Original Article

Transfusion syndromes in monochorionic multiplets: An overview

Dominic O. Osaghae, Jacob A. Unuigbe[1]

Department of Paediatrics, College of Health Sciences, Igbinedion University, Okada, Nigeria, [1]Department of Obstetrics and Gynaecology, College of Health Sciences, Igbinedion University, Okada, Nigeria

ABSTRACT

The west Africa sub-region, notably Nigeria, records the highest twin and triplet birth rates globally. Therefore, the time has come for attention to be focused on an area of gemellology, feto-fetal transfusion syndromes in multiplets, in order to attend to what the authors consider a yet-to-be-explored major significant contributor to the overall unacceptably high fetal, perinatal and neonatal losses in the region. This review examines the genetics, embryology and pathophysiology of twinning in general to provide the background to the spectrum of clinical presentations of feto-fetal transfusion syndromes. Twin-to-twin transfusion syndromes (TTTS) are unique prenatal complications of monochorionic multiplets and manifest as twin oligohydramnios polyhydramnios sequence (TOPS), twin anaemia polyhydramnios sequence (TAPS) and twin reversed arterial perfusion syndrome (TRAPS). These grave complications are associated with fetal malformations and early miscarriages as well as fetal weight and haemoglobin discordances, discordant haemodynamic changes in addition to intrauterine deaths, perinatal asphyxia, cerebral palsy and brain damage. Most importantly, the management of TTTS requires highly skilled interventions, expensive equipment, rare expertise and costly treatment options that are currently not available in Nigeria and other developing countries. Moreover, these management options are unavailable in Nigeria because considerable attention of the health system is directed at the burden of high levels of maternal, perinatal, and childhood morbidity and mortality. Regardless of these overwhelming obstetric and paediatric challenges, there is still urgent need to develop feto-maternal medicine units in the country to focus attention on the management of TTTS because of high twinning rate and attending fetal, perinatal and neonatal wastages. Furthermore, Nigeria is now witnessing an increased incidence of twin births from the rapidly developing assisted reproductive therapy centres in the country. All these provide justification for devoting attention to this unique area of perinatal care that will, on balance, be robustly cost effective. Hence, this review of transfusion syndromes in monochorionic multiplets aims to sensitize health workers and researchers in Nigeria, particularly perinatologists and feto-maternal physicians, neonatal paediatricians, as well as policy makers and other stakeholders, on the need to focus attention on the problem.

Key words: Feto-fetal; monochorionic multiplets; transfusion syndrome.

Introduction

The human uterus is probably modeled naturally for the nurture of one fetus per pregnancy, and this possibly explains why most pregnancies end up as singletons.[1] Some pregnancies, nevertheless, produce multiplets resulting in two or more fetuses. For this reason, it is not surprising that pregnancies with more than one fetus are frequently associated with complications,[2-6] such as miscarriages, pre-term pre-labour

Address for correspondence: Prof. Jacob A. Unuigbe, Department of Obstetrics and Gynaeclogy, College of Health Sciences, Igbinedion University, Okada, PMB 0006, Benin City, Nigeria.
E-mail: junuigbe@yahoo.com

Access this article online	
Website: www.tjogonline.com	Quick Response Code
DOI: 10.4103/0189-5117.192211	

How to cite this article: Osaghae DO, Unuigbe JA. Transfusion syndromes in monochorionic multiplets: An overview. Trop J Obstet Gynaecol 2016;33:135-42.

rupture of membranes (PPROM), preterm births, low birth weights as well as antepartum haemorrhage and hypertension in addition to twin-to-twin transfusion syndromes (TTTS) including twin anaemia polycythemia sequence (TAPS), TTTS and twin reversed arterial perfusion syndrome (TRAPS).

These complications demand skilled management in order to achieve successful perinatal outcomes.[5,6] At present, these specialized skills are not readily available in Nigeria and other developing countries because of high cost of setting up centres for fetal and perinatal care.[7] Consequently, a ready excuse for failure to develop this highly technical and expensive branch of perinatal care is the preponderance of other medical problems, such as infections and infestations in the newborn[8] and major obstetric complications including obstructed labour, obstetric haemorrhage, hypertensive diseases, illicit abortions, and puerperal genital sepsis.[9,10] These health hazards, all causes of very high perinatal and maternal mortality, tend to divert health institutions' attention from the development of desired skilled fetal medicine units.

It is, therefore, against this backdrop that we must consider the importance of the subject of transfusion syndromes in multiplets with reference to developing countries, notably Nigeria that records the world's highest twinning rate. In 1969, about 1 in 22 maternities in southwestern Nigeria were found to be twins. A 5-year study on the frequency of twinning in a rural community (Igbo-Ora) in western Nigeria, based on the analysis of data collected from an entire community, (population: 30000) in which there was no selection, was conducted by Nylander from 1964 to 1968.[11] In that landmark publication, Nylander reported a twinning rate of 45.1 per 1000 maternities, considered the highest to date globally.[11,12] The twinning and triplet rates in western Nigeria were found to be approximately 4 and 16 (i.e., 4^2) times the corresponding rates in the UK and USA.[12,13] Although a more recent study on a very small homogenous settlement, Candido Godoi in south Brazil, a municipality of approximately 6000 inhabitants, reported a twinning rate of 10%, this does not negate the more statistically valid observed highest rate of 4.5% from western Nigeria.[14]

Moreover, Nigeria now witnesses an increasing spate of assisted reproductive therapy (ART) in many health centres.[15] Spontaneous twins comprise one-third monochorionic (MC) twin pairs; iatrogenic twins (after ART assisted infertility treatment) double the overall twinning rate, and include, even if a smaller proportion (5%), of MC twin pairs.[16] These considerations must impact the overall MC twinning rate in Nigeria.

