# Maternal Complications following Open and Fetoscopic Fetal Surgery: a Systematic Review and Meta-Analysis

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What's already known about this topic?

- Fetal surgery, both open and fetoscopic, is now widely performed.
- Fetoscopy is perceived as safe for the mother, although specific data on maternal complications is lacking.
- Open fetal surgery is known to cause maternal morbidity, but the exact nature and frequency of complications is not well established across different centres and types of surgery.

What does this study add?

- This study estimates the nature and frequency of maternal complications following fetoscopic and open fetal surgery.
- For open fetal surgery the severe complication rate (Grade III to V according to the Clavien-Dindo classification of surgical complications) is approximately 4% and minor complication rate is 16%.
- For fetoscopic fetal surgery the severe complication rate is approximately 2% and minor complication rate is 4%.

Abstract

*Objective*

To establish maternal complication rates for fetoscopic or open fetal surgery.

*Methods*

We conducted a systematic literature review for studies of fetoscopic or open fetal surgery performed since 1990, recording maternal complications during fetal surgery, the remainder of pregnancy, delivery and after the index pregnancy.

*Results*

One hundred and sixty-six studies were included, reporting outcomes for open fetal (n=1193 patients) and fetoscopic surgery (n=9403 patients). No maternal deaths were reported. The risk of any maternal complication in the index pregnancy was 20.9% (95%CI 15.22-27.13) for open fetal and 6.2% (95%CI 4.93-7.49) for fetoscopic surgery. For severe maternal complications (Grade III to V Clavien-Dindo classification of surgical complications) the risk was 4.5% (95%CI 3.24-5.98) for open fetal and 1.7% (95%CI 1.19-2.20) for fetoscopic surgery. In subsequent pregnancies, open fetal surgery increased the risk of preterm birth but not uterine dehiscence or rupture. Nearly one quarter of reviewed studies (n=175, 23.3%) were excluded for failing to report the presence or absence of maternal complications.

*Conclusions*

Maternal complications occur in 6.2% fetoscopic and 20.9% open fetal surgeries, with serious maternal complications in 1.7% fetoscopic and 4.5% open procedures.

Reporting of maternal complications is variable. To properly quantify maternal risks, outcomes should be reported consistently across all fetal surgery studies.

Keywords:

Fetal surgery, fetoscopic surgery, maternal safety, maternal complications

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## Introduction

The last 35 years have witnessed an expansion of fetal therapy options[1 2], with surgery on the fetus, placenta, or cord now relatively common in tertiary-level fetal medicine units. Enabled by advancements in imaging, surgical instrumentation and techniques, early diagnosis and treatment of fetal anomalies is now possible for a wide range of conditions[3].

The mother has been called an "innocent bystander" in fetal surgery[4] and generally fetal therapy is almost exclusively offered to women who are healthy themselves. Fetal surgery poses risks to the mother not only during the procedure itself but also throughout the remainder of the index pregnancy, potentially during any future pregnancies and throughout the woman's entire life. Fetal surgery offers no direct medical benefit to the mother, and from an ethical perspective maternal risks should be minor and acceptable to the mother and family[5].

Information regarding safety of surgery is important for counselling and informed decision making; however, robust data on maternal complications of fetal surgery are lacking. One single-centre study of maternal outcomes following both open fetal and fetoscopic surgery performed between 1989 and 2003 found a number of short-term morbidities[6]. A systematic review of maternal complications following fetoscopic laser coagulation for twin-to-twin transfusion syndrome (TTTS) in 1785 patients treated between 1990 and 2009[7] observed an overall adverse event rate of 5.4% with severe complications in 1.0%. The aim of this study was to estimate the incidence of immediate and long-term maternal complications of fetoscopic or open fetal surgery through a systematic review of the literature.

## Methods

### *Protocol and Registration*

This systematic review was conducted in accordance with Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidance[8]. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO-CRD42017082411).

### *Eligibility criteria*

All randomised, cohort and case-controlled studies and case series reporting the results of open fetal or fetoscopic fetal surgery in humans from January 1990 to October 2018 were considered eligible. No language restrictions were applied. Systematic reviews, narrative review articles and case reports were excluded. There is no accepted numerical definition of a case series[9]. We used an empirical cut-off of at least three cases because of the rarity of some procedures and conditions searched for.

### *Search strategy*

A systematic review was conducted in MEDLINE, EMBASE and Cochrane databases using free text and Medical Subject Headings (MESH). The electronic search strategy is described in Supplement 1. Subsequently, a grey literature (first 100 hits in Pubmed and Google Scholar) search was performed, and reference lists of relevant review articles were manually checked. Covidence software (Veritas Health Innovation Ltd, Melbourne, Australia) was used to eliminate duplicate articles and manage study screening.

*Study selection*

Two authors (A.S. and L.VdV.) screened all titles and abstracts independently, excluded irrelevant studies and then independently assessed the remaining full-text articles for eligibility; disagreements were resolved by consensus. Studies were excluded if the full text was unavailable online and the abstract contained insufficient information. Studies with interventions which were not fully described or were performed on the neonate instead of the fetus were excluded. Interventions involving access to the uterus using a device with a total outer diameter of <1.5mm were excluded; this cut-off was chosen to avoid procedures performed with needles only (e.g. amniocentesis, fetal blood transfusion, thoraco- or vesicocentesis etc.). Studies of shunting were only included if the outer shunt diameter was ≥1.5mm or the shunt was inserted fetoscopically. Studies which did not report maternal outcomes were excluded. For the purpose of this study, preterm rupture of membranes (PROM), chorionic membrane separation (CMS), preterm labour, preterm delivery and gestational age at delivery, though relevant, were not considered to be maternal complications. Studies from which data could not be extracted (e.g. composite or combined outcomes given) and studies containing patient cohorts which appeared to have been published previously by the same authors were excluded.

*Data extraction*

Two authors independently extracted data (A.S. and E.B. for open fetal surgery studies, A.S. and C.F. for fetoscopic studies) and entered them into a standardised Excel (Microsoft, Washington, USA) form. Disagreements were resolved by consensus. The ex-utero intrapartum treatment (EXIT) procedure was classified as open fetal surgery. Study characteristics noted included study design, underlying fetal

condition, type of intervention, presence of a control group, gestational age at surgery and number of patients in each study. Outcomes recorded for the duration of the index pregnancy included intra-operative complications (maternal death, placental abruption, uterine bleeding/haemorrhage, blood transfusion, organ damage or anaesthetic complications), post-operative complications (classified from the end of surgery until delivery; maternal death, placental abruption, uterine bleeding/ haemorrhage, blood transfusion, sepsis, chorioamnionitis, other infections, pulmonary oedema, amniotic fluid embolism and other respiratory, gastro-intestinal, cardiac or wound problems), complications at delivery of the index pregnancy (uterine dehiscence or rupture or blood transfusion) and the need for additional treatment at any time during the pregnancy. Outcomes noted at any time following the index pregnancy (late outcomes) included fertility (number of further pregnancies, difficulty conceiving, mean time to conception), future pregnancy complications (miscarriage or pre-term delivery), complications during future deliveries (uterine dehiscence or rupture or haemorrhage at delivery), gynaecological and psychological symptoms. When a study reported “haemorrhage” or an actual blood loss of ≥1000mL we noted this as “haemorrhage”. This cut-off is an accepted definition of severe bleeding both in pregnancy[10] and post-partum[11]. If a study did not specify whether a complication occurred intra- or post-operatively (e.g. placental abruption, requirement for blood transfusion) then this was assumed to have occurred post-operatively.

