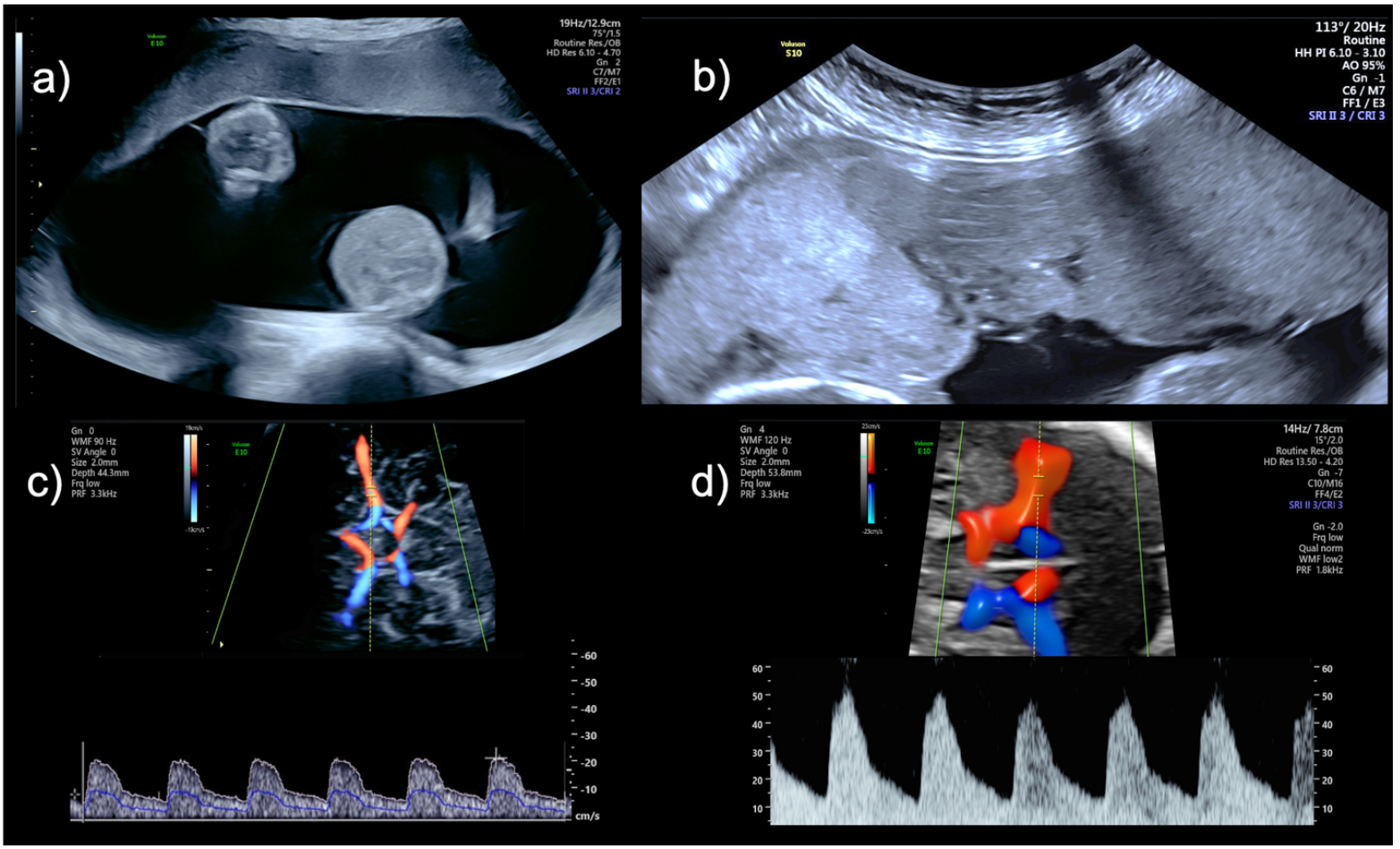

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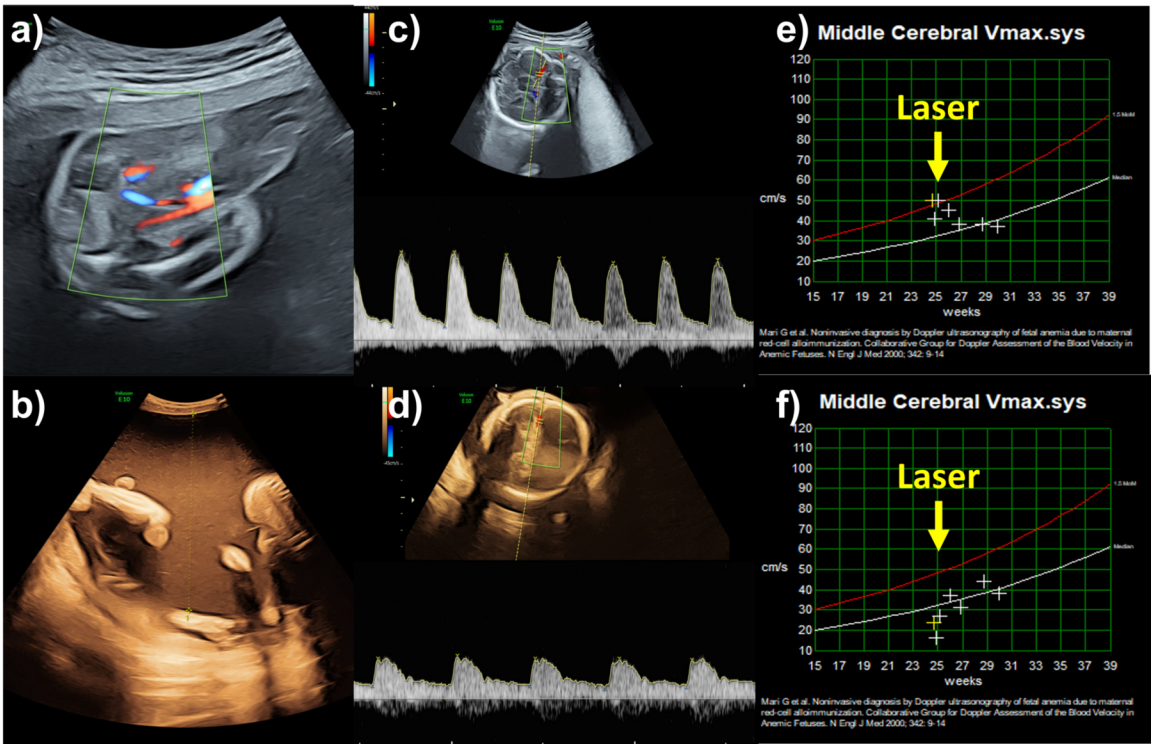

