Long-term neurodevelopmental outcome in monochorionic twin pregnancies complicated by selective intrauterine growth restriction

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1.1 Clinical scenario

This thesis is based on the clinical scenario of a thirty-one-year-old woman (G1P0) with a monochorionic, diamniotic twin pregnancy complicated by selective intrauterine growth restriction (sIUGR). She presented herself at the department of obstetrics in the Leiden University Medical Centre (LUMC) at the gestational age of 20+3 weeks after an abnormally large estimated fetal weight (EFW) discordance between the twins was detected at routine ultrasound investigation. An umbilical artery (UA) Doppler was performed. The flow patterns were described as persistently absent and reversed flows, corresponding with a type 2 Gratacós classification.

The patient was admitted to the obstetric unit at 26+2 weeks of gestation for fetal surveillance. At 28+1 weeks the fetal condition deteriorated, upon which a caesarian section was performed. Two boys were born, with birth weights of 780 g and 1466 g respectively amounting to a birth weight discordance of 48%. After careful examination of the placenta, a severe placental share discordance of 72.5% was observed. Furthermore, multiple vascular anastomoses were documented, allowing inter-fetal blood exchange (Figure 1).

The twins were admitted to the neonatal intensive care unit (NICU). They are currently being monitored extensively. The future of the children is still unsure. In order to give the parents an indication of the prognosis, it is necessary to research whether the sIUGR has complicated the development of the children and if it might affect their cognitive abilities later in life.
1.2 Introduction

Around 20% of twin gestations are monochorionic diamniotic pregnancies (MCDA), meaning that the fetuses share a placenta in the womb (1). These MC pregnancies are associated with a higher risk of perinatal adverse outcome mainly caused by the existence of vascular anastomoses on the surface of the shared placenta (1). These anastomoses give rise to an inter-fetal blood exchange, which can lead to multiple complications such as twin-twin transfusion syndrome (TTTS), twin anemia-polycythemia sequence (TAPS) or selective intrauterine growth restriction (sIUGR) (2, 3). sIUGR occurs in 10-15% of MC twin pregnancies and is associated with specific patterns of vascular anastomoses and unequal placental sharing (4).

sIUGR can be classified according to UA Doppler flow in the smaller twin, proposed by Gratacós et al. (5). Type I sIUGR is characterized by a positive UA flow, linked to a relatively benign prognosis. The anastomoses in this group are similar to uncomplicated MC pregnancies. Type II demonstrates a persistently absent or reversed UA Doppler (AREDF) and has the highest perinatal mortality and morbidity. The anastomosal pattern is mostly similar to type I, while the placental discordance is more severe. Finally, type III is defined as intermittent absent or reversed end-diastolic flow (iAREDF). The clinical course of type III is difficult to predict and therefore associated with severe neurological damage in the larger twin and an elevated risk of intrauterine demise of the smaller twin (6, 7). The different types have specific features contributing to the risk of perinatal adverse outcome and possibly long-term outcome.

Each type of sIUGR is associated with a certain pattern of anastomoses. The arterio-arterial (AA) anastomoses in particular have been linked to the pathophysiology of the disease (5). A large diameter of the AA anastomoses results in a higher amount of interfetal blood exchange, leading to higher birth weight discordance and more detrimental clinical outcomes. The diameter of the AA anastomoses is therefore correlated with the clinical evolution of the disease and in accordance with the proposed classification (2, 3, 8).

sIUGR might lead to serious complications since a feasible treatment is still unavailable. Perinatal adverse outcomes can include fetal deterioration, intrauterine fetal demise and
prematurity (9). Cerebral injury is present in approximately 8% of the MC twins with sIUGR (7) and neurological damage is prevalent, mainly among type III flows (6). Many studies have examined the neonatal and perinatal outcomes of MC twin pregnancies complicated by sIUGR. However, studies documenting the long term neurodevelopmental follow-up are scarce and often demonstrate conflicting results. The aim of this critical appraisal of a topic is to document the long-term neurodevelopmental outcomes for sIUGR twins. By doing this, the question of the parents about the long-term development of their twins in the above mentioned clinical scenario can be answered.
CHAPTER TWO – Critical appraisal of a topic

2.1 Literature search
Pubmed database was searched electronically on the 29th of March 2018. The search strategy outlined in Appendix 1 was applied to search for relevant articles on long-term neurodevelopmental outcomes for sIUGR pregnancies. The main keywords were composed of ‘selective intrauterine growth restriction’, ‘twins’, and ‘neurodevelopmental outcomes’. The search was restricted to the English and Dutch language.