The implications of increased multiple pregnancy rate are worrisome and include increased early pregnancy losses, sometimes even prior to pregnancy detection; late miscarriages; preterm births, with implied perinatal morbidity/mortality; infant morbidity/mortality; late morbidity/mortality, with implied socioeconomic burden to parents, relatives, and governments. Therefore, all these provide justification for devoting attention to this unique area of perinatal care that will, on balance, be robustly cost effective. As a result, this review of transfusion syndromes in monochorionic multiplets aims to sensitize health workers and researchers in Nigeria, particularly perinatologists and feto-maternal physicians, neonatal paediatricians, as well as policy makers and other stakeholders, on the need to focus attention on the problem.

Singletons and Multiplets

Singletons

A normal pregnancy producing a singleton is the result of the fertilization of a normal ovum and a structurally intact spermatozoon leading to the formation of a zygote.[1] The zygote subsequently undergoes further differentiation to form blastocyst that develops through different stages to the fetus. The fetus is attached by the umbilical cord to the placenta, embedded to the uterine wall and surrounded by the amniotic fluid. These structures are enclosed by two layers of membrane, an outer layer, chorion, and an inner layer, amnion. Singletons are, therefore, described as monozygotic, monochorionic and monoamniotic [Figures 1 and 2].[1]

Mechanism for the production of multiplets, zygote cleavage and chorionicity

The mechanisms for the production of twins are not well understood. While dizygotic twin results from fertilization of

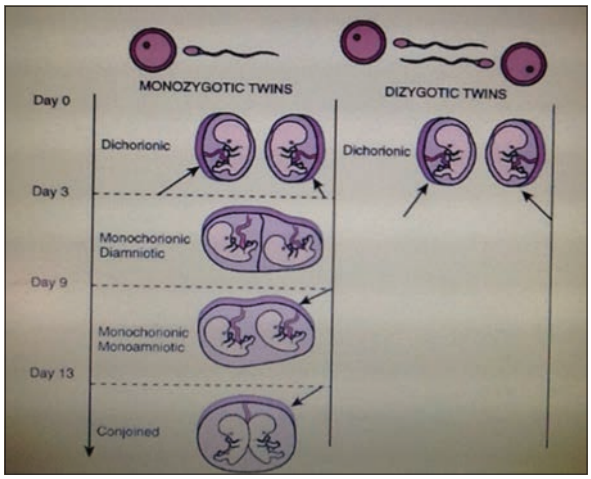

Figure 1: Zygocity and chorionicity; impact on fetal, perinatal, and neonatal outcome with late sequelae. (Liesbeth Lewi and Jan Deprest[16])

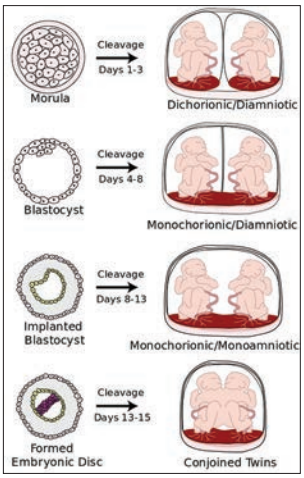

Figure 2: Chorionicity, amniosity, and conjoint twins. (Courtesy: van Vugt JMG, Shulman LP, Snijders RJM. Fetal Medicine Foundation, Netherlands, 2006)

two ova, it is reasoned that a monozygotic twin is the outcome of fertilization of an ovum followed by early cleavage into two halves that undergo further independent development.[2,3] Further, the time between fertilization and cleavage of the zygote is a determinant of the type of resultant twin. For this reason, a monozygotic twin may be either of the following: dichorionic, monochorionic diamniotic, monochorionic monoamniotic and conjoined following cleavage on the 1st, 3rd, 9th and 12th days, respectively.[16] [Figures 1 and 2].