All complications were independently graded according to the Clavien-Dindo classification of surgical complications[12] by two authors (A.S. and L.VdV.) (Supplement 2). Clavien-Dindo grade I or II complications were defined as mild; grade III to V complications were defined as severe[12].

*Quality assessment of studies*

Study quality and risk of bias were analysed by two authors (A.S. and L.VdV.) independently using a standardised form. Randomised trials were analysed using the Cochrane Collaboration's tool for assessing risk of bias[13]. Case-control studies were analysed using the Newcastle-Ottawa scale for assessing the quality of non-randomised studies[14]. Case series were analysed using the National Institutes of Health study quality assessment tool[15].

*Assessment of heterogeneity*

Methodological and clinical heterogeneity of data per study were evaluated. Variables were tested for statistical heterogeneity by applying the $I^2$ test to determine whether data could be pooled. An $I^2$ value less than 40% was taken to indicate minor heterogeneity; 40-75% moderate heterogeneity and >75% substantial heterogeneity[13].

*Meta-analysis*

Meta-analysis for all outcomes was carried out using MedCalc statistical software version 15.4 (MedCalc Software, Ostend, Belgium). Results were expressed as proportions with 95% confidence intervals (CI) as all outcomes were categorical variables. Pooled proportions were calculated using both the fixed and random effects model in case of homogeneity or heterogeneity respectively.

## Results

### *Study selection*

The electronic literature search identified 70,367 studies published between 1990 and 2018 (Figure 1); search of the grey literature and reference lists identified a further 16 studies. Following this, 48,248 studies were immediately removed as duplicates. The remaining studies (22,135) were screened by title and abstract, and a further 21,384 were excluded as irrelevant. Full texts of the remaining 751 articles were reviewed, and 585 were excluded for the following reasons: no reporting of maternal outcomes (175/585, 29.9% of studies excluded and 23.3% [175/751] of all studies assessed), insufficient information available (conference abstract/poster only or full text unavailable) (119/585, 20.3%), study design other than randomised trial, case-control trial or case series (110/585, 18.8%) and uterine access using a device <1.5mm (59/585, 10.1%). Thirty studies were translated from French (10), Spanish (7), Polish (5), German (3), Dutch (2), Portuguese (2) and Turkish (1), of which 16 were included following review. Two Chinese-language papers were identified but the full text could not be accessed online. Eventually 166 studies were included; 41 on open fetal surgery, 122 on fetoscopic surgery and three studies including both surgery types.

### *Study characteristics*

Characteristics of included studies are shown in Tables 1-3. Studies of open fetal (Table 1) and fetoscopic (Table 2) surgery are presented and analysed separately as the difference in surgical technique was considered too great for combined analysis. Seven studies specifically focused on late complications, i.e. after the index pregnancy, and are presented separately (Table 3). The majority of studies (68.1%,

113/166) were case series i.e. without a control group; 27.1% (45/166) were case control studies and 4.8% (8/166) were randomised trials.

*Risk of bias*

Quality assessment of the studies is given in Supplement 3. Most studies (139/166, 83.7%) had a low risk of bias or were high quality. All remaining studies (27/166, 16.3%) had an unclear risk of bias or were fair quality. No studies were found to have a high risk of bias or be low quality overall. For randomised trials, included studies had a high risk of bias with regards to blinding. For case control studies, included studies did not describe statistical methods well overall.

*Statistical heterogeneity*

Maternal outcome data was pooled in 64 separate meta-analyses, of which 37.5% (24/64) had no or minor heterogeneity. In 39.1% (25/64) there was moderate heterogeneity and in 23.4% (15/64) there was considerable heterogeneity. The levels of heterogeneity per outcome measure are listed in Supplement 4. As both clinical and statistical heterogeneity were found, pooled proportions were given using the random effects model for meta-analysis.

*Maternal complications in the index pregnancy - intra-operative*

Table 4 summarises maternal complications according to type of surgery performed. No maternal deaths (Clavien-Dindo grade V) due to fetal surgery were reported in any study (10,596 procedures). One study[16] reported a patient at 20 weeks' gestation experiencing a cardio-respiratory arrest *prior* to fetoscopy for laser photocoagulation. The cause was considered to be a combination of morbid obesity, spinal anaesthesia

and aorto-caval compression, and not related to the procedure which had not commenced. An immediate delivery was conducted by hysterotomy as part of maternal resuscitation and the patient made a full recovery. Another study[17] reported brief maternal seizure-like activity during open fetal surgery, which was thought to be anaesthesia-related.

Haemorrhage severe enough to prompt delivery or termination of pregnancy at the time of surgery as a life-saving procedure for the mother (Clavien-Dindo grade III) occurred in 0.92% of open fetal (95% CI 0.46-1.62) and 0.26% of fetoscopic surgeries (95% CI 0.17-0.38). Three cases[18 19 20] occurred due to placental abruption during open fetal surgery for myelomeningocele (MMC) repair, following which delivery occurred, with all three fetuses surviving. Two cases[21 22] occurred following laser photocoagulation for TTTS said to be due to “excessive bleeding from placental anastomoses” and the uterine wall respectively. Two cases[23 24] occurred during selective reduction, with haemorrhage from the uterine wall prompting delivery. Finally, one pregnancy was terminated due to bleeding from a trocar placental injury during fetoscopic MMC repair.[25]

In total, placental abruption (Clavien-Dindo grade III) occurred intraoperatively in 1.28% of open fetal (95% CI 0.73-1.98) and in 0.28% of fetoscopic surgeries (95% CI 0.18-0.39). Bleeding during the procedure was noted in 1.97% of open fetal (95% CI 0.97-3.31) and in 1.74% of fetoscopic surgery cases (95% CI 1.25-2.32). Intra-operative blood transfusion was required in 1.00% of patients undergoing open fetal surgery (95% CI 0.53-1.64) and in 0.27% undergoing fetoscopic surgery (95% CI 0.18-0.38). Intra-operative skin burns at the site of diathermy pads occurred in 0.26% of

patients (95% CI 0.17-0.37) during fetoscopic surgery; this outcome was not reported in any open fetal surgery.

*Maternal complications in the index pregnancy - postoperative*

One study on laser photocoagulation for TTTS (n=132)[26] reported a maternal death from disseminated intravascular coagulation (DIC) four weeks following an uneventful procedure. A post-mortem examination did not find any evidence of chorioamnionitis or amniotic fluid embolism and the authors therefore concluded that this death was unrelated to the procedure.

Haemorrhage severe enough to prompt return to theatre for termination or delivery of the pregnancy within 24 hours was not reported following any open fetal surgeries but occurred following 0.25% of fetoscopic procedures (95% CI 0.16-0.37). This included one[27] four hours post-fetoscopic tracheal balloon removal with no cause of the bleeding found. There were two late placental abruptions, one[28] 12 hours post-laser photocoagulation and one[29] within 24 hours of bipolar cord coagulation.

