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Mode of birth in women with low-lying placenta: protocol for a prospective multicentre 1:3 matched case–control study in Italy (the MODEL-PLACENTA study)

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ABSTRACT

Introduction The term placenta praevia defines a placenta that lies over the internal os, whereas the term low-lying placenta identifies a placenta that is partially implanted in the lower uterine segment with the inferior placental edge located at 1–20 mm from the internal cervical os (internal-os-distance). The most appropriate mode of birth in women with low-lying placenta is still controversial, with the majority of them undergoing caesarean section. The current project aims to evaluate the rate of vaginal birth and caesarean section in labour due to bleeding by offering a trial of labour to all women with an internal-os-distance >5 mm as assessed by transvaginal sonography in the late third trimester.

Methods and analysis The MODEL-PLACENTA is a prospective, multicentre, 1:3 matched case–control study involving 17 Maternity Units across Lombardy and Emilia-Romagna regions, Italy. The study includes women with a placenta located in the lower uterine segment at the second trimester scan. Women with a normally located placenta will be enrolled as controls. A sample size of 30 women with an internal-os-distance >5 mm at the late third trimester scan is needed at each participating Unit. Since the incidence of low-lying placenta decreases from 2% in the second trimester to 0.4% at the end of pregnancy, 150 women should be recruited at each centre at the second trimester scan. A vaginal birth rate ≥60% in women with an internal-os-distance >5 mm will be considered appropriate to start routinely admitting to labour these women.

Ethics and dissemination Ethical approval for the study was given by the Brianza Ethics Committee (No 3157, 2019). Written informed consent will be obtained from study participants. Results will be disseminated by publication in peer-reviewed journals and presentation in international conferences.

Trial registration number NCT04827433 (pre-results stage)

Strengths and limitations of this study

- This is the first prospective case–control study to admit women with low-lying placenta at >5 mm from the internal os to a trial of labour and to collect data regarding their rate of vaginal birth.
- The project involves 17 maternity units across Northern Italy and it will be one of the largest studies on the topic of low-lying placenta.
- A transvaginal scan, although routinely performed in women with low-lying placenta, might be uncomfortable and embarrassing for some women.
- As the outcome indicators for this study rely on clinical observations and individual diagnostic technique, only senior obstetricians will perform transvaginal scan assessment and counselling regarding the mode of birth in order to limit biases.
- Considering that placenta praevia and low-lying placenta are a relatively rare obstetric complication, the enrolment process and protocol adherence should be strictly monitored, in order to include all cases.

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INTRODUCTION

The term placenta praevia identifies a placenta that covers completely the internal os of the uterine cervix, while the term low-lying placenta is used to define a placenta that is partially implanted in the lower uterine segment with the inferior placental edge located at 1–20 mm from the internal cervical os.[1–3]

Transvaginal scanning (TVS) is the gold-standard technique for measuring the distance between the placental edge and the internal os of the cervix, the internal-os-distance (IOD).[4] The optimal timing for such measurement is suggested to be the late third trimester, that is, 36 weeks' gestation,[5] since the lower uterine segment has mostly formed at this time.[6 7] Knowledge of the IOD is crucial for choosing the most appropriate mode of birth.[2 5 8]

While there is consensus that caesarean section (CS) should be performed in case of placenta praevia, the most appropriate mode of birth in women with low-lying placenta is still controversial due to lack of robust data.[9–14] Recently, both the American and the Royal College of Obstetrics and Gynecology[5 15] have stated that for women with a third trimester asymptomatic low-lying placenta, mode of birth should be individualised based on the clinical background and the woman's preference. Conversely, the 2015 Dutch and the 2020 Canadian guidelines have suggested that a vaginal birth should be offered to all women with low-lying placenta and an IOD between 11 and 20 mm, since the likelihood of an emergency CS due to haemorrhage is low.[16] In addition, the Canadian guideline includes the possibility of a trial of labour (TOL) in women with an IOD ≤10 mm if no other risk factors, such as previous bleeding episodes <29 weeks' gestation or evidence of marginal sinus, are present.[17]

In a retrospective study, we found a 69% rate of vaginal birth in women with low-lying placenta and an IOD between 11 and 20 mm, compared with 25% in women with an IOD of 1–10 mm.[10] Based on these results, a structured protocol for counselling women with a low-lying placenta on mode of birth was implemented at our Institution in 2009. According to this protocol, a planned CS was proposed to all women with an IOD ≤10 mm at the late third trimester TVS, whereas women with an IOD between 11 and 20 mm were counselled in favour of a TOL.