An article was included when it met the pre-specified inclusion criteria, containing the following aspects: the population consisted of monochorionic twins diagnosed with sIUGR; the study design was a randomized controlled trial or a cohort study, either prospective or retrospective; the performed neurodevelopmental tests were age appropriate and no intrauterine interventions were performed, such as fetoscopic laser therapy. An article was excluded when there was co-existing TTTS or TAPS or when the study design was either a case-control study, case series, case report or systematic review and/or meta-analyses as these study designs are not fit for prognostic research. When an intrauterine intervention was performed in the study population the article was subsequently excluded, due to interference with the natural course of the disease. A full overview of the inclusion and exclusion criteria can be found in Appendix 2.

Figure 2. Flowchart of study inclusion
The search strategy yielded 298 results. The primary assessment was based on the title and the abstract, which led to the exclusion of 270 articles. Of the 28 remaining articles, 22 were excluded after thorough full-text assessment, leaving five articles to be included. This process is presented in the flowchart of study inclusion (Figure 2). The following articles were selected in this critical appraisal of a topic:


2.2 Critical evaluation

A summary of the methods of the article is presented. Next, the critical evaluation was performed according to the JAMA ‘User Guides to the medical Literature’ for Prognostic research (10), assessing the articles on three domains: validity, results and applicability. A complete overview of the study characteristics for all included articles can be found in Appendix 3.

Adegbite et al. conducted a prospective cohort study to determine the incidence of neurologic morbidity in monochorionic (MC) and dichorionic (DC) twins born between 24 and 32 weeks of gestation. They compared birth weight concordant and discordant groups. Twins were included when patient data was complete and when the pregnancy was not complicated by fetal aneuploidy, intrauterine death of both twins, congenital malformations, embryo reduction or feticide. Birth weight discordance was clearly defined as a birth weight difference of $\geq 20\%$ or a smaller twin with an abdominal circumference of $\leq 5^{th}$ centile with an abnormal UA Doppler. A total of 76 MC pregnancies were included, of which 13 were classified as birth weight discordant. All infants were followed up until the age of two years.

The main outcome measures were the incidence of cerebral palsy, diagnosed by guideline criteria of persistent abnormality of movement and posture, and developmental delay diagnosed with the Griffith’s mental developmental scale score. These were compared in relation to chorionicity, discordant birth weight, TTTS and co-twin death.

The cohort was well-defined and representative. The follow-up of this study was sufficiently long to determine the incidence of cerebral palsy and neurological disabilities, as this mostly originates from the perinatal or neonatal period. However, longer follow-up would have provided more information on neurodevelopment at school age. Furthermore, the follow-up was nearly complete with a loss-to-follow-up of 13%. This loss might lead to an underestimation of the neuromorbidity rate, as specified by the article itself. Moreover, the follow-up was elaborately described as to how many of the infants were born alive and completed follow-up. Any drop-outs or deaths were clearly described.

Although the study has a small study population and relatively short follow-up time, it has an adequate validity due to the well-defined and representative nature of the population. In addition, the follow-up was nearly complete and elaborately described. These aspects combined make the article valid.

Edmonds et al. performed a retrospective cohort study in which they studied whether poor intrauterine growth relates to impaired cognitive functions. They included 71 monozygotic twin pairs with gestational age > 32 weeks. Those with severe chronic disease such as cerebral palsy, those who received treatment for acute TTTS or were born before 32 weeks of gestational age and those who were unwell on the day of study were excluded from the analyses.

The primary outcome measures, defined as the verbal IQ and the performance IQ, were determined by administering the Wechsler Intelligence Scale for Children. Corrections for socioeconomic status, preterm birth and birth weight difference of > 0.5 kg were performed by omitting these data and repeating the analyses. Lastly, subgroup analyses were conducted to examine the verbal IQ as a function of increases in birth weight difference.

