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Management of interstitial pregnancy in the era of laparoscopy: a meta-analysis of 855 case studies compared with traditional techniques

Greg Marchand, MD, FACS, FICS, FACOG[1], Ahmed Taher Masoud, MD[1,2], Anthony Galitsky, MD[1], Ali Azadi, MD, FACOG[3], Kelly Ware, MS2[1], Janelle Vallejo, MS3[1], Sienna Anderson, BS[1], Alexa King, BS[1], Stacy Ruther, BS[1], Giovanna Brazil, BS[1], Kaitlynne Cieminski, BS[1], Sophia Hopewell, BS[1], Kaitlyn Eberhardt, BS[1], Katelyn Sainz, MD[1]

[1]The Marchand Institute for Minimally Invasive Surgery, Mesa, AZ, USA, [2]Faculty of Medicine, Fayoum University, Fayoum, Egypt, [3]Department of Urogynecology, Star Urogynecology, Peoria, AZ, USA

Interstitial pregnancy is a rare, life-threatening condition that requires high clinical suspicion for diagnosis. Most cases are discovered after complications have occurred. Many authors have described laparoscopic management. Although previous systematic reviews have compared the attributes and complications associated with interstitial pregnancy, we endeavored to complete the first systematic review and meta-analysis to compare the laparoscopic treatment of interstitial pregnancy with the open approach in the modern age of laparoscopic surgery. We systematically searched PubMed, ClinicalTrials.gov, Scopus, Web of Science, and Cochrane until June 2020 using relevant keywords and screened them for eligibility. We found a statistically significant difference in blood loss between laparoscopic and open surgery (168 mL compared to 1,163 mL). Further, cumulative meta-analysis has revealed that blood loss in laparoscopy has been decreasing over time from 1991 to 2020. Laparoscopic patients took less operative time (63.2 minutes) compared to laparotomy patients (78.2 minutes). Patients in the laparoscopic group spent less time hospitalized (3.7 days) compared to laparotomy patients (5.2 days). Our findings add strength to the position that laparoscopic approaches to interstitial pregnancy can be considered first-line in most situations. The laparoscopic approach was found to have a mean blood loss of 168 mL, and this blood loss seems to decrease over time. Increased gravidity and duration of amenorrhea are positive factors that increase bleeding during the procedure. We are unable to find enough high-quality data to significantly compare successful pregnancy following surgery or risk of mortality in these populations.

Keywords: Ectopic; Laparoscopy; Laparotomy; Meta-analysis

Introduction

Ectopic pregnancy is a pregnancy due to implantation outside the normal endometrium, and it is a rare occurrence representing about 2% of all pregnancies [1]. Many risk factors contribute to increasing the incidence of ectopic pregnancy, such as a history of ectopic gestation, tubal adhesions, history of endometriosis or pelvic inflammatory disease (PID), the use of some contraceptive devices, and previous tubal surgeries [2]. The most common sites within the fallopian tube include the ampulla (69.9%), isthmus (12%), and interstitium (2.4%) [2,3]. The term "interstitial pregnancy" is used interchangeably with "cornual pregnancy" to describe a pregnancy in the interstitium, although interstitial preg-

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Corresponding author: Greg Marchand, MD, FACS, FICS, FACOG
The Marchand Institute for Minimally Invasive Surgery, 10238 East Hampton, Street 212 Mesa, AZ 85209, USA
E-mail: www.marchandinstitute.org, gm@marchandinstitute.org
https://orcid.org/0000-0003-4724-9148

nancy may be considered a more accurate description [4]. Some authors believe the term "cornual pregnancy" should be reserved to refer to gestations in a horn of a bicornuate uterus [5-7].

Symptoms of interstitial pregnancy vary from asymptomatic to non-specific symptoms of suprapubic pain, nausea, vomiting, and vaginal bleeding [5,8]. Therefore, diagnosing interstitial pregnancy presents a challenge for obstetricians; it requires high clinical suspicion, especially in women with the aforementioned risk factors. In the last two decades, there has been a noticeable rise in the incidence of interstitial pregnancies, mainly due to the increased use of contraceptive devices and increased prevalence of PID, in addition to the major advances in imaging technologies and ultrasound [9].

Treatment of cases of interstitial pregnancy range from medical treatment to surgical interventions. Local and systemic methotrexate is the mainline for medical treatment, mainly indicated in young nulliparous women desiring future fertility [9]. Surgical interventions include laparotomy and laparoscopic management.

Recently, laparoscopy has become more common for gynecologic and obstetric procedures as a safe approach with less bleeding and improved surgical outcomes [10,11]. A study by Gyr et al. [12] compared traditional abdominal hysterectomy with minimally invasive laparoscopic hysterectomy with an ultrasonic scalpel and found that the latter reduces the need for analgesia and improves postoperative outcomes. Laparoscopy has also shown considerable efficacy in the management of mild to moderate endometriosis [13] and is considered one of the safest gynecologic operations for removing ovarian masses in adolescents [14].

We aimed to conduct this systematic review and meta-analysis to provide an updated insight into the use of laparoscopy in interstitial pregnancy, in addition to measuring its effectiveness in reducing blood loss and other complications compared to traditional techniques. We endeavored to complete the first systematic review and meta-analysis to compare the laparoscopic treatment of interstitial pregnancy with the open approach in the modern age of laparoscopic surgery.

Methods

We conducted this systematic review and meta-analysis following the guidelines reported in the Cochrane Handbook for Systematic Reviews of Interventions [15] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16].