The evaluation of 9 years of practice (2009–2018) after the introduction of this new protocol confirmed our previous results, showing a 77% rate of vaginal birth in women with an IOD between 11 and 20 mm admitted to TOL.[18] The rate of emergency CS due to haemorrhage was 16.3%. These findings are consistent with data from a recent systematic review by Jansen *et al*,[19] reporting a vaginal birth rate and an emergency CS rate of 85% and 14%, respectively, in women with an IOD between 11 and 20 mm. The authors also identified a 43% and 45% rate of vaginal birth and emergency CS due to haemorrhage in women with an IOD between 1 and 10 mm. Of note, no differences were identified between the two IOD groups in terms of maternal morbidity. Similar results were reported in a retrospective study by Wortman *et al*, who identified a substantially higher likelihood of vaginal birth in women with an IOD >5 mm compared with ≤5 mm (58% and 0%, respectively), with no significant differences among IOD subgroups (6–10 mm, 11–15 mm and 16–20 mm).[13]

Due to lack of strong scientific evidence and, in turn, specific national recommendations, most women with low-lying placenta in Italy are offered a CS as the safest mode of birth. For this reason, no Italian data are available regarding the rate of vaginal birth and maternal and neonatal outcomes in women with this condition, except for the studies mentioned above.[10 18] In addition, little is known about birth outcomes of women and neonates with a resolution of low-lying placenta, that is, IOD becomes >20 mm, during the third trimester. In particular, evidence suggests that these women might still present an increased risk of postpartum haemorrhage compared with women with a normally located placenta since the second trimester scan.[18–20]

Altogether, it appears clear that provision of robust data on this topic is mandatory in order to generate appropriate scientific recommendations regarding childbirth practice for these women in Italy as well as worldwide.

Although low-lying placenta is a rare disorder, the prevention of CS in women with this condition could contribute to reducing the overall CS rate and the immediate and future risks associated with this surgery, thus ultimately improving early and long-term maternal and neonatal outcomes.

CS is associated with an increased risk of placenta praevia in subsequent pregnancies, especially in women with a prior placenta praevia.[21] This risk rises as the number of prior CS increases.[5] Moreover, prior CS and placenta praevia are substantial risk factors for placenta accreta spectrum.[22] Placenta accreta spectrum is a life-threatening condition associated with an increased risk of severe haemorrhage, hysterectomy, blood transfusion, and maternal and perinatal death.[23]

Considering that WHO has recently called for action to prevent inappropriate CS, especially primary CS (ie, in the first pregnancy),[24] implementation of successful strategies to improve CS practice worldwide is of utmost importance. This is particularly true for Italy, which holds one of the highest primary and repeated elective CS rates among European countries.[25]

The current project proposes to offer a TOL to all women with a low-lying placenta and an IOD>5 mm as assessed by transvaginal sonography (TVS) in the late third trimester. Timing of TVS will vary according to the parity of women. TVS assessment, as well as counselling regarding mode of birth, will be performed by senior obstetricians. Data regarding birth outcomes among women with a resolved low-lying placenta (IOD becomes>20 mm) will also be collected and assessed. Women with a normally located placenta at the second trimester scan will represent the

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control group, and they will be matched to cases in a 1–3 ratio according to parity.

METHODS AND ANALYSIS

Aims of the study

The primary aim of this study is to evaluate the rate of vaginal birth and emergency CS in labour due to vaginal bleeding in women having a low-lying placenta with an IOD between 6 and 20 mm. These outcomes will be compared with those of women with a resolved low-lying placenta during pregnancy (IOD becoming >20 mm) and those of women with a normally located placenta at the second trimester scan (controls).

