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Is the laparoscopic approach a safe choice for the management of acute appendicitis in pregnant women? A meta-analysis of observational studies

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ABSTRACT

INTRODUCTION Acute appendicitis is a common and serious situation during pregnancy, because of the increased risk of fetal loss and perforation in the third trimester, as well as a diagnostic difficulty. During recent years laparoscopic approach has been introduced to clinical practice with encouraging results. The purpose of this meta-analysis is to compare the surgical and obstetrical outcomes between laparoscopic and open appendectomy during pregnancy.

MATERIALS AND METHODS MEDLINE, SCOPUS, Clinicaltrials.gov, CENTRAL and Google Scholar were searched for studies reporting on postoperative outcomes between laparoscopic and open appendectomy during pregnancy. The random effects model (DerSimonian–Laird) was used to calculate pooled effect estimates when high heterogeneity was encountered, otherwise the fixed-effects (Mantel–Haenszel) model was implemented.

RESULTS Twenty-one studies that enrolled 6276 pregnant women are included in the present meta-analysis. Of these women, 1963 underwent laparoscopic appendectomy and 4313 underwent an open appendectomy. Women who underwent laparoscopic appendectomy demonstrated an increase in fetal loss risk, while neonates of women that underwent open appendectomy presented decreased Apgar score at five minutes after birth. All the rest outcomes were similar between the two groups. The time that each study took place seemed to affect the comparison of birth weight and postoperative hospital stay between the two groups.

CONCLUSION Laparoscopic appendectomy seems to be a relatively safe therapeutic option in pregnancy when it is indicated. Thus, it should be implemented in clinical practice, always considering the experience of the surgeon in such procedures. Nevertheless, the need of new studies to enhance this statement remains crucial.

KEYWORDS

Laparoscopy – Appendicitis – Pregnancy

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Introduction

During pregnancy, appendicitis is a common non-obstetric emergency that may entail surgery. It is observed in approximately 1/1500 pregnancies,[1] representing 25% of non-obstetric operations performed in the antenatal period.[2] Incidence varies throughout the pregnancy course, ranging from 19% to 36% during the first trimester, from 27% to 60% during the second trimester and from 15% to 33% during the last three months of pregnancy.[3] Despite the fact that acute appendicitis is more common during the first and second trimesters, perforation is more common in the third trimester.[4]

Pregnant women who undergo surgery, including appendectomy, are at a higher risk of fetal loss, particularly when the operation takes place during early pregnancy and if the mother fails to receive immediate and appropriate medical attention.[5] Accurate diagnosis becomes a problem, because appendicitis is complicated by the physiological and anatomical changes that occur during pregnancy. In several cases, the signs and symptoms are similar to those of pregnancy or the onset of labour and include loss of appetite, nausea and vomiting and lower abdominal pain.[5] This can delay diagnosis and increase the risk of morbidity for both the mother and the fetus.[6]

Pregnancy was a relative contraindication to laparoscopy until recently because of the belief that the procedure would decrease uterine and fetal blood flow; thus there were concerns that it could result in miscarriage or could possibly influence fetal development.[7] Although laparoscopic appendectomy has become more popular in daily practice, some controversy still exists regarding its everyday practice in pregnancy.[8] Current data suggest that laparoscopy can be performed without complications during the three trimesters,[7,9] although the procedure may become particularly difficult at term gestation as the operating field is obstructed by the gravid uterus.[10] Since then, several studies have been published in this field that add new data, thus rendering necessary the conduct of a new meta-analysis.

In the present meta-analysis, our aim was to assess the safety and feasibility of laparoscopic appendectomy in pregnant women and to compare the perioperative surgical as well as the perinatal outcomes between laparoscopic and open appendectomy.

Materials and methods

The present meta-analysis was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the protocol of has been registered with PROSPERO (CRD42018087261).[11]

We used the Medline (1966–2018), Scopus (2004–2018), Clinicaltrials.gov (2008–2018), EMBASE (1980–2018), the Cochrane Central Register of Controlled Trials CENTRAL (1999–2018) and Google Scholar (2004–2017) databases in our primary search, together with the reference lists of electronically retrieved full-text papers. The date of our last search was 25 March 2018. Our search strategy included the text words 'laparoscopic', 'laparoscopy', 'appendectomy', 'appendicitis' and 'pregnancy' and is schematically presented in the PRISMA flow diagram (Fig 1).

The studies were selected in three consecutive stages. Following deduplication, the titles and abstracts of all electronic articles were screened by two authors (MF and CN) to assess their eligibility. The decision for inclusion of studies in the present meta-analysis was taken after retrieving and reviewing the full text of articles that were held potentially eligible. Potential discrepancies in this latter stage were resolved by the consensus of all authors.

Types of studies and patients

The eligibility criteria for the inclusion of studies were predetermined. All observational studies and randomised trials that assessed the perioperative outcomes and antenatal/perinatal outcomes of pregnant women who had laparoscopic or open appendectomy during their pregnancy course (irrespective of the trimester of pregnancy) were considered eligible for inclusion. Case reports, experimental animal studies and reviews were not considered eligible for inclusion. In addition, studies that demonstrated mixed surgical and obstetric outcomes after laparoscopic appendectomy and cholecystectomy in combination with studies that presented outcomes only after laparoscopic appendectomy during pregnancy, without comparison to the open technique, were excluded from our meta-analysis (Fig 1).

Outcome measures

Outcome measures were predefined during the design of the present meta-analysis. Fetal loss during the antenatal period was defined as the primary outcome, whereas birth weight, preterm birth, intraoperative duration of appendectomy, Apgar score at one and five minutes, duration of postoperative hospitalisation and wound infection rates were predefined as secondary outcomes.

Data tabulation

Data on variable of interest were tabulated in four structured forms. Table 1 presents the basic study characteristics, the trimesters of pregnancy, the continent of each study and diagnosis of acute appendicitis. Table 2 summarises patient characteristics: maternal age, gestational age at the time of surgery, maternal age at time of delivery, time from the start of symptoms until reaching the emergency department, laboratory findings (e.g. fever and leucocytosis) and trimester of pregnancy of each group of women. Table 3 presents the obstetric outcomes: Apgar scores at one and five minutes, birth weights, preterm birth rates, miscarriage rates, caesarean section frequency and fetal loss rates. Table 4 contains the intraoperative and postoperative parameters: interval from presentation to surgery, wound infection rates, abscess formation, intraoperative time, postoperative hospital stay, overall complications rates and histopathological type of appendix, divided into normal, phlegmonus or complicated.

