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# **BMJ Open** Microwave ablation versus radiofrequency ablation for the treatment of severe complicated monochorionic pregnancies in China: protocol for a pilot randomised controlled trial

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#### **ABSTRACT**

**Introduction** Complicated monochorionic twin pregnancies are often associated with high perinatal morbidity and mortality, some of which are severe enough to require a gestational reduction surgery to improve fetal survival and reduce disabilities. While radiofrequency ablation is currently the most commonly used procedure with higher fetal survival and fewer maternal and fetal complications compared with other surgical methods, the therapeutic effect of microwave ablation (MWA) is reported to be better, presumably due to the higher thermal effect and fewer restrictions. Currently there is limited evidence to prove the feasibility of MWA for selective reduction. The aim of this pilot study is to explore the feasibility, efficacy and safety of MWA reduction for severe complicated monochorionic pregnancies and may provide evidence for using the MWA in intrauterine surgeries extensively. Methods and analysis This is a study protocol for a parallel-design pilot randomised controlled trial. 60 eligible patients with severe complicated monochorionic pregnancies will be randomised in a ratio of 1:1 to MWA group and radiofrequency group. Patients will be followed up until 6 months of age of the retained fetal. The primary analysis will compare the rates of neonatal survival at 28 days to evaluate the effect of MWA. The study will also evaluate the safety profile of MWA including the occurrence of postoperative adverse events and maternal and fetal complications. Additional secondary outcomes to be explored include the condition of neonatal asphyxia and the growth of surviving fetus at 6 months. Outcomes will be analysed by both a frequentist and the Bayesian statistical approach. Ethics and dissemination This study was approved by the ethical review committee of the Peking University Third Hospital (Beijing, China). The results of this study will be published in peer-reviewed scientific journals and

#### INTRODUCTION

Monochorionic twins are a special type of twin pregnancy representing 20% of all multiple gestations. At the same time, the

Trial registration number NCT04014452; Pre-results.

presented at relevant academic conferences.

# Strengths and limitations of this study

- First randomised controlled trial to investigate microwave ablation for treating severe complicated monochorionic pregnancies.
- Pilot randomised controlled design to enhance the reliability of results using predetermined primary outcomes of feasibility.
- Both frequentist statistical analysis and Bayesian analysis will be used to estimate the probability of
- Clinicians and patients could not be blinded.

number of twins is constantly increasing due to the application of assisted reproductive technology. Monochorionic twins have the highest risk of fetal loss, very preterm delivery and neonatal death in different types of pregnancy<sup>2 3</sup> and have an almost five times higher risk of neurological injury after intrauterine death of the co-twin compared with their dichorionic counterparts. 45

Monochorionic twin pregnancies are at risk of twin-to-twin transfusion syndrome (TTTS), twin anemia-polycythemia sequence, selective intrauterine growth restriction (sIUGR), discordance for structural or chromosomal anomalies and twin reverse arterial perfusion (TRAP) sequence due to the various patterns of vascular anastomoses.<sup>6</sup> In many situations, selective termination of one fetus is necessary in order to optimise the chances of survival of the normal co-twin. Selective reduction of an anomalous co-fetus has been shown to reduce maternal-fetal morbidity from severe complicated monochorionic pregnancies.<sup>7 8</sup> However, due to the placental traffic vessel anastomosis in monochorionic gestations, the traditional potassium chloride injection is contraindicated for this, and other surgical methods to occlude the umbilical vessels can only be adopted. These methods include fetoscopical ligation of the umbilical cord, laser coagulation, bipolar cord coagulation (BCC), radiofrequency ablation (RFA)<sup>9</sup> and most recently, microwave ablation (MWA). 9-11 Up to now, RFA and BCC are effective and relatively safe in selective reduction having higher fetal survival rates and fewer complications, which can significantly improve the prognosis of pregnancy. 12 13 Compared with BCC, RFA has potential advantages. First, the tip diameter is smaller (1.4 mm vs 3–5 mm), so the operation can be earlier, even when amniotic fluid is less, and postoperative complications such as premature rupture of membranes and preterm birth rate are lower. Second, the operation is easier, and pregnant women can also accept the operation under local anaesthesia, reducing the discomfort of the pregnant women. <sup>14</sup> Meanwhile, MWA has been widely used for the minimally invasive treatment of most tumours as well as RFA due to its higher thermal efficiency and shorter operative time. Considering the importance of ablation cycle times in fetal reduction surgeries, 15 the microwave as a thermal ablation technique was considered as a fetal reduction technique.