Birth weight discordance was not properly defined, since it was seen as a continuous variable in this study. There was no distinction between MC or DC twins, which makes it difficult to draw conclusions on the effect of chorionicity. Furthermore, socioeconomic status was relatively high in the study population, subsequently leading to higher IQs as IQ is associated with socioeconomic status and parental education. The follow-up ranged from 7 years and 11 months to 17 years and 3 months due to the retrospective nature of the study. This range is too large to adequately compare the obtained IQ scores.

The improperly defined population that makes no distinction based on chorionicity and the large difference in follow-up time for the infants might lead to the limited use of these results in clinical practice. Consequently, the study has a low validity.

Based on prospective data from The Neuro-Developmental Outcome for Twins of the ESPRiT Study (NOTES study), Halling et al. studied the effect of a birth weight discordance greater than 20% on neurodevelopmental outcomes in MC and DC twins. The study included 119 pairs classified as growth discordant, of which 24 were MC. One hundred-eleven concordant twin pairs were recruited as controls. Twins with single fetal demise, single neonatal death, single childhood death and pairs with chromosomal abnormalities were excluded.

The Bayley Scales of Infant and Toddler Development were administered for twins between 24 and 42 months of age, in order to determine the scores for cognitive, language and motor composite as primary outcome measures. Corrections for chorionicity, gender, prematurity and birth weight were also performed to control for bias. However, the growth-discordant group was significantly younger on the day of assessment as compared to the concordant twins possibly affecting the interpretation of results.

The included twins in the study by Halling et al. were carefully described and were retrieved from a much larger prospective cohort study (11). The follow-up range was adequate, since the outcomes would have occurred between 24 and 42 months, and the follow-up rate was high, namely 79%.

Even though the follow-up time is too short to deduce information on the neurodevelopment at school age, the study is still awarded a high validity. The prospective nature of the study, the large study population, objective outcome assessment with the Bayley Scales of Infant and Toddler Development and corrections for certain prognostic factors that might introduce confounding or bias, make this study trustworthy.

The retrospective cohort study performed by Rustico et al. examined the correlation between UA Doppler findings and pregnancy course, perinatal outcome and postnatal follow-up, including neurodevelopment in a cohort consisting of 140 MC diamniotic pregnancies complicated by sIUGR, referred before 26 weeks of gestation. sIUGR was defined as a smaller twin with an EFW < 10th centile or an EFW difference ≥ 25%.

The level of neurological impairment was objectively determined by pediatric neurologist-psychiatrists according to routine care for every infant in Italy and was classified as severe, moderate or mild. Severe was associated with cerebral palsy level 3 to 5, a developmental quotient < 70, bilateral sensorineural deafness or autism. Moderate neurological impairment consisted of children with cerebral palsy level 2, a developmental quotient of 70-84, attention deficit disorder and/or hyperactivity or unilateral sensorineural deafness. Finally, mild neurological impairment contained children with minor motor deficits, isolated language impairment or transient motor delay. The results were compared within the twin pairs; the larger versus the smaller twin.

Rustico et al. clearly defines the study population. The neurodevelopmental follow-up ranged from 12 months to 7 years, which is quite broad and leads to the inability to draw conclusions about the group as a whole. However, the neurological impairment often originates from complications in the perinatal or neonatal period. Additionally, the follow-up was complete. Of the 280 infants included, 191 had complete data on the neurodevelopmental outcome. This discrepancy is caused by the perinatal death of the 89 infants.

Overall, the study has a high validity due to the clearly defined population, complete follow-up and objective assessment of the outcomes. The small study population and retrospective design should be taken into account when applying the results to clinical practice.

Swamy et al. researched the long-term cognitive outcome of birth weight discordant monochorionic twins, with birth weight discordance ≥ 20%. They used a prospectively collected database ascertained via the Northern Survey of Twins and Multiple Pregnancies. Twin pairs with cerebral palsy, either in one or both twins, or behavioral issues were excluded. Fifty-one MC twins born between January 2000 and December 2004 were included in the analysis. They also included twins with TTTS, not adhering to the pre-specified inclusion criteria of this CAT. However, as this was the case for only six twin pairs, the article was still selected due to the specific match with the question in this CAT.