Statistical analysis

Statistical meta-analysis was performed using RevMan 5.3 software. Confidence intervals (CI) were set at 95%. We calculated pooled odds ratios (OR), mean differences (MD) and 95% CI with the DerSimonian–Laird random effect model due to the significant heterogeneity in the methodological characteristics of included studies.[12] Publication bias was assessed with the funnel plot method in cases of variables that included outcomes from at least 10 studies.[13]

Sensitivity analysis

Sensitivity analyses were considered, taking into account the fact that each study may have significantly altered the results of the meta-analysis. The fixed effects model results in narrower CI and these might have accounted for non-significance. The idea behind changing the selected model is to evaluate whether, in an ideal world of no

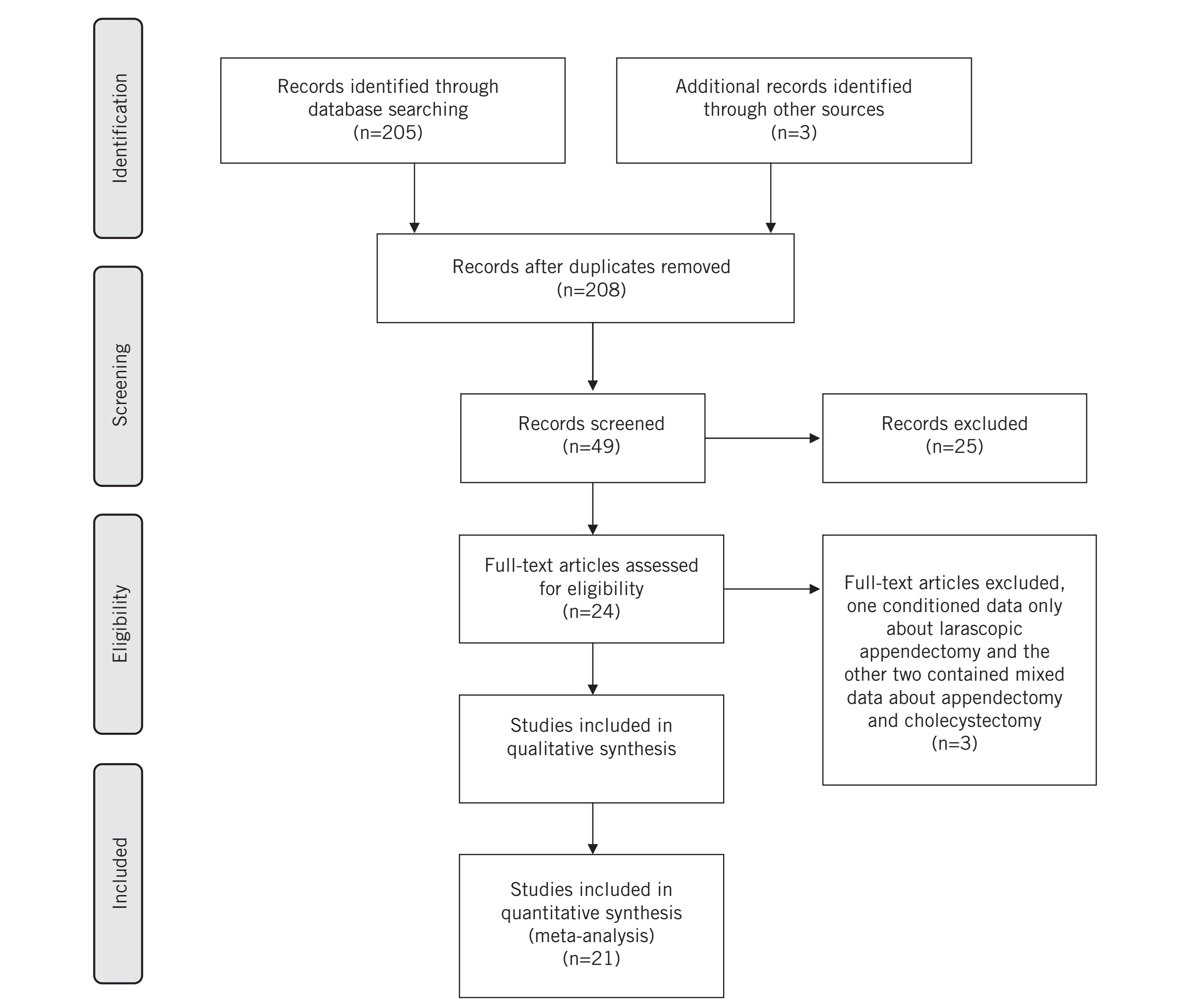

Figure 1 The PRISMA flow chart of study selection.

heterogeneity, the results of included studies would have been significant. Consequently, leave-one-out meta-analysis was performed to rule out the potential effect of individual studies on the outcomes of the primary meta-analysis. Furthermore, to study the effect of time (year of publication) we performed cumulative meta-analysis and meta-regression analysis. In addition, meta-regression analysis was performed to investigate the effect of the origin of each study on the obstetric and surgical outcomes after appendectomy. Although these analyses do not have a reference to adhere to, we believe that they are rational and that they provide a spherical approach in the field of this meta-analysis. The forest plots of the 'leave one out', cumulative meta-analysis and meta-regression analysis were produced with the Open-Meta Analyst statistical software.[14]

Quality assessment

We evaluated the quality of included studies using the risk of bias in non-randomised studies (ROBINS-I) assessment tool. The tool briefly assesses the possibility of bias that may arise due to confounding, selection, classification, attrition or selective reporting (Table 5).[15]

Results

Included studies

Twenty-one studies are included in the present meta-analysis,[16–36] which presented the postoperative and obstetric outcomes of 6276 pregnant women who underwent appendectomy under the suspicion of acute appendicitis. A total of 1963 pregnant women underwent laparoscopic appendectomy, while 4313 pregnant women underwent an open