Frequency of multiplets

The overall incidence of multiple pregnancies on a global scale has witnessed a steady rise from 1 in 100 to 1 in 70 births.[16] Moreover, there is a 40% and three-fold increase, respectively, in twinning and higher order multiple births. In addition, the incidence of monozygotic twins on the other hand is 4 per 1000 births.[17] The explanation for the increasing frequencies is not clear but some identified factors include hereditary predisposition, commonly found in dizygotic twins, ethnicity, advanced maternal age as documented increase by 2% at 35 years. Other factors include increasing parity as documented increase by 2% after four pregnancies, ovulation induction with hormones, and five to ten-fold increase in twining following ART, including blastocyst transfer, micromanipulations of the zona pellucida with intracytoplasmic sperm injection as well as assisted hatching.[18-21]

Placentation

The placenta plays key roles in the survival of the fetus through the provision of nutrients, oxygenation and gaseous exchanges, fluid and electrolyte balance and excretion of nitrogenous waste products.[22] Hence, absence of placenta is not compatible with survival of a fetus. Therefore, every fetus is attached to a placenta for survival. As a result, singletons are attached to a placenta whereas multiplets attach to either one or more placentas depending on the chorionicity of the fetus.[16] In this regard, while dichorionic twins are attached to two placentas, monochorionic twins share one placenta. The sharing of a common placenta by monochorionic twins is fraught with complications because it is associated with the development of placental anastomoses between arterial and venous blood vessels of the twins as either arteriovenous (AV) or arterioarterial (AA) anastomoses.[1,16,23]

Several studies[24-27] have demonstrated evidence from injection of dye into the placenta and visualization at fetoscopy, ultrasonography and Doppler velocimetry that vascular anastomoses occur predominantly in monochorionic twins complicated by twin-to-twin transfusion. This complication leads to dire consequences in the twins that include discordance in amniotic fluid volume, differential filling of the bladder, differential fetal growth and differential haemoglobin concentration.[16] In addition, observational studies by Senat *et al*.[28] have confirmed that such monochorionic twins are prone to increased incidence of low birth weight, neurodevelopmental impairment, cerebral palsy, renal and cardiovascular damage, perinatal death and death in infancy.

Sequence of events

The natural history of intertwin transfusions in multiplets reveals a wide range of disorders with different outcomes and progression from one stage to the next that are neither slow nor methodical or predictable but rather difficult to anticipate, can be sudden and may altogether skip stages.[29]

In multiplet transfusions, the donor and recipient fetuses make concerted efforts to maintain the body's homeostasis but the effort is undermined by the ongoing imbalance in the transfusion of blood from one twin to the other. Hence, as pregnancy progresses, the vasculature of the anastomoses increase in diameter leading to increasing volumes of blood transfused from donor to recipient with worsening of disease as gestation advances. Deterioration of fetal condition can be seen clinically and by ultrasonic screening as follows. The earliest finding relates to amniotic fluid imbalance that is evident as an oligohydramnios-polyhydramnios sequence. Then, a decreased donor and increased recipient urine output is noted by ultrasound as absence of donor bladder and enlarged recipient bladder. This observation is followed by alterations in blood flow in various vessels detected by Doppler velocimetry. Other changes that have been observed include growth restriction in the donor, cardiac dysfunction because of volume overload as well as hydrops fetalis of

the recipient and death of one or both fetuses.[16,29,30,31] The changes are summarized in Table 1.[1]

Twin-twin-transfusion syndrome

TTFS is the result of interfetal transfusion in monochorionic multiple pregnancies, occurring between 15 and 26 weeks of gestation.[31,32] Two patterns of interfetal transfusion in monochorionic multiple gestations have been described based on ultrasound studies. The most frequent pattern affects 90% of the cases and results from constant but balanced bidirectional interfetal transfusion between the twins.[16] This means that the transfusion from one twin (Baby 1 – donor) to the other (Baby 2 – recipient) is counterbalanced by the transfusion from Baby 2 (recipient) to Baby 1 (donor).

Conversely, in 10% of monochorionic twins, a chronic imbalance in net flow develops, resulting in TTTS,[32,33] and it brings about different complications in the twins. Whereas the donor develops hypovolaemia, oliguria and oligohydramnios, the recipient develops hypervolaemia, polyuria and polyhydramnios, circulatory overload and hydrops. The presence of hydramnios is detected at ultrasonic scan by the appearance of characteristic changes in the quantity of amniotic fluid contained in the sac. Thus, in the recipient there is polyhydramnios in its sac secondary to polyuria, demonstrated by the presence of a deep vertical pocket of ≥8 cm prior to 20 weeks and ≥10 cm after 20 weeks' gestation.[34-36] On the other hand, the donor twin develops oliguria and oligohydramnios demonstrated with the deepest vertical pocket measuring ≤2 cm on ultrasound scan.[34]

Based on ultrasound and Doppler studies, Quintero *et al*.[37] have described five possible stages in the progression of TTTS. Accordingly, stage I is typified by presence of hydramnios in the recipient sac but the bladder is still visible. Stage II is underlined by empty bladder of the donor twin (stuck Twin). Stage III is characterized by severely abnormal Doppler studies including absent or reversed end-diastolic flow in the umbilical artery or abnormal venous Doppler pattern in the recipient, such as reverse flow in the ductus venosus or pulsatile umbilical venous flow. Stage IV implies fetal hydrops and stage V corresponds to the death of one or both twins. The Quintero's classification[37,38] has been criticized because the five stages do not correlate with either severity of disease or time-scale for progressive deterioration of disease.[29] It has been observed that TTTS can present as stage III from the outset and stage I disease can progress to stage V without passing through stages II, III and IV. Furthermore, Lewi and Deprest[16] noted that this classification does not predict the outcome to treatment of all stages of TTTS. Hence, at best, the Quintero staging system reflects the different possible clinical manifestations that may result from a variable contribution of intertwin transfusion imbalance, hormonal factors and the degree of placental sharing. It should be noted that other conditions can also lead to growth discordance, thus confusing the picture presented by TTTS.[16] For example, in a twin gestation, oligohydramnios may be associated with a growth restricted twin that appears to be stuck, whereas polyhydramnios is absent in the larger baby. Likewise, the isolated presence of hydramnios in one sac with a normal amniotic fluid in the other certainly precludes a diagnosis of TTTS. Hence, multiplets that present with these features call for further assessment to identify the underlying cause of the discordance in fetal growth.