Literature search

We searched for published studies in four electronic databases: PubMed, ClinicalTrials.gov, Web of Science, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL) up to June 2020. We used the following strategy for our search: (Laparoscop* OR cornuostomy OR 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

All studies that met the following criteria were included: 1) patients=women with interstitial or cornual pregnancy; 2, 3) intervention with or without a comparator=all types of laparoscopic surgeries, open surgeries, or both, 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 reports). We excluded conference abstracts, non-English studies, reviews, and studies that report the effect of only one type of surgery. No restriction on age, place, or publication date was implemented.

Screening and studies selection

Retrieved citations were screened for eligibility in two steps: title and abstract screening in which preliminary eligible records from the first step entered the second one; followed by full-text screening in which the articles were assessed for all criteria to be included in our study. In addition, we manually screened the references of the included studies and previous

systematic reviews for additional or missed citations.

Data extraction

After the screening step, we extracted the following data from the eligible studies using a formatted data extraction sheet: 1) summary and baseline characteristics of the patients in each study, including study design, type of operation, number of patients, groups, age, parity, gravidity, previous ectopic pregnancy, and duration of amenorrhea, and 2) any repeated outcomes (reported by two or more studies) including postoperative hospital stay (days), operation time (minutes), blood loss (mL), postoperative pregnancy rate, and ruptured ectopic pregnancy. Data for continuous outcomes were extracted as mean and standard deviation, and dichotomous outcomes were extracted as event and total.

Quality assessment

The quality of the included studies was assessed using four tools according to the study design. We assessed the quality of cohort, case series, and case control studies using three different tools developed by the National Heart, Lung, and Blood Institute [17]. Each tool consisted of questions to assess the risk of bias and confounders. These questions were answered by "yes," "no," "not applicable," "cannot determine," or "not reported," and then each study was given a score to guide the overall rating of the quality as "good," "fair," or "poor."

We also assessed the quality of the included case reports using the Joanna Briggs Institute (JBI) critical appraisal tool for case reports. The tool is composed of some questions developed according to the CARE Guidelines for reporting case reports. These questions were answered by "yes," "no," "not applicable," or "unclear" [18]. We could not assess publication bias due to the small number of included studies according to Egger's funnel-plot-based methodologies [19].

Data synthesis

Comprehensive meta-analysis and open meta-analyst software were used to perform this meta-analysis. Continuous outcomes were pooled as the mean and standard deviation (SD). Whenever studies provided median and range, we used the methods described by Hozo et al. [20]. to transform these data to mean and SD. Dichotomous data were pooled as proportions. A random-effects model was used. We employed meta-regression models and leave-one-out meta-analysis whenever there was significant heterogeneity. In addition, a cumulative meta-analysis was used to reveal trends in the data over time.

Results

1. Literature search

We identified 96 records after searching PubMed, ClinicalTrials.gov, Web of Science, Scopus, and CENTRAL. The remaining records after removing duplicates were screened for eligibility. Two hundred studies were included in the full-text screening. We finally included 96 studies. We did not find any missing papers after screening the references of the included trials and previous systematic reviews.

2. Characteristics of the included studies

Our review included 96 studies: 65 case reports, 23 cohort studies, 6 case series, and 2 casecontrol studies conducted between 1992 and 2020 [7-115]. The included studies enrolled 885 patients. A total of 723 patients underwent laparoscopy, while 132 underwent operative laparotomy for the management of ectopic pregnancy. The median age of the included participants ranged from 19 to 42 years. A summary of the included studies and their findings and baseline characteristics of the enrolled patients is shown in Table 1.

3. Results of risk of bias assessment

According to JBI critical appraisal tool for case reports, the quality of the included reports ranged from moderate to high. Most of the included case reports did not clearly describe patient demographics. However, most of them have clearly reported patients' history, clinical presentation, diagnostic method, intervention, post-intervention status, and side effects, and provided takeaway lessons for clinical practice.

According to different NIH quality assessment tools for each study design, all case-control studies were of poor quality, while four case series were of fair quality, and the remaining two studies were of poor quality. Regarding cohort stud-

Table 1. Study characteristics

Study	Type of operation	Study design	Number of patients	Age (yr)	Gravidity	Parity	Duration of amenorrhea	Previous ectopics
Api and Api [74] (2010)	Laparoscopy	Case report	1	38	3	0+2		1
Attia et al. [75] (2005)	Laparotomy	Case report	1	34			17	
Bremner et al. [76] (2000)	Laparoscopy	Case report	1	36	4	1	8.5	2
Cai et al. [77] (2009)	Laparoscopy	Case report	1	32	5	0+4	9.5	
Casadio et al. [78] (2009)	Laparoscopy	Case report	1	27	3	2		
Chachan et al. [79] (2011)	Laparoscopy	Case report	1	36	3	1		
Chauhan et al. [80] (2006)	Laparotomy	Case report	1	40	3		12	
Chen et al. [94] (2019)	Laparoscopy	Retrospective (cohort/analysis)	14	32.8±5.9	0.7±0.7			
	Laparoscopy		26	33.0±5.5	1±0.9			
Cheng et al. [81] (2009)	Laparoscopy	Case report	1	22	2	0		
Chin et al. [82] (2004)	Laparotomy	Case report	1	29	2	0	12	
	Laparotomy		1	34	1	0	17	
Choi et al. [96] (2009)	Laparoscopy	Retrospective (cohort/analysis)	8				7.6	
Corić et al. [83] (2004)	Laparoscopy	Case report	1	42	3	2	5	
Cucinella et al. [86] (2012)	Laparoscopy	Retrospective (cohort/analysis)	5	32	1.8		7.2	1
Dendas et al. [84] (2017)	Laparotomy	Case report	1	35				
Di Tizio et al. [85] (2018)	Laparoscopy	Case report	1	26				
	Laparoscopy		1	30				
	Laparoscopy		1	38				
Divry et al. [21] (2007)	Laparotomy	Case report	1	32				
Dumesic et al. [22] (2001)	Laparotomy	Case report	1	37	3	1		
Faioli et al. [112] (2016)	Laparoscopy	Case series	3					
Gao et al. [88] (2019)	Laparoscopy	Retrospective (cohort/analysis)	9	30.1			4.3	
Garretto et al. [23] (2015)	Laparoscopy	Case report	1					
Garzon et al. [24] (2019)	Laparoscopy	Case report	1	30	2	1	12	
Gezer and Mutlu [25] (2004)	Laparoscopy	Case report	1	36	2	1	7	
Grant et al. [100] (2017)	Laparoscopy	Retrospective (cohort/analysis)	44	32.6 (NR)	3	4	6	
Grimbizis et al. [26] (2004)	Laparoscopy	Case report	1	28	3	2	7	
Grobman and Milad [27] (1998)	Laparoscopy	Case report	1	31	3	4	7	
Ghazali et al. [106] (2018)	Laparoscopy	Retrospective (cohort/analysis)	7	29.3±5.9	2.9±0.7		8.4±2.1	3
	Laparotomy		7	31.4±7.3	2.7±1.5		11.0±4.6	1
Huang et al. [108] (2005)	Laparoscopy	Case series	4				9	
Hwang et al. [113] (2011)	Laparoscopy	Case control	54	32.74±5.11		0.98±0.74	7.7±1.5	6
	Laparoscopy		34	31.12±5.99		0.82±0.90	8±2	8

