

A Systematic Review and Meta-analysis of Laparotomy Compared with Laparoscopic Management of Cornual Pregnancy

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Abstract

Background: Cornual (or interstitial pregnancy) is a rare but life-threatening condition with an incidence of about 1-4% of all types of tubal ectopic pregnancies. It can be managed by open and minimally invasive surgical techniques. Therefore, we aim to compare between laparoscopy and traditional open surgery for managing interstitial pregnancy. Methods: We systematically searched PubMed, Scopus, Web of Science, and Cochrane till May 2020 using relevant keywords and screened retrieved studies for eligibility. Data were extracted from the relevant articles and were pooled as mean difference (MD) or relative risk (RR) with a 95% confidence interval (CI), using Review Manager Software for continuous outcomes and OpenMeta [Analyst] software for windows for dichotomous outcomes. Results: We included four studies, three of which provided data eligible for meta-analysis. The duration of postoperative hospital stay was lower in the laparoscopic surgery group (MD = -1.42, 95% CI [-1.72, -0.76], $P < 0.0001$). There were no significant difference between laparoscopy and traditional open surgery in operative time (MD = -11.22, 95% CI [-42.44, 20], $P = 0.48$), blood loss (MD = -9.43, 95% CI [-214.18, 195.32], $P = 0.93$), post and intraoperative complications (RR = 1.543, 95% CI [0.201, 11.849], $P = 0.677$), and need for blood transfusion (RR = 0.774, 95% CI [0.497, 1.251], $P = 0.296$). Conclusion: Laparoscopic surgery is associated with lower postoperative hospital stay duration with no difference in terms of operation time, blood loss, post, and intraoperative complications, and need for blood transfusion compared with laparotomy.

Introduction

Interstitial pregnancy is a type of ectopic pregnancy which occurs in the uterus but outside the uterine cavity, implantation occurs in the interstitial (proximal) part of the fallopian tube at its insertion into the uterus (1-3). It's a life-threatening rare condition with an incidence of about 1-4% of all types of tubal ectopic pregnancies and approximately one time every 2500-5000 live births (4). Many risk factors may predispose to interstitial pregnancy including pelvic surgery and inflammatory diseases, tumors, anomalies of the uterus, and in-vitro fertilization (5). Many cases can be asymptomatic or present with non-specific symptoms such as vaginal bleeding and abdominal pain therefore, the diagnosis is often delayed which increases the risk of rupture (5-7). Diagnosis depends on high levels of suspicion, especially in women who have any risk factor. Interstitial and cornual pregnancy may be used as synonyms of each other as reported in some studies However, they are actually two different conditions as cornual pregnancy occurs mainly in the horn of a bicornuate uterus (6-8).

Many modalities were used for management including medical treatment such as local and systemic methotrexate, expectant, open, and minimally invasive surgical techniques (1). Choosing a treatment option

is depending on some criteria like the patient's desire for future fertility and whether the rupture has occurred or not. Medical or expectant treatment are used only in asymptomatic and hemodynamically stable patient cases (1). Surgical management is the main line of management in most cases especially in ruptured ones. These surgical options are either laparoscopy or laparotomy depending on the patient's condition and available resources. Traditionally, open surgery as laparotomy with cornual resection or hysterectomy was used but with the progression in surgical approaches, laparoscopic surgeries have shown better results compared with laparotomy (9). Laparoscopic surgery for ectopic pregnancies is done through different approaches as cornuostomy, salpingostomy, cornual resection, and mini-cornual excision (10–14). Laparoscopic surgery may have advantages over laparotomy such as lower hospital stay duration, less postoperative pain, lower blood loss, and skin incision (15,16).

Some reports have reviewed most of the treatment modalities and described a road map for the management of ectopic pregnancies but these reports include few or no interstitial pregnancy cases (1,17) and no clear evidence for selecting the most suitable surgical approach in interstitial pregnancy. Therefore, we aim to compare laparotomy with laparoscopic management of interstitial pregnancy as evidenced from published studies.

Methods

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (18). We also followed the guidelines reported in the Cochrane Handbook for Systematic Reviews of Interventions (19).