Table 1 Study characteristics

Study	Type of study	Patients (*n*)	Age (years)	Trimesters of pregnancy	Continent of origin	Diagnosis
Curet 1996[44]	Retrospective	16 vs 18	23.8 vs 22.4	1st, 2nd	USA	N/A
Gurbuz 1997[22]	Retrospective	5 vs 4	24.5 vs 24.5	1st, 2nd, 3rd	USA	Clinical manifestation, lab. findings (WBC)
Conron 1999[43]	Retrospective	12 vs 9	24.5 ± 1.8 vs 23.7 ± 1.6	1st, 2nd ,3rd	USA	N/A
Affleck 1999[16]	Retrospective	22 vs 18	N/A	1st, 2nd, 3rd	USA	N/A
Lyass 2001[25]	Prospective	11 vs 11	27 vs 30	1st, 2nd, 3rd	Asia	Clinical examination, laparoscopy
Carver 2005[17]	Retrospective	17 vs 11	23 ± 5 vs 24 ± 7	1st, 2nd	USA	N/A
McGory 2007[26]	Retrospective	454 vs 2.679	N/A	1st, 2nd, 3rd	USA	N/A
Upadhyay 2007[30]	Retrospective	4 vs 2	27 vs 27.5	1st, 2nd, 3rd	USA	Clinical examination, ultrasound
Kirshtein 2009[23]	Retrospective	23 vs 19	29.8 vs 26.8	1st, 2nd	Asia	Clinical examination, ultrasound
Sadot 2009[28]	Retrospective	48 vs 17	29.79 ± 6.2 vs 28.76 ± 5.1	1st, 2nd, 3rd	USA	Imaging studies, operative intervention
Corneille 2010[20]	Retrospective	9 vs 40	24 ± 8 vs 26 ± 6	1st, 2nd, 3rd	USA	Clinical examination, operative intervention
de Bakker 2011[33]	Retrospective	17 vs 3	32 vs 35	1st, 2nd, 3rd	Europe	N/A
Eom 2012[34]	Retrospective	15 vs 28	N/A	1st, 2nd, 3rd	Asia	N/A
Kapan 2013[35]	Retrospective	10 vs 10	27.1 vs 25	1st, 2nd, 3rd	Europe	Clinical examination, lab. findings (WBC, NEU), ultrasound
Chung 2013[19]	Retrospective	22 vs 39	29.3 ± 3.1 vs 31.4 ± 4.3	1st, 2nd, 3rd	Asia	Clinical examination, ultrasound
Peled 2014[27]	Retrospective	26 vs 59	29.2 ± 4.9 vs 27.6 ± 4.7	2nd	Asia	Clinical examination, lab. findings (WBC)
Cheng 2015[18]	Retrospective	128 vs 653	27.28 vs 27.36	N/A	Asia	N/A
Cox 2016[21]	Retrospective	894 vs 441	27.7 ± 6.2 vs 28.2 ± 6.3	N/A	USA	N/A
Laustsen 2016[24]	Retrospective	19 vs 25	30.5 vs 30.5	1st, 2nd, 3rd	Europe	Clinical examination, ultrasound
Segev 2016[29]	Retrospective	50 vs 42	28 vs 29	1st, 2nd, 3rd	Asia	Clinical examination, ultrasound, MRI
Winter 2017[31]	Retrospective	125 vs 93	27 vs 28	1st, 2nd, 3rd	Australia	Clinical examination, Operative intervention
Yoo 2016[32]	Retrospective	24 vs 56	30.2 vs 31	1st, 2nd, 3rd	Asia	Clinical examination, ultrasound, MRI
Karaman 2016[36]	Retrospective	12 vs 36	27.08 ± 5.48 vs 28.81 ± 8.35	1st, 2nd, 3rd	Europe	Clinical examination, ultrasound, lab. findings (WBC)

lab., laboratory; MRI, magnetic resonance image; N/A, not available; NEU, neutrophil count; vs, compared with; WBC, white blood cell count.

Table 2 Patient characteristics

Study	Age (years)	Gestational age (weeks)		Patient delay (hours)[a]	Fever (°C)	Leucocytosis (WBC > 10 × 10^9/l)	Trimester		
		At surgery	At delivery				1st	2nd	3rd
Curet 1996[44]	23.8 vs 22.4	N/A	38.2 vs 39.2	N/A	N/A	N/A	7 vs 8	9 vs 10	None
Gurbuz 1997[22]	24.5 vs 24.5	26 vs 17	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Conron 1999[43]	24.5 ± 1.8 vs 23.7 ± 1.6	11.5 ± 2.1 vs 24.9 ± 1.9	39.2 ± 0.7 vs 38.4 ± 0.6	N/A	N/A	N/A	N/A	N/A	N/A
Affleck 1999[16]	N/A	N/A	N/A	N/A	N/A	N/A	6 vs N/A	9 vs N/A	4 vs N/A
Lyass 2001[25]	27 vs 30	16 vs 24	40 vs 40	N/A	N/A	N/A	5 vs 2	4 vs 4	2 vs 5
Carver 2005[17]	23 ± 5 vs 24 ± 7	14 ± 5 vs 14 ± 6	38 ± 1 vs 39 ± 1	N/A	N/A	N/A	5 vs 4	12 vs 7	None
McGory 2007[26]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Upadhyay 2007[30]	27 vs 27.5	N/A	31 vs 34	N/A	N/A	N/A	0 vs 0	0 vs o	4 vs 2
Kirshtein 2009[23]	29.8 vs 26.8	12 ± 5 vs 16.2 ± 7.2	39.3 ± 1.2 vs 38.9 ± 2.6	35.9 ± 29.5 vs 24.2 ± 1 9.3	37.2 vs 37.2	11.800 vs 13.100	23 (total)	19 (total)	0 vs 0
Sadot 2009[28]	29.79 ± 6.2 vs 28.76 ± 5.1	18.1 ± 7.4 vs 24.3 ± 6.7	37.9 ± 3.5 vs 38.54 ± 1.48	34.4 ± 18.4 vs 33.7 ± 15.8	36.96 ± 0.58 vs 36.67 ± 0.82	14.220 ± 4.500 vs 13.660 ± 4000	14 vs 0	32 vs 12	2 vs 5
Corneille 2010[20]	24 ± 8 vs 26 ± 6	11 ± 6 vs 17 ± 9	38 ± 5 vs 38 ± 3	N/A	N/A	N/A	6 vs 19	3 vs 12	0 vs 9
de Bakker 2011[33]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Eom 2012[34]	N/A	15 vs 17	38 vs 39	N/A	0 vs 3	15 vs 28	N/A	N/A	N/A
Kapan 2013[35]	27,1 vs 25	17,8 vs 17,5	N/A	N/A	N/A	13.410 vs 14.430	N/A	N/A	N/A
Chung 2013[19]	29.3 ± 3.1 vs 31.4 ± 4.3	16.4 ± 5.7 vs 16.7 ± 4.8	37.1 ± 1.7 vs 38.2 ± 3.5	N/A	N/A	N/A	6 vs 8	13 vs 20	3 vs 11
Peled 2014[27]	29.2 ± 4.9 vs 27.6 ± 4.7	14.6 ± 6.9 vs 19.3 ± 7.7	37.8 ± 2.8 vs 38.6 ± 2.5	1.9 ± 1.9 vs 2.3 ± 2.6	N/A	13.100 ± 5.300 vs 13.900 ± 3.800	N/A	N/A	N/A
Cheng 2015[18]	27.28 vs 27.36	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cox 2016[21]	27.7 ± 6.2 vs 28.2 ± 6.3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Laustsen 2016[24]	30.5 vs 30.5	16 vs 22	N/A	N/A	N/A	N/A	8 vs 0	7 vs 20	4 vs 5
Segev 2016[29]	28 vs 29	16 vs 24	38 vs 39	24 vs 24	5 vs 7 (No)	38 vs 34 (No)	20 vs 6	29 vs 16	1 vs 20
Winter 2017[31]	27 vs 28	13 vs 22	N/A	N/A	N/A	N/A	67 vs 13	54 vs 58	4 vs 22
Yoo 2016[32]	30.2 vs 31	19.1 vs 20.7	38.4 vs 38.5	N/A	37.3 vs 37.1	14.700 vs 14.100	7 vs 14	15 vs 29	2 vs 13
Karaman 2016[36]	27.08 ± 5.48 vs 28.81 ± 8.35	22.42 ± 8.25 vs 25.67 ± 6.57	37.25 ± 3.41 vs 36.72 ± 4.84	N/A	N/A	13.92 ± 5.10 vs 13.62 ± 5.40	1 vs 2	7 vs 12	4 vs 22

N/A, not available; vs, compared with.
[a] Patient delay: interval from the beginning of symptoms to theatre.

