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Yolanda Maria dos Santos Martins

Into the heart of monochorionic twin pregnancies – from the placenta to the hemodynamic compromise

Até ao coração das gravidezes monocoriónicas – da placenta ao compromisso hemodinâmico.

Junho, 2010

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INTO THE HEART OF MONOCHORIONIC TWIN PREGNANCIES - FROM THE PLACENTA TO THE HEMODYNAMIC COMPROMISE

ATÉ AO CORAÇÃO DAS GRAVIDEZES MONOCORIÓNICAS - DA PLACENTA ATÉ AO COMPROMISSO HEMODINÂMICO

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ABBREVIATIONS

- Monochorionic twins: MC
- Twin-to-twin transfusion syndrome: TTTS
- Twin reversed arterial perfusion: TRAP
- Congenital heart disease: CHD
- Fetoscopic laser coagulation: FLP
- Monozygotic: MZ
- Dichorionic: DC
- Diamniotic: DA
- Monochorionic: MC
- Monoamniotic: MA
- Paracentral cord insertion:PCI
- Velamentous and marginal insertion: VMI
- Aterio-arterial anastomoses: AAA
- Veno-venous anastomoses: VVA
- Arterio-venous anastomoses: AVA
- Twin oligo-polyhydramnios sequence: TOPS
- Deepest vertical pool: DVP
- Right ventricular outflow tract obstruction: RVOTO
- Preterm Premature Rupture of the Membranes: PPROM
- Umbilical cord occlusion: UCO

RESUMO

As anastomoses vasculares placentárias são o marco das gravidezes monocoriónicas. Os dois determinantes vasculares do comportamento clínico em gémeos monocoriónicos são as combinações de inserções do cordão umbilical e as ligações vasculares da placenta entre os gémeos. Há, portanto, uma necessidade urgente de encontrar formas de diagnosticar estas anastomoses, bem como de as identificar directamente *in vivo*. A síndrome de transfusão feto-fetal (TTTS) desenvolve-se quando o fluxo sanguíneo unidirecional e descompensado de um gémeo (dador) para o outro (receptor) causa um desequilíbrio circulatório, na presença de uma anastomose profunda arterio-venosa (AVA). Esta síndrome afecta 15% das gravidezes gemelares monocoriónicas e permanece uma das afecções perinatais mais letais. O diagnóstico é feito por evidência ecográfica da sequência TOPS (sequencia de oligo-poliidramnio dos gémeos). O TTTS representa actualmente o maior desafio terapêutico de qualquer patologia fetal e mais opções válidas são ainda necessárias. O gémeo acárdico ocorre quando um gémeo não tem placentação e é perfundido de forma inversa pelo outro (twin reversed arterial perfusion, TRAP). Esta patologia afecta 1% das gravidezes monocoriónicas e tem uma elevada mortalidade perinatal. Actualmente, técnicas minimamente invasivas tratam a condição interrompendo o suprimento vascular ao gémeo acárdico e estão associadas com o melhor outcome para o gémeo "bombeador". A eficácia de qualquer tratamento fetal não pode ser completamente avaliada apenas pela sobrevivência, mas também pelos seus efeitos na morbilidade neonatal e a longo prazo. O objectivo deste artigo foi de rever a literatura publicada sobre este tema, tentando construindo pontes entre o sistema circulatório dos gémeos monochorionicos, a sua morbilidade cardíaca e as formas de orientar o tratamento.

Palavras-chave: Monozygotic twins; Heart defect; Fetofetal Transfusion; Ultrasonography, Prenatal; Fetal surgery.

ABSTRACT

Placental vascular anastomoses are landmarks of monochorionic (MC) twin pregnancies. The vascular determinants of clinical behavior in MC twins are combinations of cord insertions and the inter-twin vascular connections on and in the placenta. There is, therefore, an urgent need to find ways to diagnose the presence of these anastomoses, as well as a direct method to pinpoint these connections *in vivo*. The twin-to-twin transfusion syndrome (TTTS) develops when uncompensated unidirectional blood flow from one twin ('donor') to the other ('recipient') causes circulatory imbalance in the presence of a deep arterio-venous anastomose (AVA). It affects 15% of MC twin pregnancies and remains one of the most lethal perinatal complications. The diagnosis is made by sonographic evidence of the twin oligo-polyhydramnios sequence (TOPS). TTTS currently presents the greatest therapeutic challenge of any fetal pathology and more valuable options are still lacking. Acardiac anomaly, also known as twin reversed arterial perfusion (TRAP), occurs when one twin lacks placentation and is perfused reversely by the other. It affects 1% of MC twins and has a high perinatal mortality rate. Minimally invasive techniques that treat the condition by interrupting the vascular supply to the acardiac twin are associated with the best outcome for the pump twin. The efficacy of any fetal treatment can only be evaluated fully by assessment not only of survival, but also of its effect on the neonatal and long-term morbidity. The aim of this paper was to review the literature publicated on this subject and to try to build the bridges between the circulatory system in MC twins, their cardiac morbidity and the ways to manage it.