The study also comprises six relevant secondary objectives, which will focus especially on the phenomenon of the resolution of praevia or low-lying placenta:

1. To analyse the frequency of resolution of praevia or low-lying placenta (IOD becoming >20 mm) in relation to the placental location at the second trimester scan (anterior/posterior; praevia/low-lying) and in relation to previous uterine surgery.
2. To analyse the time needed for resolution in relation to placental location (anterior/posterior; praevia/low lying) and previous uterine surgery, and its correlation to the risk of bleeding during pregnancy and the mode of birth.
3. To analyse the frequency of marginal sinus in women with low-lying placenta and its relation to the risk of bleeding during pregnancy or labour, and to the mode of birth.
4. To analyse maternal complications, including:
   - Incidence of antepartum haemorrhage requiring hospital admission or immediate delivery.
   - Incidence of intrapartum haemorrhage requiring emergency CS.
   - Incidence of severe postpartum haemorrhage defined as bleeding ≥1000 mL following birth.
   - Incidence of severe postpartum haemorrhage requiring administration of second-line uterotonic drugs, balloon tamponade, uterine artery embolisation, ligature of uterine arteries, hysterectomy, or blood transfusion.
   - Admission to the intensive care unit.
5. To analyse neonatal complications, including:
6.
   - Incidence of preterm birth <37 weeks and <32 weeks.
   - Admission to the neonatal intensive care unit.
7. To analyse the rate of women declining the mode of birth proposed by clinicians during counselling, according to three IOD subgroups: 1–5 mm, 6–10 mm and 11–20 mm.

Study setting

The study will be conducted in Northern Italy and will involve 17 maternity units, with the Monza Brianza per il Bambino e la sua Mamma Foundation (MBBM Foundation) Onlus placed in Monza at the San Gerardo University Hospital, as coordinating unit, where all data will be collected and analysed.

The Italian birth context has a classification system for levels of maternity care, comprising first level units providing care for low-risk pregnancies or with minor complications, and second level units also taking care of women with high-risk pregnancies. Women with a persistent low-lying placenta followed in a first level unit and admitted to a TOL will be transferred to a second level unit.

Among the 17 maternity units involved in this study, 4 are first level and 12 are second level. Each unit will have a senior obstetrician as contact person, who will be responsible to conduct meetings to inform colleagues about the ongoing research, to obtain informed consent from women who accept to participate into the study, and to collect data and ensure their completeness before sending them to the coordinating unit for the planned analyses.

The coordinating unit will monitor the case reporting and completeness of data collection on a monthly basis.

The principal investigator of the coordinating unit has already organised an on-line meeting to discuss the study protocol in detail with the nominated clinician of each maternity unit involved in the study and is available in case of further queries. In addition, the principal investigator has conducted a face-to-face meeting with colleagues of the MBBM Foundation Onlus to present the study and to describe the recruitment process, and will be available to replicate it at the participating maternity units.

Study design

This research is a prospective multicentre 1:3 matched case–control study.

Although randomised controlled trials are defined as the 'gold standard' of clinical trials to measure the effectiveness of a new intervention or treatment, in this specific case that research design would have arose strong ethical issues. In the light of the recent evidence,[1 2] which recommend that women with a low-lying placenta should have a TOL, and considering that concomitantly with the rising incidence of CS births, the incidence of a placenta accreta spectrum is also rising,[22] it would not be acceptable, ethical or safe to preclude the opportunity of having a vaginal birth to women.

Recruitment and sample

The recruitment process will last 42 months, from January 2021 to November 2024, with an additional follow-up phase lasting 6 months to complete the childbearing period of the last women recruited.