Table 1: Fetal effects of multiplet transfusion syndromes (Courtesy: Skupski DW)

Oligohydramnios-polyhydramnios sequence (Amniotic fluid imbalance)
Decreased donor and increased recipient urine output, detected by ultrasound as absence and enlarged bladder in donor and recipient twins
Alterations of blood flow in various blood vessels based on Doppler velocimetry
Absent or reversed end-diastolic velocity of the umbilical artery in the donor twin
Pulsatile umbilical venous flow in the recipient twin
Absent or reversed diastolic velocity in the ductus venosus of the recipient twin
Growth restriction in the donor twin detected by estimated fetal weight determination by ultrasound
Cardiac dysfunction due to vascular volume overload in the recipient twin detected by fetal echocardiography
Hydrops fetalis of the recipient twin detected by ultrasound
Death of one or both foetuses

Pathophysiology

The pathology of feto-fetal transfusion essentially consists of abnormal intertwin placental fetal vascular anastomoses, first described as 'Chorioangiopagus Vessels' by Friedrich Schatz in his study of monochorionic pregnancies between 1875 and 1910.[1] These chorioangiopagus vessels described the placental vascular anastomoses, which were considered to be variant on the nomenclature used for the description of conjoined twins. Schatz suggested that the twins were connected by blood vessels, and this constituted the mildest form on the spectrum of what could be considered 'the conjoint twin syndrome'.[39] In essence, the 'conjoint twin syndrome' literally spans a spectrum from 'placental part sharing' to 'fetal body part sharing' [Figures 2 and 3].

The exact pathophysiology of TTTS is not clear.[16] Nevertheless, diverse mechanisms,[40-47] such as vascular anastomoses, haemodynamic and hormonal factors, have been proposed to explain the changes associated with the condition. It is for this reason that TTTS is now viewed to be more complex than just the simple transfer of blood from

one twin to the other. Thus, the development of TTTS is best explained on the basis of unique vascular anastomoses occurring in the placenta of monochorionic twins revealed by postnatal injection studies[36] and *in-vivo* fetoscopic observations,[38,48] indicating the presence of at least one unidirectional AV anastomosis as an anatomical prerequisite for the development of TTTS. Thus, placental anastomoses can be AA, AV and venovenous (VV) [Figures 3 and 4].[16]

AA and VV anastomoses are typically superficial, bidirectional vascular connections on the surface of the chorionic plate, forming direct communications between the arteries and the veins of the two fetal circulations. The direction of flow depends on the relative interfetal vascular pressure gradients. AV anastomoses are referred to as 'deep' anastomoses because they occur at the capillary level deep within the depth of the placenta, receiving arterial supply from one twin and providing well-oxygenated venous drainage to the other. Hence, the supplying artery and draining vein of the AV anastomoses can be visualized on the placental surface as an unpaired artery and vein that pierce the chorionic plate in close proximity to each other. The AV anastomoses allows flow in only one direction, and hence, may create an imbalance in interfetal transfusion leading to TTTS, unless balanced by an oppositely directed transfusion through other superficial or deep anastomoses. Hence, the presence of bidirectional AA anastomoses is believed to protect against the development of TTTS because most (84%) non-TTTS monochorionic placentas have AA anastomoses in contrast to TTTS (20%).[34,36]

Sonographically distinct TTTS is defined in 75% of cases by haematocrit difference of less than 15%. Hence, it is apt to infer that other mechanisms may explain TTTS in the other 25% with inter twin haematocrit difference of more than 15%. It has also been noted that changes expected to accompany chronic transfusion in donor and recipient twins are absent in some cases of TTTS, thus signifying that other mechanisms should be invoked to explain the findings in multiplet transfusion. In this regard, elevated erythropoietin level is expected to be demonstrated in the donor, however, this is not the case in some cases of TTTS.[40] Moreover, iron depletion and overload are absent in the donor and recipient twin accordingly.[41]

By same token, various reports[42,43] have found that placental dysfunction is associated with an increased feto-placental resistance that promotes the transfusion of blood from one twin (growth restricted) to the other (recipient). Therefore, the demonstration of decreased levels of hormones including insulin growth factor II[42] and Leptin[43] in donors as compared to values in the recipients suggests that the problem is discordant placental development rather than transfusion as cause of the discordance in growth. Furthermore, other hormonal changes occur in the recipient and donor twins involving the circulating levels of endothelin I, atrial natriuretic peptide and renin, as well as angiotensin and aldosterone.[44]