Keywords: Monozygotic twins; Heart defect; Fetofetal Transfusion; Ultrasonography, Prenatal; Chorion/ultrasonography; Congenital/therapy; Hemodynamics; Fetal surgery; Laser Coagulation.

"*I carry your heart. I carry it in my heart*". E.E. Cumminghs

INTRODUCTION

The hemodynamics of monochorionic (MC) twin pregnancies is considered enigmatic, remaining one of the most challenging problems in contemporary obstetrics. With two hearts serving one circulation, continuous intertwin transfusion is standard.[1] Placental vascular anastomoses in MC twins' pregnancies are the main cause of perinatal complications, including twin-to-twin transfusion syndrome (TTTS), twin reversed arterial perfusion (TRAP), growth abnormalities, fetal demise and adverse neurological outcomes.[2] A significant contribution to the higher morbidity and mortality is made by the increased risk of structural congenital heart disease (CHD) and of acquired cardiac complications associated with the twinning process.[3] This disproportionate mortality and morbidity is receiving increased attention, while studies from placental vasculature, cordocentesis, and fetal Doppler are enhancing our understanding of the pathophysiology of MC twins.[4] From serial amniodrainage to fetoscopic laser photocoagulation (FLP), much has been done to increase survival and diminish the perinatal complications associated with the "liaisons dangereuses".[5] The aim of this paper was to review the literature publicated on this subject and to try to build the bridges between the circulatory system in MC twins, their cardiac morbidity and the ways to manage it. We based our review article on the extensive pubmed articles research and chapters of books related to the title.

THE "BLACK BOX" OF MC PLACENTAS

Approximately one-third of twin pregnancies are monozygotic (MZ) resulting from the cleavage of a single fertilized egg. Their chorionicity depends on the timing of splitting of the fertilised egg.[6] Early division at less than 3 days post-fertilization results in dichorionic/diamniotic (DC/DA) twins (25%-30%). Later division at days 3 to 9 results in monochorionic/ diamniotic (MC/DA) twins (70%-75%) and division between days 9 and 12 results in monochorionic/monoamniotic (MC/MA) twins (1%-2%).[7] Conjoined twins must arise after day 14.[8] MC twins have a perinatal mortality rate (2.8%) nearly twice as high as DC twins and four times higher than singletons.[9]

There are two vascular determinants of clinical behavior in MC twins: combinations of cord insertions; and types, combinations and flow directions in the inter-twin vascular connections on and in the placenta.[10]

First, the umbilical cord may insert at any point into the inner surface of the hollow trophoblastic sphere. In most cases, this corresponds with the most deeply implanted (paracentral or central insertion (PCI)) portion of the trophoblast that will become the placenta proper.[11-12] Velamentous and marginal cord insertions (VMI) that don't face the endometrium are present in about 50% of MC twin pregnancies. VMI can be explained by the fact that the intercord distance is determined before implantation and the single placenta is unable to 'spin' or 'adjust' once it has implanted.[10] If cords are inserted far apart on the early disc, one might be exposed to trophotropism, a competition process that's thought to result from a battle for space between each twins' placental territories.[10, 13] When there is a combination of PCI and VMI resulting in unequal sharing of placental tissue, the centrally inserted twin commands a disproportionate amount of placental parenchyma, whereas the velamentous twin has a very small territory, as often seen in TTTS.[10-11]