The British Ability Scales: Second Edition (BASII) was used to assess cognitive function, consisting of the Early year’s battery, evaluating reasoning, memory and understanding of basic quantitative concepts, and School age battery, evaluating reasoning, memory using numerical, verbal and figural methods and processing speed. The Quick Neurological Screening Test-II (QNST) was performed to identify children with neurological disabilities that are associated with learning disabilities. All the tests were performed by a single blinded investigator. Lastly, the Strenghts and Difficulties Questionnaire (SDQ) was completed by teachers and parents and determined the behavior.

The study population was well-defined and ascertained from a prospective database. The inclusion rate was 77% after the exclusion of fifteen pregnancies, amounting to a population of 51 MC twins. Furthermore, the population was representative as it was focused on MC birth weight discordant twins, even though the study population is relatively small. Since it was a retrospective study design with included twins born between 2000 and 2004, the age at which the neurocognitive tests were performed varied possibly affecting the interpretation of results. However, the mean age at assessment was 6.3 years with a range from 4-8.7 years, not leading to any incomparability of the results.

The outcome measures (BASII, QNST) were objectively recorded by a blinded investigator, assuring unbiased assessment adding to the credibility of the results. The SDQ might be
influenced by the subjective assessment of parents and teachers which should be taken into account. The analysis of results was corrected for factors shared within twin pairs, such as gestation and sex. However, educational levels of the parents were not corrected for which might bias the results. Nonetheless, the article specified that these levels were largely similar between families and that this was the reason that they did not correct for this.

Overall, this study has a detailed specification of the population. Combined with its representative nature, the objective assessment of the outcome measures and the adequate follow-up range, the study has a high validity. Therefore, it has implications for clinical practice.
2.4 Evidence

**Adegbite et al. (2004)**

Fifteen (58%) of the discordant MC infants had a normal development and the incidence of neuromorbidity in discordant MC infants was 23%. The cerebral palsy rate was also significantly higher in discordant MC than DC infants, namely 19% and 1% respectively (p<0.05). The overall neuromorbidity in discordant MC twins was 42% as opposed to 13% in DC twins (p<0.01). Lastly, the overall incidence of neuromorbidity was significantly higher in the discordant MC twins compared with the concordant MC twins, namely 42% versus 8% (p<0.01). The study concludes that birth weight discordant MC twins have a 6-fold higher risk of cerebral palsy compared to DC twins.

**Edmonds et al. (2010)**

The dataset exhibited a spectrum of birth weights varying from 1070 to 3500 g, with differences ranging from 30 to 1480 g. After performing a regression analysis, Edmonds et al. concluded that there was a relationship between within-twin birth weight difference and verbal IQ scores with a slope of 13.0 and an intercept of -4.4 (p<0.01). Twin pairs with a birth weight difference lower than 340 g demonstrate a lower verbal IQ in the heavier twin. The opposite was true for the discordant pairs, such that the heavier twin had an advantage of 8.6 points for a 1 kg greater birth weight. Corresponding confidence intervals were presented. No significant effects of birth weight difference on performance IQ were observed. Hence, suboptimal intrauterine growth is related to impaired verbal IQ according to this study.

**Halling et al. (2015)**

Growth discordant MC twins performed lower in the language composite score (difference of 3.8 points with p=0.03), expressive language (difference of 0.8 points with p=0.02), composite motor (difference of 5.3 points with p=0.002) and scaled gross motor categories (difference of 1.1 points with p=0.001). Within-pair differences for MC twins could not be calculated with certainty due to small sample size. The smaller twin appeared to have lower neurodevelopmental scores across all domains for DC twins. The differences between the mean for MC twins and DC twins were presented with corresponding confidence interval.
Rustico et al. (2017)

Rustico et al. analyzed 140 MC twin pregnancies complicated by sIUGR, of which 65 (46%) were type I, 62 (44%) type II and 13 (9%) type III according to the UA Doppler classification. However, the neurodevelopmental outcome was not compared between the different types of the classification. The smaller twin more often demonstrated a mild neurodevelopmental impairment as opposed to the larger twin, namely 6 (7%) versus 1 (1%) infants respectively (p=0.02). The intact survival rate, calculated by dividing the number of infants without impairments by the total number of infants, was 48% for the smaller twin and 74% for the larger twin.