Table 1. Continued

Study	Type of operation	Study design	Number of patients	Age (yr)	Gravidity	Parity	Duration of amenorrhea	Previous ectopics
Kahramanoglu et al. [110] (2017)	Laparotomy	Case series	1	25	4	2		
	Laparoscopy		1	28	1	0	7	
Kalchman and Meltzer [28] (1966)	Laparotomy	Case report	1	28	1	0		1
	Laparotomy		1	29			8	1
Kasum et al. [29] (1998)	Laparotomy	Case report	1	38	5	0	14	2
Kim et al. [114] (2015)	Laparoscopy	Case control	26	32	0		6 (3-8)	
	Laparoscopy		80	31	0		6 (4-10)	
Kim et al. [101] (2016)	Laparoscopy	Retrospective (cohort/analysis)	13	31 (25-33)	1 (1-6)	0 (0-1)	7 (5)	
Ko et al. [30] (2007)	Laparoscopy	Case report	1	32	3	0		
Koukoura et al. [31] (2020)	Laparoscopy	Case report	1	39	1	0	9	
Kumakiri et al. [32] (2005)	Laparoscopy	Case report	1	38	2	0	7.4	
Lai et al. [33] (2016)	Laparotomy	Case report	1	22	2	1	12	
Lam et al. [34] (2004)	Laparotomy	Case report	1	32			12	1
	Laparotomy		1	32			9	2
Lam and Tulandi [8] (1999)	Laparoscopy	Retrospective (cohort/analysis)	22					
Lazard et al. [107] (2011)	Laparoscopy	Case series	1	41	4	3	7	
	Laparoscopy		1	32	6	3	8	
Lee et al. [35] (2011)	Laparoscopy	Case report	1	28	3	1		
Lialios et al. [36] (2008)	Laparoscopy	Case report	1	29	3	2	6.8	
Liao and Ding [37] (2009)	Laparotomy	Case report	1	29	6	0	13	
MacRae et al. [89] (2009)	Laparoscopy	Prospective cohort	10	30 (7.5)				1
	Laparotomy		1	24				
Maher and Grimwade [38] (1982)	Laparotomy	Case report	1	31	3	2	6	
	Laparotomy		1	36	5	2	13	
Marfori and Kotzen [39] (2018)	Laparoscopy	Case report	1	33	3	1	7.8	
Morita et al. [40] (1997)	Laparoscopy	Case report	1	39	4	2	6	
	Laparoscopy		1	29		0	7	
Mavrelos et al. (1996)	Laparoscopy	Retrospective (cohort/analysis)	12	37			15	
Moon et al. [103] (2000)	Laparoscopy	Retrospective (cohort/analysis)	24	33.4±5.8				
Moon et al. [104] (2010)	Laparoscopy	Retrospective (cohort/analysis)	20	28 (NR)			6.7	
Nabeshima et al. [41] (2010)	Laparoscopy	Case report	1	38	2			
Ng et al. [98] (2009)	Laparoscopy	Retrospective (cohort/analysis)	53	19-40				
Nirgianakis et al. [105] (2017)	Laparoscopy	Retrospective (cohort/analysis)	10	34.5±6.21	2.6±1.58	1.0±1.05		2