Endothelin I, a hormone derived from the vascular endothelium, is elevated in recipients and it leads to the development of peripheral vasoconstriction and hypertension. In addition, atrial natriuretic peptide, secreted by atrial myocytes, in response to filling of the atrium, is elevated in recipients leading to sodium and fluid excretion by the

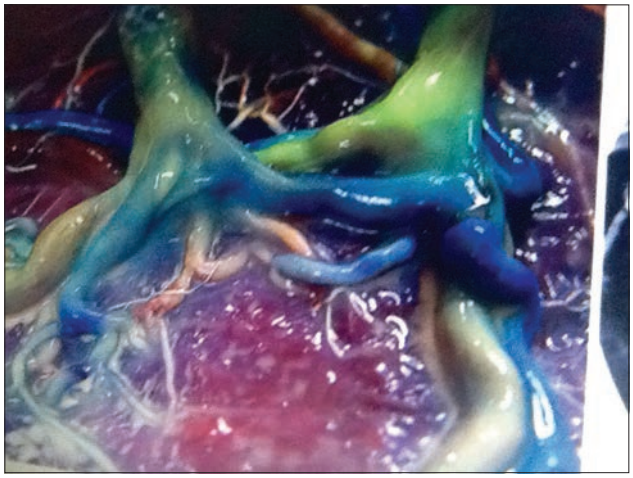

Figure 3: Monochorionic Monoamniotic Placental Angioarchitecture with Fetofetal Vascular Anastomoses; Macroscopic image of large diameter anastomoses and side-to-side insertion of umbilical cords. (Liesbeth Lewi and Jan Deprest)

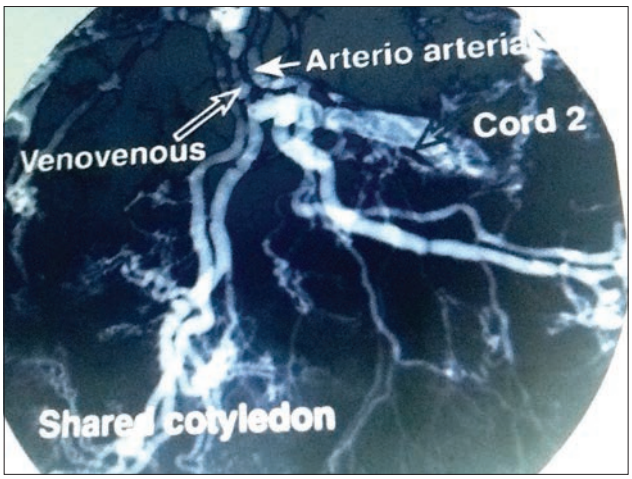

Figure 4: Angiography displaying fetofetal vascular anastomoses. Diagnostic angiography in which injection of umbilical vessels of one twin was sufficient to visualize placental vascularization of both twins owing to presence of large arterioarterial and venovenous anastomoses. In addition, approximately 50% of the placenta consisted of shared cotyledons. (Liesbeth Lewi and Jan Deprest)

kidneys of the affected twin. Moreover, there is an increased renin gene and protein in the donor kidney as compared to the recipient kidneys. These observations suggest the role of the renin-angiotensin-aldosterone mechanism in the development of TTTS.[45-47] Thus, the pathophysiology of sonographically-defined TTTS is most likely multifactorial with vascular anastomoses providing the anatomic basis, whereas haemodynamic and hormonal factors contribute in varying degrees to its clinical development.

Early detection and markers

Early identification of monochorionic twin pregnancies at increased risk of TTTS would assist patient counselling, follow-up in a fetal medicine centre and institution for timely treatment. Unquestionably, timely treatment of TTTS might improve the outcome by preventing PPROM and/or cervical shortening, important risk factors for preterm birth.[48-50] Some markers for the early identification of monochorionic twins with high risk for the development of TTTS include nuchal translucency (NT), folding of the intertwin membrane and crown rump length (CRL).

An increased nuchal translucency of $>95^{th}$ percentile in at least one fetus during 11–14 weeks examination occurs in 13% of monochorionic twins. This finding is a marker for TTTS as well as for other conditions such as chromosomal anomalies, cardiac defects and a myriad of genetic syndromes.[16] Folding of the intertwin membrane at 15–17 weeks is another sign for the prediction of TTTS.[50] It reflects the presence of oliguria and a reduced amniotic fluid in the sac of the donor. CRL difference between the twins of ≥6 mm is predictive of diagnosis of TTTS.[16] A velamentous or marginal cord insertion has been demonstrated by Fries *et al*.[51] to indicate risk for the development of TTTS.

