UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE CIÊNCIAS MÉDICAS

RAFAEL DAVI BOTELHO

REPARO DA MIELOMENINGOCELE ATRAVÉS DA MINI-HISTEROTOMIA

FETAL MYELOMENINGOCELE REPAIR THROUGH A MINI-HYSTEROTOMY

CAMPINAS
2016

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Dissertação de Mestrado apresentada ao Programa de Pós-Graduação em Tocoginecologia da Faculdade de Ciências Médicas da Universidade Estadual de Campinas, UNICAMP, para obtenção do Título de Mestre em Ciências da Saúde, área de concentração em Saúde Materna e Perinatal.

Dissertation submitted to the Program of Obstetrics and Gynecology, Faculty of Medical Sciences, University of Campinas, UNICAMP, for obtain the title of Master in Health Sciences, in the concentration area of Maternal and Perinatal Health.

ORIENTADOR: CLEISSON FABIO ANDRIOLI PERALTA

ESTE EXEMPLAR CORRESPONDE À VERSÃO
FINAL DA DISSERTAÇÃO DEFENDIDA PELO
ALUNO RAFAEL DAVI BOTELHO, E ORIENTADO PELO
PROF. DR. CLEISSON FABIO ANDRIOLI PERALTA.

CAMPINAS

2016

Agência(s) de fomento e nº(s) de processo(s): Não se aplica.

Ficha catalográfica
Universidade Estadual de Campinas
Biblioteca da Faculdade de Ciências Médicas
Maristella Soares dos Santos - CRB 8/8402

B657r

Botelho, Rafael Davi, 1978-
Reparo da mielomeningocele através da mini-histerotomia / Rafael Davi Botelho. – Campinas, SP : [s.n.], 2016.

Orientador: Cleisson Fabio Andriolli Peralta.
Dissertação (mestrado) – Universidade Estadual de Campinas, Faculdade de Ciências Médicas.

1. Meningomielocele. 2. Feto - Cirurgia. 3. Disrafismo espinhal. 4. Defeitos do tubo neural. I. Peralta, Cleisson Fabio Andriolli. II. Universidade Estadual de Campinas. Faculdade de Ciências Médicas. III. Título.

Informações para Biblioteca Digital

Título em outro idioma: Fetal myelomeningocele repair through a mini-histerotomy
Palavras-chave em inglês:
Meningomyelocele
Fetus, Surgery
Spinal disrafism
Neural tube defects
Área de concentração: Saúde Materna e Perinatal
Titulação: Mestre em Ciências da Saúde
Banca examinadora:
Cleisson Fabio Andreoli Peralta
João Renato Bennini Junior
Mario Henrique Burlacchini de Carvalho
Data de defesa: 29-08-2016
Programa de Pós-Graduação: Tocoginecologia

BANCA EXAMINADORA DA DEFESA DE MESTRADO

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A ata de defesa com as respectivas assinaturas dos membros da banca examinadora encontra-se no processo de vida acadêmica do aluno.

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Dedico este trabalho...

À energia criadora universal pelo dom da vida, pela inquietação da busca, e por ser o sustentáculo desta busca de ser e fazer algo melhor...

Agradecimentos

Ao Prof. Dr. Cleisson Fabio Peralta, pelas oportunidades diárias, pelo aprendizado constante e dedicação sem a qual este momento não seria possível, mas sobretudo pela abnegação e caráter para com a medicina e para com os pacientes, exemplo a ser seguido em cada dia de nossa caminhada.

À companheira e amiga Karina Jorge Rodrigues da Costa, irmã de coração, pelo apoio e suporte ao longo de toda a trajetória.

Aos colegas Dr. Antônio De Sales, Fabrício Lamis, Vanessa Imada e Ronaldo Rossi, companheiros indispensáveis à conclusão deste projeto.

Aos meus familiares pelo incentivo diário.

Às pacientes pelo carinho e confiança.

A todos os companheiros do CAISM, do Programa de Pós-Graduação da FCM/Unicamp e do Hospital do Coração, pelo apoio incondicional à realização deste projeto.

Enfim, a todos os amigos que de alguma forma sempre estiveram ao meu lado.

Resumo

Objetivo: Avaliar a viabilidade técnica do reparo da mielomeningocele fetal através de uma mini-histerotomia e descrever os resultados perioperatórios e perinatais de nossa experiência inicial.

Materiais e Métodos: Estudo descritivo dos casos de correção MMC fetal através de mini-histerotomias realizadas entre 2014 e 2016.

Resultados: Quarenta e cinco mulheres foram submetidas à cirurgia fetal e 87% (39/45) dos fetos operados já nasceram. Uma correcção multicamada completa do defeito fetal foi possível em todos os casos. Não houve óbitos maternos, fetais ou neonatais. Não houve complicações maternas ou fetais durante ou após a correção MMC fetal até a alta hospitalar materna. A média de idade gestacional (IG) no momento da cirurgia foi de 24,5 semanas (DP: 1,7; variação: 20,7-26,9). O comprimento médio da histerotomia foi de 3,05 cm (DP: 0,39; intervalo: 2,50-3,50). Apenas uma paciente (1/39 - 2,6%) apresentou uma separação corioamniótica. Nove pacientes (9/39 - 23,1%) tiveram ruptura prematura de membranas em uma IG mediana de 34,1 semanas (variação: 31,1-36,0). A IG média no parto foi de 35,3 semanas (DP: 2,2; variação: 27,9-39,1). Noventa e cinco por cento (37/39) das pacientes apresentou a histerorrafia intacta no momento do parto. A colocação de derivação ventrículo-peritoneal foi necessária em 7,7% (3/39) dos recém-nascidos.

Conclusão: O reparo da MMC fetal é viável através de uma mini-histerectomia. Esta abordagem parece estar associada com riscos reduzidos de parto muito pré-termo e complicações maternas, fetais e neonatais.

Palavras-chave: mielomeningocele fetal, cirurgia fetal, reparação da mielomeningocele, defeitos do tubo neural, cirurgia fetal aberta, disrafismo espinhal.

Abstract

Objective: To present the thecnical feasibility of fetal myelomeningocele (MMC) repair through a mini-hysterotomy and to describe the perioperative and perinatal results from our initial experience.

Methods: Descriptive study of cases of fetal MMC correction via mini-hysterotomies performed between 2014 and 2016.

Results: Forty-five women underwent fetal surgery and 87% (39/45) have already delivered. A complete multilayer correction of the fetal defect was possible in all of the cases. There were no maternal, fetal or neonatal deaths. No maternal or fetal complications occurred during or after fetal MMC correction until maternal hospital discharge. Average gestational age (GA) at surgery was 24.5 weeks (SD: 1.7; range: 20.7 – 26.9). The median hysterotomy length was 3.05 cm (SD: 0.39; range: 2.50 – 3.50). Only one patient (1/39 – 2.6%) experienced chorioamniotic separation. Nine patients (9/39 – 23.1%) had premature preterm rupture of membranes at a median GA of 34.1 weeks (range: 31.1 – 36.0). Average GA at delivery was 35.3 weeks (SD: 2.2; range: 27.9 – 39.1). Ninety-five percent (37/39) of our patients had an intact hysterorrhaphy site at delivery. Ventriculoperitoneal shunt placement was necessary for 7.7% (3/39) of the neonates.

Conclusion: Fetal MMC repair is feasible through a mini-hysterotomy. This approach appears to be associated with reduced risks of very preterm delivery and maternal, fetal and neonatal complications.

Keywords: fetal myelomeningocele, fetal surgery, myelomeningocele repair, neural tube defects, open fetal surgery, spinal disrafism.