Table 3 Obstetric parameters

Study	Apgar		Weight (g)	Preterm labour	Miscarriage	Caesarean section	Fetal loss
	5 minutes	1 minute					
Curet 1996[44]	9 vs 9	7 vs 8	3.290 vs 3.293	0 vs 1	0 vs 0	N/A	0 vs 0
Gurbuz 1997[22]	N/A	N/A	N/A	0 vs 0	0 vs 0	N/A	0 vs 0
Conron 1999[43]	9 ± 0.2 vs 8.8 ± 0.1	7.4 ± 0.3 vs 7.6 ± 0.3	3.360 ± 140 vs 3.270 ± 180	0 vs 0	0 vs 1	N/A	1 vs 0
Affleck 1999[16]	N/A	N/A	N/A	3 vs 2	0 vs 0	N/A	0 vs 0
Lyass 2001[25]	No statistical difference	No statistical difference	No statistical difference	0 vs 0	0 vs 0	N/A	0 vs 0
Carver 2005[17]	9 ± 0.6 vs 9 ± 0.5	8 ± 2 vs 7 ± 1	3.500 ± 500 vs 3.500 ± 400	0 vs 0	0 vs 0	2 vs 3	2 vs 0
McGory 2007[26]	N/A	N/A	N/A	1 vs 216	N/A	N/A	31 vs 88
Upadhyay 2007[30]	N/A	N/A	N/A	1 VS 0	0 vs 0	0 vs 0	0 vs 0
Kirshtein 2009[23]	10 vs 10	8.9 vs 8.7	3.165 ± 413 vs 3.118 ± 600	0 vs 0	1 vs 1	6 vs 3	0 vs 0
Sadot 2009[28]	8.97 ± 0.17 vs 9.06 ± 0.25	8.91 ± 0.29 vs 9.0 ± 0	3.298 ± 544 vs 3.311 ± 340	12 vs 3	0 vs 0	12 vs 4	1 vs 0
Corneille 2010[20]	9 ± 2 vs 9 ± 2	8 ± 2 vs 8 ± 2	N/A	1 vs 5	0 vs 3	N/A	N/A
de Bakker 2011[33]	N/A	N/A	N/A	1 vs1	N/A	N/A	1 vs 0
Eom 2012[34]	N/A	N/A	3125 vs 2780	0 vs 3	1 vs 2	0 vs 4	0 vs 0
Kapan 2013[35]	N/A	N/A	N/A	0 vs 0	0 vs 0	N/A	0 vs 0
Chung 2013[19]	9.8 ± 0.2 vs 9.9 ± 0.1	9.2 ± 0.1 vs 9.3 ± 0.2	2.810 ± 293 vs 2.790 ± 312	2 vs 4	0 vs 0	6 vs 14	0 vs 0
Peled 2014[27]	10 ± 0 vs 9.9 ± 0.1	8.9 ± 0.2 vs 8.7 ± 1.0	3.075 ± 479 vs 3.115 ± 636	5 vs 14	1 vs 0	7 vs 18	0 vs 0
Cheng 2015[18]	N/A	N/A	N/A	7 vs 74	7 vs 37	52 vs 258	N/A
Cox 2016[21]	N/A	N/A	N/A	0 vs 0	N/A	N/A	N/A
Laustsen 2016[24]	9.7 vs 9.3	8.7 vs 8.2	3.458 vs 3.366	3 vs 2	0 vs 0	N/A	0 vs 0
Segev 2016[29]	10 vs 10	9 vs 9	3.000 vs 3.400	5 vs 3	0 vs 0	N/A	2 vs 2
Winter 2017[31]	N/A	N/A	N/A	8 vs 8	0 vs 0	N/A	7 vs 0
Yoo 2016[32]	N/A	N/A	2.860 vs 2.840	2 vs 4	0 vs 0	13 vs 18	3 vs 4
Karaman 2016[36]	N/A	8.42 ± 1.08 vs 8.11 ± 1.62	3030 ± 744 vs 2944 ± 664	3 vs 9	1 vs 0	4 vs 11	1 vs 1

N/A, not available; vs, compared with.

Table 4 Surgery and postoperative parameters

Study	Surgery delay (hours)	Wound Infection	Abscess	Surgery time (minutes)	Length of Stay (days)	Overall complications	Pathology		
							Normal	Phlegmonus	Complicated
Curet 1996[44]	N/A	N/A	N/A	82 vs 49	1.5 vs 2.8	6 vs 3	N/A	N/A	N/A
Gurbuz 1997[22]	N/A	N/A	N/A	64 vs 58	1.2 vs 1.8	N/A	N/A	N/A	0 vs 0
Conron 1999[43]	N/A	N/A	N/A	51.3 ± 5.5 vs 63.5 ± 7.5	1.41 ± 0.15 vs 3.78 ± 0.74	1 vs 1	N/A	N/A	N/A
Affleck 1999[16]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lyass 2001[25]	N/A	N/A	N/A	60 vs 40	3.6 vs 5.2	1 vs 1	1 vs 6	10 vs 5	0 vs 0
Carver 2005[17]	N/A	0 vs 0	N/A	N/A	2.6 ± 1.6 vs 2.4 ± 1.4	0 vs 0	N/A	N/A	0 vs 1
McGory 2007[26]	N/A	N/A	N/A	N/A	N/A	32 vs 304	245 vs 480	122 vs 1507	86 vs 697
Upadhyay 2007[30]	N/A	N/A	N/A	N/A	N/A	1 vs 1	1 vs 0	2 vs 2	1 vs 0
Kirshtein 2009[23]	9.8 ± 7.2 vs 7.6 ± 4.6	N/A	N/A	29.9 ± 6.3 vs 28.9 ± 9.2	2.4 ± 1.7 vs 1.4 ± 0.5	0 vs 0	4 vs 1	12 vs 17	7 vs 1
Sadot 2009[28]	11.28 ± 9.55 vs 13.23 ± 7.41	1 vs 0	0 vs 1	54 ± 34 vs 55 ± 25	3.44 ± 5.4 vs 4.2 ± 2.1	2 vs 1	12 vs 3	32 vs 10	4 vs 4
Corneille 2010[20]	N/A	N/A	N/A	N/A	5 ± 4 vs 4 ± 3	1 vs 6	N/A	N/A	N/A
de Bakker 2011[33]	N/A	N/A	N/A	68 vs 59	N/A	1 vs 1	3 vs 0	8 vs 2	1 vs 1
Eom 2012[34]	N/A	0 vs 0	0 vs 1	27.5 vs 55	4 vs 5	1 vs 7	0 vs 0	11 vs 2	4 vs 6
Kapan 2013[35]	6.3 vs 5.7	N/A	N/A	59.5 VS 48.2	1.1 VS 1.1	N/A	3 vs 0	7 vs 10	0 vs 0
Chung 2013[19]	N/A	0 vs 1	1 vs 1	44.2 ± 16.4 vs 47.3 ± 14.7	4.2 ± 2.9 vs 6.9 ± 3.7	1 vs 2	2 vs 4	19 vs 29	1 vs 6
Peled 2014[27]	N/A	N/A	N/A	N/A	3.7 ± 1.1 vs 3.8 ± 1.2	1 vs 15	5 vs 10	19 vs 37	1 vs 10
Cheng 2015[18]	N/A	N/A	N/A	N/A	3.8 vs 5.5	N/A	N/A	N/A	12 vs 109
Cox 2016[21]	N/A	6 vs 17	0 vs 0	47.1 ± 20.2 vs 52.1 ± 25.1	2.3 ± 5.8 vs 3.3 ± 2.5	36 vs 31	0 vs 0	823 vs 392	71 vs 49
Laustsen 2016[24]	N/A	1 vs 6	0 vs 2	69 vs 49	2.6 vs 5.5	1 vs 9	3 vs 13	13 vs 7	3 vs 5
Segev 2016[29]	13 vs 12	0 vs 5	0 vs 0	57 vs 60	3 vs 5	4 vs 10	9 vs 11	36 vs 23	4 vs 7
Winter 2017[31]	N/A	N/A	N/A	N/A	3.7 vs 4.5	N/A	N/A	N/A	N/A
Yoo 2016[32]	N/A	3 vs 2	1 vs 4	52.8 vs 53.9	5.1 vs 8.1	4 vs 6	0 vs 0	13 vs 42	11 vs 14
Karaman 2016[36]	18.42 ± 17.15 vs 13.83 ± 13.45	0 vs 1	0 vs 1	49.42 ± 11.38 vs 38.61 ± 11.50	3.25 ± 2.45 vs 4.28 ± 3.31	0 vs 1	N/A	N/A	N/A