As one of the most recent methods to treat severe complicated monochorionic pregnancies, MWA was first reported by Prefumo<sup>10</sup> in 2013 to use for the reduction of fetal deformity. Subsequently, in 2014, six cases using MWA for the reduction of TRAP were reported. 11 After demonstration and improvement, the obstetrics and gynaecology team of Peking University Third Hospital carried out this operation for the first time in China. In the past 2 years, they have completed more than 100 operations and applied for a patent for MWA. In 45 cases of complicated single chorionic twins undergoing selective ablation with microwaves, the total fetal survival rate at 28 days was 73.3%, and no brain injury or serious complications were found. 16 In addition, the operation of microwave surgery, which neither requires the use of positive and negative electrodes to generate current nor uses electrode plates to avoid skin burns, is simpler than that of the RFA. Therefore, the application of MWA in the selective reduction of twins may be more advantageous than that of the RFA.

To sum up, RFA is currently widely used in complicated twin reduction surgeries, with a higher fetal survival rate and fewer surgical complications. At the same time, current experience suggests that MWA has similar therapeutic effects and potential advantages, which can be effectively applied. However, there are few studies on MWA and there is still no strong evidence to determine the overall perinatal benefits and the long-term neurobehavioural development of the surviving fetus.

Therefore, more studies are needed to support the use of MWA of severe complicated monochorionic pregnancies. This study is a pilot randomised controlled trial (RCT) aiming to evaluate the efficacy and safety of MWA by comparing pregnancy outcomes of complicated

monochorionic twin pregnancies undergoing selective reduction by radiofrequency versus MWA.

#### **AIMS AND OBJECTIVE**

In this study, we aim to test the hypotheses that MWA is not inferior to RFA in terms of the rate of neonatal survival in the treatment of severe complicated monochorionic pregnancies, and that MWA has additional benefits over RFA, including fewer complications, shorter length of operative time and simple procedure.

#### Specific objectives and hypotheses

#### Aim 1

To evaluate the hypothesis that the rate of fetal survival by MWA is not inferior to that by RFA, including:

1. The proportion of fetal survival at 28 days post partum.

#### Aim 2

To evaluate the hypothesis that MWA has additional benefits over RFA, including:

- 1. The duration of the reduction surgery.
- 2. The frequency of surgical injury to fetal, including central nervous system injury detected by MRI or B ultrasound at 28–32 weeks of gestation and 42 days post partum.
- 3. The rate of maternal complications, including <28 weeks of intrauterine fetal death/abortion rate, >28 weeks of intrauterine fetal death rate, premature rupture of membranes, neonatal intensive care unit (NICU) admission rate and <28 weeks, <32 weeks, <34 weeks premature delivery rate.
- 4. Growth and development of newborn babies, including birth weight, birth height, Apgar Score at 1 min and 5 min, neonatal diseases and growth of children at 6 months.

# Aim 3

To explore the risk factors for fetal death after selective reduction for complicated monochorionic pregnancies, including:

- 1. The basic characteristics of pregnant women, including maternal age, conception mode, cervical length and indications.
- The clinical factors associated with surgeries, including cycles of coagulation required, the maximal power of effective coagulation and the duration of the reduction surgery.
- 3. The situation of depression and sleep using the Edinburgh Postnatal Depression Scale and Pittsburgh Sleep Quality Index before operations, at 28 weeks of gestation.