Literature Search

We searched for published studies in four electronic databases: PubMed, Web of Science, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL) in June 2020. We used the following query for our search: ((Laparoscop* OR cornuostomy) AND (cornu* OR laparotomy OR "cornual evacuation" OR "cornual resection" OR "cornual excision" OR "wedge resection" OR "loop ligature" OR "Vicryl loop placement" OR "conical exeresis" OR hysterectomy OR salping* OR traditional OR classic* OR conventional)) AND ("interstitial pregnancy" OR "Cornual pregnancy" OR "cornual gestation" OR "interstitial gestation" OR "cornual ectopic").

Eligibility criteria

We included all studies that met the following criteria: 1) Patients: women with interstitial (cornual) pregnancy, 2) Intervention: all types of laparoscopic surgeries, 3) Comparator: all types of open surgeries, 4) Outcomes: all reported outcomes especially those regarding bleeding, operation time and hospital stay, and 5) Study design: all interventional and observational studies (Cohort, case-control, cross-sectional, case series and case report). We excluded conference abstracts, non-English studies, reviews, studies that report the effect of only one type of surgery. No restriction on age, place, and publication date.

Screening and studies selection

We screened the search results for eligibility in two steps: title and abstracts were screened then preliminary eligible records from the first step entered the second one, full-text screening in which the articles were revised for all criteria to be included in our study. We manually screened the references of the included studies, and previous systematic review, for additional or missed citations.

Data Extraction

After the screening step, we extracted the following data from the eligible studies using a previous formatted data extraction sheet: (1) Summary of the included studies including study design, sites and time, participants and main inclusion criteria, total sample size, type of laparoscopic surgery, type of traditional surgery, number of patients assigned to each type, investigations, results, conclusion of each study, (2) baseline characteristics of the patients in each study including groups, Cases number in each group, age, gestational age (days), number of symptomatic women at diagnosis, number of ruptured ectopic, parity, gravidity, and,

risk factors for developing interstitial pregnancy in recruited patients, (3) any repeated outcomes (reported by two or more studies) including postoperative hospital stay (days), operative time (minutes), blood loss (ml), post and intraoperative complications, need for blood transfusion. Data for continuous outcomes were extracted as a mean and standard deviation and dichotomous outcomes, events and total were extracted.

Quality assessment

The quality of the included studies was assessed by quality assessment tools of the National Heart, Lung, and Blood Institute (NHLBI) (20). We used a tool for observational cohort studies and another tool for a case series study. Each tool composed of some questions to assess the risk of bias and confounders. These questions were answered by “yes”, “no”, “not applicable”, “cannot determine”, or “not reported” then each study was given a score to guide the overall rating of the quality as “good”, “fair”, or “poor”. We could not assess the publication bias due to the small number of included studies according to Egger’s funnel-plot-based methodologies (21).

Data Synthesis

For continuous data, we used the inverse-variance method and the data were pooled as mean difference (MD) using Review Manager Software (version 5.3) for windows. For dichotomous data, we used the Mantel-Hanszel method and the data were pooled as relative risk (RR) using OpenMeta [Analyst] software for windows. We assessed the heterogeneity by the Chi-square test and its extent was determined by I^2 -square, such that values of $p < 0.1$ or $I^2 > 50\%$ were significant indicators of heterogeneity. We used the random-effects model to analyze heterogeneous data and fixed-effects model for the analysis of homogeneous data and performed a sensitivity analysis to solve the heterogeneity whenever detected.

Results:

Literature search

By searching PubMed, Web of Science, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL), we identified 832 records. We removed duplicates and the remaining 505 records were screened for eligibility. Only 18 studies were further included for full-text screening. We included four studies from this step. We didn’t find any missing papers after the screening of the references of the included trials and previous systematic review (223 references) and finally, we included six studies, four of them were eligible for meta-analysis. The literature search process was described in a PRISMA flow diagram in Figure (1).

Characteristics of the included studies

We included one case series study, one cross-sectional, and four retrospective cohort studies with 70 cases of interstitial ectopic pregnancy in the laparoscopic surgery group and 83 cases in the open surgery group. Summary of the included studies and their results are shown in (Table 1) and baseline characteristics of their patients are shown in (Table 2).