Table 1. Continued

Study	Type of operation	Study design	Number of patients	Age (yr)	Gravidity	Parity	Duration of amenorrhea	Previous ectopics
Oelsner et al. [42] (1993)	Laparoscopy	Case report	1	29				
	Laparoscopy		1	21				
Olagundoye et al. [97] (2000)	Laparotomy	Retrospective (cohort/analysis)	7					
	Laparoscopy		66					
	Both		33					
Oral et al. [43] (2014)	Laparoscopy	Case report	1	27				
Osuga et al. [44] (2001)	Laparoscopy	Case report	3	32	3	0	7	
Pasic et al. [45] (2002)	Laparoscopy	Case report	1	21	1	0	8	
Pedroso et al. [46] (2014)	Laparotomy	Case report	1	19	1	0	15	
Pluchino et al. [47] (2009)	Laparoscopy	Case report	1	34	1	0	7	1
Poujade et al. [48] (2009)	Laparoscopy	Case report	1	32	5		9	
Pramayadi et al. (2018)	Laparoscopy	Case report	1	35	2	1		
Quinlan and Newcombe [54] (2007)	Laparoscopy	Case report	1	40			6	
Raheem and Afifi [53] (2008)	Laparoscopy	Case report	1	35	1		8	
Rheinboldt and Ibrahim [52] (2013)	Laparoscopy	Case report	1	20	1	0		
Ron-el et al. [50] (1988)	Laparotomy	Case report	1	38			14	1
Ross et al. [55] (2006)	Laparoscopy	Case report	1	27	3	1	11	
	Laparoscopy		1	30	2	1	6	
Sagiv et al. [51] (2001)	Laparoscopy	Case report	1	21	3	1	8	1
Sagiv et al. [93] (2013)	Laparotomy	Retrospective (cohort/analysis)	5	33 (20-47)	5 (1-9)	2 (0-5)	6-17	
	Laparotomy		8					
Sahoo et al. [56] (2009)	Laparotomy	Case report	1	28	7	5+1	5	
Said [111] (2016)	Laparoscopy	Case series	1	23	1			
	Laparoscopy		1	30	4	1+2		2
	Laparoscopy		1	25			10	
	Laparoscopy		1	26	1	0	7	
Sant and Andersen [57] (2012)	Laparotomy	Case report	1	30	2	0	21	
Sarmini and Tate [58] (2005)	Laparoscopy	Case report	1	22	2	0		
Sherer et al. [59] (1995)	Laparoscopy	Case report	1	32	2	1	7	
Soriano et al. [6] (2008)	Laparoscopy	Retrospective (cohort/analysis)	11	34.3±5.8	3.7±1.8	1.5±1.4	59.1±14.7	0.5
	Laparotomy		11	35.2±4.3	4.3±2.1	1.7±1.3	49.7±8.4	
Takeda et al. [60] (2009)	Laparoscopy	Case report	1	29	3	2	7	
Tinelli et al. [61] (2010)	Laparoscopy	Case report	1	34				
	Laparoscopy		1	37		2	11	
	Laparoscopy		1	31			7	

Table 1. Continued

Study	Type of operation	Study design	Number of patients	Age (yr)	Gravidity	Parity	Duration of amenorrhea	Previous ectopics
Tulandi and Al-Jaroudi [90] (2004)	Laparotomy	Retrospective (cohort/analysis)	32					13
	Laparotomy		13					7.3±0.4
	Laparoscopy		11					5.4±1.0
Ugwumadu et al. [62] (1997)	Laparotomy	Case report	1		1		33	
Uludag et al. [92] (2018)	Laparoscopy	Retrospective (cohort/analysis)	3	30.6 (NR)	1		6	
Vicino et al. [63] (2000)	Laparoscopy	Case report	1	39	7	3		
Vilos [64] (1995)	Laparoscopy	Case report	1	31	4	2	7	
Vilos [65] (2001)	Laparoscopy	Case report	1	31			8	
Walid et al. (2010)	Laparoscopy	Case report	1	27				
Wang et al. [99] (2014)	Laparoscopy	Retrospective (cohort/analysis)	9	30.4			7.2	
Watanabe et al. [91] (2014)	Laparoscopy	Prospective cohort	13	34.6±10.2			7.6±1.3	
Weissman and Fishman [67] (1992)	Laparotomy	Case report	1	34	2	1	20	
Wood and Hurley [68] (1992)	Laparoscopy	Case report	1	27			6	
Woodland et al. [69] (1996)	Laparoscopy	Case report	1	23			8	
Xu et al. [95] (2018)	Laparoscopy	Retrospective (cohort/analysis)	14	30.9	2.21	0.14	5±7.1	
Yalçın et al. [70] (2015)	Laparoscopy	Case report	1	36	5	3	6	
Yang and Song [71] (2018)	Laparoscopy	Case report	1	41			7	
Yoong et al. [109] (2020)	Laparoscopy	Case series	12	31 (20-44)				
Zhang et al. [72] (2004)	Laparoscopy	Case report	18				5-12	
Zhang et al. [73] (2013)	Laparoscopy	Case report	2	30.43 (NR)	4,2	1.1	8, 12	
Zuo et al. [87] (2012)	Laparoscopy	Retrospective (cohort/analysis)	17	26.8 (20-35)			7.8±0.7	

Data are reported as median (range) or mean ± standard deviation, number.
NR, not reported.

ies, 13 studies were of fair quality, and 10 were poor quality.

4. Analysis of the outcomes

1) Blood loss

Laparoscopy group

Eighty-three studies reported blood loss in the laparoscopy group. The overall mean blood loss was 168 mL (confidence interval [CI] [141.3, 194.7], $P<0.001$) (Fig. 1A). There was significant heterogeneity among these studies ($I^2=98.3\%$, $P<0.001$); therefore, a meta-regression model was employed. Gravidity and the duration of amenorrhea explained most of the heterogeneity among the included studies ($R^2=44\%$ and 51%, respectively) (Supplementary Fig. 1). In addition, the cumulative meta-analysis showed a reduction in blood loss over time from 2000 to 2019 (Supplementary Fig. 2).

Laparotomy group

Data reported from 27 studies revealed a mean blood loss of 1,163 mL (CI [894.974, 1431.023], $P<0.001$) in the laparotomy group (Fig. 1B). There was no heterogeneity among

the data obtained from these studies (I^2= 0%, *P*=0.8).

2) Operative time

Laparoscopy group

Data on operative time in the laparoscopy group were reported by 52 studies. The overall mean operative time was 63.2 minutes (CI [53.5, 72.8], *P*<0.001) (Fig. 2A). However, data from these studies showed significant heterogeneity (I^2=98.3%, *P*<0.001). Interestingly, a meta-regression model that included "duration of amenorrhea" as a covariate explained 81% of the between-studies variance (R^2=81%) (Supplementary Fig. 3). Cumulative meta-analysis of operative time showed a trend increase in the cumulative mean operative time from 46.5 minutes in 1996 to 63.3 minutes in 2019 (Supplementary Fig. 4).