Placental abruption occurred in 1.80% of patients following open fetal (95% CI 1.14-2.63) and in 1.29% following fetoscopic surgery (95% CI 0.90-1.75). Post-operative blood transfusion was given to 3.36% after open fetal surgery (95% CI 1.85-5.29) and in 0.32% following fetoscopic surgery (95% CI 0.22-0.44).

Chorioamnionitis following open fetal surgery or endometritis following an EXIT procedure occurred in 4.13% of women (95% CI 3.03-5.40), and in 1.45% undergoing fetoscopic surgery (95% CI 1.06-1.90). Of those, PROM was reported to have

occurred in 47.78% following open fetal surgery (95% CI 23.01-73.16) and in 36.31% following fetoscopic surgery (95% CI 22.00-51.99). One study reported severe chorioamnionitis five days after bipolar cord coagulation[30] with septic shock and acute kidney injury which resolved leaving 70% residual renal function. Sepsis was also reported in one patient[31] with chorioamnionitis following fetoscopic laser photocoagulation and in one patient[32] following open MMC repair who developed post-operative peritonitis requiring an emergency laparotomy and delivery. Post-operative pneumonia occurred in two patients - one[33] following fetoscopic radiofrequency ablation (RFA), necessitating three days of intubation and intensive care unit (ICU) care; and one requiring ICU admission [34] following open MMC repair.

Pulmonary oedema occurred in 4.32% of open fetal surgery cases (95% CI 2.32-6.90), and in 0.63% of fetoscopic cases (95% CI 0.43-0.87). Three studies in which post-operative pulmonary oedema occurred reported on peri-operative fluid management (3/102, 2.9%) and 33 reported on the use of magnesium sulphate (33/102, 32.4%) without specifically suggesting causality. Six women required ICU admission, with four requiring intubation and ventilation; three following open fetal surgery[6 35] and three following fetoscopic surgery[36 37 38].

*Maternal complications in the index pregnancy - at delivery*

Only a few fetoscopic surgery studies (4/121 studies, 0.33%) reported findings or complications at delivery. Complications at delivery following open fetal surgery are shown in Table 4. Hysterectomy at or around the time of delivery was reported in two patients (Clavien-Dindo grade III). In one case[39], caesarean delivery following open MMC repair in a woman with two previous caesareans, intra-abdominal scarring and

friable tissue eventually resulted in hysterectomy. In the second case[38] following laser photocoagulation for TTTS and PROM, a caesarean section was performed at 33 weeks' gestation. A hysterectomy was eventually required due to haemorrhage with DIC and the patient spent five days in ICU, where she also experienced an iatrogenic pneumothorax.

Uterine rupture occurred in 0.90% of patients at delivery following open fetal surgery (excluding EXIT procedures) in the index pregnancy (95% CI 0.41-1.59), and uterine dehiscence occurred in 3.67% (95% CI 2.01-5.81). Blood transfusion was given to 1.83% of women (95% CI 1.16-2.65) at delivery following open fetal surgery.

*Overall maternal complication rates*

Table 4 displays maternal complications. In open fetal surgery there was a 4.51% severe (95% CI 3.24-5.98), a 16.26% minor complication rate (95% CI 11.17-22.09), and a total complication rate of 20.86% (95% CI 15.22-27.13). For fetoscopic surgery, the corresponding rates were: 1.66% severe (95% CI 1.19-2.20), 4.33% minor (95% CI 3.33-5.45) and 6.15% total complications (95% CI 4.93-7.49). Complication rates in the six commonest fetal surgical procedures performed are displayed in Table 5.

*Maternal outcomes following the index pregnancy (long-term)*

Table 6 shows subsequent pregnancy outcomes and long-term maternal outcomes following a pregnancy in which fetal surgery was performed. New difficulties in conceiving were described in 3.81% of women after open fetal surgery (95% CI 1.22-7.76, reported in four studies); this outcome was not reported to occur after fetoscopic surgery (three studies). Pregnancy loss prior to 24 weeks' gestation occurred in

19.95% of pregnancies conceived following open fetal surgery (95% CI 13.37-27.48, three studies) and 13.67% of pregnancies conceived after fetoscopic surgery (95% CI 9.34-18.68, three studies). Preterm birth occurred in 20.49% of pregnancies following open fetal surgery (95% CI 10.48-32.81, four studies) and in 2.12% of pregnancies following fetoscopic surgery (95% CI 0.02-9.01; three studies). Uterine rupture or dehiscence occurred respectively in 6.89% (95% CI 1.34-16.27, reported in three studies) and 11.09% (95% CI 5.34-18.59) of pregnancies following open fetal surgery. None were mentioned in fetoscopy studies.

## Discussion

In this systematic review of the literature we found an overall complication rate of approximately 21% for open fetal surgery and 6% for fetoscopic fetal surgery, of which minor complications occurred in 16% and 4% of surgeries respectively. This maternal complication rate excludes obstetric complications which may also have occurred (e.g. PROM, CMS, preterm labour and preterm delivery). Additionally, many studies of fetal surgery fail to document maternal complications. Out of 751 full-text articles reviewed, 175 (23.3%) were excluded as no maternal outcomes were stated. Although 68 of these studies focused on a specific aspect of the surgery or its neonatal outcome, 107 studies (92 fetoscopic and 15 open) involving over 9000 patients did *not* comment on the presence or absence of any complications specifically affecting the mother's health. Often the "maternal outcomes" stated meant in reality obstetric outcomes (e.g. PROM, preterm labour). We also found that maternal complications were often presented from the fetal perspective (e.g. fetal demise caused by placental abruption). Thirty included studies (18.1%) contained a statement that no adverse maternal outcomes were observed without specifying what was meant by maternal outcomes.

Among these studies were some large series, including a study of 201 patients undergoing fetoscopic tracheal balloon removal[40] and studies of 200[41] and 500[42] patients undergoing fetoscopic laser coagulation. It is unlikely that such large numbers of procedures had no maternal complications, and more likely that complications were either not perceived as serious, not reported and/or the patient follow-up was incomplete. This lack of reporting has most likely led to an underestimation of the actual risk of maternal complications in our meta-analysis. Conversely, when maternal complications were reported, there was a wide variability in which outcomes were discussed and how they were presented.

There was a severe complication rate (Clavien-Dindo grade III or IV) of 4.5% in women undergoing open fetal surgery and 1.7% undergoing fetoscopic surgery. This is in keeping with a previous multi-centre review of maternal complications following laser photocoagulation for TTTS[7] which found a 1.0% rate of severe complications and a 5.4% total rate of complications across all studies; however, when the authors only included studies which systematically assessed maternal complications as a primary or secondary outcome, this rose to 1.8% for severe and 17.4% for all complications.