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Siglas e Abreviaturas

MMC	–	Mielomeningocele, Myelomeningocele
RPMPT (PPTRM)	–	Ruptura Prematura de Membranas Pré-Termo (Premature Preterm membrane rupture)
TPPT	–	Trabalho de Parto Pré-Termo
DTN (NTD)	–	Defeito do Tubo Neural (Neural Tube defect.)
DP (SD)	–	Desvio Padrão (Standard Deviation)
IG (GA)	–	Idade Gestacional (Gestational Age)
HCOR	–	Hospital do Coração
RDB	–	Rafael Davi Botelho
VI	–	Vanessa Imada
KJRC	–	Karina Jorge Rodrigues da Costa
RRJ	–	Ronaldo Rossi Junior
AAFS	–	Antônio Afonso Ferreira de Salles
CFAP	–	Cleisson Fabio Andrioli Peralta

Sumário

1. Introdução

A disrafia espinhal aberta ou mielomemingocele (MMC) é uma malformação grave do sistema nervoso central para a qual não existe cura definitiva e que ocorre em cerca de 1/1000 recém-nascidos no Brasil. Trata-se de uma doença caracterizada por protrusão de meninges, raízes nervosas e medula através de uma abertura no arco vertebral, o que pode levar à paralisia dos membros inferiores, diferentes graus de restrição no desenvolvimento intelectual, disfunções intestinais, gênito-urinárias e ortopédicas.[1-5]

A etiologia e a fisiopatologia da doença são pouco conhecidas. No entanto, sabe-se que inicialmente ocorre um defeito primário de fechamento do tubo neural, com exposição do tecido nervoso ao ambiente intrauterino. Sem a proteção de uma pele normal, este tecido nervoso sofre dano secundário pela exposição ao líquido amniótico e trauma contra a parede uterina. A lesão na coluna, medula e raízes nervosas leva à tração do tronco cerebral contra o forame magno (Malformação de Chiari II), o que dificulta a circulação liquórica no sistema ventricular cerebral, levando a ventriculomegalia, que ocorre em aproximadamente 85% das crianças afetadas.[6,7]

Classicamente, a correção da MMC é feita logo após o nascimento. Aproximadamente 80% das crianças operadas no período neonatal necessitam da colocação de drenos ventrículo-peritoneais com intuito de impedir a piora da ventriculomegalia cerebral e assim minimizar o comprometimento no desenvolvimento intelectual.[6-10] No entanto, aproximadamente 45% das crianças que necessitam da colocação de drenos têm complicações subsequentes (obstruções, deslocamento dos drenos e infecções), o que acarreta trocas sucessivas destes drenos e piora progressiva da capacidade intelectual destes indivíduos.[6-10] As alterações cerebrais mencionadas e as complicações de seu tratamento (em especial a necessidade de colocação de drenos e a obstrução destes) são responsáveis por óbito de até 15% dessas crianças até o 5º ano de vida.[6-10]

Há pouco mais de uma década, tem sido proposta a correção intrauterina da MMC. Vários foram os motivos que levaram ao desenvolvimento deste procedimento. Como mencionado anteriormente, o dano neurológico na MMC é primariamente devido a uma anormalidade no desenvolvimento do tubo neural durante o período embrionário. No entanto, a exposição crônica deste tecido nervoso ao ambiente intrauterino (liquido amniótico, trauma contra a parede do útero, pressão hidrodinâmica sobre o tecido nervoso sem a proteção de uma pele normal) piora a lesão neurológica. Esta teoria é chamada de teoria das duas agressões (*the two-hit hypothesis*)[11-14], sendo várias as observações que a suportam.[11-14] Alguns estudos sobre avaliação histológica desses defeitos de fechamento da coluna demonstram que o tecido nervoso exposto diretamente ao líquido amniótico (medula, meninges e raízes nervosas) apresenta diferentes graus de perda de tecido neural, ao mesmo tempo que as porções menos expostas (cornos ventrais e dorsais, especialmente das porções proximais da lesão) têm aspecto histológico normal. Além disso, vários estudos observacionais têm demonstrado que grande parte dos fetos com MMC que apresentam movimentos em membros inferiores em exames ultrassonográficos, não apresentam função motora logo após o nascimento.[11-14] Estes aspectos reforçam a teoria das duas agressões e suportam a racionalidade da correção pré-natal da MMC. O fechamento intrauterino do defeito tem a finalidade de minimizar a segunda agressão, minimizando a exposição do tecido nervoso ao ambiente uterino, e assim melhorar o prognóstico neurológico dessas crianças.

Após uma série de estudos experimentais que demonstraram reversão do Chiari II em modelos animais com MMC operadas intrautero,[15-18] foram iniciados estudos em seres humanos. Inicialmente, algumas séries de casos demonstraram redução significativa da necessidade de colocação de drenos ventrículo-peritoneais após o nascimento nas crianças que haviam sido operadas no período pré-natal, principalmente pela reversão intrauterina do Chiari II.[19-24] Estes resultados positivos levaram ao desenvolvimento de um ensaio clinico randomizado nos Estados Unidos da América, chamado de *MOMs trial (Management of Myelomeningocele study),* cujos resultados foram publicados no periódico *The New England Journal of Medicine*, em 2011.[25] Neste estudo, 183 gestantes cujos fetos apresentavam MMC foram randomizadas para o tratamento intrauterino (correção da MMC através de

histerotomia – abertura no útero) ou para o tratamento pós-natal (grupo controle - conduta expectante durante a gestação e correção da MMC no neonato). Os principais critérios para inclusão das pacientes neste estudo foram: idade gestacional entre 18 e 26 semanas, MMC com nível superior da lesão entre T1 (primeira vértebra torácica) e S1 (primeira vértebra sacral), ausência de outras malformações fetais graves ou anomalias cromossômicas, presença de Chiari II e ausência de tortuosidades graves na coluna fetal. O estudo necessitou ser finalizado após o recrutamento de 183 gestantes pois a análise estatística intermediária demonstrou resultados neurológicos significativamente melhores para as crianças operadas no pré-natal através de uma cirurgia aberta para o reparo intrauterino da MMC, em comparação àquelas que foram tratadas após o nascimento.[25,26]

A correção do defeito no feto era feita através de histerotomia corporal de 6 a 10 cm de comprimento, com finalidade de permitir adequada exposição da lesão fetal para que o neurocirurgião pudesse realizar a clássica cirurgia de fechamento por camadas da MMC. Houve significativa redução na necessidade de instalação de drenos ventrículo-peritoneais no grupo da cirurgia fetal (40%) em relação às crianças operadas após o nascimento (82%), devido à reversão do Chiari II ainda na vida fetal,[25] e melhora pontuações neurológicas globais e motoras de lactentes[26]. O grupo das crianças submetidas à cirurgia intrauterina também apresentou, até o seguimento de 30 meses, significativo aumento na chance de deambular sem uso de órteses e melhora significativa no desenvolvimento intelectual, quando comparado ao grupo de crianças que foram operadas após o nascimento. [26]

Apesar dos resultados favoráveis para a criança, a cirurgia fetal foi acompanhada de algumas complicações maternas controláveis, mas não negligenciáveis. As mais frequentemente observadas foram a RPMPT (46%), o TPPT (38%), deiscência completa ou parcial da histerotomia observada no momento da resolução da gravidez (30%), separação cório-amniótica (26%), necessidade de transfusão sanguínea materna no parto (9%), edema agudo de pulmão (6%) após a cirurgia fetal e descolamento prematuro de placenta (6%) durante a cirurgia fetal. Essas complicações acabaram por limitar a difusão da cirurgia fetal para

mielomeningocele em todo o mundo.[25]

A cirurgia aberta para MMC fetal, classicamente realizada através da histerotomia corporal de 6 a 10 cm, permite a correção em multicamadas do DTN, conforme realizada no pós-natal [26-31]. Com o objetivo de minimizar o acesso necessário para a correção da disrafia fetal e, portanto, diminuir a morbidade materna, alguns grupos têm testado a abordagem endoscópica [32-37]. No entanto, os resultados neurológicos após estes procedimentos aparentemente menos invasivo não são bem conhecidos, e as taxas de RPMPT, parto prematuro e deiscência da cicatriz fetal / neonatal requerendo reoperação pós-natal, são ainda muito elevados.[32-37]

Tendo em vista que os resultados adversos maternos são as maiores preocupações referentes à abordagem intrauterina da correção fetal da disrafia espinhal, inovações técnicas com intuito de minimizar estas complicações seriam bem-vindas. Assim, sendo, descrevemos uma modificação da cirurgia aberta clássica para MMC fetal, em que a mesma correção multicamada do defeito da coluna vertebral é realizada através de uma histerotomia de 2,5 - 3,5 cm. Os principais objetivos deste estudo são avaliar a viabilidade téncica desta abordagem, os resultados perioperatórios e perinatais de nossa experiência inicial.

2. Objetivos

2.1. Geral:

Avaliar a viabilidade técnica do reparo da mielomeningocele fetal através de uma mini-histerotomia e descrever os resultados perioperatórios e perinatais de nossa experiência inicial.