Swamy et al. (2018)

The general conceptual ability assessed with the BASII was 108.4 in the heavier twin and 105.4 in the lighter twin (p=0.005). Also, there were significant differences for mathematics and memory among individual subtests. When an abnormal Doppler flow was present (intermittent/persistently reversed or absent), the general conceptual ability of the smaller twin was 7 points lower than the heavier twin (p=0.04).

No neurological signs were observed with the QNST. The ratings of the SDQ for parents and teachers were largely similar, reporting the same number of lighter twins as heavier twins to have behavioral problems.

Thus, this study concludes that the small twin of a birth weight discordant pair has a significant long-term neurocognitive disadvantage. Memory and mathematical skills demonstrated the largest differences.
2.5 Commentary

The study populations of the included articles were relatively similar with regard to study type, study population including chorionicity, in- and exclusion criteria (except for Swamy et al. who excluded cases with cerebral palsy), and the definition of birth weight discordance. However, the follow-up periods differed significantly between the studies and the outcome measures were variable including either IQ or neurological impairment. Thus, the evidence level of the included articles is of moderate quality. A moderate quality of evidence suggests that further research will have a significant impact on the confidence of the estimates of the outcomes.

The pooled results of the included studies can be applied to the patients in the above-mentioned scenario based on the definition of birth weight discordance, chorionicity, and patient population. The twins in the clinical scenario had a birth weight discordance of 48% and were delivered at 28+1 weeks gestational age, which makes them compatible with Adegbite et al., Halling et al., Rustico et al. and Swamy et al. In Edmonds et al., the included twins were born > 34 weeks of gestation, which is not similar to the clinical scenario. Furthermore, Edmonds et al. did not make a distinction between MC and DC pregnancies, which makes the results difficult to relate the results to our case. All articles demonstrate that there is a higher incidence of neurological or cognitive impairment in birth weight discordant MC twins with a disadvantage for the smaller twin. These results can be used to offer the parents counseling about the incidence of neurodevelopmental impairment in their sIUGR twins.

2.6 Bottom line

The neonatologist should discuss the increased incidence of neuromorbidity and neurodevelopmental impairment of the sIUGR twins in the long-term with the parents in the clinical scenario. Exact risks cannot be estimated since larger, more elaborate research is still necessary to give enough certainty, but it is proven in the literature that there is a higher prevalence of neurodevelopmental impairment in birth weight discordant MC twins.
CHAPTER THREE – Discussion

3.1 Discussion

This literature evaluation presented evidence that sIUGR twins are at substantial risk of neurodevelopmental impairment in the long-term. Five articles researching the impact of birth weight discordance on cognitive abilities all concluded that the prevalence of neuromorbidity was higher in the MC birth weight discordant twins. However, there are differences in study design and methodology between the articles which should be taken into consideration when comparing and assessing the results.

Concerning the UA Doppler classification, a review by Buca et al. (12) evaluated the outcomes of sIUGR pregnancies according to the UA Doppler pattern in a systematic review and meta-analysis. They concluded that type II and type III sIUGR are at higher risk of abnormal brain imaging compared with type I sIUGR based on thirteen included studies. Furthermore, a systematic review by Lopriore et al. (7) documented an incidence of 8% of cerebral injury in sIUGR twins mainly affecting the larger twin. These results demonstrate that specific UA Doppler classifications are linked to certain cerebral and neurological outcomes. Research on whether this is the case for long term neurodevelopmental impairment is still lacking.

The elevated risk of neurodevelopmental impairment has clinical consequences. The current recommendation is to extensively monitor twins with sIUGR, mainly perinatally since the neurological and cerebral damage most often originates from this period. Moreover, routine cognitive and developmental evaluations will have to be performed to control and manage the possible impairments and effectively respond with adequate treatment or education.