In almost all studies of fetal surgery reviewed, long-term maternal follow up was not described. The seven studies that did so had a wide variation in the parameters described. Fertility does not appear to be negatively affected by fetal surgery, with the rates of de novo difficulties for conceiving in this review (3.81% following open fetal surgery and none following fetoscopic surgery) being comparable, if not less, than published rates of secondary infertility in the general population[43]. Similarly, the rates of miscarriage described (19.85% following open fetal and 13.67% following fetoscopic

surgery) are similar to rates of spontaneous miscarriage in women who have not undergone fetal surgery [44] [45] [46]. Epidemiological studies[47] have suggested a worldwide preterm birth rate of 11.1% with a rate of 8.6% in "developed regions"[47]. In the US and UK it is estimated at 9.8%[48] and 7.3%[49] respectively. The preterm birth rate in this review following open fetal surgery (20.49%) is higher than the usual prevalence, but not higher following fetoscopic surgery (2.12%). Open fetal surgery was followed by uterine rupture or dehiscence in 6.89% and 11.09% of subsequent pregnancies respectively, which is in line with published rates of rupture (6.2%) and dehiscence (12.5%) following a classical caesarean section[50]. Conversely, no uterine ruptures were reported following fetoscopic surgery.

This study included the commonest fetal procedures and, from a maternal perspective, involved similar surgical manipulations yet variable operating times. We included studies from multiple centres worldwide and attempted to identify the non-English literature. It is therefore likely that these results are generalisable to fetal surgery performed outside the included studies. An obvious weakness of this systematic review is that most studies did not include a control group. Furthermore, we decided to pool data for meta-analysis despite having high heterogeneity in some results. Another weakness is the extraction of patient data from papers, which is prone to error given the variable reporting; it is possible that some patients had more than one complication and this was not noted or cumulative rates were as a consequence miscalculated.

This systematic review has identified a significant rate of maternal complications, which should be discussed with patients before embarking on fetal surgery. Large

studies allow an estimation of the likelihood of these events, insomuch as the cases in these series are unselected and consecutive. Our systematic review search strategy may have missed relevant yet rare complications. For example, a letter to a journal editor describing maternal convulsions during general anaesthesia[51] was excluded as a case report according to our criteria. In this circumstance, it appears the patient was also part of the cohort of a study that was included[17], but it is possible that other rare events reported as case series have been missed. An international, prospective registry of fetal and fetoscopic surgery, such as the Eurofoetus[52] and NAFTNet[53] registries, would be the best way to accurately determine complication types and rates and avoid missing rare complications.

Conclusion

The maternal risks of fetal surgery are accepted by many patients and healthcare professionals for the possible benefit to the fetus[54 55]. This systematic review finds that studies of fetal surgery focus on the fetal outcomes of the procedure, and many fail to describe maternal complications. Fetal surgery comes at a risk to the mother, which may be underestimated by fetal therapists due to under-reporting and variable reporting quality. In order to properly quantify maternal risks, outcomes should be reported consistently across all studies of fetal surgery, preferentially in prospective registries.

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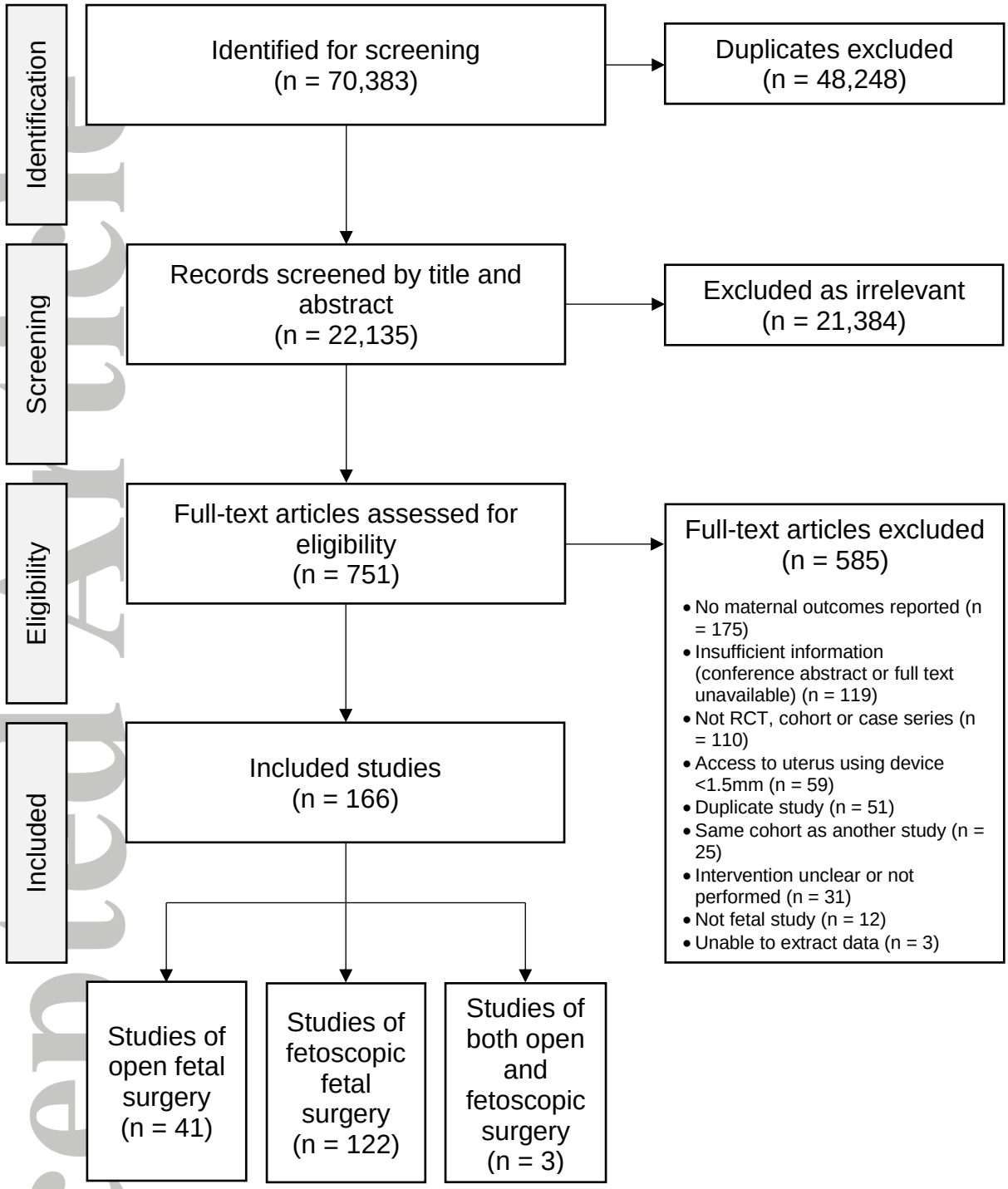


Figure 1: Flow diagram of study selection adapted from PRISMA 2009[8]

Table 1: Included studies of open fetal surgery.