2.2. Específicos:

Descrever a viabilidade técnica da correção da mielomeningocele fetal através da mini-histerotomia.

Descrever os resultados perioperatórios associados à correção da mielomeningocele fetal através da mini-histerotomia.

Descrever os resultados perinatais após a correção da mielomeningocele fetal através da mini-histerotomia.

3. Artigo

Artigo enviado para a revista Fetal Diagnosis and Therapy

From: <fdt@karger.com>

Subject: Fetal Diagnosis and Therapy Submission Received

Date: 11 de junho de 2016 18:42:04 BRT

To: <botelhord@gmail.com>

Dear Dr. Rafael Davi Botelho:

Dr. Cleisson Peralta has submitted a manuscript entitled "Fetal myelomeningocele repair through a mini-hysterotomy.", in which you are listed as co-author, to "Fetal Diagnosis and Therapy".

The submission will now be checked by the editorial office, and Dr. Cleisson Peralta will receive a confirmation mail from the editorial office soon.

With kind regards,

Editorial Office

From: <fdt@karger.com>

Date: Sat, Jun 11, 2016 at 6:42 PM

Subject: Fetal Diagnosis and Therapy Submission Received

To: cfaperalta@gmail.com

Dear Dr. Cleisson Peralta:

Thank you for submitting your manuscript entitled "Fetal myelomeningocele repair through a mini-hysterotomy." to "Fetal Diagnosis and Therapy"; the submission number is: 7323. Your submission will now be checked by the editorial office. Once this has been done, you will receive a confirmation mail from the editorial office.

If you have any queries please send an email to: fdt@karger.com.

With kind regards,

Editorial Office

Fetal myelomeningocele repair through a mini-hysterotomy.

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Running head: Mini-hysterotomy for myelomeningocele repair

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ABSTRACT

Objective*:* To present the thecnical feasibility of fetal myelomeningocele (MMC) repair through a mini-hysterotomy and to describe the perioperative and perinatal results from our initial experience.

Methods: Descriptive study of cases of fetal MMC correction via mini-hysterotomies performed between 2014 and 2016.

Results*:* Forty-five women underwent fetal surgery and 87% (39/45) have already delivered. A complete multilayer correction of the fetal defect was possible in all of the cases. There were no maternal, fetal or neonatal deaths. No maternal or fetal complications occurred during or after fetal MMC correction until maternal hospital discharge. Average gestational age (GA) at surgery was 24.5 weeks (SD: 1.7; range: 20.7 – 26.9). The median hysterotomy length was 3.05 cm (SD: 0.39; range: 2.50 – 3.50). Only one patient (1/39 – 2.6%) experienced chorioamniotic separation. Nine patients (9/39 – 23.1%) had premature preterm rupture of membranes at a median GA of 34.1 weeks (range: 31.1 – 36.0). Average GA at delivery was 35.3 weeks (SD: 2.2; range: 27.9 – 39.1). Ninety-five percent (37/39) of our patients had an intact hysterorrhaphy site at delivery. Ventriculoperitoneal shunt placement was necessary for 7.7% (3/39) of the neonates.

Conclusion*:* Fetal MMC repair is feasible through a mini-hysterotomy. This approach appears to be associated with reduced risks of very preterm delivery and maternal, fetal and neonatal complications.

Key words: fetal myelomeningocele, fetal surgery, myelomeningocele repair, neural tube defect, open fetal surgery, spinal dysraphism.

Introduction

Recent studies have demonstrated that infants who undergo an in-utero repair of a myelomeningocele (MMC) through an open surgery have better neurological outcomes than those who are treated after birth [1]. The fetal operation significantly reduces the need for postnatal ventriculoperitoneal shunting and improves infants' global and motor neurological scores [1]. Maternal morbidity is not negligible in the fetal treatment group, as observed by high rates of premature preterm rupture of membranes (PPTRM), preterm labor, chorioamniotic separation, dehiscence of the hysterorrhaphy and the need for maternal transfusion at delivery [1].

Classically, open surgery for fetal MMC is performed through a 6 – 10 cm hysterotomy to allow for the multilayer correction of the neural tube defect (NTD) as would be performed postnatally [1-6]. With the purpose of minimizing access to the fetus and therefore decreasing maternal morbidity, some research groups have tested an endoscopic approach [7-12]. However, neurological outcomes after these apparently less invasive procedures are not well known, and the rates of PPTRM, preterm delivery and dehiscence of fetal/neonatal scars requiring postnatal reoperation are still very high.

We describe a modification of the classic open surgery for fetal MMC in which the same multilayer correction of the spinal defect is performed through a 2.5 – 3.5 cm hysterotomy. The main purposes of this study are to present the feasibility and technical details of this approach and to describe the perinatal results from our initial experience.

Material and Methods

This is a descriptive study of consecutive cases of fetal MMC correction via mini-hysterotomies performed at The Heart Hospital – São Paulo - Brazil between October 2014 and April 2016. All women eligible for fetal surgery were thoroughly educated about the benefits and disadvantages of both fetal and neonatal corrections of the MMC. The patients who opted for the fetal treatment were aware of the technical modifications proposed by our multidisciplinary team and signed a specific informed

consent form before the surgery. The ethics committee for medical research at The Heart Hospital approved this study.

The inclusion criteria for fetal surgery were as follows: 1. Singleton pregnancy; 2. Gestational age (GA) from 18^{+0} to 26^{+6} weeks; 3. MMC with an upper anatomical level from T1 to S1 and the presence of a Chiari II malformation; 4. No chromosomal abnormality or fetal anatomical defect other than the MMC and associated alterations; 5. No previous history of prematurity or a short cervix of less than 25 mm in size during the current pregnancy; 6. No fetal scoliosis of more than 30^{0}; 7. Easy access to the tertiary referring center for follow-up and/or emergency assistance after fetal surgery; 8. No serious maternal disease that could significantly increase the surgical risk; and 9. No positive maternal serology for HIV or hepatitis B and C.

All of the surgeries were performed by the same multidisciplinary team (RDB, VI, KJRC, RRJ, AAFS and CFAP) according to the following steps: 1. Maternal anesthesia was induced by thiopental, fentanyl and rocuronium. 2. A Pfannestiel incision was performed, and the uterus was dislodged from the abdominal cavity. 3. The fetus was gently moved by external manipulation guided by ultrasound so that the spinal defect was located against the uterine wall free of the placenta; until adequate fetal positioning was achieved, low doses of midazolan and remifentanil were used to maintain the uterine tone and maternal-fetal anesthesia. 4. A 2.5 – 3.5 cm hysterotomy was performed with an electric blade at least 2 cm away from the border of the placenta, above the fetal defect. The membranes were sutured to the inner layer of the myometrium and a neonatal Ankeney® retractor (Schobell Industrial, Rio Claro, SP, Brazil) was used to hold the hysterotomy walls (Figure 1). At this stage, midazolam was replaced by inhaled sevoflurane, and the remifentanil infusion was readjusted. Uterine relaxation was optimized by the use of nitroglycerin, and from this moment, maternal haemodynamics were carefully controlled by fluid infusion and the use of inotropic agents. Fetal heart rate was continuously monitored by ultrasound, and an umbilical artery Doppler was checked throughout the procedure. 5. Two neurosurgeons operated on the fetus using a microscope while one of the fetal medicine specialists carefully held and manipulated the fetus to properly expose the

MMC (Figure 2). Because the size of the MMC was often larger than the hysterotomy orifice, the fetus had to be constantly and carefully moved so that a specific portion of the lesion could be observed by the neurosurgeons. 6. The neural placode was dissected, and the defect was closed in separate layers (Figure 2). 7. Uterine suture was performed in two layers (Figure 2), and before the last stitch was tightened, the physiologic solution was returned to the amniotic cavity until the amount of fluid was considered normal according to ultrasound. 8. After the surgery, the patient was kept in the intensive care unit for at least 12 hours and then transferred to a common infirmary, where she was kept under observation for at least three days. 9. Nifedipine (20 mg tid) and vaginal progesterone (200 mg) were used from the end of the surgery until delivery.

After hospital discharge, the patient was maintained in close proximity to the institution where delivery was planned to occur, and the patient was evaluated every two weeks by a maternal-fetal medicine specialist until the end of the pregnancy.