Results of Risk of Bias Assessment

Two cohort studies had a fair quality according to NIH quality assessment tool for Observational Cohort and Cross-Sectional Studies. The other two cohort studies and the only cross-sectional study were poor quality. The only case series study was fair in quality according to the NIH quality assessment tool for case series studies. For more details and answers to all assessment questions in each study, see supplementary table 1 for cohort studies and table 2 for a case series study.

Analysis of Outcomes

Postoperative hospital stay (days)

The pooled mean difference (MD) showed that laparoscopic surgery was significantly associated with less hospital stay duration than open surgery (MD = -1.42 days, 95% CI [-1.72, -0.76], $P > 0.0001$); Fig.2. Pooled results were homogenous ($P = 0.88$, $I^2 = 0\%$).

Operation time (minute)

The pooled effect estimate revealed no significant difference between laparoscopic surgery and open surgery in terms of operative time (MD = -11.22 minutes, 95% CI [-42.44, 20], $P = 0.48$); Fig.3 (A). Pooled results were heterogeneous ($P = 0.03$, $I^2 = 73\%$) and the detected heterogeneity was best resolved after excluding Hwang et.al. 2010 ($P = 0.44$). Homogeneous results favored the laparoscopy group by a shorter operation time of 28 minutes compared with laparotomy (MD = -28.72, 95% CI [-53.62, -3.81], $P = 0.02$); Fig.3 (B).

Blood loss (ml)

The pooled mean difference (MD) showed no significant difference between laparoscopic surgery and open surgery in terms of blood loss (MD = -9.43, 95% CI [-214.18, 195.32], $P = 0.93$); Fig.4. Pooled results were homogenous ($P = 0.39$, $I^2 = 0\%$).

Post and intraoperative complications

The pooled relative risk (RR) revealed no significant difference between laparoscopic surgery and open surgery in terms of post and intraoperative complications (RR = 1.543, 95% CI [0.201, 11.849], $P = 0.677$); Fig.5. Pooled results were homogenous ($P = 0.645$, $I^2 = 0\%$).

Need for blood transfusion

The pooled mean difference (MD) showed no significant difference between laparoscopic surgery and open surgery in terms of need for blood transfusion (RR = 0.677, 95% CI [0.431, 1.062], $P = 0.089$); Fig.6. Pooled results were homogenous ($P = 0.409$, $I^2 = 0\%$).

Qualitative evidence

For pregnancy outcome as reported by Sagiv et. al (22), three out of five women undergoing laparotomy, became infertile, one underwent a tubal ligation, and only one woman became pregnant and delivered by cesarean section. But out of women eight managed by laparoscopy, three women were undesirable for pregnancy, one not reported, one had an early miscarriage, and three became pregnant and delivered by cesarean section.

Tulandi et. al (23) reported that in patients managed by laparoscopy, hemoperitoneum encountered was 1385.7 ± 978.8 mL in the laparotomy group and 460.0 ± 70.7 mL in the laparoscopy group. In the laparotomy group, no patient needed any subsequent treatment but in the laparoscopy group, the first treatment failed in one patient and needed methotrexate as subsequent treatment.

Warda et. al (24) presented four cases of interstitial pregnancy, the first case was a 36-year-old woman treated with cornuostomy by laparotomy and then she received a third intracytoplasmic sperm injection cycle then she delivered an intact female after a pregnancy period devoid of any complications. The other three cases aged 30, 30, and 36 years were treated with laparoscopic cornuostomy and removal of products of conception. They also underwent another in-vitro fertilization cycle then they delivered without any complications and with no adverse neonatal outcomes.

Discussion

We found that laparoscopic surgery was significantly associated with less postoperative hospital stay period and less operation time than open surgery. However, we found no difference between both types in terms of blood loss, post and intraoperative complications, and need for blood transfusion.

Our results were consistent with other studies published in the literature. Laparoscopic surgery has many advantages such as minimal skin incision and a little hospital stay period, preserve the uterus for future fertility, improved and fast recovery and less postoperative pain (7,9), but also it has some minor disadvantages like hematomas of the abdominal wall occurring near the incisions, some abdominal or pelvic infections but Serious laparoscopy complications are rare (25).