# METHODS AND ANALYSIS

#### Overview

The study will be a single-centre, parallel-design pilot RCT. Sixty severe complicated monochorionic pregnant



Table 1 Schedule of enrolment, interventions and assessments Study period **Enrolment Allocation Treatment** Follow-up First visit **Enter group** Within 3 within within days after 7 and 30 28 weeks 42 days post 6 months **Timepoint** 24 hours 24 hours admission days **Delivery** partum post partum pregnant **Enrolment:** Eligibility screen X Informed X consent X Basic information Randomisation X X Allocation Interventions: X Microwave ablation Radiofrequency X ablation Assessments: Surgical X X process Χ X Depression and X sleep Maternal X X Χ complications X X X X Pregnancy outcome Fetal survival X

women who need a selective reduction will be randomised in a 1:1 ratio to MWA or RFA. We hypothesise that non-inferiority of MWA as compared with RFA in terms of the rate of fetal survival. The schedule of enrolment, interventions and assessments is summarised in table 1, and the flow diagram of the study is presented in figure 1.

#### Patient and public involvement

Patients and the public were not directly consulted in the development of the research questions or outcome measures. Patients were not involved in designing, recruiting or conducting studies. Results of the final study will be disseminated to all study participants by phone calls. The burden of intervention will be taken by the patients and our findings.

#### Recruitment

Peking University Third Hospital in China will conduct this trial. Potential trial participants will be screened from the daily outpatients. Screening will be applied only to eligible participants requiring selective reduction, based on guidelines for clinical management of twin pregnancies. Informed consent will be obtained on the day of study recruitment. Only a well-trained clinical coordinator, the principal investigator or an associate investigator will obtain consent. Details of the protocol will be discussed with the potential participants at the time after the first visit if they need a selective reduction. These individuals will then be approached with the informed consent form. Recruitments are expected to occur over a 10-month period, commencing in July 2019.

#### **Inclusion criteria**

- 1. Complicated monochorionic pregnancies women.
- 2. Having the indication of selective reduction (as delineated in more detail in box 1).
- 3. The reduction surgery should be done after 15 weeks of gestation.
- 4. Willingness to participate in the trial and having provided written consent.

# **Exclusion criteria**

 Preoperative examinations show that patient is not appropriate to undergoing reduction surgeries, such as the acute infection of the organ system, especially the urinary system.

<sup>\*</sup>At any time the retained fetal death occurs, follow-up should be terminated.

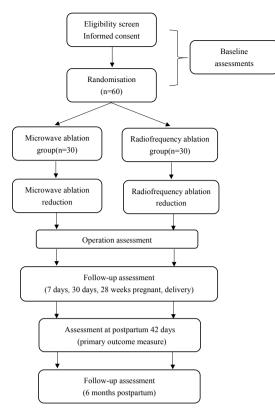


Figure 1
Flow diagram of the study.

Figure 1 Flow diagram of the study.

- 2. Patients need to accept acute reduction surgeries due to the progress of the disease and the surgery cannot be scheduled.
- 3. Other diseases that may affect the experimental results: neuropsychiatric diseases and congenital diseases.

# Box 1 Indication of selective reduction

- Twin malformation inconsistency: one fetus did not have obvious abnormalities as seen in ultrasound examination, but the other one was found with severe malformation.
- 2. Twin reversed arterial perfusion: the diagnosis of it was confirmed as the presence of inverse direction of blood flow in the aorta of the acardiac twin.
- 3. Type II or III of sIUGR: it was defined as an estimated fetal weight (EFW) of less than the 10th centile in one twin or an intertwin EFW discordance ≥25%. EFW discordance was calculated as (EFW of the larger twin–EFW of the smaller twin)÷EFW of the larger twin×100%. Classification of sIUGR was based on the Doppler waveforms in the umbilical arteries as described by Gratacos.
- 4. Stage III or IV of TTTS rejecting the laser coagulation of placental blood vessels under fetal microscopy, or failing after it, or placenta completely covers the anterior uterine wall. TTTS was diagnosed based on the presence of deepest vertical pocket of amniotic fluid in the donor ≤2 and ≥8 cm in the recipient before 20 weeks of gestation and ≥10 cm after 20 weeks. The Quintero staging system was used to assess the severity of TTTS.
- Three or more fetuses with monochorionic pregnancies requiring reducing the number of fetuses.