N/A, not available; vs, compared with.

Table 5 Risk of bias in non-randomised studies of interventions (ROBINS-I) tool

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Curet 1996[44]	Serious	Low	Low	Moderate	Low	Low	Moderate
Gurbuz 1997[22]	Serious	Low	Low	Low	Low	Low	Moderate
Conron 1999[43]	Serious	Low	Low	Low	Low	Low	Moderate
Affleck 1999[16]	Serious	Low	Low	Moderate	Low	Low	Moderate
Lyass 2001[25]	Moderate	Low	Low	Low	Low	Low	Low
Carver 2005[17]	Moderate	Low	Low	Low	Low	Low	Low
McGory 2007[26]	Moderate	Moderate	Low	Low	Low	Low	Moderate
Upadhyay 2007[30]	Moderate	Low	Low	Low	Low	Low	Low
Kirshtein 2009[23]	Moderate	Low	Low	Low	Low	Low	Low
Sadot 2009[28]	Low	Low	Low	Low	Low	Low	Low
Corneille 2010[20]	Serious	Low	Low	Low	Low	Low	Moderate
de Bakker 2011[33]	Moderate	Low	Low	Low	Low	Low	Low
Eom 2012[34]	Serious	Moderate	Low	Low	Low	Low	Moderate
Kapan 2013[35]	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
Chung 2013[19]	Low	Low	Low	Low	Low	Low	Low
Peled 2014[27]	Low	Low	Low	Low	Low	Low	Low
Cheng 2015[18]	Low	Low	Low	Low	Low	Low	Low
Cox 2016[21]	Moderate	Low	Low	Moderate	Low	Low	Moderate
Laustsen 2016[24]	Moderate	Low	Low	Low	Low	Low	Moderate
Segev 2016[29]	Low	Low	Low	Low	Low	Low	Low
Winter 2017[31]	Low	Low	Low	Low	Low	Low	Low
Yoo 2016[32]	Moderate	Moderate	Low	Moderate	Low	Low	Moderate
Karaman 2016[36]	Low	Moderate	Low	Low	Low	Moderate	Moderate

appendectomy. The enrolled patients, who were divided into two groups ('laparoscopic' and 'open'), according to the surgical technique they underwent, presented no difference in terms of age, gestational age at the operation time, gestational age at the delivery time, delay until they were taken to theatre, fever, leucocytosis and trimester of pregnancy (Table 2).

Outcome of interest

Our analysis outlined a statistically significant increase in fetal loss rates during laparoscopic appendectomy compared with open appendectomy (OR 2.11, 95% CI 1.44–3.09, P = 0.0001; Fig 2).

Secondary outcomes

On the other hand, no difference was observed in terms of birth weight at the time of delivery (MD 7.32, 95% CI –92.38 to 107.02, P = 0.89; Fig 3) and preterm birth rates (OR 0.72, 95% CI 0.40 to 1.29, P = 0.27; Fig 4) between patients who underwent open and laparoscopic appendectomy. Intraoperative times did not differ between open and laparoscopic appendectomy (MD 0.33, 95% CI –5.47 to 6.14, P = 0.91; Fig 5). There was a statistically significant decrease in Apgar score at five minutes after delivery in the babies of women who had undergone open appendectomy compared with those of women who had undergone laparoscopic appendectomy during pregnancy (MD –0.09, 95% CI –0.17 to –0,02, P = 0.01; Fig 6). On the other hand, Apgar score at one minute after delivery showed no difference (MD 0.10, 95% CI –0.17 to 0.38, P = 0.46; Fig 7).

The surgical parameters after appendectomy were similar between the two groups two. More specifically, no difference was observed in terms of postoperative hospital stay duration (MD –0.47, 95% CI –1.24 to 0.30, P = 0.24; Fig 8) or wound infection rates (OR 0.47, 95% CI 0.15 to 1.48, P = 0.20; Fig 9) after open and laparoscopic appendectomy during pregnancy.

Sensitivity analysis

A cumulative effect was observed that tended to stabilise the results of our study in terms of OR and 95% CI after 2012, indicating that current knowledge has been established since that time, and that the latter studies do not tend to significantly alter the results of the cumulative analysis (Suppl. figure 1).