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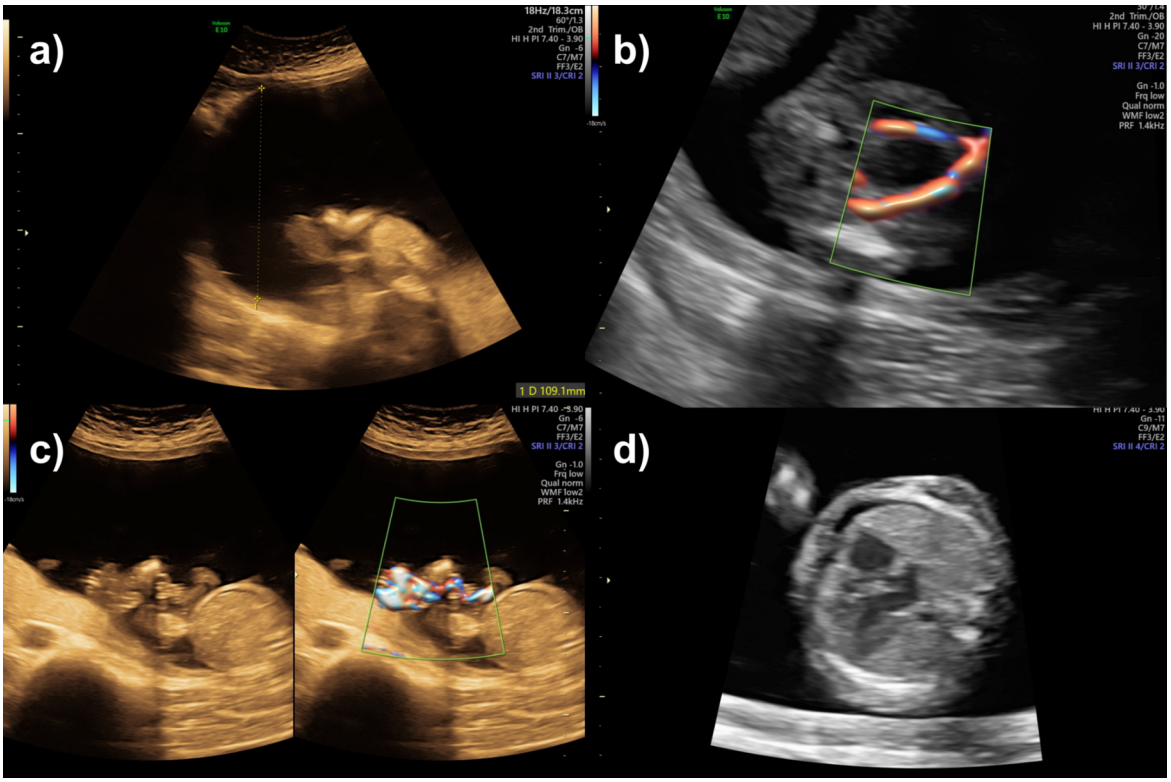