#### Sample size

The purpose of this pilot RCT is to explore the feasibility and evaluate the efficacy and safety of MWA reduction for severe complicated monochorionic pregnancies. According to previous studies, the rate of neonatal survival at 28 days of RFA ranged from 63.6% to 88.6% (average 76.0%). Based on the preliminary date of our department, the rate of neonatal survival at 28 days was nearly 73.3% in patients treated with MWA. Thus, a sample size of 878 patients (439 in each group) would be required with a 5% (two-sided) type I error and a power of 80% using a 10% non-inferiority margin. However, based on the feasibility and the intent to provide pilot dates to full sample sizes and statistical plans, 30 participants in each group and a total of 60 participants will be recruited for this trial.

#### **Randomisation and allocation concealment**

Sixty participants who meet eligibility requirements and provide informed consent will be assigned in a ratio of 1:1 to the treatment group and the control group. Patients will be allocated to each group according to a randomisation schedule using SAS V.9.4 with a random block size of 6. The statistician will seal the randomisation codes in sequentially numbered opaque envelopes and send them to the research centres. Allocations will be concealed until participants sign the informed consent, at which time the interventionalist will access the allocation code.

#### Blinding

In this research, it is not feasible to conceal the allocation from the surgical operators. In addition, it is not possible to prevent participants from knowing if they have received MWA reduction or RFA reduction. The treatment and assessment will be performed independently. The outcome assessors and the data statistical analysts will be blinded to the treatment allocation throughout the study.

#### Intervention

All participants of this trial will have the same preoperative preparation and postoperative treatment regardless of the assigned groups.

#### Microwave ablation group

Participants in the MWA group will receive the surgery by an ECO-100E MWA therapy apparatus and an electrode needle. The patients will be placed in a supine position with conventional abdominal disinfection spread cloth, local anaesthesia with 1% lidocaine and a 2mm incision made on the skin. Under the guidance of continuous ultrasound, an electrode needle with a frequency of 2450 MHz will be inserted into the abdominal cavity of the fetus to be attenuated, as close as possible to the umbilical cord entrance. The distance between the electrode tip and the fetal abdominal wall, the back and the uterine wall will be measured. Choose different power according to the size of the tire body, set the power as 30–40 W, last for 3 min as a cycle. During the ablation process, ultrasound



real-time will monitor the umbilical cord blood flow of the reduced fetus. If the umbilical blood flow does not disappear, one more cycle will be added. During the ablation process, colour doppler ultrasound will continuously monitor the umbilical cord blood flow. At the same time, the operation through the temperature measurement in real-time monitoring of the amniotic fluid temperature, the temperature setting is 40°C, and when the temperature reached the alarming value, the melting automatically stops. The reduced fetal heart rate and the retained fetal heart rate, umbilical artery blood flow and the middle cerebral artery blood flow will be observed after the surgery.

#### Radiofrequency ablation group

Participants in the RFA group will receive the surgery by a S-1500 RFA system and a SLIM 17G radiofrequency needle. The patients will be placed in a supine position with the electrode board pasted on the lateral thigh, while the conventional abdominal disinfection cloth will be applied, and 1% lidocaine will be given for local anaesthesia. Under the guidance of continuous ultrasound, the radiofrequency needle will be quickly transdermal inserted into the umbilical cord at the inner part of the fetal abdominal wall. After confirming the correct position of the radiofrequency needle tip with colour doppler, the umbrella-shaped needle claw will open to determine the position of the needle claw again. Turn on the RFA generator and the power will start from 20 W and increase by 10 W/min. Keep heating until the machine stops automatically. The umbilical cord blood flow will be observed. If it does not disappear, another circulation will be added. During the ablation process, colour doppler ultrasound will be used to continuously monitor the umbilical cord blood flow. If it is confirmed that the umbilical cord blood flow is completely blocked, the radiofrequency will be stopped. The reduced fetal heart rate and the retained fetal heart rate, the umbilical artery blood flow and the middle cerebral artery blood flow will be observed after the surgery.

