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ORIGINAL ARTICLE

WILEY PRENATAL DIAGNOSIS

Fetal myelomeningocele surgery: Only treating the tip of the iceberg

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Abstract

Objective: Fetal myelomeningocele (fMMC) surgery improves infant outcomes when compared with postnatal surgery. Surgical selection criteria and the option of pregnancy termination, however, limit the number of cases that are eligible for prenatal surgery. We aimed to quantify what proportion of cases could ultimately benefit from fetal therapy.

Methods: We retrospectively reviewed all cases of fMMC referred to a large tertiary care center over a 10-year period and assessed their eligibility for fetal surgery, pregnancy termination rates, and actual uptake of the surgery.

Results: Of 158 cases, 67 (42%) were ineligible for fetal surgery based on surgical exclusion criteria. Eleven fetuses (7%) had chromosomal anomalies, 10 of which (91%) had other anomalies on ultrasound. Thirty-four patients had a combination of maternal and fetal contraindications. Of the remaining 91 eligible cases (58%), 45 (49%) pregnancies were terminated, leaving only 46 (29% of initial 158 cases) as potential candidates for fetal repair. Actual uptake of fetal surgery was 15% (n = 14 of 91), but this increased after a national program was started.

Conclusion: Only a minority of fMMC cases will ultimately undergo fetal surgery. These numbers support the centralization of care in expert centers.

1 | INTRODUCTION

Fetal myelomeningocele (fMMC) is a common congenital central nervous system anomaly with an incidence of approximately 3-4 per 10 000 live births in countries with folic acid supplementation programs.[1] The condition has an 8% infant mortality rate[2] and leads to considerable morbidity, with lifetime healthcare costs exceeding $600 000 (2002 US dollars) amongst survivors.[3] Typically, spina bifida is treated postnatally, but since the publication of the Management of Myelomeningocele Study (MOMS)[4] in 2011, fMMC surgery has become a clinical option for patients as the trial demonstrated improved motor function, less hindbrain herniation, and decreased need for surgical procedures for hydrocephalus with prenatal surgery compared with postnatal closure.

Since the publication of the MOMS trial, the number of centers offering fMMC surgery has increased significantly, particularly in the USA, thereby increasing regional access, but potentially diluting the expertise of individual centers. Although there are no good data to support how many centers are needed and what a minimal number of cases per center should be to ensure competency, it is important to note that the total number of women undergoing fMMC surgery will likely be much smaller than the total number of cases of fMMC as many couples will still choose to terminate the pregnancy or to continue the pregnancy with postnatal treatment for several reasons. For

example, the surgery is typically reserved for healthy mothers and singleton fetuses without associated structural or genetic anomalies, similar to the selection criteria used in the MOMS trial.[4,5] Additionally, not all patients who are surgical candidates will consent to the procedure, as the surgery has significant risks, both for the index pregnancy and for future pregnancies,[6,7] and entails significant lifestyle modifications (eg, relocation for the surgery and limited physical activity) with potential financial implications.

The aim of this study was to estimate the number of cases of fMMC that would be candidates for fMMC repair in Canada and to estimate how many of those would likely opt for the procedure.

What is already known about this topic?

- Typically, fetal myelomeningocele is treated postnatally, but since 2011, antenatal surgery has become a clinical option.

What does this study add?

- Availability of a national fetal surgery program increases the uptake of fetal surgery for fetal myelomeningocele compared with international referral.
- After exclusion of cases for surgical reasons or because the parents opt to terminate the pregnancy, 29% of cases is ultimately eligible for fetal surgery.
- We provide numbers that allow estimating the need for local fetal surgery programs for fetal myelomeningocele. These numbers can be extrapolated to other countries but will need to be adjusted for disease incidence and pregnancy termination rates, which vary regionally.