Second, the MC twin placenta has a vascular equator roughly equidistant between the cord insertions.[10] The equator defines two zones of placental parenchyma perfused by each twin that aren't

always equal.[12] The chorion surface vessels may show a dispersal pattern (fine networks of progressively decreasing diameters starting at the cord insertion) in the larger portion and a magistral pattern (course from the cord to the placenta edge without diminishing in diameter) in the smaller. These patterns may be occasioned by type of cord insertion.[4] The primitive villous circulation develops independently of the fetal cardiovascular system. As fetal veins and arteries grow out from the umbilical cord on to the surface of the placenta, they capture cotyledons and connect with the underlying primitive villous sinusoids via scattered foramina in the chorionic plate, one for each cotyledon.[10] These anastomoses can be superficial with a very low resistance, arterio-arterial anastomoses (AAA) or veno-venous anastomoses (VVA), or deep with high resistance, arterio-venous anastomoses (AVA). These interfetal connections are present in 95–98% of MC twin placentas.[10] The majority of them contain one AAA, seldom more. In contrast, VVAs are much rarer, probably because of spontaneous thrombosis/sclerosis, but, when present, there may be several per placenta. VVAs are particularly dangerous because they permit large and rapid flows at low resistance.[10]

MC twin placental asymmetry has been described as unequal sharing of venous return zones, unequal allocation of parenchyma and discordant vascular perfusion zones, but a precise definition is lacking. The clinical consequences of this asymmetry depend on the degree of placental share.[4] There's therefore an urgent need to find ways to diagnose the presence of AAAs and AVAs as well as a direct method to pinpoint them *in vivo*.[12]

For improved outcomes of the twins, the diagnosis should be made as early as possible, so that treatment can be planned before end-stage disease is reached, commonly at 20–24 weeks gestation.[10] Chorionicity and amniocity can be reliably recorded by 7 menstrual weeks using transvaginal ultrasonography.[4] The distinction between MC and DC twins is by identification of the 'twin peak' (or 'lambda') sign by the first-trimester ultrasound. All patients with MC twin pregnancies should be counselled about the symptoms of polyhydramnios and should be seen approximately biweekly. Each antenatal visit during the 3rd trimester should document the fetal well-being of both twins. Given the increased risk of fetal demise after 32–33 weeks' gestation, the frequency of antenatal visits should be at

least biweekly and preferably include Doppler velocimetry of the umbilical artery and middle cerebral artery.[14]

Different forms of TTTS have been described. Acute perimortem TTTS occurs after fetal demise and is due to the acute exsanguination from the surviving twin into the low-pressure circulation of the dead cotwin. Consequences for the survivor include cerebral impairment and preterm delivery. Acute perinatal TTTS may occur during birth and is the result of rapid blood loss via the superficial anastomoses due to blood pressure differences associated with uterine contractions or changes in fetal position. It can probably also occur when the umbilical cord of one twin is clamped quickly after birth and a large volume of blood in the placenta flows to the other child. Both acute forms of TTTS are mediated through superficial anastomoses. Chronic TTTS, the most common form, develops when uncompensated unidirectional blood flow from one twin ('donor') to the other ('recipient') causes circulatory imbalance[1] in the presence of a deep AVA. It occurs usually during the second trimester and affects 15% of MC twin pregnancies.[6, 15] It remains one of the most lethal perinatal complications, with an 80–100% mortality rate and a 15–50% risk of disability in survivors without treatment.[2]

(In this review when using the abbreviation "TTTS", the authors are referring to "chronic TTTS".)

Etiology

After Schatz's suggestion that TTTS was due to unbalanced inter-twin transfusion via AVA[16], Sebire *et al*.[17] hypothesized that it results from a progressive, but asymmetric, reduction of bidirectional AVAs.[18] A single AVA in the absence of other effective connections dooms the twins to early and severe TTTS. There are two routes by which flow in the causative AVA can be compensated: by an AVA in the opposite direction; and by surface AAAs or VVAs that allow to establish a dynamic equilibrium. Fortunately, the majority of MC placentas contain complex combinations of these anastomoses that don't permit imbalance and the development of TTTS. The presence of an AAA largely protects against the

development of TTTS; TTTS that occurs in the presence of an AAA or bidirectional AVAs is usually mild.[10]

Many hypothesis may explain why TTTS doesn't manifest in the first trimester:[17-18] the placenta is still in the process of expanding and its size is much larger relative to the fetus facilitating compensation for imbalances; in the second trimester, the recipient's villous capillaries distend under an increased luminal pressure[18-19]; colloid osmotic pressure and viscosity in fetal blood increases as gestation progresses[18, 20]; and, the fetal kidneys aren't fully functional at 12 weeks when the skin is still highly permeable to amniotic fluid.[18]

Placental vascular diameter, vascular resistance, flow paterms, vascular distribution patterns and alterations of the endothelin and the renin-angiotensin system have also been implicated in the pathogenesis of TTTS.[21-22] According to Lopriore *et al.*[15] other mechanisms may produce TTTS such as loss of protein, compression of vessels, *in utero* placental insufficiency and differential production of growth factors.