Women are enrolled according to the inclusion criteria identifying the study population (cases): minimum age of 18 years, singleton pregnancy, presence of praevia or low-lying placenta confirmed by TVS at the second trimester scan at 19–23 weeks or after accessing the Maternity Triage for vaginal bleeding at <32 weeks of gestation (not

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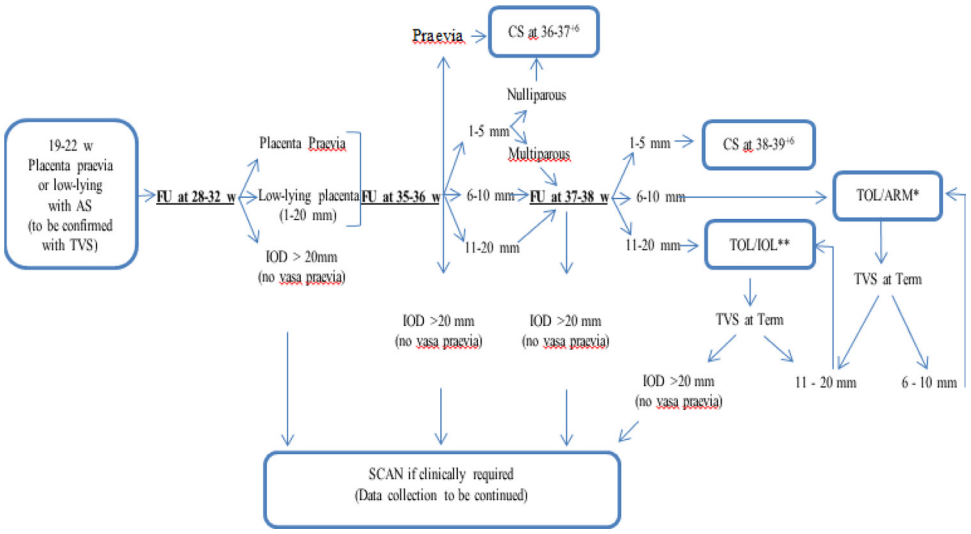

Figure 1 Flow chart: participants' antenatal care and follow-up scans. *Trial of labour, the onset of labour could be spontaneous or induced through an artificial rupture of membranes, otherwise the woman should undergo a CS between 41 and 41+5 weeks. ** Trial of labour, a pharmacological induction of labour is allowed. ARM, artificial rupture of membranes; AS, abdominal scan; CS, caesarean section; FU, follow-up; IOL, induction of labour; IOD, internal os distance; TVS, transvaginal sonography; TOL, trial of labour; w: weeks.

requiring an emergency CS). Women with a normally located placenta at the second trimester scan will represent the control group. After the inclusion of one case, three women with a normally located placenta will be recruited, according to the parity of the case (eg, CASE=nulliparous woman with low-lying placenta; CONTROLS=3 nulliparous women with normal placentation).

The exclusion criteria are: suspected or confirmed placenta accreta spectrum; vaginal bleeding requiring emergency CS; women declining participation.

Women will be approached to participate in the study by theobstetrician who will perform the second trimester scan between 19 and 23 weeks. All women presenting a placenta located on the lower uterine segment at the transabdominal scan will undergo evaluation by a TVS and, if praevia or low-lying placenta is confirmed, they will then be contacted by one of the team researchers. The women will be fully informed about the study and will be given an information leaflet containing the contact details of the principal investigator. Finally, the researcher will ask to sign the informed consent. Participants will attend follow-up scans to assess potential IOD modifications and resolution of a low-lying placenta (figure 1). IOD will be assessed at approximately 37 weeks' gestation to start discussing about the mode of birth; subsequent assessment will be defined according to woman's IOD value and parity.

Participants allocated to the control group will be recruited from general antenatal clinics and will be offered the same midwifery and obstetric care as they would normally receive, in line with usual practice.

Data collection tool

Data will be collected online using an Electronic Data Capture (EDC) system developed in collaboration with the University of Milano-Bicocca Clinical Research Office.

Google Form Module was employed to generate the EDC, assuring maintenance of data confidentiality by automatic generation of a research code for each enrolled woman by means of an electronic document. For every new subject to enrol, the electronic document will provide a research code constituted by the site code + '-'+the progression number starting from one, for example, MB-1. A paper logbook containing both the research code and the personal data of the enrolled woman will be kept separately, in a locked cabinet accessible only by the principal investigator of the maternity unit.

The EDC is constituted by three different modules to collect data regarding maternal general characteristics, medical and obstetric history, ultrasound scans and clinical course of the index pregnancy, labour and birth outcomes, and neonatal outcomes. At the beginning of each module, the investigator will input the research code, thus guaranteeing data tracing between different modules for the data belonging to the same subject. The module regarding the index pregnancy provides different sessions to enter data about the ultrasound scan at recruitment and all the follow-up scans. Birth outcomes will be differentiated based on mode of birth: planned CS, prelabour emergency CS, emergency CS in labour and vaginal birth.

