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# Complicated multiple pregnancy referral, treatment and outcomes at the NSW Fetal Therapy Centre

## Abstract

*Objectives:* To determine the indications for referral, sonographic workload, diagnoses and outcomes of women with a multiple pregnancy referred to the New South Wales Fetal Therapy Centre (NSW FTC).

*Methods:* Retrospective cohort study of twin and higher order multiple (HOM) pregnancies referred to the NSW FTC at the Royal Hospital for Women (RHW) Department of Maternal Fetal Medicine (MFM), Sydney from January 2007 to December 2009.

*Results:* There were 176 twin pregnancies (138 monochorionic diamniotic, 29 dichorionic diamniotic and nine monoamniotic), and 26 HOMs referred (23 triplet and three quadruplet pregnancies). Indications for referral were: twin to twin transfusion syndrome (TTTS) 103 women, fetal anomaly 31 women, intrauterine growth restriction (IUGR) 12 women, serial surveillance of twins or HOM 37 women, and fetal reduction of HOM (nine women). In 80.2% the pathological referral diagnosis was confirmed. The average number of ultrasounds was five (range 1–24), with 90 women (45%) receiving invasive therapy. Thirty-five percent (71) of referrals were from outside Sydney, including eight interstate and 11 overseas referrals. Two-thirds of out of area referrals were able to return to their referral hospital for birth: 95 women (47%) delivered at RHW.

*Conclusion:* TTTS was the most common reason for referral, with a high concordance between referral and initial diagnosis. RHW accepted a large number of out of area referrals, in keeping with its role as the NSW FTC. Twin and HOM pregnancy referrals represent a significant workload for the department, with many women also requiring invasive therapy.

*Keywords:* multiple pregnancy, pregnancy complications, higher order multiples, twins, ultrasound.

## Introduction

In Australia in 2010 there were 4675 multiple births, 98.4% of which were twin pregnancies and 1.6% higher order multiple (HOM).<sup>1</sup> Multiple pregnancy accounts for approximately 1.6% of all births in Australia at greater than 20 weeks gestation.<sup>1</sup> The proportion of multiple births, both twins and HOM, has overall increased markedly in the last two decades due to assisted reproductive therapy (ART), delay in childbearing and a higher proportion of older mothers,<sup>2</sup> but has recently stabilised or slightly decreased.<sup>3</sup> It is well known that multiple gestations are at higher risk for adverse perinatal outcomes, especially with the decreasing average gestational age at delivery as plurality increases.<sup>4</sup> Accordingly, more monitoring and increased contact with health care professionals, including ultrasound services, are needed for women with multiple pregnancies.

The majority of fetal complications of multiple pregnancy, including those requiring invasive therapy, occur in monochorionic placentation.<sup>5</sup> Approximately 30% of monochorionic diamniotic (MCDA) twins have at least one

of twin-twin transfusion syndrome (TTTS), selective intrauterine growth restriction (sIUGR), twin-anaemia polycythaemia syndrome (TAPS), fetal death, or fetal anomaly.<sup>5</sup> Of these, TTTS is most common, occurring in approximately 15% of MCDA twin pregnancies.<sup>5</sup> It is fatal in 80% of untreated cases, and is the basis for the recommendation to monitor MCDA pregnancies by ultrasound every two weeks from 16 weeks.<sup>6</sup> Growth discordance is also common (and may overlap with TTTS), with up to 15% of MCDA pregnancies affected.<sup>5</sup> Any difference greater than 25% in biometric measurements or estimated fetal weight between twin or triplet fetuses should be regarded as clinically important.<sup>7</sup> Due to the rarity of MCMA and HOM gestations, the literature is composed of case reports or small series, which provide limited evidence as to the most effective management of these cases.<sup>7</sup> Tertiary centres therefore base management on this evidence combined with local experience rather than clinical trial evidence.<sup>8</sup>

Maternal Fetal Medicine (MFM) is a subspecialty of obstetrics and gynaecology. The Royal College of Obstetricians and Gynecologists

(RCOG) recommends referral to an MFM department for all triplet pregnancies, and all monochorionic monoamniotic (MCMA) twin pregnancies, as they are associated with increased risks compared with other multiple pregnancies.<sup>9</sup> They also recommend that multiple pregnancies complicated by discordant fetal growth, fetal anomaly, discordant fetal death or TTTS be referred to MFM, due to increased risks and complicated management.<sup>7</sup> This referral may create significant potential psychological and social impact, due to separation from family and support networks as a consequence of travel to a tertiary centre, as well as the underlying pregnancy complications and adverse outcomes that lead to a referral.