Diagnosis

The original neonatal criteria for TTTS (i.e. at least 5 g/dl of hemoglobin concentration difference and at least 20% of birthweight discordance) have been abandoned because they often failed to apply.[2]

Between 16 and 26 weeks of gestation, the diagnosis is made by sonographic evidence of twin oligo-polyhydramnios sequence (TOPS).[15] The donor becomes hypovolaemic and develops oliguria and oligohydramnios[23] (deepest vertical pool (DVP) of amniotic fluid of maximum 2.0 cm [24-25]), also known as the 'stuck twin' sequence.[23] Hypervolaemia triggers polyuria and polyhydramnios in the recipient (DVP of at least 8.0 or 10 cm before or after 20 weeks of gestation, respectively[24-25]), which can develop high-output cardiac failure and hydrops.[2] Other criteria include umbilical artery intertwine differences of 0.4 or greater for systolic/diastolic ratio and demonstration of the transplacental shunt.[4]An uncommon form of TTTS referred to as twin anemia–polycythemia sequence, with severe anemia in one twin and

polycythemia in the other without the characteristically associated TOPS seen in the classical TTTS, has been described.[15]

Doppler investigation demonstrates signs of congestive heart failure in severe cases due to hypervolemia in recipients (negative or reverse a-wave in the *ductus venosus*, pulsatile umbilical venous flow, tricuspid regurgitation) and signs of decreased venous return due to hypovolemia and increased placental resistance in donors.[2, 26] Fetal echocardiography should be performed to exclude myocardial hypertrophy or signs of right ventricular outflow tract obstruction (RVOTO) in the recipient.[26]

The early prediction of the occurrence of TTTS in the first trimester by intertwin discordance in measurements of nuchal translucency thickness, ductus venosus blood flow and crown–rump length remains a challenge.[2, 26-29]

Although its prognostic value has not been established, cardiac profiling may be used as an early marker as well as a diagnostic tool for TTTS.[30]

Rare differential diagnoses of TTTS include other causes of discordant polyhydramnios (such as fetal anomalies and infections) and other reasons for discordant oligohydramnios (such as intrauterine growth retardation, renal malformations and preterm premature rupture of the membranes (PPROM)).[26]

Staging of severe TTTS

In 1999, Quintero *et al.*[31] introduced a staging system with prognostic value, describing the pathophysiological development of TTTS. Stage I represents the most benign form of TTTS with polyhydramnios of the recipient and oligohydramnios of the donor, with its' bladder still visible. In Stage II the donor is 'stuck' and its' bladder is no longer visible. Stage III describes forms with severely abnormal Doppler flow patterns: absent or reverse end-diastolic flow in the umbilical artery of the donor and/or venous abnormalities in the recipient. Stage IV is characterized by development of fetal hydrops. Stage V describes the fetal demise of one or both twins.[2, 6, 24, 26, 32-33]

During expectant management of patients with TTTS, there may be no progression between stages, sequential change, or non-sequential progression of disease.[32]

Complications

When considering CHD in MC twins, primary structural cardiac anomalies must be distinguished from acquired cardiac manifestations due to hemodynamic changes.[34] CHD occurs 12 times more frequently in TTTS twins than in the general population.[35] The MZ twinning process itself may increase the incidence of CHD, by the unequal division of the inner cell mass resulting in discordant cardiovascular anatomy.[36]

When TTTS occurs, 55–100% of recipients present with signs of cardiac compromise[37] including hypertension[38-40], (bi-)ventricular hypertrophic cardiomyopathy [36, 41-42], tricuspid regurgitation[43], ventricular hypokinesia[30], abnormal flow patterns in the DV[30], and most importantly RVOTO[36, 44].