Leaving one out meta-analysis outlined that Peled *et al*[27] [MD –0.09, 95% CI –0.17 to –0.02, P = 0.011] affected significantly the comparison of Apgar score at five minutes between women who had undergone open appendectomy during pregnancy compared with those who had undergone laparoscopic appendectomy (Suppl. figure 2). In addition, Sadot *et al*[28] (OR 0.66, 95% CI 0.45 to 0.98, P = 0.039), Laustsen *et al*[24] (OR 0.67, 95% CI 0.46 to 0.99, P = 0.043) and Segev *et al*[29] (OR 0.67, 95% CI 0.45 to 0.99, P = 0.044) could influence the comparison of preterm labour rates between the two groups of patients ((Suppl. figure 3). All studies that provide data about fetal loss rates could affect the comparison of that outcome between women who underwent open and laparoscopic appendectomy during pregnancy (P < 0.001),[16, 17, 19, 22–25, 27–36] except from Mc Gory *et al*[26] (OR 1,58, 95% CI 0.75 to 3.33, P = 0.23; Suppl. Table 2). Yoo *et al*[32] had a strong effect on the comparison of wound infection rates after open and laparoscopic appendectomy during pregnancy (OR 0.25, 95% CI 0.12 to 0.52, P < 0.001; Suppl. Table 2). Finally, Kirshtein *et al*[23] influenced the comparison of postoperative duration of

Study or subgroup	Laparoscopic Events	Laparoscopic Total	Open Events	Open Total	Weight	Odds ratio M-H, random, 95% CI	Year
Gurbuz 1997	0	5	0	4		Not estimable	1997
Affleck 1999	0	22	0	18		Not estimable	1999
Lyass 2001	0	11	0	11		Not estimable	2001
Carver 2005	2	17	0	11	1.5%	3.71 [0.16, 84.92]	2005
McGory 2007	31	454	88	2679	82.7%	2.16 [1.41, 3.29]	2007
Upadhyay 2007	0	4	0	2		Not estimable	2007
Sadot 2009	1	48	0	17	1.4%	1.11 [0.04, 28.43]	2009
Kirshtein 2009	0	23	0	19		Not estimable	2009
de Bakker 2011	1	17	0	3	1.3%	0.64 [0.02, 19.11]	2011
Eom 2012	0	15	0	28		Not estimable	2012
Kapan 2013	0	10	0	10		Not estimable	2013
Chung 2013	0	22	0	39		Not estimable	2013
Peled 2014	0	26	0	59		Not estimable	2013
Karaman 2016	1	12	0	36	1.8%	3.18 [0.18, 55.19]	2016
Laustsen 2016	0	19	0	25		Not estimable	2016
Segev 2016	2	50	2	42	3.7%	0.83 [0.11, 6.18]	2016
Yoo 2016	3	24	4	56	5.9%	1.86 [0.38, 9.02]	2016
Winter 2017	7	125	0	93	1.9%	1.84 [0.67, 209.90]	2016
Total (95% CI)		**904**		**3125**	**100.0%**	**2.11 [1.44, 3.09]**	
Total events	48		95				

Heterogeneity: Tau² = 0.00; Chi² = 3.12, df = 7 (P = 0.87); I² = 0%
Test for overall effect: Z = 3.81 (P = 0.0001)

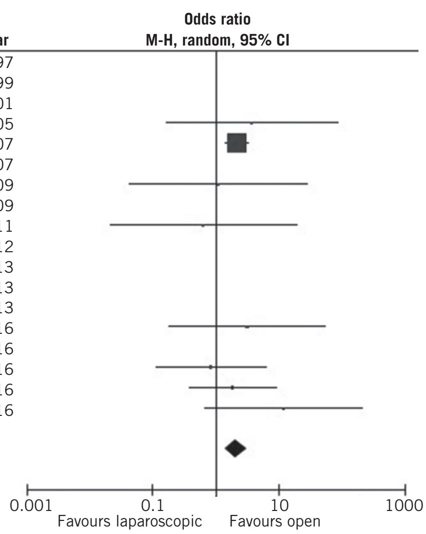

Figure 2 Odds ratio according to fetal loss rate. The overall effect was statistically significant (P < 0.0001); vertical line, no difference point between two groups; squares, odds ratios; diamonds, pooled odds ratio for all studies; horizontal lines, 95% confidence interval, CI; M-H, Mantel–Haenszel model.

Study or subgroup	Laparoscopic Mean	SD	Total	Open Events	SD	Total	Weight	Mean difference IV, random, 95% CI	Year
Carver 2005	3,500	500	17	3,500	400	11	8.8%	0.00 [–335.21, 335.21]	2005
Sadot 2009	3,298	544	48	3,311	340	17	20.0%	–13.00 [–236.17, 210.17]	2009
Kirshtein 2009	3,165	413	23	3,118	600	19	9.8%	47.00 [–271.24, 365.24]	2009
Chung 2013	2,810	293	22	2,790	312	39	40.4%	20.00 [–136.78, 176.78]	2013
Peled 2014	3,075	479	26	3,115	636	59	16.5%	–40.00 [–285.43, 205.43]	2013
Karaman 2016	3,030	744	12	2,944	664	36	4.4%	86.00 [–387.55, 559.55]	2016
Total (95% CI)			**148**			**181**	**100.0%**	**7.32 [–92.38, 107.02]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.37$, df = 5 ($P = 1.00$); $I^2 = 0\%$
Test for overall effect: Z = 0.14 ($P = 0.89$)

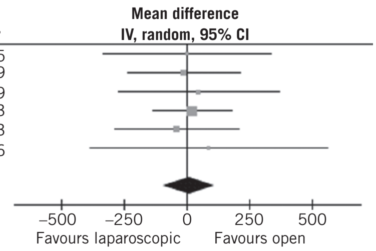

Figure 3 Odds ratio according to neonatal birth weight at time of delivery. The overall effect was not statistically significant ($P > 0.05$); vertical line, no difference point between two groups; squares, odds ratios; diamonds, pooled odds ratio for all studies; horizontal lines, 95% confidence interval, CI; IV, weighted mean difference.

Study or subgroup	Laparoscopic Events	Total	Open Events	Total	Weight	Odds ratio M-H, random, 95% CI	Year
Gurbuz 1997	0	5	0	4		Not estimable	1997
Affleck 1999	3	22	2	18	5.9%	1.26 [0.19, 8.52]	1999
Lyass 2001	0	11	0	11		Not estimable	2001
Carver 2005	0	17	0	11		Not estimable	2005
McGory 2005	1	454	216	2679	5.7%	0.03 [0.00, 0.18]	2007
Upadhyay 2007	1	4	0	2	2.3%	2.14 [0.06, 77.54]	2007
Sadot 2009	12	48	3	17	8.3%	1.56 [0.38, 6.36]	2009
Kirshtein 2009	0	23	0	19		Not estimable	2009
Corneille 2010	1	9	5	40	4.7%	0.88 [0.09, 8.56]	2010
de Bakker 2011	1	17	1	3	2.9%	0.13 [0.01, 2.88]	2011
Eom 2012	0	15	3	28	3.0%	0.24 [0.01, 4.86]	2012
Peled 2014	5	26	14	59	9.9%	0.77 [0.24, 2.40]	2013
Kapan 2013	0	10	0	10		Not estimable	2013
Chung 2013	2	22	4	39	6.4%	0.88 [0.15, 5.21]	2013
Cheng 2014	7	128	74	653	12.2%	0.45 [0.20, 1.01]	2014
Cox 2016	0	894	0	441		Not estimable	2015
Laustsen 2016	3	19	2	25	6.0%	2.16 [0.32, 14.41]	2016
Yoo 2016	2	24	4	56	6.5%	1.18 [0.20, 6.93]	2016
Segev 2016	5	50	3	42	7.8%	1.44 [0.32, 6.44]	2016
Winter 2017	8	125	8	93	10.7%	0.73 [0.26, 2.01]	2016
Karaman 2016	3	12	9	36	7.7%	1.00 [0.22, 4.52]	2016
Total (95% CI)		**1935**		**4286**	**100.0%**	**0.72 [0.40, 1.29]**	
Total events	54		348				