Overall, sIUGR is associated with impaired neurocognitive development in both twins. More extensive research focused specifically on sIUGR twins is necessary to conclude this with more certainty. The research should be in a prospective follow-up setting, preferably with a large cohort of MC twins with a long follow-up until school age. A stratification according to UA Doppler classification might offer insight into the risk of long-term neuromorbidity per type of sIUGR. When the progression of the neurocognitive abilities is properly
documented, a management protocol can be formed in order to take adequate measures and optimize the development of twins with sIUGR.
References


APPENDIX 1 – Literature search

<table>
<thead>
<tr>
<th>Naam Student</th>
<th>Sophie Groene</th>
</tr>
</thead>
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<tr>
<td>Werkgroep</td>
<td>3</td>
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<td>Datum</td>
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1. **Zoekvraag**

“What is the long-term prognosis and neurodevelopmental outcome of monochorionic twin pregnancies complicated by selective intrauterine growth restriction (sIUGR)?”

<table>
<thead>
<tr>
<th>Component/concept</th>
<th>PICO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient/Population</td>
<td>Monozygotic monochorionic twins</td>
</tr>
<tr>
<td>Intervention</td>
<td>sIUGR</td>
</tr>
<tr>
<td>Comparison/Control</td>
<td>No sIUGR</td>
</tr>
<tr>
<td>Outcome</td>
<td>Prognosis, neurodevelopmental outcome</td>
</tr>
</tbody>
</table>

**Component 1: Selective intrauterine growth restriction**

weight discordant”[Tw] OR “Discordant birth weight”[Tw] “Growth discordance”[Tw] OR “Growth discordant”[Tw]

**Component 2: Twins**


**Gecombineerde strategie (component 1 + 2)**


**Aantal gevonden referenties: 1024**

**Datum: 29-3-18**

**Relevante van de gevonden referenties:** Het aantal referenties is te hoog om door te lezen, maar op de eerste pagina staan al een aantal zeer relevante en specifieke referenties toegespitst op sIUGR.

**Aanpassing zoekstrategie:**

De zoekstrategie is aangepast omdat er 1024 referenties werden gevonden. Dit is te veel om door te zoeken naar relevante referenties. De zoekstrategie moet worden aangepast om efficiënter te kunnen zoeken.

Methode: Component toegevoegd.

**Component 3: Outcomes (prognosis, neurodevelopmental outcomes)**


**Nieuwe zoekstrategie (component 1 + 2 + 3):**


Aantal referenties: 298

Datum: 29-3-18

Relevantie: Erg relevant en specifiek over sIUGR. Ook voldoende referenties om te doorzoeken.

Verschil met oorspronkelijke strategie: Veel minder referenties, beter te overzien en specifiek voor het gekozen onderwerp.

De zoekstrategie zoals bovenstaand (aantal gevonden referenties: 298) levert voldoende artikelen op die gebruikt kunnen worden voor het schrijven van de CAT. Daarom is deze zoekstrategie uiteindelijk toegepast.

Geïncludeerde artikelen


## APPENDIX 2 – Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>Population of monochorionic sIUGR or birth weight discordant twins</td>
<td>Population of monochorionic twins diagnosed with sIUGR and co-existing twin-twin transfusion syndrome (TTTS) or twin anemia polycythemia sequence (TAPS)</td>
</tr>
<tr>
<td>Follow-up studies (cohort studies, both prospective and retrospective), randomized controlled trials</td>
<td>Case-control studies, systematic reviews and/or meta-analyses, case series, case report</td>
</tr>
<tr>
<td>Age-appropriate neurodevelopmental tests</td>
<td>Inappropriate neurodevelopmental tests</td>
</tr>
<tr>
<td>No interventions in the study population</td>
<td>Interventions in the study population, such as fetoscopic lasertherapy</td>
</tr>
<tr>
<td>English or Dutch articles</td>
<td>Articles in any other language than stated in the inclusion criteria</td>
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</table>
## APPENDIX 3 – Evidence table