The following variables were evaluated: maternal and fetal characteristics at the time of surgery, such as maternal and gestational ages; previous history of neural tube defects; parity; body mass index; upper level position of the MMC; the presence of ventriculomegaly, inferior limb deformity and normal movements (subjective evaluation); the size of the lateral ventricle; and placental position. Perioperative variables, such as the hysterotomy length (incision size); total operative time (maternal skin-to-skin); duration of the fetal surgery; the occurrence of maternal and/or fetal complications during and/or after the surgery; and total length of stay in the hospital. Variables obtained from the maternal hospital discharge after fetal surgery until delivery included changes in the fetal ventricle size; the reversal of the Chiari II malformation; the presence of fetal inferior limb deformities and movements (subjective evaluation); the occurrence of chorioamniotic separation, fetal death and PPTRM; GA at PPTRM; and the time intervals between fetal surgery and birth and between PPTRM and delivery. Peripartum variables included GA at the time of delivery; the occurrence of maternal and/or fetal complications during the caesarean section; the condition of the hysterorrhaphy site; and the neonatal Apgar scores and weight. Neonatal variables until hospital discharge, such as the condition of the scar at the MMC repair site; the

results of the transfontanelar ultrasound and/or brain MRI scans; the need for ventriculoperitoneal shunting; global and motor neurological status; the occurrence of neonatal death or any other complication; and total length of stay in the hospital were recorded.

Fetal ventriculomegaly was diagnosed when the width of the lateral ventricle at the level of the parieto occipital fissure was greater than 10 mm. The largest measurement between the two sides was considered for analysis. During the follow-up after fetal surgery, a significant change was defined as a difference of more than 1 mm in the lateral ventricle diameter from the time of surgery to the last ultrasound evaluation before delivery.

A complete reversal of the fetal Chiari II malformation after MMC repair was recorded when both normal anatomy and measurements of the cerebellum (transverse cerebellar diameter and craniocaudal diameter of the vermis) were obtained by ultrasound. In addition, the cerebellum and the pons were required to be located completely above the foramen magnum in a midsagittal view of the brain, and the cisterna magna had to be measurable in a standard suboccipital view. A partial reversal of the Chiari II malformation was defined when the cerebellum fastigium was visible above the foramen magnum in a midsagittal view by ultrasound but portions of the cerebellum could still be observed below the level of the foramen magnum. In addition, improved visualization of the transverse cerebellum anatomy in relation to the preoperative image was required. The cisterna magna was obliterated and therefore was not measurable.

Continuous variables were described using averages and standard deviations (SD) or medians and ranges when appropriate, and categorical data were described using absolute and relative frequencies. The Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA), version 21.0, was used for the analyses.

Results

During the study period, 45 women underwent fetal surgery for MMC through a mini-hysterotomy. A complete multilayer correction of the fetal defect was possible in all of the cases. No maternal or fetal complications occurred during or after fetal MMC correction until maternal hospital discharge, apart from one case (1/45 – 2.2%) of pneumonia that was most likely acquired prior to maternal admission. Two patients (2/45 – 4.4%) reported a previous sibling with NTD. At the time of this analysis, 39 women (39/45 – 86.6%) had delivered. Maternal and fetal characteristics at the time of MMC repair are described in table 1. Considering all of the cases, the mean GA at surgery was 24.5 weeks (SD: 1.7; range: 20.7 – 26.9). The most frequently observed upper anatomical levels of the lesions were from L1 to L4. Thirty-two fetuses (32/45 – 71.1%) exhibited ventriculomegaly, and the average lateral ventricle diameter was 11.4 mm (SD: 3.1; range 4.0 – 20.0). The majority of the fetuses (34/45 – 77.8%) had apparently normal inferior limb movements, and 42.2% (19/45) presented with inferior limb deformities, mainly clubfoot.

The perioperative variables were similar considering all of the patients and only those who have delivered. The median hysterotomy length was 3.05 cm (SD: 0.39; range: 2.50 – 3.50). The total operative time and time taken to perform the MMC repair were 3.44 h (SD: 0.71; range: 1.50 – 4.57) and 1,90 h (SD: 0,72; range: 0.50 – 3.50), respectively. The average maternal length of stay in the hospital was 3.55 days (SD: 1.56; range: 4 – 11).

Variables obtained from maternal hospital discharge after fetal surgery to delivery are presented in table 2. There were no fetal demises and only one patient (1/39 – 2.6%) experienced chorioamniotic separation, which was not followed by olygohydramnios. There was a decrease or stabilization in the fetal cerebral lateral ventricle size in 22 cases (22/39 – 56.4%), and 34 fetuses (34/39 – 87.1%) exhibited a complete or partial reversal of the Chiari II malformation. The average time interval from fetal surgery to delivery was 10.9 weeks (SD: 2.3; range: 5.7 – 17.9). Nine patients (9/39 – 23.1%) had PPTRM at a median GA of 34.1 weeks (range: 31.1 – 36.0). No patients delivered more than one week after the rupture of the membranes.

Peripartum variables are presented in table 3. All deliveries occurred by caesarean section at an average GA of 35.3 weeks (SD: 2.2; range: 27.9 – 39.1). The indications for delivery included signs of labor and/or rupture of membranes in 36 patients (36/39 – 92.3%), severe pre-eclampsia in two patients (2/39 – 5.2%) and placental abruption in one patient (1/39 – 2.6%). There were no fetal or neonatal deaths and no cases of maternal bleeding requiring transfusion.

The neonatal variables until hospital discharge are displayed in table 4. All neonates survived, and the median length of stay in the hospital was 5 days (range: 2 - 75). Two neonates (2/39 – 5.1%) exhibited partial skin dehiscence at the repair site with no fluid leakage; one neonate required complementary repair. Thirty-seven neonates (37/39 – 94.9%) underwent transfontanellar ultrasound and/or MRI scans. Information about the Chiari II malformation obtained by MRI was available for 35 neonates. Complete and partial reversal of the Chiari II malformation was observed in 33.3% (13/39) and 43.6% (17/39) of cases, respectively. Ventriculoperitoneal shunt placement was necessary for 7.7% (3/39) of the neonates. Unilateral or bilateral clubfoot and normal inferior limb movements and strength were observed in 22 (22/39 – 56.4%) and 18 (18/39 - 46.2%) neonates, respectively. Five neonates (5/36 – 12.8%) presented with neurogenic bladder, and one neonate had necrotizing enterocolitis requiring segmental enterectomy.

Discussion

This study demonstrated that fetal MMC repair through a mini-hysterotomy is feasible and safe for the mother, the fetus and the neonate.

The rationale for fetal MMC correction originated in the two-hit hypothesis, which proposes that the neurological damage of this disease is primarily due to abnormal embryonic development followed by chronic exposure of the neural tissue to the intrauterine environment [13-15]. This theory has led to a series of experimental studies in animals and humans, which demonstrated in-utero reversal of the Chiari II malformation after fetal NTD correction [16-19].

The assumption that fetal MMC correction could improve postnatal neurological outcomes compared to neonatal surgery was confirmed by the results of the MOMs trial (Management of Myelomeningocele study) [1]. After a 30-month follow-up period, a significant reduction in the need for ventriculoperitoneal shunting was observed in the fetal surgery group (40%) in comparison to children undergoing surgery after birth (82%), due to prenatal reversal of the Chiari II malformation. Children who underwent intrauterine surgery had a significantly higher chance of walking independently and a significant improvement in neurological scores when compared to children undergoing operations in the neonatal period. Despite the presence of favorable outcomes for the children, prenatal surgery was associated with a higher maternal morbidity, evidenced by the rates of PPTRM (46%), preterm labor (38%), complete or partial dehiscence of the hysterorrhaphy (30%), chorioamniotic separation (26%), the need for maternal blood transfusion at delivery (9%) and acute pulmonary edema (6%).

Focusing mainly on the reduction of maternal morbidity, we aimed to minimize the size of the hysterotomy so that the NTD could be repaired as was performed in the MOMs trial. The main differences in fetal access were the size of the hysterotomy (present study: 2.5 – 3.5 cm; MOMs trial: 6.0 to 10 cm) and the fact that we did not use staplers to secure the borders of the hysterotomy. Instead, after the myometrium was incised using an electric blade, the membranes were attached to the inner third of the incised tissue using a running suture.