2 | METHODS

After approval of the study by the Mount Sinai Hospital Research Ethics Board (REB #17–0087-C), we retrospectively reviewed all cases of fMMC referred to the fetal medicine unit at Mount Sinai Hospital, Toronto, Canada between March 2008 and March 2018. Mount Sinai Hospital serves as a referral center for fetal anomalies for the Greater Toronto Area (6.4 million inhabitants) and is the largest fetal therapy center in the country. We have been discussing the option of fMMC surgery with all eligible patients since 2011, and this has become a standard available option in Canada since October 2014.[8] Initially, fMMC surgery was available through referral to a center in the United States, but, since June 2017, fMMC surgery has been offered in Toronto.

A search of the fetal medicine, radiology, pathology, and genetics databases was carried out to identify all women referred for an fMMC. Patients with closed neural tube defects or anencephaly were excluded. For each patient, data were extracted from inpatient and outpatient electronic medical records including ultrasound reports, MRI, perinatal, cytogenetic, and pathology reports.

Maternal background variables included age, ethnicity, body mass index (BMI), preconceptual folic acid use, significant maternal chronic illnesses that would pose a contraindication for safe fetal surgery or general anesthesia, previous uterine surgeries or uterine anomalies, drug use, gravidity, parity, previous preterm birth or other pregnancy complications, and previous personal or family history of a neural tube defect.

For the current pregnancy, we recorded mode of conception, pregnancy complications such as gestational diabetes and hypertension, gestational age at diagnosis and referral, multiple pregnancies, cervical length, upper level of the vertebral defect, presence of Chiari II malformation, ventriculomegaly or talipes, and other intracranial or extracranial anomalies and genetic results. For those who did not undergo invasive testing during pregnancy, we obtained genetic testing at delivery. Timing of MMC surgery (prenatally or postnatally) was recorded.

For each case, we assessed potential eligibility for fMMC surgery using the same inclusion and exclusion criteria as in the MOMS study.[4] Inclusion criteria for surgery were maternal age of at least 18 years, a singleton pregnancy, gestational age between 19 and 25.9 weeks gestation at assessment, myelomeningocele with the upper boundary located between T1 and S1, and evidence of hind brain herniation and normal fetal karyotype. Exclusion criteria included a body mass index (BMI) $\geq$ 35 kg/m^2, maternal medical diseases that would constitute a contraindication for general anesthesia and surgery, previous hysterotomy in the active uterine segment, risk of preterm birth including short cervix and history of previous preterm birth, placental abruption, and any fetal anomaly not related to myelomeningocele and severe kyphosis (>30^o).

2.1 | Statistics

Statistical analysis was carried out using Prism for Windows version 5.00 (Graph Pad Software, La Jolla, CA, USA). Distribution of the data was assessed using the D'Agostino and Pearson omnibus normality test. For normally distributed data, results are expressed as mean ± standard deviation. We calculated the ratio of patients undergoing fetal surgery over the number of patients potentially eligible for fetal surgery, as well as the ratio of patients undergoing termination of pregnancy over those potentially eligible for fetal surgery for three time epochs: before availability of fetal surgery (ie, before publication of the MOMS trial in 2011), after introduction of fetal surgery but before its availability in Canada (2011-June 2017; during this time period, patients were offered fetal surgery but had to travel to the United States for the procedure), and after introduction of fetal surgery in Canada (June 2017-March 2018). The incidences of "reasons for ineligibility" were compared between patients who continued the pregnancy and those who terminated using Fisher's exact test.

3 | RESULTS

We retrieved a total of 158 pregnancies complicated by fMMC. We have seen an important increase in the number of referrals since the

start of our fMMC surgery program in June 2017, with 26 cases seen over a 9-month period, whereas annual numbers fluctuated between seven and 18 cases per year prior to that.

Baseline characteristics are presented in Table 1. Of note, this was a relatively healthy multiparous population, with none of the women having medical conditions precluding surgery and none carrying hepatitis B or C or HIV. The mean BMI at the time of assessment was 25.2 ± 5.5 kg/m^2. The incidence of class I obesity (BMI 30-34.9 kg/m^2) was 9.5% (n = 15), class II (BMI 35-39.9 kg/m^2) 5.1% (n = 8), and class III (BMI ≥40 kg/m^2) 1.3% (n = 2). Ninety-two percent (n = 145) used folic acid prior to conception.