The New South Wales Fetal Therapy Centre (NSW FTC) is based at The Department of MFM at RHW. It is a multidisciplinary unit led by MFM subspecialists including those with specific training in invasive fetal therapy, and includes sonographers, midwives, neonatologists, geneticists, and social workers. The NSW FTC functions as the NSW referral centre for laser therapy for twin-twin transfusion syndrome. It also accepts referrals for high-risk pregnancies including complicated twin pregnancies and higher-order multiples (HOM). Referrals are received from NSW, interstate as well as internationally. The centre provides a number of ultrasound-guided fetal therapy procedures including fetal intravascular transfusions, bladder and pleural shunts, embryo reduction and radiofrequency ablative therapy, in line with recommendations that such specialised care is restricted to a small number of centres where operators have expertise and full support services are available.<sup>10</sup>

The current study was undertaken to determine the reason for referral, sonographic workload, diagnosis and pregnancy outcome of women with a multiple pregnancy referred to the New South Wales Fetal Therapy Centre (NSW FTC).

## Methods

We performed a retrospective cohort study of women with twins and HOM pregnancy referred to the NSW FTC, at the Department of Maternal Fetal Medicine RHW, Sydney between February 2007 and December 2009. All twin and higher order multiple pregnancies referred to the NSW FTC were identified from the Viewpoint database (GE Healthcare).

The primary outcomes studied were the number of women referred, reason for referral and care received. Other exploratory variables included demographic characteristics and baseline pregnancy characteristics. Clinical outcomes, including birth at RHW versus birth at referral hospital, gestational age at birth, and maternal and fetal outcomes were also collected. Workload was recorded through number of visits and ultrasounds, invasive therapy required and details of this therapy. Staging of Twin to twin transfusion was performed according to Quintero staging defined as: Stage I, polyhydramnios in recipient twin, donor twin with severe oligohydramnios but with visible bladder in donor twin; Stage II, polyhydramnios in recipient twin, donor twin stuck, bladder in donor twin not visible, diastolic flow present in the umbilical artery and forward flow in the ductus venosus; Stage III, poly/oligohydramnios, bladder in donor twin not visible, and critically abnormal Doppler studies; Stage IV, presence of ascites or frank hydrops (fluid in two or more cavities) in either fetus; Stage V, demise of either fetus.<sup>11</sup> Selective IUGR was diagnosed

**Table 1:** Maternal and pregnancy characteristics of multiple pregnancies referred to the NSW FTC.

Patient Characteristics	n = 202 N	%
Mean Maternal age $\pm$ standard deviation (SD), years	31.8 $\pm$ 5.5	
<b>Country of birth</b>		
Australian born	108	53.5
Other	51	25.2
Unknown	43	21.3
<b>Referral from</b>		
Royal Hospital for Women	50	24.8
Within Sydney	81	40.1
Outside of Sydney	71	35.1
Regional	52	25.8
Interstate	8	4.0
International	11	5.5
Body Mass Index*, mean $\pm$ SD	25.2 $\pm$ 6.8	
<b>Parity</b>		
Nulliparous	98	48.5
Multiparous	93	46.0
Unknown	11	5.4
<b>Type of pregnancy</b>		
Twins	176	87.1
DCDA	29	14.4
MCDA	138	68.3
MCMA	9	4.5
Triplets	23	11.4
Quadruplets	3	1.5

\*BMI was known for 112 women, DCDA = dichorionic diamniotic MCDA = monochorionic diamniotic MCMA = monochorionic monoamniotic

as smallest fetus < 10th centile for gestational age (Hadlock twin curves in Viewpoint database)<sup>12</sup> and other fetus(es) 25th centile for gestational age or greater. Growth discordance was identified as for ongoing surveillance if an intertwin difference of 20–25% in EFW was identified, and considered a confirmed diagnosis if discrepancy of > 25% in EFW was present.<sup>5</sup>

Databases utilised for this data collection included Viewpoint (GE Healthcare), Obstetrix (NSW Department of Health), eMR (Cerner Systems), and medical records. Data was analysed using Excel spreadsheet and SPSS software Version 21 (IBM Corporation). Chi-squared test and Fisher exact test were used to test as appropriate for significant differences between categorical variables. Student's t-test and ANOVA were used as appropriate to compare continuous variables. All tests were two-sided, and statistical significance was defined as a probability value of < 0.05. Appropriate adjustment was made for multiple comparisons.

The study was approved as low-risk research by the local institutional ethics committee, the South Eastern Sydney Local Health District Human Research Ethics Committee (HREC 08/168).