We compared our data (39 cases with neonatal results) to data from the post-MOMs experience, which focused on the perinatal results rather than on a longer-term follow-up of the infants. Our inclusion criteria for fetal MMC repair were comparable, as were most of the maternal and fetal characteristics at the time of fetal surgery, summarized as follows (present series x post-MOMs experience): average GA at surgery (23.3 x 24.5 weeks); most frequent upper level of the MMC (L1 – L4: 74.2% x 87.0%); average size of the larger lateral cerebral ventricle (11.3 x 10.6 mm); and presence of talipes (38.5% x 15.0%).

In terms of perioperative variables, there were differences in total operative time (3.44 x 1.31 h), the frequency of patch use (0.0% x 20%) and the need for fetal resuscitation (0.0% x 5.0%). Most likely, the longer operative time in the current study reflected our decision to not use staplers and patches. This decision could support our purpose to demonstrate that fetal MMC correction is feasible through a smaller hysterotomy, even for more challenging (larger) defects. One observation that we cannot fully explain is the lack of cases requiring fetal resuscitation in our series.

Concerning the variables evaluated from the time of maternal hospital discharge to delivery, the rates of PPTRM (23.1% x 32.3%) and chorioamniotic separation (2.6% x 22.9%) were lower in the current study. This finding can be attributed to not only the size of the hysterotomy but also to the way in which the membranes are attached to the myometrium. In the current study, 22 (22/39 - 56%) fetuses experienced a decrease or stabilization in the lateral ventricle size, and 34 (34/39 - 87.1%) exhibited a complete or partial reversal of the Chiari II malformation.

Despite a similar average GA at delivery (35.3 x 34.3 weeks), the distribution of deliveries according to GA intervals was different. The rate of late preterm deliveries (after 34 complete weeks) was higher in the current study (82.2 x 54.2%), and only 5.1% (2/39) of our patients delivered before 32 weeks (one at 27.9 weeks, and the other at 31.9 weeks). In the post-MOMs evaluation, there were four (4/96 – 4.2%) extreme preterm deliveries, which occurred two weeks after the fetal MMC repair. In the present study, similar to the post-MOMs evaluation, the average time interval between fetal surgery and birth was approximately 11 weeks. However, none of our patients delivered less than 5.7 weeks after the MMC repair. Two other aspects that deserve recognition are perinatal mortality and dehiscence at the hysterotomy site observed at delivery. In the current study, there were no perinatal deaths (versus 6.1% in the post-MOMs experience) and 94.9% (37/39) of our patients had an intact hysterotomy site at delivery (versus 50.6 in the post-MOMs experience). The impact of the lower incidence of uterine scar dehiscence on future pregnancies is unknown.

The only important difference in the neonatal variables was the rate of ventriculoperitoneal shunt placement prior to hospital discharge, which was higher in the current study than in the post-MOMs evaluation (7.7% x 2.4%). Interestingly, the rates of complete or partial reversal of the Chiari II malformation on the MRI scans in both studies were similar (76.9% x 79.5%). One explanation could be that in in the present study, the neonates were followed by different neurology teams using different criteria for the indication of ventriculoperitoneal shunting. The values in the current study are still within an acceptable shunt rate, which will be re-evaluated in at least 30 months to determine if it approaches the results reported in the MOMs trial.

The frequency of major adverse events, such as maternal pulmonary edema, the need for maternal transfusion at the time of fetal surgery or delivery, the need for fetal resuscitation, or the incidence of fetal or neonatal death, was 17 among 100 cases in the post-MOMs experience, whereas only one (1/39 – 2.6%) of our patients experienced placental abruption close to the time of delivery.

The main weaknesses of our study are the small number of patients, the short follow-up period and uneven criteria for ventriculoperitoneal shunting.

In conclusion, we propose that fetal MMC repair is feasible through a mini-hysterotomy. This approach appears to be associated with reduced risks of very preterm delivery and maternal, fetal and neonatal complications when compared to the classical hysterotomy procedure for fetal MMC repair.

Acknowledgement

This study was sponsored by the Charity Project Fetal Cardiology PROADI, NHS, Ministry of Health, Brazil.

References

1. Adzick NS, Thom EA, Spong CY, Brock III JW, Burrows PK, Johnson MP, Howell LJ, Farrell JA, Dabrowiak ME, Sutton LN, Gupta N, Tulipan NB, D'Alton ME, Farmer

DL, for the MOMS Investigators. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med 2011; 364:993-1004.

2. Tulipan N, Hernanz-Schulman M, Bruner JP. Reduced hindbrain herniation after intrauterine myelomeningocele repair: a report of four cases. Pediatr Neurosurg 1998; 29:274–278.
3. Adzick NS, Sutton LN, Crombleholme TM, Flake AW. Successful fetal surgery for spina bifida. Lancet 1998; 352:1675–1676.
4. Sutton LN, Adzick NS, Bilaniuk LT, Johnson MP, Crombleholme TM, Flake AF. Improvement in hindbrain herniation by serial fetal MRI following fetal surgery for myelomeningocele. J Am Med Assoc 1999; 282:1826–1831.
5. Bruner JP, Tulipan N, Paschall RL, et al. Intrauterine repair of myelomeningocele, 'hindbrain restoration' and the incidence of shunt-dependent hydrocephalus. J Am Med Assoc 1999; 282:1819–1825.
6. Johnson MP, Adzick NS, Rintoul N, et al. Fetal myelomeningocele repair: shortterm clinical outcomes. Am J Obstet Gynecol 2003; 189:482–487.
7. Bruner JP, Tulipan NB, Richards WO. Endoscopic coverage of fetal open myelomeningocele in utero. Am J Obstet Gynecol 1997; 176:256–257.
8. Pedreira DA, Zanon N, de Sá RA, Acacio GL, Ogeda E, Belem TM, Chmait RH, Kontopoulos E, Quintero RA. Fetoscopic single-layer repair of open spina bifida using a cellulose patch: preliminary clinical experience. J Matern Fetal Neonatal Med. 2014; 27:1613-1619
9. Kohl T. Percutaneous minimally invasive fetoscopic surgery for spina bifida aperta. Part I: surgical technique and perioperative outcome. Ultrasound Obstet Gynecol. 2014; 44:515-524.
10. Degenhardt J, Schürg R, Winarno A, Oehmke F, Khaleeva A, Kawecki A, Enzensberger C, Tinneberg HR, Faas D, Ehrhardt H, Axt-Fliedner R, Kohl T. Percutaneous minimal-access fetoscopic surgery for spina bifida aperta. Part II: maternal management and outcome. Ultrasound Obstet Gynecol. 2014; 44:525-531.
11. Graf K, Kohl T, Neubauer BA, Dey F, Faas D, Wanis FA, Reinges MH, Uhl E, Kolodziej MA. Percutaneous minimally invasive fetoscopic surgery for spina bifida aperta. Part III: neurosurgical intervention in the first postnatal year. Ultrasound Obstet Gynecol. 2016; 47:158-161.
12. Pedreira DA, Zanon N, Nishikuni K, Moreira de Sá RA, Acacio GL, Chmait

RH, Kontopoulos EV, Quintero RA. Endoscopic surgery for the antenatal treatment of myelomeningocele: the CECAM trial. Am J Obstet Gynecol. 2016 ; 214:111.e1-111.e11.

13. Meuli M, Meuli-Simmen C, Hutchins GM, Seller MJ, Harrison MR, Adzick NS. The spinal cord lesion in human fetuses with myelomeningocele: implications for fetal surgery. J Pediatr Surg 1997; 32:448–452.
14. Korenromp MJ, Van Good JD, Bruinese HW, Kriek R. Early fetal movements in myelomeningocele. Lancet 1986; 1:917–918.
15. Sival DA, Begeer JH, Staal-Schreinemachers AL, Vos-Niel JM, Beekhuis JR, Prechtl HF. Perinatal motor behaviour and neurological outcome in spina bifida aperta. Early Hum Dev 1997; 50:27–37.
16. Meuli M, Meuli-Simmen C, Yingling CD, et al. Creation of myelomeningocele in utero: a model of functional damage from spinal cord exposure in fetal sheep. J Pediatr Surg 1995; 30:1028–1032.
17. Meuli M, Meuli-Simmen C, Hutchins GM, et al. In utero surgery rescues neurologic function at birth in sheep with spina bifida. Nat Med 1995; 1:342–347.
18. Meuli M, Meuli-Simmen C, Yingling CD, et al. In utero repair of experimental myelomeningocele saves neurologic function at birth. J Pediatr Surg 1996; 31:397–402.
19. Bouchard S, Davey MG, Rintoul NE,Walsh DS, Rorke LB, Adzick NS. Correction of hindbrain herniation and anatomy of the vermis after in utero repair of myelomeningocele in sheep. J Pediatr Surg 2003; 38:451–8.
20. Moldenhauer JS, Soni S, Rintoul NE, Spinner SS, Khalek N, Martinez-Poyer J, Flake AW, Hedrick HL, Peranteau WH, Rendon N, Koh J, Howell LJ, Heuer GG, Sutton LN, Johnson MP, Adzick NS. Fetal myelomeningocele repair: the post-MOMS experience at the Children's Hospital of Philadelphia. Fetal Diagn Ther. 2015; 37:235-240.