Fetal risks

TTTS that is not recognized early and treated accordingly can lead to nearly 100% mortality. However, improvement in prenatal and neonatal care has reduced mortality to approximately 60%. Some complications include abortion, extreme preterm birth, hydramnios and fetal death from cardiac failure in the recipient and poor perfusion in the donor. In addition, chronic haemodynamic imbalance leads to substantial cerebral and cardiac sequelae in survivors. Both recipient and donor are at risk for antenatally acquired cerebral lesions. In donor twins, hypovolemia, hypotension and anaemia may induce cerebral hypoxia and brain damage. Conversely, hyperviscosity and cardiac failure in the donor may impair cerebral perfusion. Hence, the reported incidences of cerebral palsy and major neurological deficiencies in TTTS are 6–23%.[52,53]

Management options

Several treatment options utilized in the management of TTTS include serial amniodrainage, fetoscopic laser coagulation, septostomy and selective feticide.[54-56] Amniodrainage is a palliative procedure and involves the iatrogenic reduction of the volume of amniotic fluid. It is useful in the treatment of mild cases of TTTS such as stages I and II by prolonging the pregnancy and improving the fetal condition through the reduction of the intrauterine pressure.

Fetoscopic laser coagulation (fetoscopic laser occlusion of chorioangiopagus vessels, FLOC) is superior to amniodrainage in the management of all stages of TTTS because the procedure permits the disruption of the vascular connections between the twins, thereby terminating the circulation of blood from one twin to the other.[55-58] Flimsy or minimal fetofetal vascular connections, which may be primary antenatally or secondary to FLOC, can result in TAPS that is treatable postnatally by blood transfusion of donor twin with blood obtained from the recipient twin.[59] Despite this uncommon complication, laser coagulation is the recommended firstline treatment for TTTS because it leads to better survival rates and neurological outcome.[54,60]

Septostomy is still being used in the treatment of some cases of TTTS and involves the dissolution of the amnion between the donor and recipient twins leading to a single sac, thus reducing pressure surrounding the babies. Septostomy does not possess survival advantage over amniodrainage or laser coagulation. Selective feticide is achieved by cord occlusion but does not arrest the transfusion of blood from one twin to the other. It is the treatment of choice in cases associated with discordant anomalies and imminent fetal death, as well as in pregnancies in which laser coagulation is difficult because full inspection of the vascular equator is technically not feasible.

Conclusion

At present, there is paucity of published literature on the subject of transfusion syndromes in monochorionic multiplets in sub-Saharan Africa and Nigeria in particular. Setting up appropriate perinatology units and collaboration with established centres in Europe, North America and Asia will facilitate growth and success of such units. The extensive work and volume of publications from the North American Fetal Therapy Network (NAFTNet), the Eurofoetus consortium and the USFetus organisation in the last decade[61] show the power of collaboration with the success achieved on this subject.