#### **Postprocedural follow-up**

Patients will be followed up at the 7th and 30th days after the surgical reduction. Meanwhile, they will be followed up four more times (28 weeks pregnant; delivery; 42 days post partum; 6 months post partum) until the retained fetal is 6 months old or death occurs (table 1).

All study-related procedures, including recruitments, enrolments, the preprocedure and postprocedure monitoring, as well as the postprocedure follow-up will be performed in by phone or in the outpatient clinic. Data to be recorded are summarised in box 2.

## Criteria for withdrawal of participants

In the event a study subject elects to be withdrawn from the study and requests for their data to be withdrawn as well, we will comply.

### Box 2 Study data acquisition

#### 1. Preprocedure data:

- 1.1. Demographic data (age, height, weight, gestational week, education, smoking, drinking and depression).
- 1.2. Early pregnancy screening information (blood biochemistry, ultrasonic testing, prenatal screening and diagnosis).
- 1.3. Anamnesis.
- 1.4. Indication of selective reduction.
- 1.5. Preoperative basic examination date (blood biochemistry, ultrasonic testing).
- 1.6. Depression and sleep data (Edinburgh Postnatal Depression Scale, Pittsburgh Sleep Quality Index).
- 2. Procedure-related data:
  - 2.1. Surgery gestational week.
  - 2.2. The site of placenta.
  - 2.3. Cycle index and time.
  - 2.4. Total operation time.
  - 2.5. Intraoperative amniotic fluid temperature.
  - 2.6. Intraoperative adverse events.
  - 2.7. Ultrasonic testing of postoperative pregnant women and retained fetuses.
- 3. Postprocedure data:
  - 3.1. Complications of surgery at 1 week and 1 month.
  - 3.2. Late pregnancy screening information (oral glucose tolerance test, blood biochemistry, ultrasonic testing and MRI, depression and sleep).
- 4. Pregnancy outcome:
  - 4.1. Parturient examination data (blood biochemistry, ultrasonic testing).
  - 4.2. Intrapartum situation data (delivery way, complication, fetal gender, fetal height, fetal weight, fetal head circumference, NICU admission, Apgar Score, disease of newborn).
  - 4.3. The rate of neonatal survival at 28 days (primary outcome).
  - 4.4. Depression and sleep data (Edinburgh Postnatal Depression Scale, Pittsburgh Sleep Quality Index).
  - 4.5. Growth of the children at 6 months (height, weight, parenting, breastfeeding, 1-day feeding record).

#### **Study outcomes**

The primary outcome of the study is the rate of neonatal survival at 28 days collected until 42 days post partum. The secondary outcomes of the study will include: (1) the frequency of surgical injury to fetuses: defined as the central nervous system injury detected by MRI or B ultrasound at 28-32 weeks of gestation and 42 days post partum; (2) postoperative complication rates: defined as <28 weeks of intrauterine fetal death/abortion rate, >28 weeks of intrauterine fetal death rate, the rate of premature rupture of membranes, NICU admission rate and <28 weeks, <32 weeks, <34 weeks premature delivery rates; (3) situations of surgical process, including cycles of coagulation required, the maximal power at effective coagulation and the duration of the reduction surgery; (4) situation of depression and sleep: defined as the score of Edinburgh Postnatal Depression Scale and Pittsburgh Sleep Quality Index before operations, at 28 weeks of gestation and after postnatal and (5) growth and development of infants: defined as birth weight, birth height,



Apgar Score at 1 min and 5 min, neonatal diseases and growth of children at 6 months.