Cardiovascular disorders in recipients may result from increased preload due to chronic hypervolemia or from increased afterload[35, 45] due to high levels of angiotensin II, endothelin or their receptors, or decreased expression of nitric oxide, nitric oxide synthase or their receptors. Recently, renin mRNA and protein have been shown to be underexpressed and overexpressed in recipient and donor kidneys, respectively.[22, 46-47] Chronic hypovolaemia of the donor results in upregulation of the renin-angiotensin system. The transfusion of this increased renin to the recipient might further contribute to recipient hypertension[36], and affect its myocardial compliance. Progressive right ventricular hypertrophy might develop in conjunction with pulmonary infundibular stenosis, leading to acquired 'congenital' pulmonary stenosis or even pulmonary atresia.[42, 44] As a consequence of the hypertrophy, recipients have diastolic dysfunction, as evidenced by elevated myocardial performance indices.[48] Ventricular performance might become so dysfunctional that hydrops fetalis develops.[2] Furthermore, changes take place in the coronary arteries to favour supply to the right ventricle whose workload increases disproportionately. The long term effects of this fetal coronary pathology in an apparent normal survivor of TTTS aren't known. Cardiac lesions affecting the recipient in this way are additional to primary structural lesions and may be temporary and reversible or progressive, both during the pregnancy and after birth.[3]

In contrast to these developments in recipients, acquired cardiac pathology of the donor is usually minimal.[3] In donors, the decreased blood flow in the ascending aorta is considered to be due to the hypovolemic circulation, which may result in acquired coarctation of the aorta.[34]

TTTS associated morbidities include intra-uterine growth restriction or hypoxia in donors, polycythemia in recipients and prematurity in both fetuses.[23] Neurologic disorders in surviving MC twins can be caused partly by prematurity and partly by aberrant fetal haemodynamics that affect organ perfusion. On the other hand, cardiac and renal structural changes are attributable entirely to the vascular structures of the placenta.[10]

There is a paucity of long-term follow up studies of survivors of TTTS.

Treatment

TTTS currently presents the greatest therapeutic challenge of any fetal pathology.[22]

Serial amnioreduction aimes at the reduction of polyhydramnios and thus the intrauterine pressure, sequentially improving uteroplacental perfusion, alleviating maternal symptoms and prolonging the pregnancy.[2] Amnioreduction for treating TTTS should be reserved to the following indications: refusal or when FLP is not available, when FLP is contraindicated or technically difficult to perform and after 28 weeks' gestation (mainly to prolong pregnancy).[14] Complications include a procedure-related risk of delivery (4%).[9, 23-24] and PPROM, preterm labour, infection and placental abruption(15–20%).[2] It's associated with a significant risk (16%) of severe neurological sequelae in survivors, neonatal renal failure (8%) and necrotizing enterocolitis (3%).[49] Cardiac problems occur frequently.[41-42, 50] Furthermore, it doesn't address the underlying pathophysiology, fails in one-third of the cases and in over half the pregnancies there's one fetal loss.[22]

Umur *et al.*[51] demonstrated that septostomy allows amniotic fluid to be swallowed by the donor with minimal effects on its growth and blood volume.[24, 52] The Istanbul international *ad hoc* committee[14] defined that septostomy is no longer indicated for treatment of TTTS.

It was DeLia *et al.*[53-54] that first described the FLP of vessels crossing the intertwin membrane, which wouldn't only arrest the shunting of blood but also halt the transfer of potential vasoactive mediators.[55] The nonselective FLP technique photocoagulates all vessels crossing the intertwin membrane. This may be problematic as the intertwin membrane often bears no relationship to the vascular equator and vessels not responsible for TTTS may be sacrificed, resulting in a higher death rate of the donor from acute placental insufficiency.[55-57] Most recently, a selective approach to FLP, described by Quintero *et al.*[57], photocoagulates only direct AAAs and VVAs.[55-56] Potential post-operative complications include haemorrhage from the entry point, persistent fluid leakage, PPROM, placental abruption and infection.[2] Donor anuria and absent end diastolic flow can disappear, and recipients show reappearance of positive velocities during atrial contraction, and even resolution of hydrops, indicating a restitution of right cardiac function after the procedure.[58] Also, the donor experiences an increase in umbilical vein blood volume and flow accompanied by a state of right heart overload, which is in agreement with the notion that FLP reverses blood flow. Furthermore, tricuspid regurgitation disappeared in 45% of fetuses.[59-60] The incidence of CHD in survivors treated with FLP is low but still higher than in the general population, which warrants close cardiac monitoring during fetal and neonatal life.[35] If there's persistence of high placental vascular resistance in the donor, growth restriction may persist. The presence of deep AVAs that couldn't be identified suggest that TTTS would continue[61] which could have significant long-term haemodynamic effects.[18] Side effects of FLP include miscarriage (5-23%)[23, 62-64], fetal demise (5%), transient hydropic signs of the donor (25%)[60], severe preterm delivery (29%)[25], recurrence of TTTS (1.4-10%) and isolated intertwin discordant hemoglobin levels.[23, 63, 65-66] Pre-operative abnormal umbilical artery doppler with absent or reverse end diastolic flow is predictive of loss of the donor following laser and, when it develops following the procedure, of recipients demise.[24] Contraindications of FLP include gestational age > 26 weeks, abnormal genetic studies, ruptured or detached membranes, prior septostomy ,short or dilated cervix, preterm labor and placenta previa.[32] Cervical length before selective FLP bears a negative correlation with outcome following the procedure and should be considered during preoperative counseling.[14] The increase in the donors' cardiothoracic