Laparotomy group

Three studies reported data on operative time in the laparotomy group. No significant heterogeneity (I^2= 0%, *P*=0.3) was found among these studies, and the overall mean operative time was 78.2 minutes (CI [68.2, 88.2], *P*<0.001) (Fig. 2B).

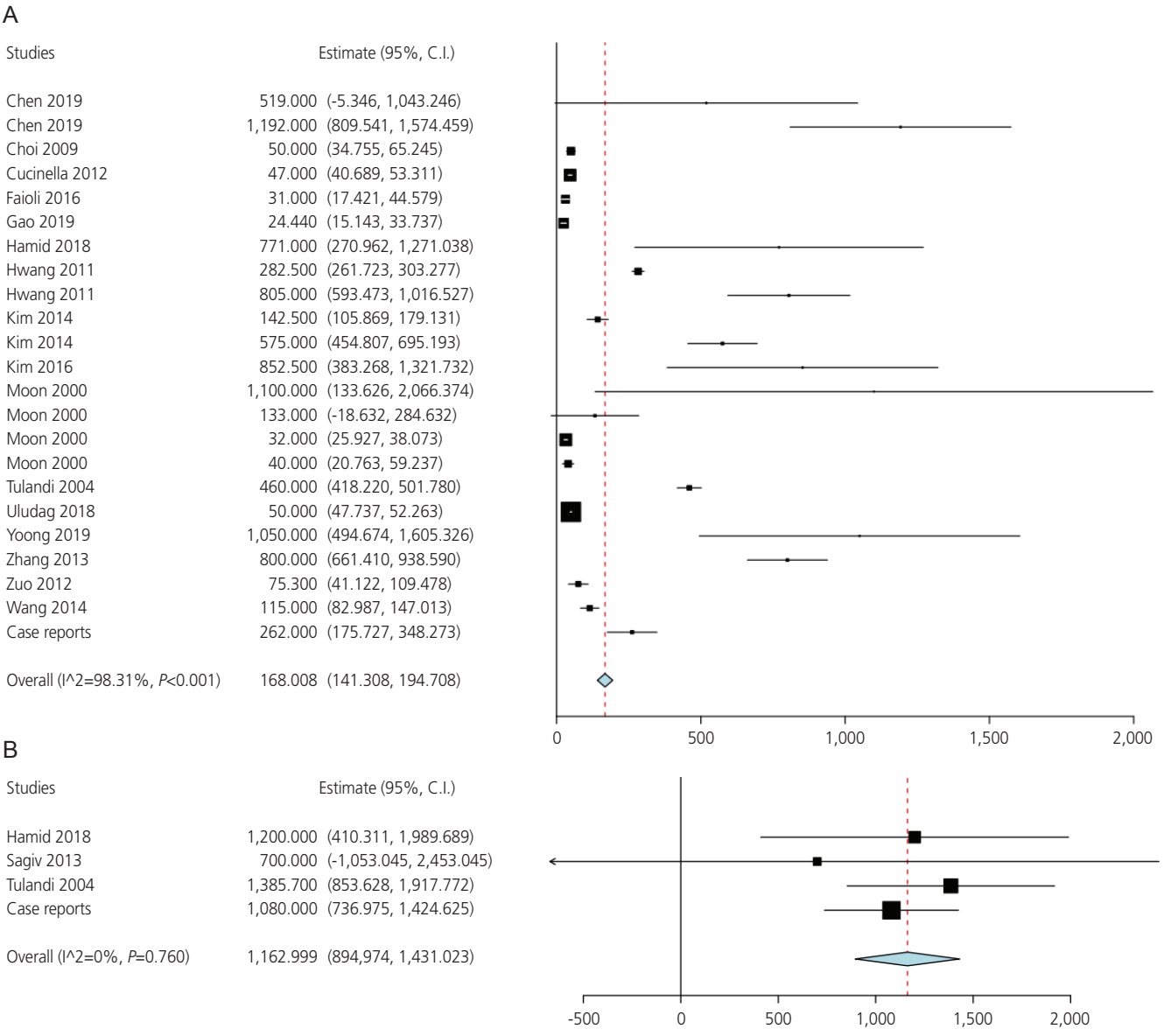

Fig. 1. Blood loss in the laparoscopy (A) and laparotomy (B) groups.

3) Hospital stay

Laparoscopy group

Data on hospital stay in the laparoscopy group were reported by 48 studies. The overall mean hospital stay was 3.7 days (CI [2.7, 4.7], *P*<0.001) (Fig. 3A). Considerable heterogeneity existed among the included studies (I^2=98%, *P*<0.001). A meta-regression model that included "gravidity" and "year of the study" as covariates explained 95% of the between-studies heterogeneity (R^2=0.95) (Supplementary Fig. 5).