Financial support and sponsorship
Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Skupski DW. TTTS: Where did we come from? Distant History. In: Skupsi DW, editor. Twin-To-Twin Transfusion Syndrome. 1st ed. New Delhi, London, Philadelphia, Panama: Jaypee Brothers Medical Publishers (P) Ltd; 2013. p. 3-15.
2. Scher A, Petterson B, Blair E, Ellenberg JH, Grether JK, Haan E, *et al*. The risk of mortality or cerebral palsy in twins: A collaborative population based study. Paediatr Res 2002;52:671-81.
3. Lewi L, Jani J, Blickstein I, Huber A, Gucciardo L, Van Mieghem T, *et al*. 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.
4. Lewi L, Gucciardo L, Van Mieghem T, de Koninck P, Beck V, Medek H, *et al*. Monochorionic diamniotic twin pregnancies: Natural history and risk stratification. Fetal Diagn Ther 2010;27:121-33.
5. Glinianaia SV, Pharaoh PO, Wright C, Rankin JM; Northern Region Perinatal Mortality Survey Steering Group. Fetal or infant death in twin pregnancy: Neurodevelopmental consequence for the survivor. Arch Dis Child Fetal Neonatal Ed 2002;86:F9-15.
6. Blickstein I. Do multiple gestations raise the risk of cerebral palsy? Clin Perinatol 2004;31:395-408.
7. Ugwu OR, Egri Okwaji MT. Perinatology in the Tropics. In: Azubuike JC, Nkaginieme KE. editord. Paediatrics and Child Health in a Tropical Region. 2nd ed. University of Port Harcourt Press; 2007. p. 157-60.
8. Osaghae DO, Sule G, Ogieva R. Admissions and outcome of newborns in Benin City. Niger Hosp Pract 2013;11:45-9.
9. UNFPA. Trends in Maternal Mortality (http//www.unfpa.org/maternal-health) Updated November, 2015.
10. Unuigbe, JA, Orhue AA, Oronsaye AU. Maternal mortality at the University of Benin Teaching Hospital, Benin-City, Nigeria., 1973-1985. Trop J Obstet Gynaecol 1988;1:13-8.
11. Nylander PP. The frequency of twinning in a rural community in Western Nigeria. Ann Hum Genet 1969;33:41-4.
12. Nylander PP. Twinning in Nigeria. Acta Genet Med Gemellol 1970;19:457-64.
13. Nylander PP. The incidence of triplets and higher multiple births in some rural and urban populations in Western Nigeria. Ann Hum Gen 1971;34:409-15.
14. Matte U, Le Roux MG, Benichou B, Moisan J, Giuglani R. Study on possible increase in twinning rate at a small village in South Brazil. Acta Genet Med Gemellol 1996;45:431-7.
15. Ikechebelu JI. Assisted Reproductive Technique (ART): The state of the Art in Nigeria. Int J Med Health Dev 2003;8:1-6.
16. Lewi L, Deprest J. Fetal problems in multiple pregnancies. In: James D, Steer PJ, Weiner CP, Gonik B, Crowther CA, Robson SC, editors. High Risk Pregnancy: Management Options. 4th ed. St Louis, MO 63403: Elsevier Saunders; 2011. p. 405-36.
17. Bulmer MG. The Biology of Twinning in Man. Clarendon Oxford; 1970.
18. Derom C, Derom R. The East Flanders Prospective Twin Survey. In: Blickstein I, Keith LG, editors. Multiple Pregnancy. 2nd ed. London: Taylor & Francis; 2005. p. 39-47.
19. Alikani M, Cekleniak NA, Walters E, Cohen J. Monozygotic twinning following assisted conception: An analysis of 81 consecutive cases. Hum Reprod 2003;18:1937-43.
20. Chow JS, Benson CB, Racowsky C, Doubilet PM, Ginsburg E. Frequency of a monochorionic pair in multiple gestations: Relationship to mode of conception. J Ultrasound Med 2001;20:757-60.
21. De Catte L, Camus M, Foulon W. Monochorionic high-order multiple pregnancies and multifetal pregnancy reduction. Obstet Gynecol 2002;100:561-6.
22. Levene MI. Fetal physiology, assessment of fetal well-being and adaptation to extra-uterine life. In: Levene IM, Tudehope D, Thearle MJ, editors. Essentials of Neonatal Medicine. 2nd ed. Blackwell science; 1996. p. 6-16.
23. Lewi L, Van Schoubroeck D, Gratacós E, Witters I, Timmerman D, Deprest J. Monochorionic diamniotic twins: Complications and management options. Curr Opin Obstet Gynecol. 2003; 15: 177-194
24. Fisk NM, Duncombe GJ, Sullivan MH. The basic and clinical of twin-twin transfusion syndrome. Placenta 2009;30:379-90.
25. Kaufmann P, Mayhew TM, Charnock-Jones DS. Aspects of human fetoplacental vasculogenesis and angiogenesis. Changes during normal pregnancy. Placenta 2004;25:114-26.
26. Diehl W, Hecher K, Zikulnig L, Vetter M, Hackelöer BJ. Placental vascular anastomoses visualized during fetoscopic laser surgery in severe mid-trimester twin–twin transfusion syndrome. Placenta 2001;22:876-81.
27. Arabian B, Baschat A. Colour injection and digital angiography. In: Skupski DW, editor. Twin-To-Twin Transfusion Syndrome. 1st ed. London: Jaypee Brothers Medical Publishers; 2013. p. 45-56.
28. 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.
29. Rossi AC, D'Addario V. The efficacy of Quintero staging system to assess the severity of twin-twin transfusion syndrome treated with laser therapy: A systematic review with meta-analysis. Am J Perinatol 2009;26:537-44.
30. Delia JE, Fisk N, Hecher K, Machin G, Nicolaides K, Hyett J, *et al*. Twin-to-twin transfusion syndrome – debates on etiology, natural history and management. Ultrasound Obstet Gynecol 2000;16:210-3.
31. Xueju W, Pengbo Y, Ying W, Yangyu Z, Yuan W. Placental characteristics of monochorionic twin pregnancy complicated with selective fetal growth restriction (Chinese). Chin J Perinat Med 2015;18:260-5.
32. Acosta-Rojas R1, Becker J, Munoz-Abellana B, Ruiz C, Carreras E, Gratacos E, *et al*. Catalunya and Balears Monochorionic Network: Twin chorionicity and the risk of adverse perinatal outcome. Int J Gynecol Obstet 2007;96:98-102.
33. Lewi L, Jani J, Blickstein, Huber A, Gucciardo L, Van Mieghem T, *et al*. 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.
34. Denbow ML, Cox P, Taylor M, Hammal DM, Fisk NM. Placental angioarchitecture in monochorionic twin pregnancies: Relationship to fetal growth, feto-fetal transfusion syndrome, and pregnancy outcome. Am J Obstet Gynecol 2000;182:417-4.
35. Lewi L, Cannie M, Bliekstein I, Jani J, Huber A, Hecher K, *et al*. Placental sharing, birthweight discordance, and vascular anastomoses in monochorionic diamniotic twin placentas. Am J Obstet Gynecol 2007;197:587.
36. Bermudez C, Becerra CH, Bornick PW, Allen MH, Arroyo J, Quintero RA. Placental types and twin-twin transfusion syndrome. Am J Obstet Gynecol 2002;187:489-94.
37. Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M. Staging of twin-twin transfusion syndrome. J Perinatol 1999;19:550-5.
38. Xueju W, Yuan W, Pengbo Y, Yangyu Z. Placental characteristics of twin-to-twin transfusion syndrome (Chinese). Natl Med J China 2015;95:1323-7.
39. Obladen M. Unequal but monozygous: A history of twin-twin transfusion syndrome. J Perinat Med 2010;38:121-8.
40. Bajoria R, Ward S, Sooranna SR. Erythropoietin in monochorionic twin pregnancies in relation to twin-twin transfusion syndrome. Hum Reprod 2001;16:574-80.
41. Bajoria R, Lazda EJ, Ward S, Sooranna S. Iron metabolism in monochorionic twin pregnancies in relation to twin-twin transfusion syndrome Hum Reprod 2001;16:567-73.