Details on the index pregnancy are listed in Table 1. There was an overrepresentation of multiple pregnancies with an incidence of 9.5% (14 twins, one triplet pregnancy). Diagnosis was typically made at the time of the anatomy screening ultrasound with mean gestational age (GA) at diagnosis of 19.9 ± 3.0 weeks. Eighty-three percent of lesions were at a lumbar level. Sixty percent (n = 95) of our study population had ventriculomegaly. Out of those cases, mild (10-12 mm), moderate (12–14.9 mm), and severe ventriculomegaly (≥15 mm) were seen at presentation in 41.1%, 30.5%, and 28.4% of cases, respectively. In total, 31 fetuses (20%) had other anomalies unrelated to the MMC on ultrasound (Table 2).

Fetal karyotyping or chromosomal microarray were available for 150 fetuses (95%), either from amniocentesis or postnatal testing. Abnormal results were identified in 11 fetuses (7%): six cases of trisomy 18, two cases of triploidy, one case of trisomy 13, and two cases of pathogenic copy-number variants on microarray results, 10 of whom had additional anomalies detected on ultrasound (Table 3).

In the total cohort of 158 cases, 83 (53%) opted for termination of pregnancy. Of the remaining 75, 46 (which is 29% of the initial cohort of 158) were potential candidates for fetal surgery. Reasons for exclusion from fMMC surgery are presented in Table 4.

Forty-seven cases were seen prior to the publication of the MOMS trial (2008-2010). In this subgroup, 30 (64%) would have been eligible for fetal surgery, and 18 of those (60%) elected to stop the pregnancy, leaving 12 potential surgical candidates (26% of the initial cohort). The termination rate amongst ineligible cases was 53% (n = 9 of 17).

TABLE 1 Baseline characteristics of the study population

Variable	Result
Maternal age in years (mean ± SD)	31.37 ± 5.84
GA at diagnosis in weeks (mean ± SD)	19.89 ± 2.97
Ethnic background, n (%)	
Black	13 (8.23)
White	119 (75.32)
Asian	21 (13.29)
East Asian	5 (3.16)
Gravidity, median (range)	2 (1-10)
Parity, median (range)	1 (0-6)
BMI in kg/m^2 (mean ± SD)	25.2 ± 5.5
Current smoker, n (%)	8 (5.1)
Pregestational diabetes, n (%)	1 (0.6)
Hepatitis B or C or HIV positive, n (%)	0 (0)
Medical diseases that contraindicate surgery or anesthesia, n (%)	0 (0)
Number of patient with previous history of caesarean section, n (%)	29 (18.4)
Previous uterine surgeries other than caesarean section, n (%):	28 (17.7)
Dilatation and curettage, n	27
Excision of uterine septum, n	1
Total number of uterine anomalies, n (%)	3 (1.9)
Previous history of preterm birth <37 weeks and/or previous history of cervical incompetence, n (%)	6 (3.8)
Either parent with family history of NTD, n (%)	9 (5.7)
Previous history of baby with NTD, n (%)	4 (2.5)
Mode of conception:	
Spontaneous, n (%)	147 (93.0)
Ovulation induction, n (%)	7 (4.4)
In vitro fertilization, n (%)	4 (2.5)
Multiple pregnancies, n (%)	15 (9.5)
Folic acid use, n (%)	146 (92.4)

Abbreviations: BMI, body mass index; GA, gestational age; NTD, neural tube defect.