# **Data collection and management**

Data will be collected after acquiring the signed consent from the participants. The collected data will be recorded on the Case Report Form (CRF) by a trained research assistant or study investigators. The whole process of the trial will be regularly monitored to ensure the quality of the trial.

The study will collect baseline demographic information including age, sex, height, body weight, medical comorbidities, the highest educational status, smoking and drinking status as well as sleep quality after participants sign the informed consent during the first visit. The gynaecologist will fill out the treatment forms, including the detailed surgical procedures and intraoperative findings, information about postoperative pregnant women and retained fetuses. After discharge, trained outcome assessors will complete the follow-up forms by phone or in the outpatient clinic. The patients are required to provide the information on the prenatal testing at 12 and 28 weeks of gestation. Any missing data require an explanation from the investigators. The completed CRF will be reviewed by an authorised investigator. A double-entry method will be used for abstracting data from the CRF. At the end of the study, the database will be sent to the statistician for statistical analysis.

#### **Statistical analysis**

The intention-to-treat analysis will be performed in all participants without major protocol violations. Initial descriptive summary of the data will be performed. Data will be expressed as means with SD, medians with IQR, percentages and proportions as appropriate.

A two-sided significance level will be set at 5%, and the multiple imputation method will be adopted for missing at random data. SPSS V.25.0 will be used for statistical analysis. Continuous data will be analysed by independent sample t-test or one-way analysis of variance.  $\chi^2$  test or Fisher's exact test will be used for nominal data. As to the primary outcome, we use non-inferiority tests, take a one-sided test of 2.5%, a non-inferiority value of 10%. The effect of multivariable for clinical improvement will be analysed by logistical regression.

In this small pilot study, some treatment effects that could be considered important may not be statistically significant. As a result, Bayesian analyses will also be performed to estimate the probability of benefit. Neutral, weakly informative priors will be used for the treatment effect, for example, for binary outcomes, the prior relative risk will be centred at 1.0 with 95% prior interval of 0.5–2.0. Depending on the results of the pilot, the need for a larger trial will be assessed.

#### **Ethics and dissemination**

This study was approved by the ethical review committee of the Peking University Third Hospital (Beijing, China).

Patients will be fully informed about the trail as well as given written informed consent prior to randomisation. Recruitment of participants started in July 2019. The duration of the trial is expected to be 2 years.

The results of this study will be published in peerreviewed scientific journals and presented at relevant academic conferences.

#### **DISCUSSION**

Severe complicated monochorionic pregnancies require reduction surgeries to reduce fetal mortality and abnormalities. Therefore, the safest and most effective surgical procedure is advocated. Currently, RFA is considered to be the safest surgical procedure, but the procedure is long and complicated.

The number of ablation cycles can greatly affect the fetal death. Meanwhile, MWA has higher thermal efficiency and shorter operative time which may improve fetal survival. So far, it remains uncertain which procedure is the optimal surgical technique. An RCT is needed to solve clinical equipoise concerning the two surgical procedures. Hence we designed the trial to explore and evaluate the feasibility and efficacy of MWA in the treatment of severe complicated monochorionic pregnancies compared with RFA.

The sample size of this pilot study is 30 per each group, which may be underpowered to confirm the hypothesis of the study. Further study will be required to draw a definitive conclusion of the effectiveness of MWA for severe complicated monochorionic pregnancies. The result of this preliminary study will become a basis to design a full-scale RCT to conclude this issue.

In summary, this study is the first RCT designed to explore and evaluate whether MWA is an alternative treatment modality for severe complicated monochorionic pregnancies, and whether it results in nearly equal efficacy, fewer complications, shorter length of operative time in comparison with RFA.

**Contributors** YW is the principle investigator and has led all stages of the study design. JX and ZC drafted the manuscript. JX, ZC, TW, XW participated in the design of the study and the protocol writing. All of the authors read and approved the final submitted manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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