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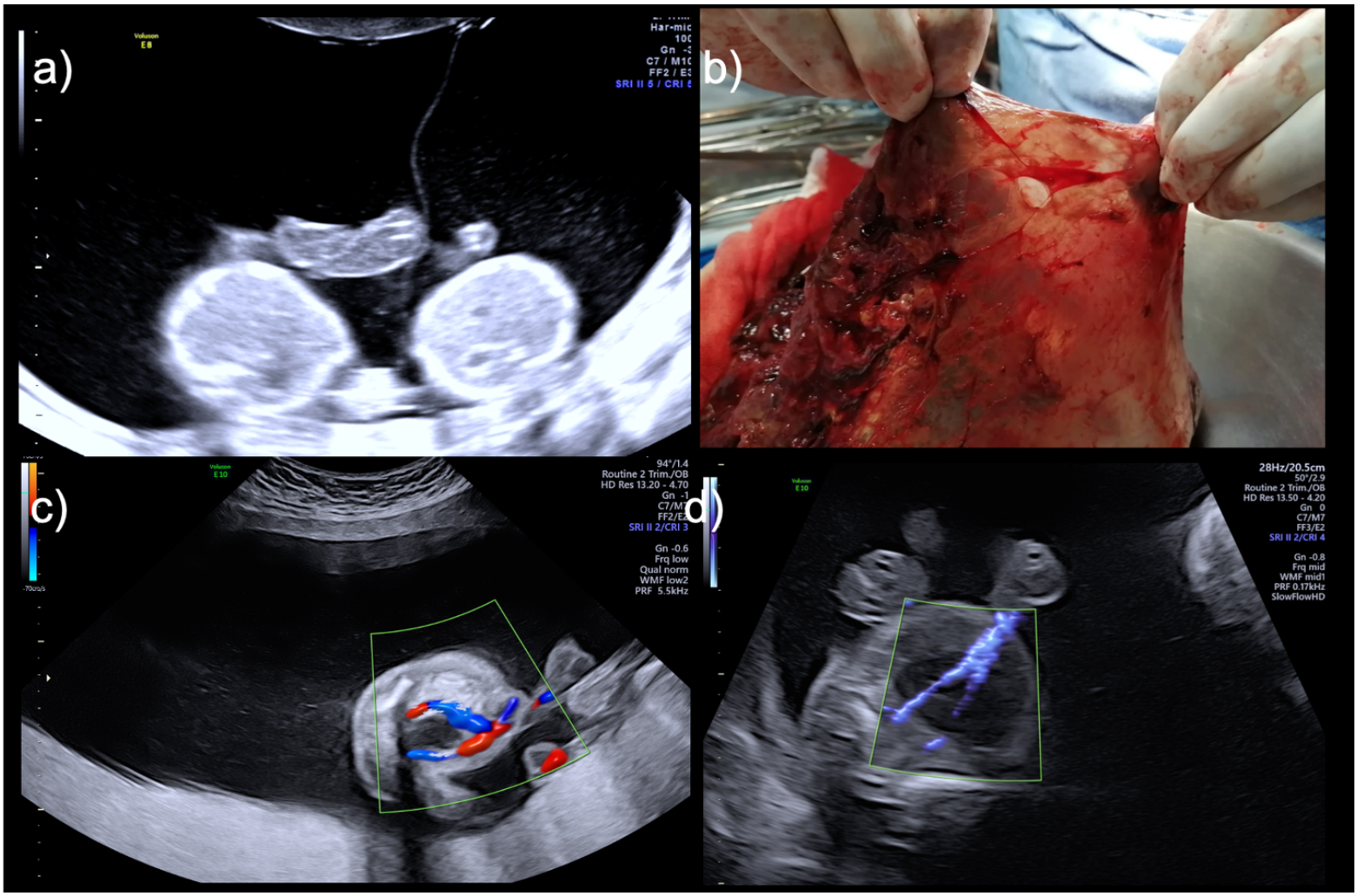

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