ratio after FLP is of special interest because cardiac involvement of donors hasn't been reported very often.[37] This can be explained by: a state of transient volume overload that iniciates a process of cardiovascular remodeling; intrauterine growth restriction that may affect cardiothoracic ratio measurements; cardiac hypertrophy; vasoactive factors that now remain in the donors' own circulation; residual anastomoses that may initiate reversal of TTTS; and fetal anemia.[37]

Selective feticide may be considered when delivery of both twins alive isn't possible or severe distress or anomaly of one twin threatens the other.[2] Techniques such as embolization, cord ligation, external cord compression, radiofrequency and both monopolar and bipolar diathermy of the cord have been described.[24, 67-71] Thrombogenic substances, such as alcohol, coils or enbucrilate gel, are now contraindicated due to a high incidence of loss of both twins.[72] FLP of the cord or the vessels at the root of the cord has been used successfully between 16 and 20 weeks of gestation.[72] Bipolar energy has been used to occlude the cord between 17 and 25 weeks gestation.[72] After 26 weeks of gestation, because the cord is too large, the technique of choice is cord ligation, with survival rates of about 70%.[72] A recently described minimally invasive technique, radiofrequency ablation[73], uses high-energy radio waves to cause the coagulation and can be performed under ultrasound guidance.[72] Even though the recipient is now generally targeted, there're still indications for occluding the donors' cord such as brain lesions, severe cardiac dysfunction, the cord of the recipient is too big (>26 weeks) or edematous to be technically feasible.[22]

When indicated and permitted, selective termination of an anomalous twin in a MC pair is best accomplished by bipolar cord occlusion.[14] The available risk assessments of unexpected fetal death after 32–33 weeks are difficult to compare but seem to suggest an increased risk of mortality. No solid evidence exists to advocate an elective preterm birth (at -36 weeks) to avoid intrauterine death. The Istanbul *ad hoc* committee [14], however, is unanimous about elective delivery of MC twins at 36–37 weeks.

Induction of labor is reasonable in cases with Quintero's stage 5 and double fetal death, whereas follow-up of the survivor seems appropriate after a single fetal demise.[14]

TRAP

Acardiac anomaly, when one twin lacks placentation and is perfused reversely by the other, occurs approximately in 1/35 000 pregnancies and in 1% of MC twins[74-75] and has a perinatal mortality rate for the healthy cotwin in the range of 35- 55%.[76]

According to the TRAP sequence hypothesis, developed by Van Allen *et al*.[77], poorly oxygenated and nutrient-poor blood flows retrogradely in the acardiac twins' umbilical artery via a single AAA. It passively follows a course through the iliac arteries at subnormal pulse pressures to preferentially perfuse the caudal rather than the cephalad structures, explaining why these develop worse.[78] The blood flow then returns to the pump-twins' circulation via a single VVA. However, this hypothesis fails to explain the mechanism leading to the persistence of the single AAA and lack of placentation. Also, it neither explains the development of a pseudoacardiac twin nor why some acardiac twins have a three-vessel cord.[78]

Of note, the AAA that's integral to the TRAP sequence may not always be present, as reported by Shih *et al*.[78-79] An acardiac twin is more often observed in a MA placenta probably because of the smaller distance between the umbilical cord insertions and the subsequently lower resistance in anastomosing vessels.[6]

Alternative etiologic theories have postulated that the primary event is a disturbance in cardiac embryogenesis causing retrograde flow in the affected twin[80], that only survives due to anastomoses that form secondarily after fetal demise. This has been contradicted by the demonstration of fetal heartbeats in early gestation, with subsequent reversal of umbilical blood flow and disappearance of cardiac activity.[81] Also, cytogenetic analyses have failed to demonstrate any consistent chromosomal abnormality.[82]