The nominated clinician at each participating Maternity Unit will be trained to use the EDC system before the commencement of the study and the PI will provide the full list of the study team and related contact information; only study team members will be granted access to the system.

The EDC system was designed to reduce data entry errors and to guarantee the highest data quality according to data integrity principles: ranges for numerical fields

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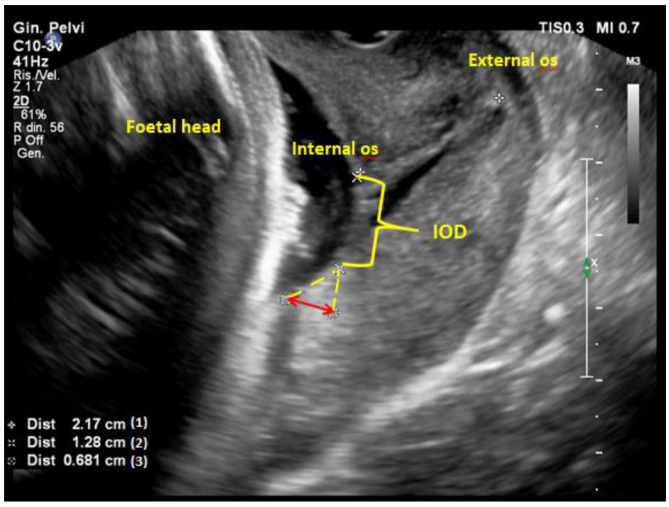

Figure 2 TVS evaluation of low-lying placenta. cervical length of 2.17 cm (1); IOD of 1.28 cm (2); placental edge thickness of 0.681 cm (3) shown by the red arrow; the angle between the basal and chorionic plates is identified by the yellow dotted lines. IOD, internal os distance; TVS, transvaginal sonography.

(no number accepted outside the provided ranges), dates collected by date fields, radio-buttons, checkboxes, drop-down menus, and dynamic behaviours (eg, previous CS collectable only if previous uterine surgery was declared).

Data will be automatically back-upped by Google Drive servers every time data are edited (inputted, modified, or deleted) and the history changes will be always accessible to the system administrator. To prevent accidental data loss due to accidental deletion, sync malfunctions, and hacking, data will be duplicated and stored in a different location twice a week (Monday 9:00 and Friday 18:00 GMT).

All data entered in the EDC system can be exported in formats compatible with the statistical analysis software to allow the planned analyses.

A data monitoring committee was not deemed necessary for the current study due to the following reasons: (1) we do not anticipate any disadvantage or risk in taking part in this research; (2) participation in the study is voluntary and women will be free to withdraw from the study at any time, continuing routinely obstetric care and (3) participation in the study will be temporally limited to the duration of pregnancy.

Data collection process

A senior obstetrician will perform the TVS as scheduled (figure 1), after inviting the woman to empty her bladder.

The assessment will include:

- The measurement of the IOD (first calliper on the internal cervical os and second calliper on the inferior edge of the placental tissue). In case of a marginal sinus, the distance between the internal cervical os and the marginal sinus will also be assessed.
- The cervical length.
- The placental edge thickness, measured within 1 cm from the meeting point between the basal and the chorionic plate. The placental edge will be considered 'thick' if this measurement is >1 cm or if the angle formed at the meeting point between the basal and the chorionic plate is >45°.

Figure 2 depicts how to assess the above-mentioned measurements.

Sample size considerations

The study by Wortman *et al*[13] included 53 women with low-lying placenta who were offered a vaginal birth. The authors identified a 58% rate of vaginal birth among women with an IOD >5 mm compared with 0% in women with an IOD ≤5 mm. No substantial differences in the rate of vaginal birth were observed in women with IOD of 6–10 mm, 11–15 mm and 16–20 mm.