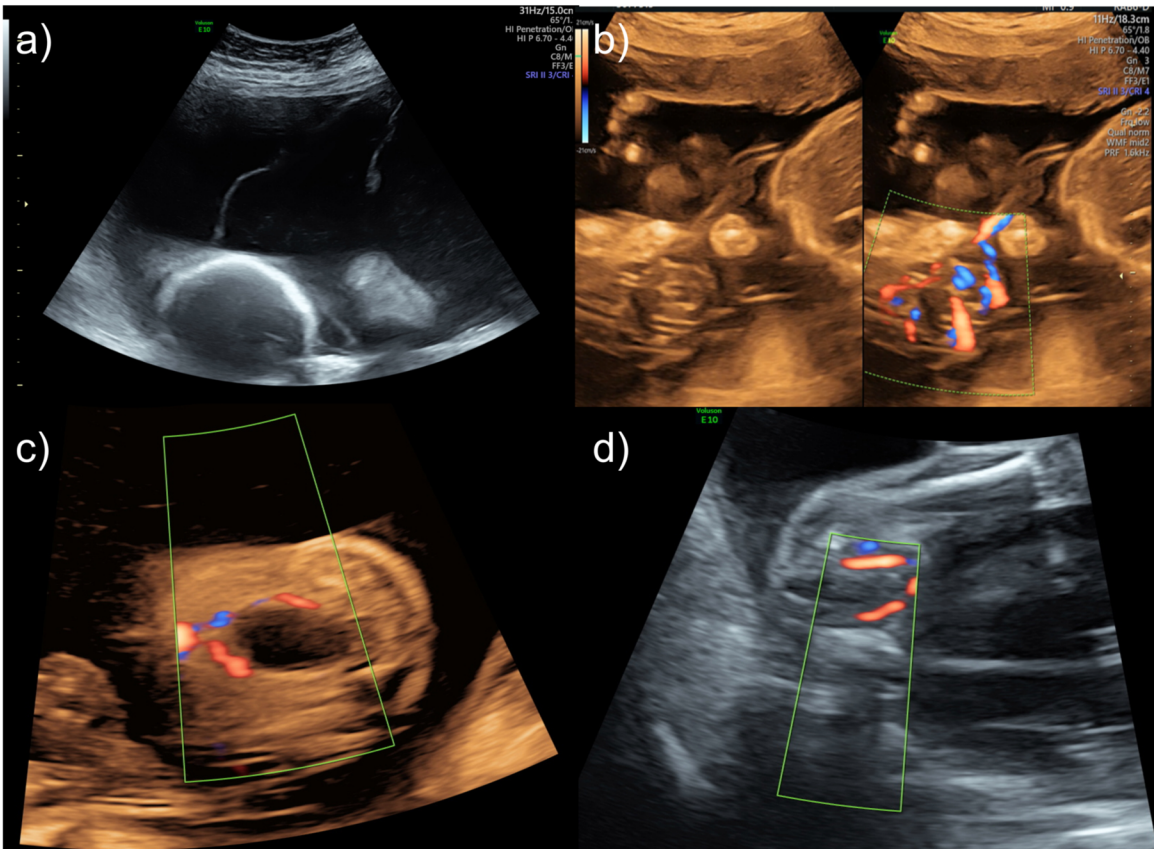

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