**Table 2:** Indication for multiple pregnancy referral, diagnosis and treatment provided by NSW FTC at the Royal Hospital for Women (RHW).

	n = 202	(%)
Mean gestation $\pm$ SD at first visit (weeks) (n = 201)	20.1 $\pm$ 5.5	
<b>Main indication for referral</b>		
TTTS	103	51.0
Serial surveillance #	40	19.8
Fetal anomaly	31	15.3
IUGR	11	5.4
Fetal reduction	8	4.0
Short cervix	2	1.0
Other	7	3.5
<b>Initial diagnosis at RHW</b>		
TTTS	85	42.1
Fetal anomaly	33	16.3
IUGR	19	9.4
Fetal reduction	10	5.0
Short cervix	4	2.0
"Pre"-TTTS/fluid discordance	7	3.5
Single intrauterine demise	2	1.0
Other	8	4.0
Normal	34	16.8
<b>Concordance diagnosis (n = 162)<sup>*</sup></b>		
RHW diagnosis = referral diagnosis	130	80.2
Abnormal RHW scan but different diagnosis	20	12.3
No abnormality seen at 1st RHW visit	12	7.4
<b>Mean number of visits/ ultrasounds</b>		
Range	1–24	
<b>Invasive procedures performed</b>		
Laser for TTTS	60	
Amnioreduction for TTTS	8	
Amnioreduction (not for TTTS)	1	
Fetal reduction	24	
Cerclage	3	
Pleuro-amniotic Shunt	1	
Intrauterine transfusion	1	
Total procedures performed <sup>°</sup>	98	
<b>Total number of women received invasive procedure</b>	91	45.0

<sup>\*</sup> Gestational age of one woman unknown# Surveillance of: HOM pregnancies (n = 15), MCMA/query MCMA twins (n = 9), MCDA twins with discordant NT (n = 5), MCDA with no known complications (n = 6), Other (n = 5)

<sup>\*</sup> Patients referred for routine surveillance/high-risk status only not included in diagnosis concordance data

<sup>°</sup> Women may have had  $\geq$  1 procedure

TTTS = twin to twin transfusion syndrome IUGR = intrauterine growth restriction

## Results

There were 202 women referred (176 twins, 23 triplets, 3 quadruplets) with a multiple pregnancy over the 35 month period. Demographic characteristic of the women are shown in Table 1.

**Table 3:** Birth outcomes of women referred to NSW FTC with a multiple pregnancy.

	n = 202 women N	(%)
<b>Delivery location</b>		
Royal Hospital for Women	95	47.0
Elsewhere	107	53.0
<b>Delivery details obtained</b>		
<b>Median Gestational age at birth in weeks<sup>*</sup></b>	34.2	
Interquartile Range (weeks)	31–36.1	
<b>Livebirth<sup>*</sup></b>	222	88.1
<b>Birthweight mean and SD<sup>*</sup></b>	1952 $\pm$ 684g	
<b>Mode of birth<sup>*</sup></b>		
Caesarean Section	183	72.6
Vaginal birth	52	20.6
Unknown	17	6.7

<sup>\*</sup> Of 252 fetuses where birth outcomes were known

Indication for multiple pregnancy referral, diagnosis made and treatment provided by the NSW FTC are illustrated in Table 2. TTTS, serial surveillance for high-risk multiple pregnancy (e.g. HOM, monoamniotic twins), and suspected fetal anomaly were the commonest reasons for referral. Over 80% of those referred with a pathological diagnosis had that precise diagnosis confirmed at the time of first ultrasound at the RHW: 12% had a different pathological diagnosis made, and in 7% of cases no pathological diagnosis was made at the first visit. Most women required more than one visit, with a mean of five visits (range 1–24). Average time from first visit to the NSW FTC to discharge back to the referring centre was 5.2 weeks.

Ninety-one (45%) women referred received an invasive procedure, with some women having more than one procedure. Eleven fetal reductions were performed from twins to singletons, for severe TTTS or secondary to severe sIUGR. Seven fetal reductions were performed for triplets – five were three to two, and two were three to one. Both triplet pregnancies reduced to singletons contained a monochorionic placenta, with one of these pairs discordant for anomaly. Two sets of quadruplets had multifetal pregnancy reduction of four to two, and one spontaneously reduced from four to three.

Birth outcomes of women referred to NSW FTC with a multiple pregnancy are shown in Table 3. Less than half (47%) of women delivered at RHW, and most women referred from outside RHW (66%) delivered at their home hospital. Some birth/outcome data was available for 126 women (62.4%). In the HOM pregnancies, median gestation at delivery was 35 weeks for reduced pregnancies and 32.5 weeks for non-reduced pregnancies. In comparison, the mean gestation at birth of twin pregnancies being seen through the RHW regular antenatal clinic (ANC) across the same time frame was 36.6 weeks (vs. the 32.1 week gestation of NSW FTC multiples), all ANC twins > 20 weeks were liveborn (compared to 88% for NSW FTC multiples), and mean birthweight was 2502 g (vs. 1952g for



NSW FTC multiples). The twins cared for in the antenatal clinic were predominantly dichorionic diamniotic (81%).