Table 1. Maternal and fetal characteristics at the time of myelomeningocele repair

Maternal characteristics		
	All cases n = 45	Delivered n = 39/45 (86.6%)
Age, years – Average (SD); range	29.6 (5.7); 18.2 – 43.0	30.1 (5.7); 18.7 – 43.0
BMI – Average (SD); range	26.6 (4.5); 19.5 – 36.4	26.8 (4.7); 19.5 – 36.4
Parity – n (%)		
Multiparous	32 (71.1)	29 (74.4)
Nuliparous	13 (28.9)	10 (25.6)
Gestational age, weeks – Average (SD); range	24.5 (1.7); 20.7 – 26.9	24.5 (1.8); 20.7 – 26.9
Fetal and placental characteristics		
MMC upper anatomical level – n (%)		
T10 / T12	3 (6.7)	3 (7.6)
L1 / L2	14 (31.1)	12 (30.7)
L3 / L4	17 (37.8)	17 (43.5)
L5 / S1	11 (24.4)	7 (17.9)
Presence of ventriculomegaly – n (%)	32 (71.1)	26 (66.6)
Lateral ventricle diameter, mm – Average (SD); range	11.4 (3.1); 4.0 – 20.0	11.3 (3.2); 4.0 – 20.0
Presence of inferior limbs' deformity – n (%)	19 (42.2)	15 (38.5)
Presence of inferior limbs' movements – n (%)	35 (77.8)	30 (76.9)
Placental position – n (%)		
Anterior	20 (44.4)	18 (46.2)
Posterior	22 (48.9)	20 (51.3)
Other	3 (6.7)	1 (2.6)

Table 2. Variables evaluated from fetal myelomeningocele repair until delivery

Variables from fetal surgery to delivery	n = 39
Change in fetal cerebral lateral ventricle size – n (%)	
Increased	17 (43.6)
Decreased	6 (15.4)
Stabilized	16 (41.0)
Reversal of the Chiari II malformation – n (%)	
Complete	10 (25.6)
Partial	24 (61.5)
None	5 (12.8)
Presence of inferior limbs' deformity – n (%)	14 (35.9)
Presence of inferior limbs' movements – n (%)	28 (71.8)
Time interval between fetal surgery and delivery, weeks – Average (SD); range	10.9 (2.3); 5.7 – 17.9
Premature preterm rupture of membranes – n (%)	9 (23.1)

Table 3. Peripartum variables

Peripartum variables	n = 39
Gestational age at delivery weeks – Average (SD); range	35.3 (2.2; 27.9 – 39.1)
> 36^{+6} weeks – n (%)	9 (23.1)
34^{+0} – 36^{+6} weeks – n (%)	23 (59.1)
32^{+0} – 33^{+6} weeks – n (%)	5 (12.8)
< 32^{+0} weeks – n (%)	2 (5.1)
hysterorrhaphy	
Intact – n (%)	37 (94.9)
Complete dehiscence – n(%)	0 (0.0)
Partial dehiscence – n (%)	2 (5.1)
Thinning – n (%)	0 (0.0)
Neonatal Apgar scores	
1^{st} minute – Median (range)	8 (7 - 10)
5^{th} minute – Median (range)	9 (8 – 10)
Neonatal weight, grams – Average (SD)	2493 (531; 1100 - 3740)

Table 4. Neonatal variables until hospital discharge

Neonatal variables	n = 39
Reversal of the Chiari II malformation on MRI – n (%)	
Complete	13 (33.3)
Partial	17 (43.6)
None	5 (12.8)
Not imaged	4 (10.3)
Ventriculoperitoneal shunting – n (%)	3 (7.7)
Presence of clubfoot – n (%)	22 (56.4)
Inferior limb movements – n (%)	
Normal	18 (46.2)
Reduced	16 (41.0)
None	5 (12.8)
Other complications – n (%)	
Neurogenic bladder	5 (12.8)
Peri intraventricular haemorrhage	1 (2.6)
Necrotizing enterocolitis	1 (2.6)

Figure 1. a. The aspect of the mini-hysterotomy after the membranes are sutured to the inner third of the myometrium. b. Microscope view of the fetal myelomeningocele after placement of the Ankeney® retractor.

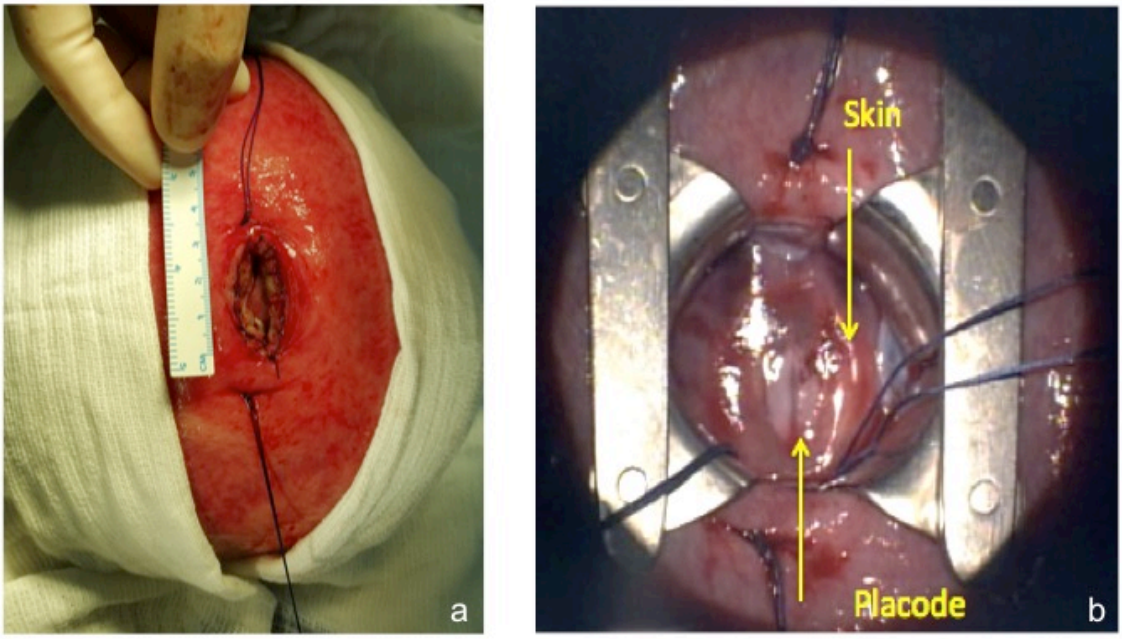

Figure 1

Figure 2. a. Microscope view of the fetal myelomeningocele correction via mini-hysterotomy. b. Final aspect of the hysterorrhaphy.