Heterogeneity: $Tau^2 = 0.56$; $Chi^2 = 26.65$, df = 14 ($P = 0.02$); $I^2 = 47\%$
Test for overall effect: Z = 1.11 ($P = 0.27$)

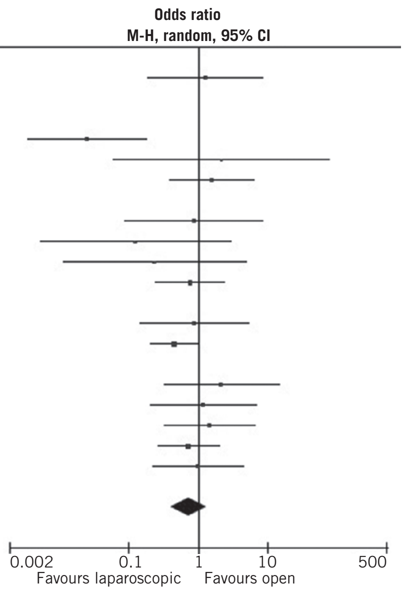

Figure 4 Odds ratio according to preterm birth rate. The overall effect was not statistically significant ($P > 0.05$); vertical line, no difference point between two groups; squares, odds ratios; diamonds, pooled odds ratio for all studies; horizontal lines, 95% CI.

hospital stay (MD –0.73, 95% CI –1.40 to –0.05, $P = 0.035$; Suppl. Table 2).

Meta-regression analysis outlined that passing years only affected the comparison of neonatal birth weight ($P = 0.011$) and the comparison of postoperative hospital stay after open and laparoscopic appendectomy during pregnancy ($P = 0.044$; Suppl. Table 2). The continent of origin of the studies did not affect any comparison between the two groups of patients.

Quality assessment

According to the ROBINS-I tool, 7 studies presented a low possibility of bias due to confounding, 10 studies presented moderate possibility and 6 studies presented a serious possibility of bias; 18 studies presented a low possibility of bias in selection of participants into the study, while 5 presented a moderate possibility. All 23 studies presented a low possibility of bias in classification of interventions and in measurements of outcomes. In addition, 19 studies presented a low possibility of bias due to missing data, while 4 presented a moderate possibility; 21 studies had a low possibility of bias in selection of the reported result, while 2 had a moderate possibility. Finally, 11 studies presented a low possibility of overall bias, while 12 studies presented a moderate possibility of overall bias (Suppl. figure 4).

Discussion

Emergency surgical procedures such us appendectomy or cholecystectomy during pregnancy remained a concern for

	Laparoscopic			Open				Mean difference	
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, random, 95% CI	Year
Kirshtein 2009	29.9	6.3	23	28.9	9.2	19	24.4%	1.00 [−3.87, 5.87]	2009
Sadot 2009	54	34	48	55	25	17	9.7%	−1.00 [−16.29, 14.29]	2009
Chung 2013	44.2	16.4	22	47.3	14.7	39	18.4%	−3.10 [−11.36, 5.16]	2013
Cox 2016	47.1	20.2	894	52.1	25.1	441	27.7%	−5.00 [−7.69, −2.31]	2015
Karaman 2016	49.42	11.38	12	38.61	11.5	36	19.8%	10.81 [3.36, 18.26]	2016
Total (95% CI)			**999**			**552**	**100.0%**	**0.33 [−5.47, 6.14]**	

Heterogeneity: $Tau^2 = 29.80$; $Chi^2 = 17.57$, df =4 ($P = 0.001$); $I^2 = 77\%$
Test for overall effect: Z = 0.11 ($P = 0.91$)

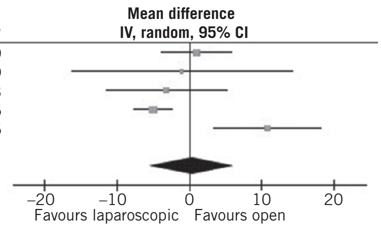

Figure 5 Odds ratio according to intraoperative duration during appendectomy. The overall effect was not statistically significant ($P > 0.05$); vertical line, no difference point between two groups; squares, odds ratios; diamonds, pooled odds ratio for all studies; horizontal lines, 95% confidence interval, CI; IV, weighted mean difference.

	Laparoscopic			Open				Mean difference	
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, random, 95% CI	Year
Carver 2005	9	0.6	17	9	0.5	11	3.1%	0.00 [−0.41, 0.41]	2005
Sadot 2009	8.97	0.17	48	9.06	0.25	17	31.6%	−0.09[−0.22, 0.04]	2009
Corneille 2010	9	2	9	9	2	40	0.2%	0.00 [−1.45, 1.45]	2010
Chung 2013	9.8	0.2	22	9.9	0.1	39	65.1%	−0.10 [−0.19, −0.01]	2013
Peled 2014	10	0	26	9.9	0.1	59		Not estimable	2013
Total (95% CI)			**122**			**166**	**100.0%**	**−0.09 [−0.17, −0.02]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.24$, df = 3 ($P = 0.97$); $I^2 = 0\%$
Test for overall efect: Z = 2.54 ($P = 0.01$)

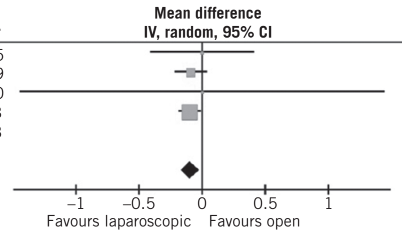

Figure 6 Odds ratio according to Apgar score five minutes after delivery. The overall effect was statistically significant ($P = 0.01$); vertical line, no difference point between two groups; squares, odds ratios; diamonds, pooled odds ratio for all studies; horizontal lines, 95% confidence interval, CI; IV, weighted mean difference.