## Discussion

This study outlines the role of the NSW FTC as a quaternary referral centre for review and management of complex multiple gestations, with referral in the majority of cases back to the referring institution for birth. In this study we found the most common reason for multiple pregnancy referral to the NSW FTC was suspected TTTS ( $n = 103$ ), which reflects the NSW FTC service's expertise in assessing TTTS and providing invasive procedures such as selective laser photocoagulation of the communicating vessels (SLPCV) for TTTS. Multiple pregnancies discordant for anomaly (15%), and pregnancies complicated by sIUGR (5%) were less common reasons for referral. The high concordance between the referral diagnosis for TTTS and other conditions reflected the appropriateness of referrals to the centre. Most (81%) of the 85 pregnancies complicated by TTTS required invasive procedures in the form of SLPCV, amnioreduction, or bipolar cord ablation.

Stage 1 twin to twin transfusion syndrome may regress, progress to a higher stage or stay the same, and prediction of progression and the time period in which it will change can be difficult.<sup>13</sup> During the time period studied, SLPCV was primarily reserved for stage 2–4 TTTS at 16–26 weeks, while stage 1 TTTS was treated with expectant management, which may explain the number of ultrasounds that some women received. A randomised controlled trial is currently underway to evaluate the role of SLPCV versus conservative management for stage 1 TTTS in Europe.<sup>14</sup>

It is well recognised that clinical care should aim to minimise the number of hospital visits, provide care as close to home as possible, and provide continuity of care within and between hospitals.<sup>7</sup> Against this is balanced the need to concentrate expertise in specialised procedures, such as SLPCV for TTTS, such that the best possible clinical outcomes can be obtained.<sup>10,15,16</sup> The NSW FTC received a high proportion of referrals from outside Sydney ( $n = 71$ , 35%), with 19 of these coming from interstate ( $n = 8$ ) or overseas ( $n = 11$ ). Ten of 11 overseas referrals were from New Zealand, and as laser therapy for TTTS is now available at Auckland Hospital, international referrals are now rare. Despite the complexity of referrals, most patients could be discharged back to their home hospital to deliver.

The sonographic workload for the NSW FTC from multiple pregnancy referrals is high, with an average of five ultrasound scans (range 1–24), often over a short period of time (1–2 weeks), per referral. Additionally, each referral involves NSW FTC subspecialist involvement (and often fetal therapy expertise/associated theatre time) and support services for these complicated pregnancies including specialised midwifery, genetic, neonatal, and social worker input. To deliver best care to these patients therefore requires both specialised infrastructure and considerable resources. Unfortunately, these are poorly remunerated under current funding models: the NSW FTC attracts no additional funding from NSW or the Local Health District to enable it to provide this specialised multidisciplinary care, and allowable outpatient billings under Medicare are usually less than \$250 even for a first visit/ultrasound of several hours duration.<sup>17</sup>

As expected, comparison of NSW FTC and ANC multiple pregnancy outcomes highlighted the high risk nature of NSW FTC patients. The lower-risk, predominantly dichorionic diamniotic (DCDA) twins cared for in the ANC (81% DCDA in ANC vs. 16% DCDA in MFM) were on average born a month later and 550 g heavier. Survival (for those for whom birth outcome was available) was also superior in ANC patients. This emphasises that even with appropriate referral and treatment at a facility with TTTS outcomes comparable to any published international literature, there remains significant mortality and morbidity in MCDA twins.

The limitations of this study include incomplete demographic information, secondary to lack of detail in the Obstetrix database; in particular use of ART, BMI and smoking status were poorly reported. A further limitation is the limited availability of birth data for those not delivering at RHW. Attempts were made to gather birth details from Obstetrix, eMR, medical records and by contacting referring hospitals. All birth details were obtained for those that delivered at RHW ( $n = 95$ ), but a significant proportion who delivered elsewhere were not able to be obtained ( $n = 76$ ), in part due to privacy requirements and separate access requests being required for each hospital from whom follow-up data was required. In future, we plan to seek prospective approval for follow-up of all NSW FTC patients so that more complete and reliable outcome data is obtained. All higher order multiple delivery details were obtained, and it was found that reduced pregnancies delivered at advanced gestations, which is in keeping with other studies.<sup>18</sup>

## Conclusion

Multiple pregnancy referrals to the NSW FTC generate a substantial sonographic and multidisciplinary workload for the centre, particularly TTTS assessment and treatment but also multiple pregnancies discordant for anomaly or with sIUGR. There was genuine demand for FTC services, reflected in a high concordance between referral and initial diagnosis and a large number of appropriate out of area referrals. Despite the stabilising Australian multiple pregnancy rate, the NSW FTC workload may continue to increase due to appropriate first trimester identification of chorionicity, and subsequent early identification and referral of potentially treatable conditions such as TTTS. Ideally, appropriately targeted funding would be available to meet the needs of our referral population and help maintain the standard of care the NSW FTC provides.

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