Laparotomy is the second line of management when there is no laparoscopic expertise or when adequate closure or hemostasis cannot be achieved by laparoscopic surgery. However, it has a lot of risks ranging from the general risks of anesthesia and surgery to incisional hernia, infections, bleeding, and injury of pelvic or abdominal organs. Also, it is accompanied by longer hospital stay periods as reported in some studies (26,27).

Two previous systematic reviews have described a road map for nearly all medical and surgical options and they recommended using laparoscopic surgery in most conditions (1,17).

A previous meta-analysis compared between laparoscopy and laparotomy for ectopic pregnancy and concluded that laparoscopy is better than laparotomy. However, contrary to our results, they found no difference between laparoscopy and laparotomy in terms of operation time which we found was lower in the laparoscopic group. Additionally, they found that intraoperative blood loss was lower in the laparoscopy arm compared with laparotomy (28).

Some studies compared different laparoscopic approaches, the study by Lee et. al 2016 (29) compared laparoscopic cornual resection and laparoscopic cornuotomy and found no significant difference between them in hemoglobin levels after the operation and persistent interstitial pregnancy and incidence of major complications but the operation time was significantly shorter for cornuotomy than that for cornual resection. Also, Gasparria et. al 2018 (30) compared conventional versus single port laparoscopy and found no difference between them in hemoglobin levels, need for blood transfusions, operation time, length of hospital stay period, and post- and intra-operative complications.

In a cost-effectiveness comparison between laparoscopic and laparotomy, Gray et. al 1995 (31) showed that at lower costs, laparoscopy produced final outcomes comparable to those of laparotomy. Also Ghazali et. al 2018 (27) stated that laparoscopy was associated with financial savings.

We included all studies comparing laparoscopic surgery with laparotomy in interstitial ectopic pregnancy patients. Additionally, most of our results were homogenous and we managed to solve the heterogeneity detected among studies.

However, we have some limitations in our study such as: 1- Small number of the included studies and small sample size. 2- The lack of data about long term effect. 3- All of the included studies were observational which are considered at low level of evidence.

Conclusion

Our analysis shows that in women with interstitial ectopic pregnancy, management with laparoscopic surgery is associated with lower postoperative hospital stay duration and operation time with no difference in terms of blood loss, post and intraoperative complications, and need for blood transfusion.

Further studies especially interventional studies with longer follow up duration and larger sample size are needed to produce more valid results and till that we recommend using laparoscopic surgery if available as it has some advantages over open surgery.

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Contribution to authorship: Greg Marchand gathered the idea and reviewed the whole work starting from search to final writing, Ahmed Taher Masoud performed statistical analysis and wrote the statistical part of the results as well as reviewing the writing process, Katelyn Sainz, Ali Azadi, and Kelly Ware searched all databases for possible included studies and screened the retrieved results, Janelle Vallejo, Sienna Anderson, and Alexa King performed the data extraction and risk of bias assessment for included studies, Asya Osborn, and Stacy Ruther wrote the introduction section, Giovanna Brazil wrote the methods section, Kaitlyne Cieminski, and Sophia Hopewell wrote the results section and served as the second team for screening and data extraction of outcomes and baseline tables, Lisa Rials, and Akarshi Brar collected and discussed our results with previous works and research papers.

Details of ethics approval: This Manuscript has been reviewed by the institutional IRB board at Marchand Institute and was found to be exempt from IRB review. (May 2020, IRB#05-2020-084)

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Figure Legend:

Figure 1. PRISMA flow chart

Figure 2. Mean difference (MD) in Postoperative hospital stay

Figure 3. Mean difference (MD) in Operative Time

Figure 4. Mean difference (MD) in Blood loss

Figure 5. Postoperative and intraoperative complications

Figure 6. Blood Transfusion

Table Legend:

Table 1: Complete summary of the included studies and their findings

Table 2: Baseline characteristics of enrolled patients in the included studies

Conclusion of the study	Results	Investigation	Type of Traditional surgery, (n)	Type of Laparoscopic surgery, (n)	Total cases n	Participants and main inclusion criteria	Sites and time	Study design	St ID
Laparoscopic cornual resection is a feasible approach with favorable surgical and long-term pregnancy outcomes.	Compared with laparotomy, laparoscopic cornual resection showed shorter operative time (median 40 vs. 70 min), less blood loss (150 vs. 400 ml) and shorter hospital stay (2 vs. 4 days).	Transvaginal ultrasound scan	Laparotomy with cornual resection, (3)	Laparoscopic cornual resection, (7)	17	Patients with intrauterine pregnancy along with feature of a co-existing interstitial pregnancy: - A gestational sac visualized high in the fundus. - not surrounded by 5 mm of myometrium in all planes. -a gestational sac seen separately and < 1 cm from the most lateral edge of the uterine cavity.	Nanjing Drum Tower Hospital, China. Records from July 2010 to December 2015	Retrospective analysis	Ji 20

Conclusion of the study	Results	Investigation	Type of Traditional surgery, (n)	Type of Laparoscopic surgery, (n)	Total cases n	Participants and main inclusion criteria	Sites and time	Study design	St ID
Laparoscopic cornual resection is a safe and less invasive procedure with a reasonable complication rate and shorter hospital stay.	There were no statistically significant differences between the two groups for the mean operation time, estimated blood loss, blood loss of more than 1000 mL, blood transfusion requirements, and complications. The mean number of postoperative hospital days was shorter in the laparoscopy group than in the laparotomy group (4.53 ± 1.44 days versus 5.89 ± 1.86 days, respectively; $P < 0.001$).	Transvaginal ultrasound scan	Open cornual resection, (54)	Laparoscopic cornual resection, (34)	88	Patients with interstitial pregnancy who were treated with open cornual resection or laparoscopic cornual resection.	The Korea University Medical Center, South Korea. Records from January 1998 to October 2009	Retrospective analysis	HY 20

Conclusion of the study	Results	Investigation	Type of Traditional surgery, (n)	Type of Laparoscopic surgery, (n)	Total cases n	Participants and main inclusion criteria	Sites and time	Study design	St ID
Laparoscopic cornual resection (cornuotomy) is a safe and less invasive procedure with a comparable complication rate. It has shown that it is feasibility and should be considered as initial treatment in managing those cases in trained hand surgeons.	The duration of hospitalization and mean operating time were both significantly shorter in the LC group than in the OC group (1.43 ± 0.54 versus 2.57 ± 0.79 and 61.4 ± 15.7 min versus 97.1 ± 38.2 min, respectively, P < 0.05). There were no statistically significant differences between both groups for the estimated blood loss, requirement of blood transfusion, complications, and future fertility.	Physical examination, transvaginal sonography, full blood count, and serum human chorionic gonadotrophin (hCG) levels.	Open cornuotomy, (7)	Laparoscopic cornuotomy, (7)	14	Patients with interstitial pregnancy who were treated with open cornual resection or laparoscopic cornual resection.	Putrajaya Hospital, Putrajaya, Malaysia. Records from January 2005 to December 2014,	Retrospective cohort	20

Conclusion of the study	Results	Investigation	Type of Traditional surgery, (n)	Type of Laparoscopic surgery, (n)	Total cases n	Participants and main inclusion criteria	Sites and time	Study design	St ID
A change from diagnosis later in pregnancy and laparotomy to more conservative treatment, mainly by laparoscopy, suggests a possibly better subsequent pregnancy rate.	The first four women, with significant hemoperitoneum, were treated by laparotomy. Of the next 10 women, four were selected for medical treatment with methotrexate. Only one case was treated successfully. The other six women had laparoscopic treatment. Of nine laparoscopies, one was converted to laparotomy due to excessive blood loss during the procedure. Of nine women desiring a child, three were infertile, whereas six conceived with an	Transvaginal ultrasound scan	Laparotomy, (5)	Laparoscopy, cornuostomy, encircling, or salpingectomy, (8)	14	Patients with interstitial pregnancy who were treated with laparotomy, medical treatment with systemic methotrexate, or laparoscopy.	Wolfson Medical Center, Holon, and 2Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel. Records from June 1997 to June 2007.	Retrospective cohort	20