| Category | First author and year of publication | Condition | Procedure | Study design | No. of patients |
|---|---|---|---|---|---|
| EXIT | Barthod 2013[56] | Neck mass, CHAOS | EXIT | Case series | 5 |
| | Cass 2013[57] | Lung mass, mediastinal mass | EXIT | Case series | 9 |
| | Chen 2018[58] | Omphalocele | EXIT | Case control | 7 |
| | Dahlgren 2004[59] | Head or neck tumour | EXIT | Case series | 4 |
| | Flake 2000†[35] | CDH | EXIT | Case series | 15 |
| | George 2007[60] | Skeletal dysplasia, micrognathia | EXIT | Case series | 3 |
| | Hedrick 2003[61] | Multiple | EXIT | Case series | 43 |
| | Hedrick 2005[62] | Lung lesions | EXIT | Case series | 9 |
| | Kern 2007[63] | CCAM, hydrothorax | EXIT | Case series | 5 |
| | Kornacki 2017[64] | Neck mass, CHAOS | EXIT | Case series | 4 |
| | Kunisaki 2007[65] | CDH | EXIT | Case control | 14 |
| | Laje 2012[66] | Cervical teratoma | EXIT | Case series | 17 |
| | Laje 2013[67] | Neck mass | EXIT | Case series | 4 |
| | Laje 2015[68] | Cervical lymphatic mass | EXIT | Case series | 13 |
| | Lazar 2011[69] | Neck mass | EXIT | Case series | 12 |
| | Noah 2002[70] | Not stated | EXIT | Case control | 34 |
| | Pellicer 2007[71] | Neck mass | EXIT | Case series | 3 |
| | Stoffan 2012[72] | CDH | EXIT | Case control | 7 |
| | Tuncay Ozgunen 2010[73] | Neck mass | EXIT | Case series | 3 |
| | Zamora 2013†‡[74] | MMC, lung mass, SCT | EXIT | Case series | 26 |
| MMC | Bennett 2014[34] | MMC | Neurosurgical repair | Case control | 43 |
| | Botelho 2017[75] | MMC | Neurosurgical repair | Case series | 45 |
| | Bruner 1999[18] | MMC | Neurosurgical repair | Case control | 29 |
| | Bruner 2000*[76] | MMC | Neurosurgical repair | Case control | 4 |
| | Farmer 2003[77] | MMC | Neurosurgical repair | Case series | 12 |
| | Friszer 2016[78] | MMC | Neurosurgical repair | Case series | 3 |
| | Johnson 2016[79] | MMC | Neurosurgical repair | Randomised | 91 |
| | Marenco 2013[80] | MMC | Neurosurgical repair | Case series | 4 |
| | Moldenhauer 2015[39] | MMC | Neurosurgical repair | Case series | 100 |
| | Moron 2018[19] | MMC | Neurosurgical repair | Case series | 237 |
| | Ochsenbein-Kolble 2017[20] | MMC | Neurosurgical repair | Case control | 30 |
| | Sinskey 2017[17] | MMC | Neurosurgical repair | Case series | 47 |
| | Soni 2016[81] | MMC | Neurosurgical repair | Case series | 88 |
| | Zamlynski 2014[32] | MMC | Neurosurgical repair | Case control | 46 |
| CDH | Flake 2000†[35] | CDH | Tracheal occlusion | Case series | 15 |
| | Harrison 1990[82] | CDH | Diaphragm repair | Case series | 6 |
| | Harrison 1993[83] | CDH | Diaphragm repair | Case series | 14 |
| | Harrison 1998*[84] | CDH | Tracheal occlusion | Case control | 13 |
| CCAM | Adzick 2003[85] | CCAM | Lung resection | Case series | 22 |
| SCT | Hedrick 2004[86] | SCT | Debulking | Case series | 4 |
| Mixed | Golombeck 2006†*[6] | MMC, CCAM, SCT | Mixed | Case control | 79 |
| | Longaker 1991[87] | LUTO, CDH, SCT, CCAM | Mixed | Case series | 17 |
| | Zamora 2013†‡[74] | MMC, lung mass, SCT | Mixed | Case series | 7 |
| **TOTAL** | | | | **43 studies** | **1193 patients** |

† Studies including patients undergoing a primary fetal and later an EXIT procedure.

* Studies including both open and fetoscopic procedures, also included in Table 2

‡ Studies including immediate and late complications, also included in Table 3

CCAM - congenital cystic adenomatoid malformation, CDH - congenital diaphragmatic hernia, CHAOS - congenital high airway obstruction syndrome, EXIT - ex-utero intrapartum treatment, LUTO - lower urinary tract obstruction, MMC - myelomeningocele, SCT - sacrococcygeal teratoma

Table 2: Included studies of fetoscopic surgery.

| Category | First author and year of publication | Condition | Procedure | Study design | No. of patients |
|---|---|---|---|---|---|
| Multiple pregnancy complications treated with laser | Aboudiab 2017[88] | TTTS | Laser photocoagulation | Case series | 18 |
| | Baschat 2013[89] | TTTS | Laser photocoagulation | Case control | 147 |
| | Chalouhi 2016[90] | TTTS (triplets) | Laser photocoagulation | Case series | 22 |
| | Chang 2006[21] | TTTS | Laser photocoagulation | Case series | 27 |
| | Chang 2016[91] | TTTS | Laser photocoagulation | Case control | 100 |
| | Chmait 2013[31] | TTTS | Laser photocoagulation | Case control | 318 |
| | Chmait 2017[92] | TTTS | Laser photocoagulation | Case series | 19 |
| | Crombleholme 2007[93] | TTTS | Laser photocoagulation | Randomised | 20 |
| | De Lia 1995[94] | TTTS | Laser photocoagulation | Case series | 26 |
| | De Lia 1999[95] | TTTS | Laser photocoagulation | Case series | 67 |
| | De Lia 2009[96] | TTTS (triplets) | Laser photocoagulation | Case series | 10 |
| | Deprest 1998[97] | TTTS | Laser photocoagulation | Case series | 6 |
| | Draga 2016[98] | TTTS | Laser photocoagulation | Case series | 37 |
| | Duron 2014[36] | TTTS | Laser photocoagulation | Case control | 85 |
| | Ek 2012[99] | TTTS | Laser photocoagulation | Case series | 67 |
| | Habli 2009[100] | TTTS | Laser photocoagulation | Case series | 152 |
| | Has 2014[101] | TTTS | Laser photocoagulation | Case series | 85 |
| | Hecher 2000[41] | TTTS | Laser photocoagulation | Case control | 200 |
| | Hernandez-Andrade 2011[102] | TTTS | Laser photocoagulation | Case series | 35 |
| | Huber 2008[22] | TTTS | Laser photocoagulation | Case control | 176 |
| | Ishii 2014[103] | TTTS (triplets) | Laser photocoagulation | Case series | 16 |
| | Ishii 2015[104] | sFGR | Laser photocoagulation | Case series | 10 |
| | Lanna 2017[105] | TTTS | Laser photocoagulation | Case control | 373 |
| | Lecointre 2017[106] | TTTS | Laser photocoagulation | Case control | 200 |
| | Malshe 2017[107] | TTTS | Laser photocoagulation | Case series | 203 |
| | Martinez 2012[42] | TTTS | Laser photocoagulation | Case series | 500 |
| | Middeldorp 2007[108] | TTTS | Laser photocoagulation | Case series | 100 |
| | Miyadahira 2018[109] | sFGR | Laser photocoagulation | Case control | 67 |
| | Molina-Garcia 2009[110] | TTTS, sFGR | Laser photocoagulation | Case series | 22 |
| | Morris 2010[111] | TTTS | Laser photocoagulation | Case series | 164 |
| | Mullers 2015[16] | TTTS | Laser photocoagulation | Case series | 105 |
| | Nakata 2016[37] | TTTS | Laser photocoagulation | Case series | 6 |
| | Nguyen 2012[112] | TTTS | Laser photocoagulation | Case series | 98 |
| | Ozawa 2017[113] | Amniotic fluid discordance | Laser photocoagulation | Case series | 11 |
| | Papanna 2010[114] | TTTS | Laser photocoagulation | Case control | 48 |
| | Papanna 2012[115] | TTTS | Laser photocoagulation | Case control | 163 |
| | Peeters 2014[116] | TTTS | Laser photocoagulation | Case control | 338 |
| | Persico 2016[117] | TTTS | Laser photocoagulation | Case series | 106 |
| | Quintero 2000[118] | TTTS | Laser photocoagulation | Case control | 92 |
| | Quintero 2001[119] | sFGR | Laser photocoagulation | Case series | 11 |
| | Rossi 2008[120] | TTTS | Laser photocoagulation | Case control | 266 |
| | Ruano 2009[121] | TTTS | Laser photocoagulation | Case series | 19 |
| | Ruegg 2018[122] | TTTS | Laser photocoagulation | Case control | 37 |
| | Rustico 2012[38] | TTTS | Laser photocoagulation | Case series | 150 |
| | Said 2008[123] | TTTS | Laser photocoagulation | Case series | 10 |
| | Senat 2004[124] | TTTS | Laser photocoagulation | Randomised | 72 |
| | Sepulveda 2007[125] | TTTS | Laser photocoagulation | Case series | 33 |
| | Shamshirsaz 2015[126] | TTTS | Laser photocoagulation | Case control | 55 |
| | Slaghekke 2014[127] | TTTS | Laser photocoagulation | Randomised | 274 |
| | Taniguchi 2015[128] | TTTS | Laser photocoagulation | Case series | 3 |
| | Tchirikov 2011[129] | TTTS | Laser photocoagulation | Case control | 80 |