The simplest classification system of acardiac twins differentiates between pseudoacardius, with evidence of a rudimentary cardiac structure, and holoacardius, where no such structure is present. A more detailed classification separates cases into four groups[75]: acardius acephalus, the most common form,

with a well-developed lower body but a deformed upperpart; acardius anceps, the most developed form, where the fetus has a well developed body, but only a partially formed head and face; acardius acormus, very rare, where only the head is developed; and acardius amorphus, where the fetus is a shapeless mass of tissue containing no recognizable organs, but has some form of axial structure.[78] This classification has no correlation with pregnancy outcome and offers no implications for management. A more practical classification system is needed.[78]

The acardiac twin threatens the survival of the co-twin by three mechanisms: an increased haemodynamic demand due to the systemic shunt leading to congestive heart failure and polyhydramnios; chronic hypoxaemia and growth restriction; and the increasing size of the hydropic acardiac twin may lead to a significant increase in intrauterine volume, with PPROM and preterm delivery.[76]

Fetal death puts the healthy one at risk, due to feto-fetal hemorrhage over the anastomoses.[83] The perinatal sequelae for the pump twin include cardiac failure and fetal hydrops (28%), polyhydramnios (51%)[84], preterm delivery (75%)[84] and intrauterine demise (25%)[72]. Because of the high perinatal mortality rate, it's important to diagnose acardiac anomaly as early as possible.[78]

Features visualized on ultrasound that point to the diagnosis include biometric discordance, absence of identifiable cardiac pulsation in one twin, poor definition of the head, trunk and upper extremities, deformed lower extremities, marked and diffuse subcutaneous edema and abnormal cystic areas in the upper part of the body of the affected twin. The demonstration of arterial blood circulating in a paradoxical direction, flowing towards the acardiac twin and in a caudal-to-cranial direction in the abdominal aorta, establishes the diagnosis. This retrograde flow has been documented by color Doppler ultrasound[85-89], three-dimensional ultrasound[78, 90], postmortem placental and fetal angiography and umbilical cord blood gas analyses.[91] The presence of cardiac motion in a fetus with suspected TRAP sequence doesn't exclude the diagnosis as it may result from a rudimentary heart or transmitted pulsation from the pump twin.[92-94] Differential diagnosis of acardiac anomaly include single intrauterine death of one abnormal MC twin, intra-amniotic or placental tumors.[94]

Once acardiac anomaly is diagnosed, the pregnancy should be classified according to prognostic factors.[78] The ratio between the abdominal or trunk circumference of the acardiac and the abdominal circumference of the pump twin, and its' evolution, has been used for prognostic evaluation.[78] The assessment of blood flow in the umbilical artery of the acardiac twin by measurement of the impedance[89], pulsatility[95] or resistance[96] indices as compared to the findings in the umbilical artery of the pump twin have shown a relationship with poor perinatal outcome. However, the most important factor indicating the need for intervention has been the appearance of signs of cardiovascular compromise in the pump twin. Wong and Sepulveda[78] proposed a classification based on acardiac/pump twin abdominal circumference ratio and signs of fetal compromise of the pump twin to recommend intervention.[76]

To assess the impact of the acardiac twin on the cardiovascular status of the pump twin, two modalities should be used: first, two-dimensional ultrasound should be used to look for physical signs of early cardiovascular deterioration, specifically polyhydramnios, cardiomegaly and pericardial effusion; second, color Doppler ultrasound should be used to look for tricuspid regurgitation, reverse flow in the ductus venosus, pulsation in the umbilical vein and high peak velocity of middle cerebral artery flow secondary to fetal anemia. The presence of any of these features predicts a poor prognosis.[78]

Treatment

Nowadays, there's consensus that minimally invasive techniques that treat the condition by interrupting the vascular supply to the acardiac twin are associated with the best outcome and pose the fewest maternal risks.[78] These techniques can be divided into umbilical cord occlusion (UCO) and intrafetal ablation treatments.