42. Bajoria R, Gibson MJ, Ward S, Sooranna SR, Neilson JP, Westwood M. Placental regulation of insulin-like growth factor axis in monochorionic twins with chronic twin-twin transfusion syndrome. J Clin Endocrinol Metab 2001;86:3150-5.
43. Sooranna SR, Ward S, Bojaria R. Discordant fetal leptin levels in monochorionic twins with chronic midtrimester twin-twin transfusion syndrome. Placenta 2001;22:392-8.
44. Bajoria R, Ward S, Chatterjee R. Natriuretic peptides in the pathogenesis of cardiac dysfunction in the recipient fetus of twin-to-twin transfusion syndrome. Am J Obstet Gynecol 2002;186:121-7.
45. Mahieu-Caputo D, Meulemans A, Martinovic J, Lacoste M, Cai Y, Narcy F, *et al*. Twin-to-twin teransfusion syndrome. Role of the fetal renin-angiotensin system. Am J Pathol 2001;156:629-36.
46. Kilby MD, Platt C, Whittle MJ, Oxley J, Lindop GB. Renin gene expression in fetal kidneys of pregnancies complicated by twin-twin transfusion syndrome. Pediatr Dev Pathol 2001;4:175-9.
47. Galea P, Bargye O, Wee L, Jain V, Sullivan M, Fisk NM. The placenta contributes to activation of the renin angiotensin system in twin-twin transfusion syndrome. Placenta 2008;29:734-42.
48. de Lia JE, Carr MH. Pregnancy loss after successful laser surgery for previable twin-twin transfusion syndrome (letter). Am J Obstet Gynecol 2002;187:517-8.
49. Robyr R, Boulvain M, Lewi L, Huber A, Hecher K, Deprest J, *et al*. Cervical length as a prognostic factor for preterm delivery in twin-twin transfusion syndrome treated by fetoscopic laser coagulation of chorionic plate anastomoses. Ultrasound Obstet Gynecol 2005;25:37-41.
50. Sebire NJ, Souka A, Skentou H, Geerts L, Nicolaides KH. Early prediction of severe twin-to-twin transfusion syndrome. Hum Reprod 2010;15:2008-10.
51. Fries MH, Goldstein RB, Kilpatrick SJ, Golbus MS, Callen PW, Filly RA. The role of velamentous cord insertion in the aetiology of twin-twin transfusion syndrome. Obstet Gynecol 1993;81:569-74.
52. Lopriore E, van Wezel-Meijler G, Middeldorp JM, Sueters M, Vandenbussche FP, Walther FJ. *et al*. Incidence, origin and character of cerebral injury in twin-to-twin transfusion syndrome treated with fetoscopic laser surgery. Am J Obstet Gynecol 2006;194:1215-20.
53. Bejar R, Vigliocco G, Gramajo H, Solana C, Benirschke K, Berry C, *et al*. Antenatal origins of neurological damage in newborn infants in multiple gestations. Am J Obstet Gynecol 1990;162:1230-6.
54. 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.
55. 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.
56. van Gemert MJ, Umur A, Tijssen JG, Ross MG. Twin-twin transfuision syndrome: Etiology, severity and rational management. Curr Opin Obstet Gynecol 2001;13:193-206.
57. Skupski DW, Gurushanthaiah K, Chasen S. The effect of treatment of twin-twin transfusion syndrome on the diagnosis to delivery interval. Twin Res 2002;5:1-4.
58. Graef C, Ellienrieder B, Hecher K, Hackeloer BJ, Huber A, Bartmann P. Long-term neurodevelopmental outcome of 167 children after intrauterine laser treatment for severe twin-twin transfusion syndrome. Am J Obstet Gynecol 2006;194:303-8.
59. Osaghae DO, Unuigbe JA. Twin Anemia Polycythemia Sequence (TAPS): Postnatal correction of severe anemia in donor twin by transfusion of blood evacuated from the recipient polycythemic twin. Trop J Obstet Gynaecol April; 33:113-9.
60. Xueju W, Guangwu X, Yuan W, Pengbo Y, Yangyu Z. Clinical effect of fetoscopic laser occlusion of chorioangiopagus vessels for twin-to-twin transfusion syndrome (Chinese). Chin J Obstet Gynecol 2014;49:886-93.
61. Johnson MP; NAFTNet. The North American Fetal Therapy Network (NAFTNet): A new approach to collaborative research in fetal diagnosis and therapy. Semin Fetal Neonatal Med 2010;15:52-7.