TABLE 2 Characteristics of the index pregnancy

Variable	Result
Cervical length, mm (mean ± SD)	38.1 ± 6.6
Placental location	
Anterior, n (%)	88 (55.7)
Posterior, n (%)	66 (41.8)
Lateral, n (%)	2 (1.3)
Previa, n (%)	2 (1.3)
Associated anomalies, n (%)	31 (19.6)
Total number of isolated fMMCs, n (%)	117 (74.1)
Chiari malformation, n (%)	138 (87.3)
Ventriculomegaly, n (%)	95 (60.1)
Ventriculomegaly, mm (mean ± SD)	11.4 ± 4.8
Closed lesion, n (%)	2 (1.3)
Open lesion, n (%)	156 (98.7)
Talipes on ultrasound:	
Total, n (%)	42 (26.6)
Unilateral, n (%)	12 (28.6)
Bilateral, n (%)	30 (71.4)
First open level of the spinal defect:	
Thoracic, n (%)	14 (8.9)
L1-L2, n (%)	15 (9.5)
L3-L4, n (%)	59 (37.3)
L5-S1, n (%)	57 (36.1)
Lower than S1	13 (8.2)
Spinal angulation >30°, n (%)	3 (1.9)
Abnormal karyotype or microarray, n (%)	11 (7.3)
Sex	
Female, n (%)	78 (49.4)
Male, n (%)	80 (50.6)

Abbreviation: fMMC, fetal myelomeningocele.

TABLE 3 Associated anomalies not related to spina bifida seen on ultrasound

Type of the anomaly	Number of cases
Craniofacial anomalies	
Absent corpus callosum (ACC)	3
Dany Walker malformation (DWM)	2
Encephalocele	1
Bilateral cleft lip	1
Cleft palate	1
Micrognathia	2
Hypertelorism/hypotelorism	3
Hypoblastic nasal bone	2
Cardiovascular anomalies	
Hypoblastic left heart syndrome (HLHS)	1
Ventricular septal defect (VSD)	5
Tetralogy of fallout (TOF)	2
Atrioventricular septal defect (AVSD)	1
Pulmonary atresia	1
Overriding of the aorta	1
Double outlet right ventricle	1
Thoracic anomalies	
Congenital diaphragmatic hernia (CDH)	1
Gastrointestinal anomalies	
Omphalocele	3
Absent stomach	1
Two vessel cord (2VC)	5
Liver and spleen calcifications	1
Genitourinary anomalies	
Bladder extrophy	1
Renal agenesis	2
Multicystic dysplastic kidneys (MDK)	1
Limb malformations	
Clenched hands	3
Bilateral clinodactyly	2
Rocker bottom feet	2

Note: 22 patients had multiple anomalies.

Between the publication of the MOMS trial in 2011 and the start of our local fMMC surgery program in June 2017, we identified 85 cases, of which 45 (53%) were eligible for fetal repair. Twenty-three of the latter (51%) chose to terminate the pregnancy, leaving 22 potential surgical candidates (26% of initial cohort). Of these, only four (18% or 5% of the cohort of 85) underwent fMMC repair in the United States. The termination rate amongst ineligible cases was 60% (n = 24 of 40).

We identified 26 cases between the start of our local fetal surgery program in June 2017 and March 2018. Of these, 16 (62%) were eligible for fetal repair. Four of the latter (25%) underwent pregnancy termination. Of the remaining 12 cases, nine (75% or 35% of the cohort of 26) underwent the surgery. The termination rate amongst ineligible cases was 50% (n = 5 of 10).

4 | DISCUSSION

In this large series of fMMC cases from a Canadian tertiary referral center, we demonstrate that, after exclusion of ineligible cases and those opting for pregnancy termination, nearly one-third were potential candidates for fetal surgery.

The main reasons for exclusion from fMMC surgery were associated fetal anomalies and abnormal karyotype results. As expected, these findings were also associated with a higher pregnancy termination rate. In comparison with the MOMS trial, we had a similar number of exclusions for previous preterm birth (3.7% vs 3.6% in MOMS)[4] but lower exclusion rates for a high BMI (6% vs 10%) or significant maternal morbidity (0% vs 4.5%).