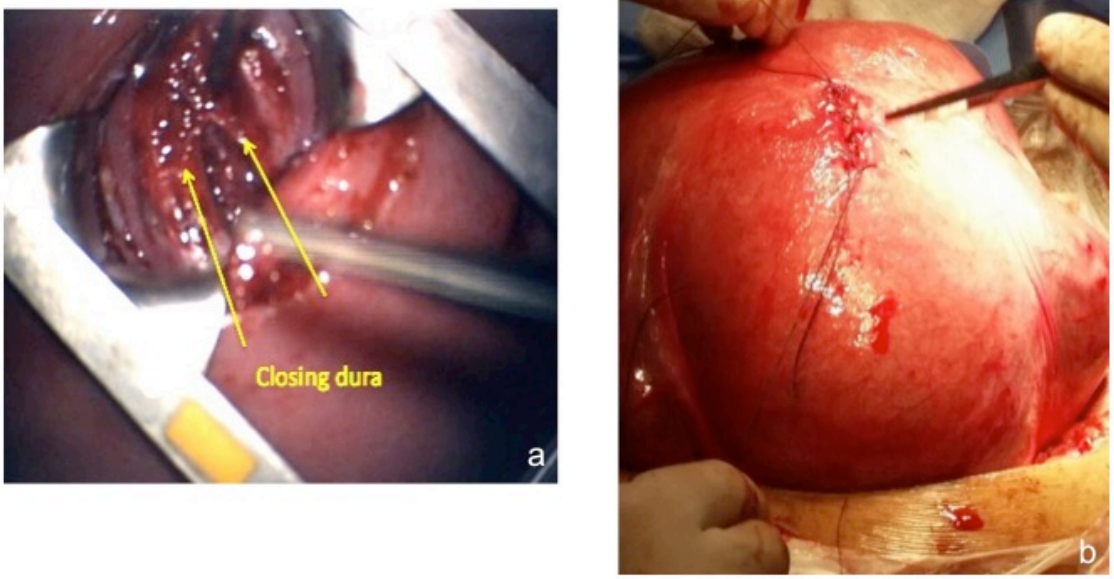

Figure 2

4. Conclusão

A correção da MMC fetal através da mini-histerotomia foi possível em todos os casos, o que demonstra a viabilidade técnica da cirurgia.

A correção da MMC fetal através da mini-histerotomia desmonstrou-se segura para a gestante e o feto, não tendo sido observadas complicações graves intra ou pós-operatórias.

Não houve complicações graves maternas ou neonatais decorrentes da correção da mielomeningocele fetal por meio da mini-histerotomia.

5. Referências Bibliográficas

1. Mitchell LE, Adzick NS, Melchionne J, Pasquariello PS, Sutton LN, Whitehead AS. Spina bifida. Lancet 2004;364:1885–95.

2. Hutchins GM, McGowan KD, Blakemore KJ. Spinal dysraphia: not a neural tube defect? Am J Hum Genet 1992;51:A319.

3. Edmonds LD, James LM. Temporal trends in the prevalence of congenital malformations at birth based on the birth defects monitoring program, United States, 1979–1987. MMWR CDC Surveill Summ 1990;39:19–23.

4. Lary JM, Edmonds LD. Prevalence of spina bifida at birth – United States, 1983–1990: a comparison of two surveillance systems. MMWR CDC Surveill Summ 1996;45:15–26.

5. Shaw GM, Jensvold NG, Wasserman CR, Lammer EJ. Epidemiologic characteristics of phenotypically distinct neural tube defects among 0.7 million California births, 1983–1987. Teratology 1994;49:143–9.

6. Oakeshott P, Hunt GM. Long-term outcome in open spina bifida. Br J Gen Pract 2003;53:632–6.

7. Hunt GM. Open spina bifida: outcome for a complete cohort treated unselectively and followed into adulthood. Dev Med Child Neurol 1990;32:108–88.

8. Dias MS, McLone DG. Hydrocephalus in the child with dysraphism. Neurosurg Clin N Am 1993;4:715–26.

9. McLone DG. Results of treatment of children born with a myelomeningocele. Clin Neurosurg 1983;30:407–12.

10. Caldarelli M, DiRocco C, LaMarca F. Shunt complications in the first postoperative year in children with meningomyelocele. Childs Nerv Syst 1996;12:748–54.

11. Hutchins GM, Meuli M, Meuli-Simmen C, Jordan MA, Heffez DS, Blakemore KJ. Acquired spinal cord injury in human fetuses with myelomeningocele. Pediatr Pathol Lab Med 1996;16:701–12.

12. Meuli M, Meuli-Simmen C, Hutchins GM, Seller MJ, Harrison MR, Adzick NS. The spinal cord lesion in human fetuses with myelomeningocele: implications for fetal surgery. J Pediatr Surg 1997;32:448–52.

13. Korenromp MJ, Van Good JD, Bruinese HW, Kriek R. Early fetal movements in myelomeningocele. Lancet 1986;1:917–8.

14. Sival DA, Begeer JH, Staal-Schreinemachers AL, Vos-Niel JM, Beekhuis JR, Prechtl HF. Perinatal motor behaviour and neurological outcome in spina bifida aperta. Early Hum Dev 1997;50:27–37.

15. Meuli M, Meuli-Simmen C, Yingling CD, et al. Creation of myelomeningocele in utero: a model of functional damage from spinal cord exposure in fetal sheep. J Pediatr Surg 1995;30:1028–32.

16. Meuli M, Meuli-Simmen C, Hutchins GM, et al. In utero surgery rescues neurologic function at birth in sheep with spina bifida. Nat Med 1995;1:342–7.

17. Meuli M, Meuli-Simmen C, Yingling CD, et al. In utero repair of experimental myelomeningocele saves neurologic function at birth. J Pediatr Surg

1996;31:397–402.

18. Bouchard S, Davey MG, Rintoul NE,Walsh DS, Rorke LB, Adzick NS. Correction of hindbrain herniation and anatomy of the vermis after in utero repair of myelomeningocele in sheep. J Pediatr Surg 2003;38:451–8.

19. Bruner JP, Tulipan NB, Richards WO. Endoscopic coverage of fetal open myelomeningocele in utero. Am J Obstet Gynecol 1997;176:256–7.

20. Tulipan N, Hernanz-Schulman M, Bruner JP. Reduced hindbrain herniation after intrauterine myelomeningocele repair: a report of four cases. Pediatr Neurosurg 1998;29:274–8.

21. Adzick NS, Sutton LN, Crombleholme TM, Flake AW. Successful fetal surgery for spina bifida. Lancet 1998;352:1675–6.

22. Sutton LN, Adzick NS, Bilaniuk LT, Johnson MP, Crombleholme TM, Flake AF. Improvement in hindbrain herniation by serial fetal MRI following fetal surgery for myelomeningocele. J Am Med Assoc 1999;282:1826–31.

23. Bruner JP, Tulipan N, Paschall RL, et al. Intrauterine repair of myelomeningocele, ‘hindbrain restoration’ and the incidence of shunt-dependent hydrocephalus. J Am Med Assoc 1999;282:1819–25.

24. Johnson MP, Adzick NS, Rintoul N, et al. Fetal myelomeningocele repair: shortterm clinical outcomes. Am J Obstet Gynecol 2003;189:482–7.

25. Adzick NS, Thom EA, Spong CY, Brock III JW, Burrows PK, Johnson MP, Howell LJ, Farrell JA, Dabrowiak ME, Sutton LN, Gupta N, Tulipan NB,

D'Alton ME, Farmer DL, for the MOMS Investigators. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med 2011; 364:993-1004.

26. Moldenhauer JS, Soni S, Rintoul NE, Spinner SS, Khalek N, Martinez-Poyer J, Flake AW, Hedrick HL, Peranteau WH, Rendon N, Koh J, Howell LJ, Heuer GG, Sutton LN, Johnson MP, Adzick NS. Fetal myelomeningocele repair: the post-MOMS experience at the Children's Hospital of Philadelphia. Fetal Diagn Ther. 2015; 37:235-240.

27. Tulipan N, Hernanz-Schulman M, Bruner JP. Reduced hindbrain herniation after intrauterine myelomeningocele repair: a report of four cases. Pediatr Neurosurg 1998; 29:274–278.

28. Adzick NS, Sutton LN, Crombleholme TM, Flake AW. Successful fetal surgery for spina bifida. Lancet 1998; 352:1675–1676.

29. Sutton LN, Adzick NS, Bilaniuk LT, Johnson MP, Crombleholme TM, Flake AF. Improvement in hindbrain herniation by serial fetal MRI following fetal surgery for myelomeningocele. J Am Med Assoc 1999; 282:1826–1831.

30. Bruner JP, Tulipan N, Paschall RL, et al. Intrauterine repair of myelomeningocele, 'hindbrain restoration' and the incidence of shunt-dependent hydrocephalus. J Am Med Assoc 1999; 282:1819–1825.

31. Johnson MP, Adzick NS, Rintoul N, et al. Fetal myelomeningocele repair: shortterm clinical outcomes. Am J Obstet Gynecol 2003; 189:482–487.

32. Bruner JP, Tulipan NB, Richards WO. Endoscopic coverage of fetal open myelomeningocele in utero. Am J Obstet Gynecol 1997; 176:256–257.