### Table 1 Summary of study characteristics and results of the included studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Year</th>
<th>Study design</th>
<th>Population</th>
<th>Definition birth weight discordance</th>
<th>Neurodevelopmental evaluation</th>
<th>Outcome measures</th>
<th>Follow-up time</th>
<th>Results</th>
</tr>
</thead>
</table>
| Adegbite et al. | United Kingdom   | 2004 | Prospective cohort    | 76 MC twin pairs born between 24 and 32 weeks of gestation, of which 13 birth weight discordant | ≥ 20% birth weight discordance or smaller twin with abdominal circumference of ≤ 5th centile with an abnormal umbilical artery Doppler | Griffith’s mental development scale score                                       | Overall incidence of cerebral palsy and minor neurologic disabilities          | 2 years                   | Incidence of cerebral palsy (p<0.05):  
  - Discordant MC twins = 19%  
  - Discordant DC twins = 1%  
  Overall neuromorbidity (p<0.01):  
  - Discordant MC twins = 42%  
  - Discordant DC twins = 13%  
  Overall neuromorbidity (p<0.01):  
  - Discordant MC twins = 42%  
  - Concordant MC twins = 8% |
| Edmonds et al.  | United Kingdom   | 2010 | Retrospective cohort  | 71 monozygotic twin pairs born > 32 weeks of gestation | Birth weight discordance not defined, birth weight difference as a continuous variable | Wechsler Intelligence Scale for Children                                     | Verbal IQ, performance IQ                                                     | Between 7 years 11 months and 17 years 3 months | Relationship between within-twin birth weight difference and verbal IQ score  
  - Slope 13.0 and intercept -4.4 (p<0.01).  
  Heavier twin advantage of 8.6 points for 1 kg greater birth weight in discordant pairs |
| Halling et al.  | Ireland          | 2015 | Prospective cohort    | 119 pairs of growth discordant twins, of which 24 birth weight discordant MC twin pairs | ≥ 20% birth weight discordance                                                                               | Bayley Scales of Infant and Toddler Development                           | Bayley Scale scores (cognitive composite, language composite, motor composite, language expressive scaled, language receptive scaled, motor fine scaled, motor gross scaled) | Between 24 and 42 months | Growth discordant MC twins  
  - 3.8 points lower in language composite score (p=0.03),  
  - 0.8 points lower in expressive language (p=0.02),  
  - 5.3 points lower in composite motor (p=0.002)  
  - 1.1 point lower in scaled gross motor categories (p=0.001) |
| Rustico et al.  | Italy            | 2017 | Retrospective cohort  | 140 MC twin pregnancies complicated by sIUGR     | EFW < 10th percentile in the smaller twin or EFW difference ≥ 25%                                            | No developmental test                                                       | Level of neurological impairment (severe, moderate, mild)                     | Between 12 months and 7 years | Mild neurodevelopmental impairment (p=0.02)  
  - Smaller twin = 7%  
  - Larger twin = 1% |
<table>
<thead>
<tr>
<th>Swamy et al.</th>
<th>United Kingdom</th>
<th>2018</th>
<th>Retrospective cohort</th>
<th>51 MC twins</th>
<th>≥ 20% birth weight discordance</th>
<th>British Ability Scales: Second Edition, Quick Neurological Screening: Test-III, Strengths and Difficulties Questionnaire</th>
<th>BASII scores, QNST scores, SDQ scores</th>
<th>Between 4 and 8.7 years, with a mean of 6.3 years</th>
<th>BASII general conceptual ability scores (p=0.005)</th>
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<td>BSII scores, QNST scores, SDQ scores</td>
<td>Between 4 and 8.7 years, with a mean of 6.3 years</td>
<td>BSII general conceptual ability scores (p=0.005)</td>
<td>- Heavier twin = 108.5</td>
<td>- Lighter twin = 105.4</td>
</tr>
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## APPENDIX 4 – Abbreviation table

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>sIUGR</td>
<td>Selective intrauterine growth restriction</td>
</tr>
<tr>
<td>MC</td>
<td>Monochorionic</td>
</tr>
<tr>
<td>DC</td>
<td>Dichorionic</td>
</tr>
<tr>
<td>EFW</td>
<td>Estimated fetal weight</td>
</tr>
<tr>
<td>NICU</td>
<td>Neonatal intensive care unit</td>
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<td>Absent/reversed end diastolic flow</td>
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<tr>
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<td>Intermittent absent/reversed end diastolic flow</td>
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<td>Quick Neurological Screening Test</td>
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