| | | | | | |
|---|---|---|---|---|---|
| | Teoh 2013[130] | TTTS | Laser photocoagulation | Case series | 49 |
| | Thia 2017[131] | TTTS | Laser photocoagulation | Case series | 5 |
| | Ville 1997[132] | TTTS | Laser photocoagulation | Case series | 132 |
| | Ville 1998[26] | TTTS | Laser photocoagulation | Case control | 44 |
| | Weingertner 2011[133] | TTTS | Laser photocoagulation | Case series | 100 |
| | Wilson 2016[134] | TTTS | Laser photocoagulation | Case series | 151 |
| | Yamamoto 2005[28] | TTTS | Laser photocoagulation | Case series | 175 |
| | Yang 2010[135] | TTTS | Laser photocoagulation | Case series | 30 |
| | Zaretsky 2018[136] | TTTS | Laser photocoagulation | Case series | 749 |
| | Zhao 2016[137] | TTTS | Laser photocoagulation | Case control | 62 |
| Multiple pregnancy complications treated with selective reduction | Bebbington 2012[138] | TTTS, TRAP, sFGR, discordant anomaly | RFA | Case control | 146 |
| | Berg 2014[139] | TRAP | RFA | Case control | 7 |
| | Delabaere 2013[23] | TTTS, TRAP, sFGR, discordant anomaly | BCC, cord compression, cord ligation | Case series | 30 |
| | Deprest 2000[140] | TTTS, TRAP | BCC | Case series | 10 |
| | Gallot 2003[24] | TTTS, TRAP | CO | Case series | 11 |
| | Gouverneur 2009[141] | TTTS, TRAP, sFGR, discordant anomaly | BCC, laser cord photocoagulation | Case series | 54 |
| | Gul 2008[142] | TTTS, TRAP, discordant anomaly | BCC | Case series | 9 |
| | Has 2014[143] | TTTS, TRAP, sFGR, discordant anomaly | BCC | Case series | 71 |
| | He 2010[144] | TTTS, TRAP, sFGR, discordant anomaly | BCC | Case series | 14 |
| | Ilagan 2008[145] | TTTS, TRAP, discordant anomaly | BCC | Case series | 27 |
| | Jelin 2010[146] | TRAP | RFA | Case control | 7 |
| | King 2017[147] | TRAP, discordant anomaly | Laser cord photocoagulation | Case series | 43 |
| | Lanna 2012[148] | TTTS, TRAP, sFGR, discordant anomaly | BCC | Case series | 118 |
| | Lee 2013[149] | TRAP | RFA | Case series | 98 |
| | Lewi 2006[30] | TTTS, TRAP, sFGR, discordant anomaly | Laser cord photocoagulation | Case series | 80 |
| | Moise 2008[33] | TTTS, discordant anomaly | RFA | Case series | 9 |
| | Nobili 2013[150] | Discordant anomaly | BCC | Case series | 48 |
| | Paramasivam 2010[151] | TTTS, TRAP, sFGR, discordant anomaly | RFA | Case series | 35 |
| | Peng 2016[152] | TTTS, TRAP, sFGR, discordant anomaly, TAPS | BCC | Case control | 93 |
| | Quintero 1996[153] | TTTS, TRAP, discordant anomaly | CO | Case series | 13 |
| | Quintero 2006[154] | TRAP | CO or laser photocoagulation | Case control | 51 |
| | Roman 2010[155] | TTTS, TRAP, sFGR, discordant anomaly | RFA | Case control | 60 |
| | Schou 2018[156] | TTTS, TRAP, sFGR, discordant anomaly | BCC | Case control | 102 |
| | Sugibayashi 2016[157] | TRAP | RFA | Case series | 40 |
| | Takano 2015[158] | TRAP | Laser photocoagulation +/- transection of cord (MCMA) | Case series | 10 |
| | Taylor 2002[29] | TTTS | BCC | Case series | 15 |
| | Tsao 2002[159] | TRAP | RFA | Case series | 13 |
| | Zhang 2018[160] | TRAP | RFA | Case series | 25 |
| CDH | Deprest 2005[161] | CDH | FETO | Case series | 20 |