In a recent publication, we reported that 77% of women with an IOD between 11 and 20 mm give birth vaginally when allowed to labour.[18] A similar rate (85%) was reported by a Jansen *et al* in their systematic review and meta-analysis.[19]

At the MBBM Foundation Onlus, approximately six women per year are found to have a low-lying placenta at the time of birth, one of whom has an IOD between 6 and 10 mm.[10 18]

A sample size of 30 women with an IOD >5 mm at the late third trimester TVS is needed at each participating maternity unit to reach a 95% statistical power with an alpha risk of 5% in assessing the primary outcome of the study. Since the incidence of low-lying placenta decreases from 2% in the second trimester to 0.4% at the end of pregnancy, 150 women should be recruited at each participating centre at the second trimester scan. A vaginal birth rate ≥60% in women with a low-lying placenta and an IOD of >5 mm will be considered appropriate to start routinely admitting to labour these women in clinical practice.

Statistical analyses

Data will be analysed using STATA/MP V.15.0 and SPSS V.26.0.

Descriptive statistics will be performed for all variables evaluated in the study population. Variables will be described by mean and SD if normally distributed, otherwise by median and IQR; proportions will be used for categorical variables.

Comparison among study groups, as defined by the IOD value assessed at the last TVS, will be performed by parametric and non-parametric tests for quantitative variables, whereas categorical variables will be compared using Pearson's χ^2 test or Fisher's exact test as appropriate.

The analyses for the primary outcome measure will be performed among women admitted to labour. A multivariate analysis will be conducted to assess the association between obstetric variables and birth outcomes.

A $p<0.05$ and a 95% CI not including the unit will be considered significant.

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Data analysis will last 6 months. Findings will be discussed with the contact person of each maternity unit before dissemination.

Patient and public involvement

Women were not involved.Women and their partners will be involved as participants after a detailed explanation of the study by a team researcher and will be fully informed about findings of the study.

We have planned to develop a Youtube information video to improve knowledge regarding low-lying placenta among women and their partners. In addition, we aim to produce education leaflets for expecting parents to raise awareness on normal birth and the importance of preventing a CS.

ETHICS AND DISSEMINATION

Ethical considerations

Developed as a consequence of the Declaration of Helsinki, Ethical Principles regarding the conduct of clinical research involving humans (World Medical Association-WMA, 1964) and of the Oviedo Convention (EU, 1997) are viewed as mandatory by the Italian NHS Research Ethics Committee.

Participants involved in this study will be fully informed about the aim of the research and will be asked to sign an individual written consent form. Women will be free to decline participation or to withdraw at any time. Data will be stored securely on laptops that will be password protected and at the completion of the study disposed of properly (Data Protection Code, 2003; GDPR, 2018).

Ethical approval for this study was obtained from the Brianza Ethics Committee (No 3157, 16 December 2019) prior to the commencement of the research. All respondents will be provided the name, telephone number and email of the principal investigator and the Institutional Review Board's contact details, in case of any question about the study.

Dissemination plan

The target audience for this study includes different stakeholders: clinicians, in particular obstetricians and midwives, policy-makers, healthcare managers, researchers, and the public, especially women in their reproductive age.

The findings from this study would make a significant contribution to the understanding of this controversial topic; information gathered from this study will inform clinical guidelines and healthcare policies, in order to promote an evidence-based practice and to improve the health of mothers and their neonates.

The dissemination plan includes the presentation of abstracts and findings at national and international scientific meetings, as well as the publication in peer-reviewed journals in the field of maternal and fetal medicine.

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Contributors SO and PV conceptualised the study, contributed to project development and critically revised the manuscript. EC contributed to the acquisition of data for the work, drafted and critically revised the manuscript. IVT and AA contributed to the acquisition of data for the work, edited and critically revised the manuscript. LA contributed to the design of the study and critically revised the manuscript. AL, AI, AP, IC, BB. EF, VS, MG, GV, SB, CB, AM, FL, CLP, EM, MC, LV, MS, FP, MP, MC, MV, GDM, AG, AP, CC, MB, SL, FP, CZ, VP, AC, EB, PA, LP, MT, FS, AM, FF and GC contributed to the acquisition of data for the work, revised critically the manuscript, gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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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 applicable.

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