Laparotomy group

Fifteen studies (12 case reports and 3 case series) were included in the meta-analysis for hospital stay in the laparotomy group (Supplementary Fig. 6). The summary estimate for mean hospital stay was 5.2 days (CI [3, 7.4], *P*<0.001) (Fig. 3B). There was significant heterogeneity among these studies (I^2=96%, *P*<0.001). When the study by Ghazali et al. [106]

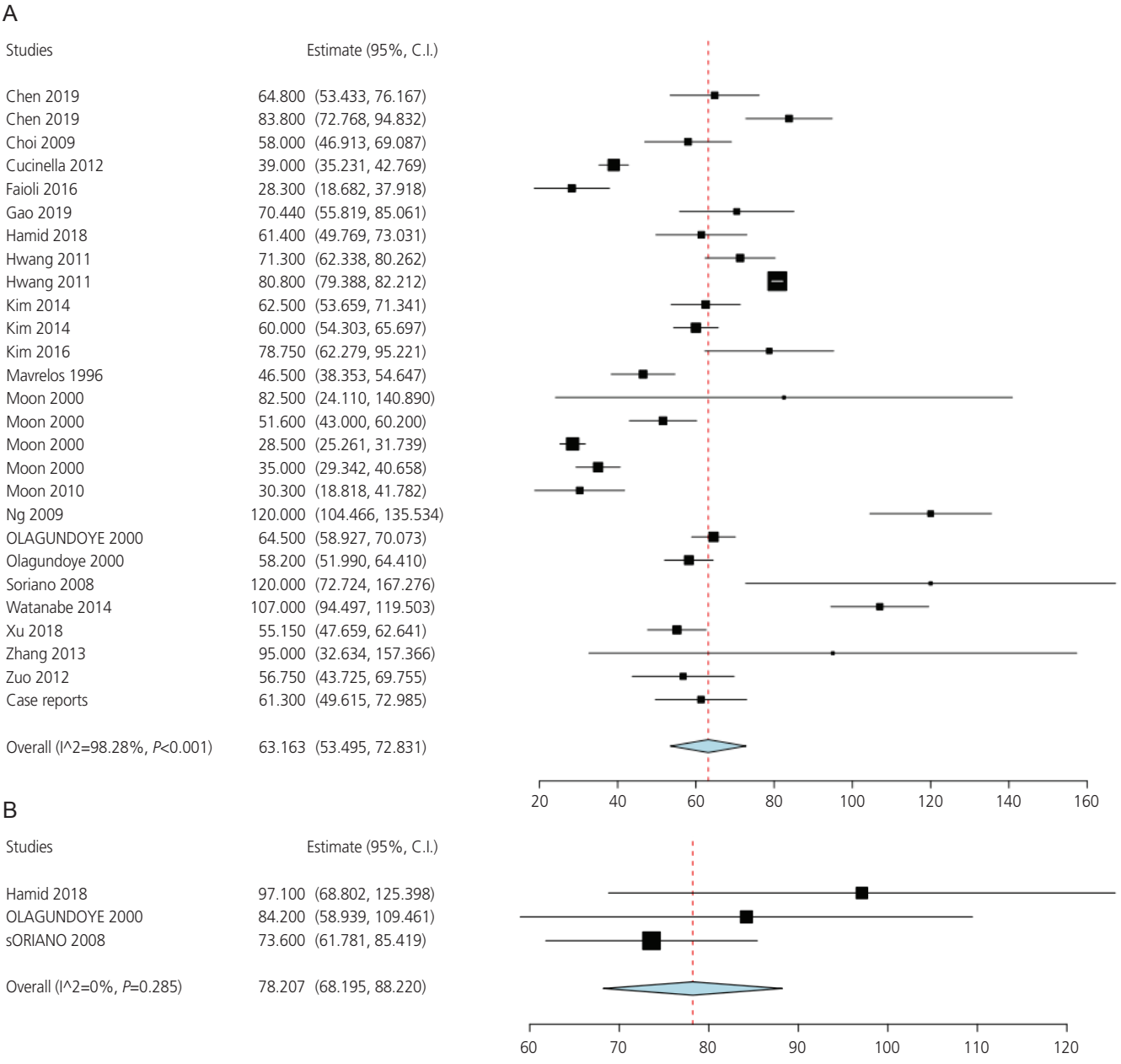

Fig. 2. Operative time in the laparoscopy (A) and laparotomy (B) groups.

(2018) was removed in a leave-one-out meta-analysis, heterogeneity was minimal (I^2=0%, *P*=0.5) (Supplementary Fig. 7).

4) Incidence of rupture

Laparoscopy group

Six studies provided analyzable data for the incidence of rupture in the laparoscopy group. The summary effect size was 0.51 (CI [0.2, 0.8], *P*<0.001) (Fig. 4A). There was significant heterogeneity among these studies (I^2=91%, *P*<0.001). When the study of Watanabe et al. (2014) [91] was removed in a leave-one-out meta-analysis, heterogeneity was minimal (I^2=0%, *P*=0.7) (Supplementary Fig. 8).

Laparotomy group

Only two studies that included 20 patients reported data on the incidence of ectopic rupture in the laparotomy group. The overall effect estimate was 0.77 (CI [0.59, 0.95], *P*<0.001). No significant heterogeneity was found (I^2=0%, *P*=0.4) (Fig. 4B).

5) Future pregnancy rate

Laparoscopy group

Data on future pregnancy rates were provided by 10 studies. The summary effect estimate was 0.62 (CI [0.42, 0.82], *P*<0.001). Significant heterogeneity was observed among these studies (I^2=86.4%, *P*<0.001), and a meta-regression model was fitted to explain this heterogeneity. The duration of amenorrhea and sample size were responsible for almost all the heterogeneity among the effect estimates (R^2=1).

Laparotomy group

The available studies provided no data on the future pregnancy rate in the laparotomy group.