Actual uptake of fMMC surgery amongst eligible cases was 18% when it required a cross-border referral but increased to 75% when the intervention became available locally. The latter number is much higher than that reported by Ovaere et al[9] and by Mazzone et al[10] in two European cohort studies, where only six of 14 (42.8%) eligible patients and 56 of 106 (53%) eligible patients, respectively, underwent the intervention. It is also higher than the numbers reported by Moldenhauer et al[11] in the United States after the MOMS trial, where only 29% of those eligible for surgery underwent the procedure. The latter is at least partly explained by cultural differences, where our series reports lower pregnancy termination rates than those seen in the Ovaere cohort (53% vs 75%, respectively), but may also reflect the referral pattern where only patients who truly are committed to the surgery are referred.

However, an increase in uptake of care is also expected to take place when care becomes available locally, as international travel for care, with its associated financial costs and family disruption, will dissuade many patients from opting for fMMC repair. We also expect to see a further increase in uptake of fMMC surgery if a minimally invasive fetoscopic approach, which has a potential to reduce maternal morbidity, becomes available.[12,13]

We saw an apparent decrease in pregnancy termination rates amongst patients eligible for surgery since the introduction of our program. This finding might reflect a referral bias, if only cases planning to continue the pregnancy and motivated to undergo fMMC surgery were actually referred. These changes in termination rates, however, may also be the result of a change in patient perception. We nevertheless strongly try to avoid presenting the surgery as an alternative to pregnancy termination,[14] but rather as an additional option for those who have decided to continue the pregnancy, as the residual risks for ventriculo-peritoneal shunting and motor dysfunction remain high,[15] and the effect on bladder function is still unclear.[16,17]

When extrapolating our results to the Canadian setting, with an estimated 150 fMMC cases annually,[18] about 50 cases would be eligible for surgery yearly, and nine (18% uptake) to 38 (75% uptake) cases would actually undergo the intervention. This supports the existence of one national center to concentrate expertise. Locally, we obtained a commitment consensus from all fetal centers in Canada to concentrate the expertise by referring all cases of fMMC eligible for antenatal repair to Toronto. Given that fMMC surgery saves about $20 000 per case compared with postnatal surgery,[19] this also represents a considerable cost saving for the health care system.

TABLE 4 Reasons for exclusion as candidates for fetal myelomeningocele surgery

	Total cohort N = 158	Termination N = 83	No termination N = 75	*P* value[a]
Maternal age < 18 years	2	1	1	0.73
Multiple pregnancies	15	10	5	0.19
BMI ≥35 kg/m^2	9[b]	5	4	0.56
Maternal medical diseases that contraindicate general anesthesia and surgery	0	0	0	1.00
Risk of preterm birth including short cervix and history of previous preterm birth	6	2	4	0.29
Uterine anomalies	2[c]	1	1	0.73
Gestational age > 25.9 weeks at assessment	7	1	6	0.06
Absence of hind brain herniation	20	9	11	0.45
Fetal anomaly unrelated to spina bifida	31	21	10	0.04
Fetal kyphosis > 30°	3	2	1	0.54
Abnormal fetal karyotype	11	9	2	0.04
Myelomeningocele with the upper boundary not located between T1 and S1	13	6	7	0.42

Abbreviation: BMI, body mass index. Note: 34 patients had multiple reasons for exclusion.

[a]*P* value for comparison between termination and no termination.

[b]Total number of patients with BMI ≥ 35 kg/m^2 is 10, but one of them, with BMI of 39 kg/m^2, underwent fetal neural tube defect (NTD) repair after extensive counseling about the risks.

[c]Total number of patients who had uterine anomalies was three but only two patients were excluded as one patient underwent a hysteroscopic uterine excision.

In summary, we here provide numbers that allow to estimate the need for local fetal surgery programs for fMMC. These numbers can be extrapolated to other countries but will need to be adjusted for baseline MMC incidence and pregnancy termination rates, both of which can vary regionally.[1,20]

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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