Conclusion of the study	Results	Investigatio(n)	Type of Traditional surgery, (n)	Type of Laparoscopic surgery, (n)	Total cases n	Participants and main inclusion criteria	Sites and time	Study design	St ID
Ipsilateral salpingectomy, previous ectopic pregnancy, and in vitro fertilization are predisposing factors for interstitial pregnancy. Contrary to previous belief, rupture of interstitial pregnancy occurs relatively early in pregnancy. In selected patients, laparoscopic cornual excision is a viable treatment option.	Persistently elevated serum human chorionic gonadotropin levels were found in one patient after laparoscopic cornual excision, and she was successfully treated with methotrexate. Fourteen cases (43.7%) of rupture of interstitial pregnancy were found. This included five cases (15.6%) of heterotopic pregnancy; all were the results of in vitro fertilization, and all ruptured at the time of diagnosis. Subsequent pregnancy was achieved	Transvaginal ultrasound scan and laparoscopy and laparotomy.	Laparotomy, (13)	Laparoscopy, (11)	32	Patients with interstitial pregnancy who were treated with laparotomy, methotrexate, or laparoscopy.	- Cases from 1999 to 2002.	Cross sectional	Tu 20

Conclusion of the study	Results	Investigation	Type of Traditional surgery, (n)	Type of Laparoscopic surgery, (n)	Total cases n	Participants and main inclusion criteria	Sites and time	Study design	Study ID
Progressively conservative surgical measures are being used to treat interstitial pregnancy successfully, with no negative impact on subsequent pregnancies.	Subsequent successful reproductive outcomes are presented.	Transvaginal ultrasound and diagnostic laparoscopy	Cornuostomy by laparotomy, (1)	Laparoscopic cornuostomy and removal of products of conception, (3)	4	Cases of interstitial ectopic pregnancy	-	Case series	Ward 2014 (24)

Table (1) shows a complete summary of the included studies and their findings.

Article ID	Groups	Cases, n	Age, mean (SD)	Outcome
Jiang 2018 (24)	laparoscopic cornual resection	7	30.71 (3.04)	5
	Laparotomy with cornual resection	3	27.67 (2.52)	4
Hwang 2010 (26)	laparoscopic cornual resection	34	31.12 (5.99)	5
	Open cornual resection	54	32.74 (5.11)	5
Ghazali 2018 (27)	Laparoscopic cornuotomy	7	29.3 (5.9)	-
	Open cornuotomy	7	31.4 (7.3)	-
Sagiv 2013 (22)	Laparoscopy	8	34.38 (5.83)	4
	Laparotomy	5	31.8 (6.91)	7
Tulandi 2004 (23)	Laparoscopy	11	32.6 (5.66)	3
	Laparotomy	13		5
Warda 2014 (27)	Laparoscopic cornuostomy and removal of products of conception.	3	32 (3.46)	-
	Cornuostomy by laparotomy	1	36	-

Table (2) shows baseline characteristics of enrolled patients in the included studies.

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Figure 1. PRISMA flow chart .docx available at <https://authorea.com/users/326713/articles/454518-a-systematic-review-and-meta-analysis-of-laparotomy-compared-with-laparoscopic-management-of-cornual-pregnancy>

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Figure 2. Mean Difference in Hospital Stay.docx available at <https://authorea.com/users/326713/articles/454518-a-systematic-review-and-meta-analysis-of-laparotomy-compared-with-laparoscopic-management-of-cornual-pregnancy>

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Figure 3. Mean Difference in Operative Time.docx available at <https://authorea.com/users/326713/articles/454518-a-systematic-review-and-meta-analysis-of-laparotomy-compared-with-laparoscopic-management-of-cornual-pregnancy>

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Figure 4. Mean Difference in Blood Loss.docx available at <https://authorea.com/users/326713/articles/454518-a-systematic-review-and-meta-analysis-of-laparotomy-compared-with-laparoscopic-management-of-cornual-pregnancy>

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Figure 5. Postoperative and Intraoperative Complications.docx available at <https://authorea.com/users/326713/articles/454518-a-systematic-review-and-meta-analysis-of-laparotomy-compared-with-laparoscopic-management-of-cornual-pregnancy>

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Figure 6. Blood Transfusion.docx available at <https://authorea.com/users/326713/articles/454518-a-systematic-review-and-meta-analysis-of-laparotomy-compared-with-laparoscopic-management-of-cornual-pregnancy>