Discussion

Our analysis showed less blood loss in the laparoscopic group (168 mL) than in laparotomy patients (1,163 mL). An

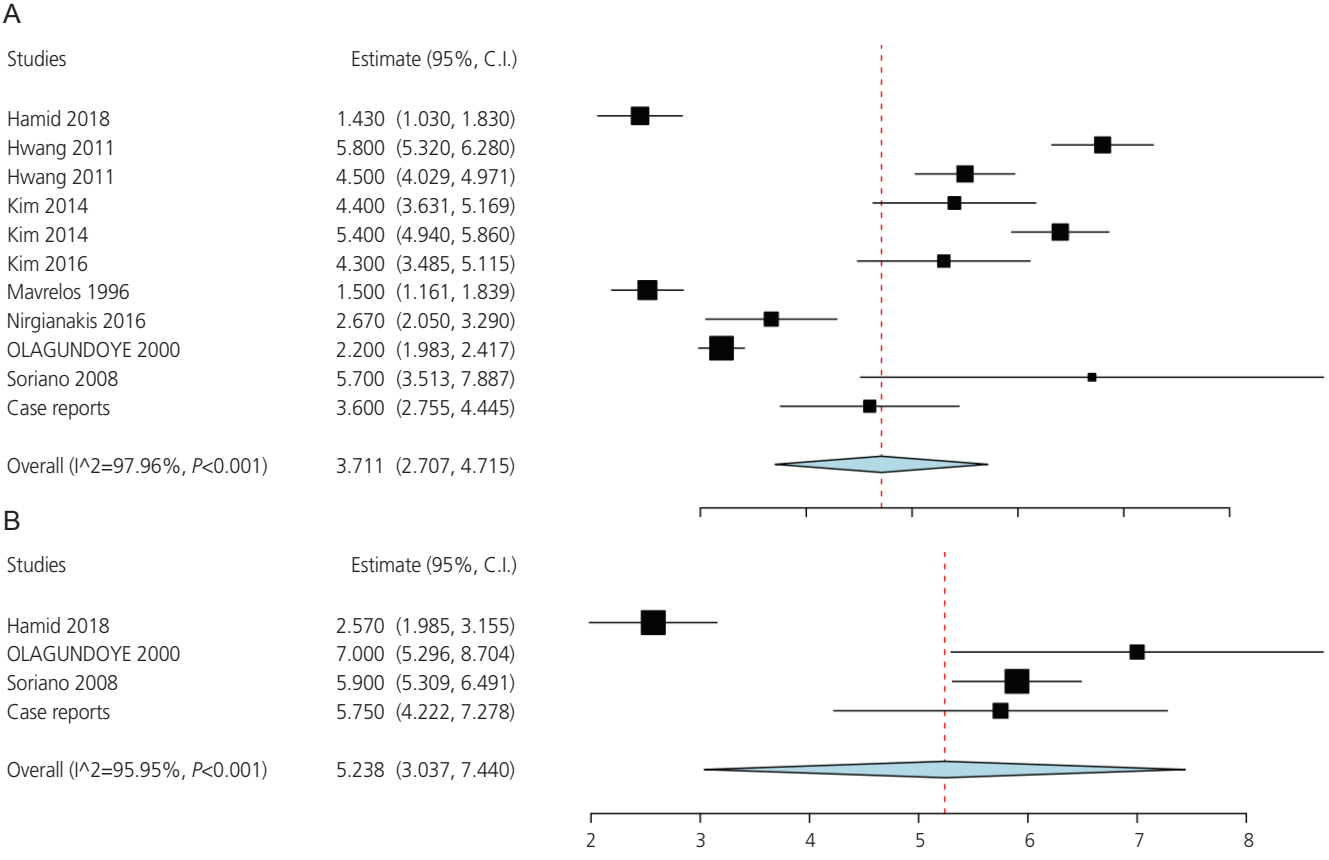

Fig. 3. Length of hospital stay in the laparoscopy (A) and laparotomy (B) groups.

increased duration of amenorrhea and gravidity is associated with increased blood loss in laparoscopic patients. Interestingly, blood loss in laparoscopy has been decreasing over time, as shown by cumulative meta-analysis. This is consistent with the nature of laparoscopic operations. Laparoscopic patients took less operative time (63.2 minutes) compared to laparotomy patients (78.2 minutes). However, the mean operative time for the laparoscopic approach is actually increasing over time. Patients in the laparoscopic group spent less time hospitalized (3.7 days) compared to laparotomy patients who spent 5.2 days in the hospital on average. More recently performed studies and women with higher gravidity were both associated with a shorter hospital stay for patients in the laparoscopic group.

Laparotomy patients had a higher incidence of ectopic pregnancy rupture (77%) than patients who underwent laparoscopic surgery (51%). However, we could not employ a meta-regression model because of the low number of studies. The study by Watanabe et al. [91] (2014) significantly contributed to this heterogeneity as it reported a much lower incidence of ruptured ectopic pregnancy (0/13) than in other studies.

Only two previous systematic reviews have discussed the different management strategies, including laparoscopy and laparotomy [103,104]. These studies discussed and compared most medical and surgical options, but stopped short of a direct meta-analysis of the laparoscopic versus open approach. This is likely because these systematic reviews predate most of the high-quality data we were able to utilize to complete this analysis, being published in 2000 and 2010, respectively. Outside of isolating for interstitial pregnancy, many authors have completed reviews comparing open and laparoscopic ectopic pregnancies. For example, a meta-analysis by Gao et al. [116] compared laparoscopy and laparotomy for ectopic pregnancy and showed similar results regarding blood loss. However, they found no difference between laparoscopy and laparotomy in terms of operation time, which we found was lower in the laparoscopic group.