UCO has a 78–84% survival rate[83] and can be achieved using either ultrasound or fetoscopy. Alcoholsoaked suture material[97] and other thrombogenic agents have been used to achieve vascular occlusion.[89] Thermocoagulation techniques, both monopolar[98-99] and bipolar[100-101] have been successfully performed under ultrasound guidance. Bipolar coagulation has the theoretical advantage that

the electrical current passes only between the two blades of the forceps.[100] Techniques employing fetoscopy have included ligation of the umbilical cord or FLP of the cord vessels of the acardiac twin.[76] These techniques are associated with a failure rate of about 10%, and an increased risk of postoperative rupture of membranes, infection and bleeding of the normal twin.[70, 102] In addition, the difficult access and identification of the umbilical cord, particularly in cases with anterior placentas, requires occasionally amnioinfusion and amniotomy with the potential risk of pseudomonoamnionicity and cord entanglement.[78] The main complications are bleeding from the vascular anastomoses, leading to IUFD and PPROM. [103] Hydropic umbilical cord of an acardiac twin in the mid-trimester or beyond may cause considerable technical difficulties for cord coagulation with the need for additional application of bipolar forceps.[103] The main disadvantages of UCO techniques are presented by anatomy: the cord of the pump twin can be inadvertently damaged; identifying the umbilical artery of the acardiac twin is crucial to avoid the intravascular transfer of any ablative material into the circulation of the pump twin; and the umbilical cord of the acardiac twin is often short, thin and structurally abnormal, making it vulnerable to rupture or bleeding.[78]

In contrast, an intrafetal approach targets the abdominal aorta or pelvic vessels of the acardiac twin, which are easily identified regardless of cord condition, placental location, amniotic fluid volume and position of the acardiac twin. The use of color doppler ultrasound has facilitated this method. Intrafetal ablation has been achieved with variety of techniques, including alcohol chemosclerosis[104-108], monopolar thermocoagulation[98-99, 109], ultrasound-guided Nd :YAG laser[110-112] and radiofrequency[73]. Alcohol chemosclerosis[104-108] should only be used when where no alternatives are available and only in acardiac pregnancies with deterioration on serial surveillance or with poor prognostic factors.[94] Monopolar diathermy can be performed in early pregnancy with risk of thermal injury to the surrounding tissues.[94] Interstitial laser can be applied intrafetally [110-112] with ultrasound guidance carrying no risk of inadvertent cautery burns as the energy is applied only at the tip of the laser fiber.[78] Radiofrequency ablation uses radiofrequency energy that's applied only to the tip after deployment into tissue avoiding

injury to the co-twin and surrounding tissues.[78] There is a theoretical risk of increasing rates of PPROM and preterm delivery[94] but it appears to be a relatively safe and effective technique.[78]

Acording to a recent review of the literature[94] once treatment is indicated, intrafetal ablation seems to be superior to UCO techniques as it's technically easier (i.e. lower technical failure rate), safer (i.e. lower preterm delivery or PPROM before 32 weeks) and more effective (i.e. longer treatment – delivery interval and higher rate of clinical success). Although the less favorable results of UCO could be attributed to the relatively higher aggressiveness and complexity of fetoscopic procedures, there was no significant difference in the primary outcomes between the fetoscopic and the ultrasound-guided techniques suggestting that the route of approach, rather than the use of larger instruments and more complex and lengthy techniques, is the primary determinant of the outcome of acardiac pregnancies treated invasively.[94]

Finally, the timing of intervention remains controversial. Some advocate early prophylactic treatment of all acardiac pregnancies at about 16 weeks if there's still blood flow demonstrated in the acardiac twin.[78, 110] Treatment at this early stage would also preclude the difficulty in achieving cessation of blood flow in larger and sometimes hydropic acardiac twins. Opponents, on the other hand, would argue that at least half of the cases won't require any treatment as the acardiac twin may experience spontaneous cessation of blood flow while others with relatively small size won't result in any pregnancy complication.[94] Due to the rarity of the condition and the heterogeneity of its' presentation, no single technique has been shown to be unequivocally optimal.[78, 113]

In MA twins, because of the high incidence of cord entanglement, FLP following intrafetal ablation has been recommended.[72]

CONCLUSION

In conclusion, the angioarchitecture of MC placentas determines perinatal outcome, occurrence of TTTS and fetal growth.[114] In addtition to the risk of TTTS itself, MC twins have a significantly increased risk of cardiac anomalies, whether primary structural lesions or acquired lesions as a result of the hemodynamics of the placenta.[3] This justifies offering a detailed cardiac assessement for all MC twins, inicially to establish normal anatomy and then to check for any envolving lesions or cardiac dysfunction in pregnancies complicated by TTTS.[3] The efficacy of any fetal treatment of TTTS can be evaluated fully not only by assessment of survival, but also of the effects on the neonatal and long-term morbidity.[56] The lack of an animal model and the difficulties involved in investigating human fetal pathophysiology further hamper therapeutic advances.[115]

CONFLICT OF INTEREST STATEMENT

None declared.

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