33. Pedreira DA, Zanon N, de Sá RA, Acacio GL, Ogeda E, Belem TM, Chmait RH, Kontopoulos E, Quintero RA. Fetoscopic single-layer repair of open spina bifida using a cellulose patch: preliminary clinical experience. J Matern Fetal Neonatal Med. 2014; 27:1613-1619.

34. Kohl T. Percutaneous minimally invasive fetoscopic surgery for spina bifida aperta. Part I: surgical technique and perioperative outcome. Ultrasound Obstet Gynecol. 2014; 44:515-524.

35. Degenhardt J, Schürg R, Winarno A, Oehmke F, Khaleeva A, Kawecki A, Enzensberger C, Tinneberg HR, Faas D, Ehrhardt H, Axt-Fliedner R, Kohl T. Percutaneous minimal-access fetoscopic surgery for spina bifida aperta. Part II: maternal management and outcome. Ultrasound Obstet Gynecol. 2014; 44:525-531.

36. Graf K, Kohl T, Neubauer BA, Dey F, Faas D, Wanis FA, Reinges MH, Uhl E, Kolodziej MA. Percutaneous minimally invasive fetoscopic surgery for spina bifida aperta. Part III: neurosurgical intervention in the first postnatal year. Ultrasound Obstet Gynecol. 2016; 47:158-161.

37. Pedreira DA, Zanon N, Nishikuni K, Moreira de Sá RA, Acacio GL, Chmait RH, Kontopoulos EV, Quintero RA. Endoscopic surgery for the antenatal treatment of myelomeningocele: the CECAM trial. Am J Obstet Gynecol. 2016 ; 214:111.e1-111.e1

6. Anexos

6.1 – Parecer da Comissão de Pesquisa do DTG/CAISM

UNICAMP

Comissão de Pesquisa do DTG / CAISM

Campinas, 09 de junho de 2016.

Protocolo nº: 34/2016

O protocolo de pesquisa *"Avaliação dos resultados cirúrgicos e perinatais da correlação da mielomeningocele fetal por meio da mini-histerotomia"* do pesquisador Rafael Davi Botelho, foi aprovado pela Comissão de Pesquisa do DTG/CAISM em 09/06/2016.

Atenciosamente,

PROF. DR. LUIZ CARLOS ZEFERINO
Presidente da Comissão de Pesquisa do DTG/CAISM

Rua Alexander Flemming, n.º101 – Cidade Universitária Zeferino Vaz – Campinas-SP
Fone: (19) 3521-9400
comissaopesquisa@caism.unicamp.br

6.2 – Parecer da Comissão de Pesquisa do Hospital do Coração – HCOR

HOSPITAL DO CORAÇÃO/ ASSOCIAÇÃO DO SANATÓRIO SÍRIO - ASS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação dos Resultados Cirúrgicos e Perinatais da Correção da Mielomeningocele Fetal Por Meio da Mini-Histerotomia

Pesquisador: RAFAEL DAVI BOTELHO

Área Temática:

Versão: 2

CAAE: 55497916.7.0000.0060

Instituição Proponente: Hospital do Coração/ Associação do Sanatório Sírio

Patrocinador Principal: Hospital do Coração/ Associação do Sanatório Sírio

DADOS DO PARECER

Número do Parecer: 1.536.963

Apresentação do Projeto:

A mielomeningocele acomete cerca de 1/1000 nascidos vivos no Brasil. Segundo os resultados do ensaio clínico randomizado conhecido como MOMs trial (Management of Myelomeningocele Study – A randomized trial of prenatal versus postnatal repair of myelomeningocele, N Engl J Med. 2011, 17;364:993-1004), a correção do defeito no feto permite melhores resultados neurológicos pós-natais do que os obtidos com a cirurgia neonatal. No entanto, a cirurgia fetal, classicamente realizada através de histerotomia corporal com 6 – 10 cm de comprimento, oferece riscos à gestante. Estes riscos (sangramento materno, descolamento de placenta, rotura prematura pré-termo de membranas e trabalho de parto pré-termo)
têm dificultado a disseminação da técnica em todo o mundo. Assim sendo, o objetivo principal do presente estudo é descrever os resultados cirúrgicos e perinatais da correção da mielomeningocele fetal realizada através de histerotomia corporal com extensão máxima de 3,5 cm. A modificação técnica (tamanho da incisão no útero) em relação à histerotomia clássica utilizada no MOMs trial.

Objetivo da Pesquisa:

Objetivo Primário:

Avaliar a viabilidade da correção da mielomeningocele fetal através da mini-histerotomia e os resultados perinatais desta cirurgia.

Endereço: Rua Abrão Dib, 50 - Térreo
Bairro: Paraíso **CEP:** 04.004-030
UF: SP **Município:** SAO PAULO
Telefone: (11)3886-4688 **Fax:** (11)3886-4689 **E-mail:** etica.pesquisa@hcor.com.br

Objetivo Secundário:
Descrever a viabilidade da correção da mielomeningocele fetal através da mini-histerotomia.
Descrever as complicações perioperatórias associadas à correção da mielomeningocele fetal através da mini-histerotomia.
Descrever as complicações perinatais após a correção da mielomeningocele fetal através da mini histerotomia.

Avaliação dos Riscos e Benefícios:
Benefícios: A mini-histerotomia para correção da mielomeningocele fetal associa-se a menos riscos de complicações perioperatórias do que os observados após a histerotomia clássica descrita no MOMs trial. Risco mínimo por se tratar de estudo retrospectivo.

Comentários e Considerações sobre a Pesquisa:
Estudo observacional descritivo retrospectivo no qual os resultados perioperatórios e perinatais da correção da mielomeningocele fetal através da mini-histerotomia serão avaliados por meio de revisão dos prontuários médicos das gestantes e dos recém-nascidos.
Os dados obtidos dos prontuários das gestantes e dos recém-nascidos serão registrados em uma planilha do programa Excel para Windows (Microsoft® Corporation, Redmond, WA, E.U.A.).

Considerações sobre os Termos de apresentação obrigatória:
Adequadamente apresentados, alteração solicitada efetuada.

Recomendações:
Sem recomendações.

Conclusões ou Pendências e Lista de Inadequações:
Sem pendência.

Considerações Finais a critério do CEP:
O CEP HCor informa que a partir desta data de aprovação, é necessário o envio de relatórios semestrais (no caso de estudos pertencentes à área temática especial) e anuais (em todas as outras situações). É também obrigatório, a apresentação do relatório final, quando do término do estudo.

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Continuação do Parecer: 1.536.963

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_705253.pdf	10/05/2016 09:09:26		Aceito
Projeto Detalhado / Brochura Investigador	Projeto_Meningomielocelele1.pdf	26/04/2016 14:54:06	RAFAEL DAVI BOTELHO	Aceito
Folha de Rosto	fls_rosto_plataformabrasil_meningomielocele.pdf	26/04/2016 14:53:28	RAFAEL DAVI BOTELHO	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Aspectos_eticos_Justificativa_de_ausencia_de_termo_de_consentimento.pdf	25/04/2016 22:19:57	RAFAEL DAVI BOTELHO	Aceito
Cronograma	CRONOGRAMA.pdf	25/04/2016 22:14:48	RAFAEL DAVI BOTELHO	Aceito
Outros	TERMO_DE_COMPROMISSO_DE_UTILIZACAO_DE_DADOS.pdf	25/04/2016 22:12:53	RAFAEL DAVI BOTELHO	Aceito
Outros	Cadastro_dos_Pesquisadores.pdf	25/04/2016 22:10:18	RAFAEL DAVI BOTELHO	Aceito
Outros	ANUENCIA_DA_AREA_ENVOLVIDA.pdf	25/04/2016 22:05:24	RAFAEL DAVI BOTELHO	Aceito
Declaração de Pesquisadores	DECLARACAO_DE_RESPONSABILIDADE_DO_INVESTIGADOR_PRINCIPAL.	25/04/2016 21:41:39	RAFAEL DAVI BOTELHO	Aceito
Declaração de Instituição e Infraestrutura	DECLARACAO_DE_INFRA_ESTRUTURA.pdf	25/04/2016 21:40:07	RAFAEL DAVI BOTELHO	Aceito
Brochura Pesquisa	Projeto_Meningomielocelele.pdf	25/04/2016 21:35:42	RAFAEL DAVI BOTELHO	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SAO PAULO, 10 de Maio de 2016

Assinado por:
Sergio Domingos Vieira
(Coordenador)

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