Both techniques have some advantages and drawbacks. Laparoscopy is a minimally invasive surgery and is associated with improved cosmesis, shorter hospital stay, faster recovery, less postoperative pain, and a higher rate of preservation of the uterus [6,98,117]. A laparoscopic approach, however, also has some drawbacks such as higher incidences of hematomas of the abdominal and abdominal or pelvic infections, although major complications are rarely reported [118]. There was not sufficient data to meaningfully analyze all possible laparoscopic techniques separately, and it is likely

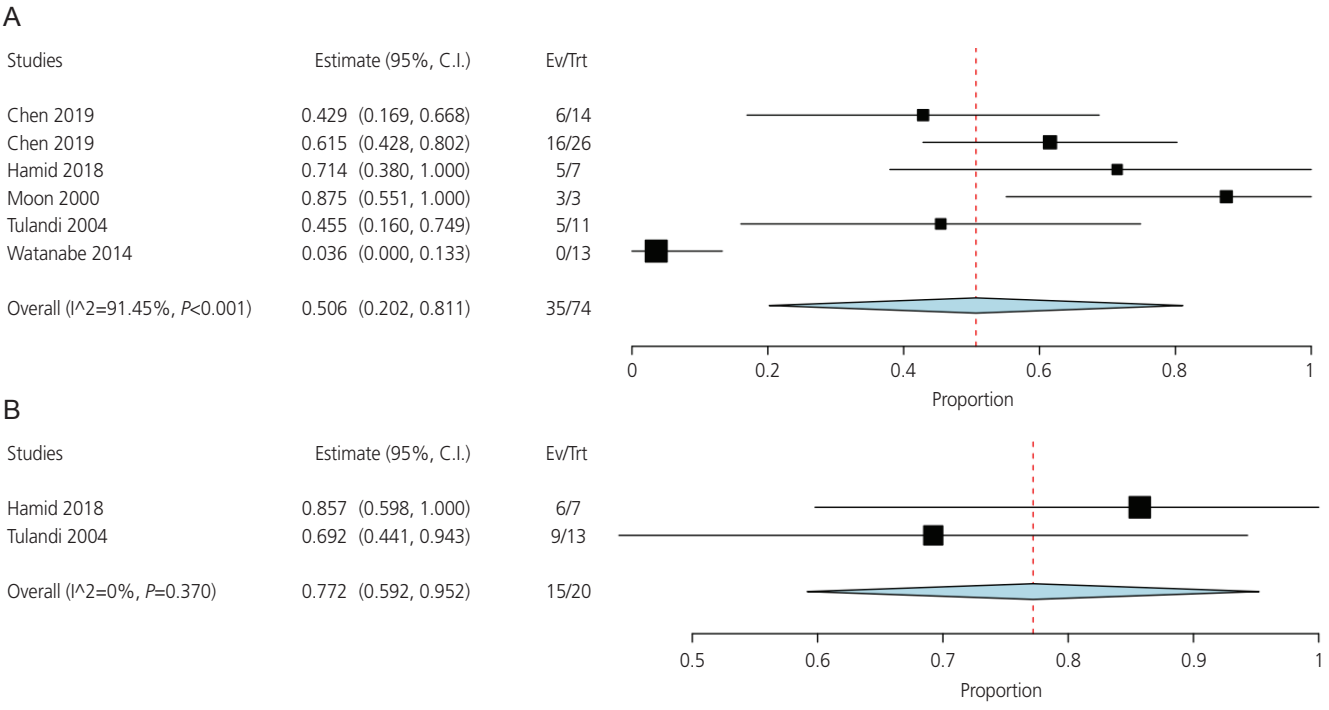

Fig. 4. Incidence of rupture in the laparoscopy (A) and laparotomy (B) groups.

that the increased operative time for laparoscopic procedures from 1996 to 2019 was a result of more complex procedures and the advent of robotic-assisted laparoscopy.

Laparotomy is also a widely used management technique, especially when adequate closure or hemostasis cannot be achieved by laparoscopy, and when surgeons without laparoscopic expertise are available. Laparotomy, however, has multiple risks including the general risks of anesthesia and surgery, incisional hernia, serious infections, bleeding, and injury of pelvic or abdominal organs. All of these are reported more often in open approaches [106,113].

We included all studies reporting data regarding the safety and efficacy of laparoscopic surgery or laparotomy (or both) in the management of interstitial or cornual ectopic pregnancy patients, as indicated in our PRISMA flow chart (Supplementary Fig. 9). Additionally, most of the heterogeneity detected among the studies was managed. The quality of most of the included studies was fair, and a large number of studies entered the analysis, which increases the generalizability of the results. A cumulative meta-analysis was also used to reveal trends in the data over time.

Limitations of this study would include the lack of data regarding long-term effects, as we were able to find little or no data regarding late complications or overall survival. We reported what little we did find with regard to future pregnancy following surgical intervention. Another limitation is that all of the included studies were observational, which is generally considered at a low level of evidence. Lastly, the authors admit that the possibility of publication bias affecting results also exists.

Conclusion

Our analysis supports laparoscopy as the mainline surgical option for patients with interstitial pregnancy. Laparoscopy was associated with an average blood loss of 168 mL, a mean operative time of one hour, and an average hospitalization time of 3.7 days. Our review shows that complications decrease over time. Interestingly, our analysis showed that both increased gravidity and duration of amenorrhea are positive risk factors leading to increased bleeding. Compared with laparotomy, management with laparoscopic surgery is associated with less blood loss, less operative time, and a shorter hospital stay. Laparotomy is also associated with a higher incidence of rupture of ectopic pregnancy.

Further interventional studies with a larger sample size and longer follow-up duration are needed to produce more valid results. We believe as the first systematic review to address this topic, our findings add strength to the position that laparoscopic approaches to interstitial pregnancy can be considered first-line in most situations.

Supplementary materials

Supplementary materials associated with this article can be found online at https://doi.org/10.5468/ogs.20299.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Ethical approval

The study was performed in accordance with the principles of the Declaration of Helsinki.

Patient consent

Written informed consent and the use of images from patients are not required for the publication.

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Condensation

Many authors have described laparoscopic management of interstitial pregnancy. We performed the first systematic review of modern laparoscopy to assess the appropriateness of the laparoscopic approach as first-line management.

IRB approval

Found exempt at the Marchand Institute July 2020 IRB Meeting (2020-04-855).

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