| | | | | | |
|---|---|---|---|---|---|
| | Harrison 1998*[84] | CDH | Tracheal clip | Case control | 8 |
| | Harrison 2003[162] | CDH | FETO | Randomised | 11 |
| | Jani 2005[163] | CDH | FETO | Case series | 24 |
| | Jani 2006[164] | CDH | FETO | Case series | 28 |
| | Jani 2009[165] | CDH | FETO | Case series | 210 |
| | Jimenez 2017[40] | CDH | Fetoscopic balloon removal | Case control | 201 |
| | Kosinski 2017[166] | CDH | FETO | Case series | 28 |
| | Manrique 2008[167] | CDH | FETO | Case control | 11 |
| | Peralta 2011[168] | CDH | FETO | Case series | 8 |
| | Persico 2017[169] | CDH | FETO | Case series | 21 |
| | Ruano 2012[170] | CDH | FETO | Case control | 35 |
| | Ruano 2012[171] | CDH | FETO | Randomised | 20 |
| | Ruano 2013[172] | CDH | FETO | Case control | 17 |
| MMC | Arens 2017[173] | MMC | Patch | Case series | 59 |
| | Belfort 2017[174] | MMC | Single layer suture (skin + dura) | Case series | 22 |
| | Bruner 2000*[76] | MMC | Maternal skin graft | Case control | 4 |
| | Degenhardt 2014[175] | MMC | Patch | Case series | 51 |
| | Kohn 2018[176] | MMC | Patch | Case series | 34 |
| | Pedreira 2014[177] | MMC | Patch + skin suture | Case series | 4 |
| | Pedreira 2016[178] | MMC | Patch + skin suture | Case series | 10 |
| | Verbeek 2012[179] | MMC | Patch | Case control | 19 |
| | Ziemann 2018[180] | MMC | Patch | Case series | 65 |
| LUTO | Morris 2013[181] | LUTO | Vesicoamniotic shunting | Randomised | 16 |
| | Ruano 2010[182] | LUTO | Cystoscopy | Case control | 11 |
| | Welsh 2003[183] | LUTO | Cystoscopy | Case series | 13 |
| Shunts | Cavalheiro 2011[184] | Ventriculomegaly | Shunting | Case series | 30 |
| | Mallman 2017[185] | Hydrothorax | Shunting | Case series | 78 |
| Mixed | Golombeck 2006*[6] | TTTS, TRAP, CDH, LUTO | Mixed | Case control | 99 |
| | Kohl 2006[27] | MMC, CDH, CHAOS | Mixed | Case series | 16 |
| | Kohl 2010[25] | MMC, TTTS, CDH, CHAOS, ABS | Mixed | Case series | 37 |
| | Nivatpumin 2016[186] | TTTS, LUTO, CDH, TRAPS | Mixed | Case series | 152 |
| | Peralta 2010[187] | TTTS, CDH, TRAP | Mixed | Case series | 56 |
| **TOTAL** | | | | **122 studies** | **9403 patients** |

* Studies including both open and fetoscopic procedures, also included in Table 1

BCC - bipolar cord coagulation, CDH - congenital diaphragmatic hernia, CHAOS - congenital high airway obstruction syndrome, CO - cord occlusion, FETO - fetoscopic endoluminal tracheal occlusion, LUTO - lower urinary tract obstruction, MCMA - monochorionic monoamniotic, MMC - myelomeningocele, RFA - cord radiofrequency ablation, sFGR - selective fetal growth restriction, TAPS - twin anaemia-polycythaemia sequence, TO - tracheal occlusion, TRAP - twin reversed arterial perfusion sequence, TTTS - twin-to-twin transfusion syndrome.

Table 3: Included studies of open and fetoscopic surgery focusing on late complications.

| First author and year of publication | Type of surgery | Condition | Study design | Number of patients |
|---|---|---|---|---|
| Farrell 1999[4] | Open | CDH, CCAM, LUTO, SCT, | Case series | 45 |
| Thom 2016[188] | Open | MMC | Randomised | 87 |
| Wilson 2010[189] | Open | MMC, CCAM, CDH, SCT, mediastinal teratoma | Case series | 47 |
| Zamora 2013‡[74] | Open | MMC, lung mass, SCT, EXIT | Case series | 33 |
| Gregoir 2016[190] | Fetoscopic | CDH | Case control | 89 |
| Le Lous 2018[191] | Fetoscopic | TTTS | Case control | 122 |
| Vergote 2018[192] | Fetoscopic | TTTS | Case control | 92 |
| **TOTAL** | | | **7 studies** | **515 patients** |

‡ Studies including immediate and late complications, also included in Table 1

CCAM - congenital cystic adenomatoid malformation, CDH - congenital diaphragmatic hernia, EXIT - ex-utero intrapartum treatment, LUTO - lower urinary tract obstruction, MMC - myelomeningocele, SCT - sacrococcygeal teratoma, TTTS - twin-to-twin transfusion syndrome

Table 4: Maternal complications occurring with open or fetoscopic fetal surgery.

| | **Severe complications** | | | | **Minor complications** | | **All complications** |
|---|---|---|---|---|---|---|---|
| Clavien-Dindo classification | IV (requiring ICU care) | | III (requiring surgical intervention) | | I-II (requiring treatment) | | I - IV |
| **Open surgery n = 1193** | *Complication* | *n* | *Complication* | *n* | *Complication* | *n* | |
| | Severe infection | 2 | Haemorrhage requiring delivery | 3 | Bleeding during procedure | 13 | |
| | Pulmonary oedema | 4 | Placental abruption | 28 | Transfusion during/after procedure | 41 | |
| | Complete heart block†[a] | 1 | Bowel obstruction | 1 | Chorioamnionitis/ endometritis | 45 | |
| | | | Wound drainage | 2 | Other infections†[b] | 8 | |
| | | | Uterine rupture | 5 | Pulmonary oedema | 50 | |
| | | | Laparotomy/ dehiscence repair | 1 | Transfusion at delivery | 17 | |
| | | | Caesarean hysterectomy | 1 | | | |
| | | | | | | | |
| | **TOTAL SEVERE: 4.51% (95% CI 3.24-5.98)** | | | | **TOTAL MINOR: 16.26% (95% CI 11.17-22.09)** | | **ALL COMPLICATIONS: 20.86% (95% CI 15.22-27.13)** |
| **Fetoscopic surgery n = 9403** | Maternal cardiac arrest and delivery by hysterotomy | 1 | Sepsis requiring delivery | 1 | Bleeding during procedure | 165 | |
| | Severe infection | 2 | Haemorrhage requiring delivery | 8 | Transfusion during/after procedure | 16 | |
| | Pulmonary oedema | 3 | Placental abruption | 159 | Venous thromboembolism†[c] | 2 | |
| | Lung collapse | 1 | | | Chorioamnionitis | 114 | |
| | DIC + Caesarean hysterectomy | 1 | | | Other infections†[d] | 2 | |
| | Amniotic fluid embolism | 2 | | | Pulmonary oedema | 45 | |
| | | | | | Upper GI bleed†[e] | 1 | |
| | | | | | Diathermy skin burns | 4 | |
| | | | | | “Epidural headache” + blood patch | 1 | |
| | | | | | Wound hernia | 1 | |
| | | | | | Pleural effusions | 1 | |
| | | | | | | | **ALL COMPLICATIONS: 6.15% (95% CI 4.93-7.49)** |
| | **TOTAL SEVERE: 1.66% (95% CI 1.19-2.20)** | | | | **TOTAL MINOR: 4.33% (95% CI 3.33-5.45)** | | |

Pooled proportions calculated using random effect model for meta-analysis

n: number of women

†[a] Complete heart block considered to be tocolysis-related (magnesium sulphate)

†[b] Other infections in open surgery: wound (6), chest (1), urinary tract (1)

†[c] Venous thromboembolism: confirmed pulmonary embolism (1); suspected PE with confirmed deep vein thrombosis (1)

†[d] Other infections in fetoscopic surgery: wound (1), chest (1)

†[e] Upper GI bleed considered to be tocolysis-related (indomethacin)

Table 5: Maternal complications according to type of fetal surgery in the six most common procedures.

| | **Severe complications** | | | | **Minor complications** | | **All complications** |
|---|---|---|---|---|---|---|---|
| Clavien-Dindo classification | IV (requiring ICU care) | | III (requiring surgical intervention) | | I-II (requiring treatment) | | I - IV |
| **EXIT n = 237** | *Complication* | *n* | *Complication* | *n* | *Complication* | *n* | |
| | | | Placental abruption | 5 | Bleeding during procedure | 11 | |
| | | | | | Transfusion during/after procedure | 19 | |
| | | | | | Endometritis | 10 | |
| | | | | | Wound infection | 5 | |
| | | | | | | | |
| | **TOTAL SEVERE: 3.62% (95% CI 1.69-6.24)** | | | | **TOTAL MINOR: 17.53% (95% CI 9.86-26.86)** | | **ALL COMPLICATIONS: 20.19% (95% CI 4.93-7.49)** |
| **Open MMC repair n = 779** | Severe infection | 2 | Haemorrhage requiring delivery | 3 | Bleeding during procedure | 1 | |
| | Complete heart block | 1 | Placental abruption | 16 | Transfusion during/after procedure | 5 | |
| | Pulmonary oedema | 1 | Bowel obstruction | 1 | Chorioamnionitis | 21 | |
| | | | Uterine rupture | 4 | Other infections[†a] | 2 | |
| | | | Caesarean hysterectomy | 1 | Pulmonary oedema | 15 | |
| | | | | | Transfusion at delivery | 16 | |
| | | | | | | | |
| | **TOTAL SEVERE: 3.35% (95% CI 1.70-5.53)** | | | | **TOTAL MINOR: 6.63% (95% CI 3.63-10.45)** | | **ALL COMPLICATIONS: 11.54% (95% CI 7.73-15.99)** |
| **Fetoscopic MMC repair n = 268** | | | Placental abruption | 6 | Bleeding during procedure | 3 | |
| | | | | | Chorioamnionitis | 10 | |
| | | | | | Pulmonary oedema | 5 | |
| | | | | | | | |
| | **TOTAL SEVERE: 2.75% (95% CI 0.56-6.52)** | | | | **TOTAL MINOR: 9.04% (95% CI 3.27-17.40)** | | **ALL COMPLICATIONS: 12.49% (95% CI 4.83-23.06)** |
| **FETO (insertion or** | | | Placental abruption | 4 | Bleeding during procedure | 1 | |
| | | | | | Transfusion during/after procedure | 1 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **fetoscopic removal of balloon) n = 634** | | | | | Chorioamnionitis | 7 | **ALL COMPLICATIONS: 3.44% (95% CI 0.98-7.32)** |
| | | | | | Wound infection | 1 | |
| | | | | | Pulmonary oedema | 3 | |
| | | | | | | | |
| | **TOTAL SEVERE: 1.08% (95% CI 0.23-2.54)** | | | | **TOTAL MINOR: 2.39% (95% CI 0.71-5.02)** | | |
| **Fetoscopic laser photo-coagulation n = 6746** | Maternal arrest and delivery | 1 | Haemorrhage requiring delivery | 2 | Bleeding during procedure | 148 | **ALL COMPLICATIONS: 5.86% (95% CI 4.33-7.61)** |
| | Pulmonary oedema | 3 | Sepsis requiring delivery | 1 | Transfusion during/after procedure | 9 | |
| | Lung collapse | 1 | Placental abruption | 130 | VTE†b | 2 | |
| | Amniotic fluid embolism | 2 | | | “Epidural headache” + blood patch | 1 | |
| | DIC + Caesarean hysterectomy | 1 | | | Chorioamnionitis | 68 | |
| | | | | | Pulmonary oedema | 11 | |
| | | | | | Upper GI bleed†c | 1 | |
| | | | | | Wound hernia | 1 | |
| | | | | | | | |
| | **TOTAL SEVERE: 1.51% (95% CI 0.91-2.25)** | | | | **TOTAL MINOR: 4.03% (95% CI 2.73-5.56)** | | |
| **Fetoscopic selective reduction n = 1239** | Severe infection | 2 | Haemorrhage requiring delivery | 3 | Bleeding during procedure | 10 | **ALL COMPLICATIONS: 5.20% (95% CI 3.00-7.96)** |
| | | | Placental abruption | 14 | Diathermy skin burns | 4 | |
| | | | | | Chorioamnionitis | 19 | |
| | | | | | Chest infection | 1 | |
| | | | | | Pleural effusion | 1 | |
| | | | | | | | |
| | **TOTAL SEVERE: 1.98% (95% CI 0.97-3.35)** | | | | **TOTAL MINOR: 3.00% (95% CI 1.68-4.68)** | | |

Pooled proportions calculated using random effect model for meta-analysis

n: number of women

†a Other infections in MMC surgery: chest (1), urinary tract (1)

†b Venous thromboembolism: confirmed pulmonary embolism (1); suspected PE with confirmed deep vein thrombosis (1)

[†c] Upper GI bleed considered to be tocolysis-related (indomethacin)

EXIT - ex-utero intrapartum treatment, FETO - fetoscopic endoluminal tracheal occlusion, MMC - myelomeningocele, DIC - disseminated intravascular coagulation

Table 6: Long-term maternal complications following open and fetoscopic fetal surgery

| | | **Open surgery†a** % (95% CI) | **Fetoscopic surgery†a** % (95% CI) |
|---|---|---|---|
| **Conception** | Women attempting further pregnancy | 50.11 (21.55-78.63) | 51.76 (18.63-84.03) |
| | Women conceiving further pregnancy | 48.33 (26.74-70.26) | 48.20 (31.46-65.16) |
| | New sub-fertility | 3.81 (1.22-7.76) | NR |
| **Pregnancy outcomes** | Miscarriage | 19.95 (13.37-27.48) | 13.67 (9.34-18.68) |
| | Pre-term delivery | 20.49 (10.48-32.81) | 2.12 (0.02-9.01) |
| | Uterine rupture | 6.89 (1.34-16.27) | 0 |
| | Uterine dehiscence | 11.09 (5.34-18.59) | NR |
| | Excessive bleeding at delivery | 6.84 (2.16-13.88) | 5.52 (2.83-9.03) |
| **Non-pregnancy** | Abdominal pain | 6.38†b | 9.01 (3.84-16.06) |
| | Abnormal menstrual bleeding | NR | 6.54 (3.43-10.57) |
| | Gynaecological surgery†c | 8.68 (1.81-19.96) | NR |
| | Psychological symptoms | 9.09†b | 32.56 (7.70-64.58) |

Pooled proportions calculated using random effect model for meta-analysis

NR - not reported

†a Variable denominator as not all outcomes were reported by all studies

†b No meta-analysis possible as reported by single study

†c Gynaecological surgery following open fetal surgery: endometrial ablation (1), hysterectomy (6): caesarean hysterectomy (1), ovarian cysts+/-menstrual disorder (2), fibroids (1), unknown reason (2)