	Laparoscopic			Open				Mean difference	
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, random, 95% CI	Year
Carver 2005	8	2	17	7	1	11	5.5%	1.00 [−0.12, 2.12]	2005
Sadot 2009	8.91	0.29	48	9	0	17		Not estimable	2009
Corneille 2010	8	2	9	8	2	40	3.4%	0.00 [−1.45, 1.45]	2010
Chung 2013	9.2	0.1	22	9.3	0.2	39	47.5%	−0.10 [−0.18, −0.02]	2013
Peled 2014	8.9	0.2	26	8.7	1	59	33.9%	0.20 [−0.07, 0.47]	2013
Karaman 2016	8.42	1.08	12	8.11	1.62	36	9.6%	0.31 [−0.50, 1.12]	2016
Total (95% CI)			**134**			**202**	**100.0%**	**0.10 [−0.17, 0.38]**	

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 8.92$, df = 4 ($P = 0.06$); $I^2 = 55\%$
Test for overall efect: Z = 0.74 ($P = 0.46$)

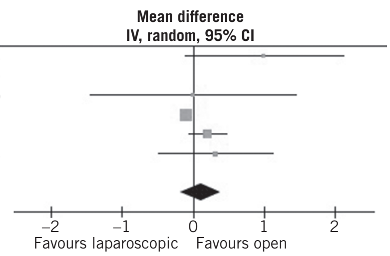

Figure 7 Odds ratio according to Apgar score one minute after delivery. The overall effect was not statistically significant ($P > 0.05$); vertical line, no difference point between two groups; squares, odds ratios; diamonds, pooled odds ratio for all studies; horizontal lines, 95% confidence interval, CI; IV, weighted mean difference.

surgeons and gynaecologists for many years. The overlapping symptoms of these two conditions with the early symptoms of pregnancy and the possible serious complications of a late diagnosis form the necessity for a safe and immediate surgical intervention, without considering the trimester of the pregnant woman or the preferred surgical procedure, open or laparoscopic, as a contraindication. Our meta-analysis outlines that women who had undergone laparoscopic appendectomy during pregnancy, had almost double the risk of fetal loss during delivery compared with women who underwent open appendectomy, regardless of the trimester of pregnancy. Nevertheless, the higher rate of complicated appendicitis among patients who underwent laparoscopic appendectomy could serve as a confounding factor, which possibly led to a weighted prognosis both for the mother and the fetus, resulting in increased fetal loss rate for the laparoscopic group. In addition, open appendectomy during pregnancy seems to be associated with a lower Apgar score at five minutes after the delivery of the neonate compared with the laparoscopic appendectomy. However, despite the fact that the difference in five-minute Apgar score after birth between the groups of women was

Study or subgroup	Laparoscopic Mean	Laparoscopic SD	Laparoscopic Total	Open Mean	Open SD	Open Total	Weight	Mean difference IV, random, 95% CI	Year
Carver 2005	2.6	1.6	17	2.4	1.4	11	14.4%	0.20 [–0.92, 1.32]	2005
Kirshtein 2009	2.4	1.7	23	1.4	0.5	19	17.4%	1.00 [0.27, 1.73]	2009
Sadot 2009	3.44	5.4	48	4.2	2.1	17	9.6%	–0.76 [–2.58, 1.06]	2009
Peled 2014	3.7	1.1	26	3.8	1.2	59	18.9%	–0.10 [–0.62, 0.42]	2013
Chung 2013	4.2	2.9	22	6.9	3.7	39	10.4%	–2.70 [–4.38, –1.02]	2013
Cox 2016	2.3	5.8	894	3.3	2.5	441	19.4%	–1.00 [–1.45, –0.55]	2015
Karaman 2016	3.25	2.45	12	4.28	3.31	36	9.9%	–1.03 [–2.79, 0.73]	2016
Total (95% CI)			**1042**			**622**	**100.0%**	**–0.47 [–1.24, 0.30]**	

Heterogeneity: $Tau^2 = 0.74$; $Chi^2 = 31.29$, df = 6 ($P < 0.0001$); $I^2 = 81\%$
Test for overall effect: Z = 1.19 ($P = 0.24$)

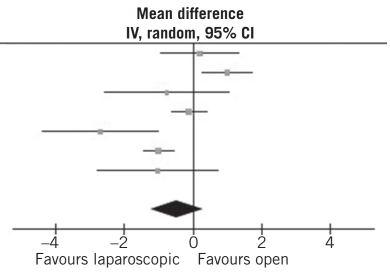

Figure 8 Odds ratio according to postoperative interval of hospital stay. The overall effect was not statistically significant ($P > 0.05$); vertical line, no difference point between two groups; squares, odds ratios; diamonds, pooled odds ratio for all studies; horizontal lines, 95% confidence interval, CI; IV, weighted mean difference.

Study or subgroup	Laparoscopic Events	Laparoscopic Total	Open Events	Open Total	Weight	Odds Ratio M–H, random, 95% CI	Year
Carver 2005	0	17	0	11		Not estimable	2005
Sadot 2009	1	48	0	17	9.1%	1.11 [0.04, 28.43]	2009
Eom 2012	0	15	0	28		Not estimable	2012
Chung 2013	0	22	1	39	9.2%	0.57 [0.02, 14.60]	2013
Cox 2016	6	894	17	441	28.4%	0.17 [0.07, 0.43]	2015
Karaman 2016	0	12	1	36	9.1%	0.95 [0.04, 24.78]	2016
Segev 2016	0	50	5	42	10.6%	0.07 [0.00, 1.26]	2016
Lausten 2016	1	19	6	45	15.3%	0.36 [0.04, 3.22]	2016
Yoo 2016	3	24	2	56	18.2%	3.86 [0.60, 24.75]	2016
Total (95% CI)		**1101**		**715**	**100.0%**	**0.47 [0.15, 1.48]**	
Total events	11		32				

Heterogeneity: $Tau^2 = 0.96$; $Chi^2 = 10.88$, df = 6 ($P = 0.09$); $I^2 = 45\%$
Test for overall effect: Z = 1.29 ($P = 0.20$)

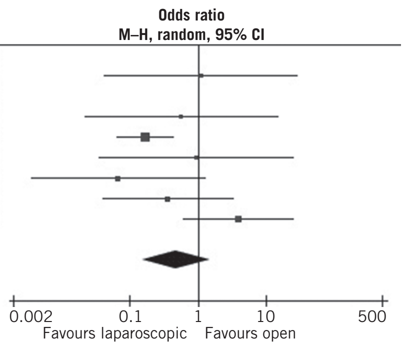

Figure 9 Odds ratio according to wound infection rate after appendectomy. The overall effect was not statistically significant ($P > 0.05$); vertical line, no difference point between two groups; squares, odds ratios; diamonds, pooled odds ratio for all studies; horizontal lines, 95% confidence interval, CI; M-H, Mantel–Haenszel model.

statistically significant, it seemed to be clinically insignificant, as this difference is quite small and only one study with 60 patients analysed the five-minute Apgar score and presented a statistically significant decrease for the open group.[19]

On the other hand, all the remaining obstetric outcomes at delivery, such as Apgar score at one minute after delivery, birth weight of the neonatal and preterm birth rates, as well as all surgical outcomes during and after appendectomy, such as wound infection rates, intraoperative duration and postoperative hospital stay duration, seemed to present no correlation with the type of surgical. Furthermore, the passage of time was an important factor that affected the comparison of neonatal birth weight and postoperative hospital stay interval between the two groups, while the continent of origin of each study had no effect.

Our findings are in accordance with previous studies that examined the outcomes after laparoscopic appendectomy in pregnancy. In a previous meta-analysis, Bakker *et al* demonstrated an increase in fetal loss rate for pregnant women who underwent laparoscopic appendectomy compared with those who had open surgery, while all other obstetric and surgical outcomes (preterm labour rate, postoperative hospital stay, wound infection rates, neonatal birth weight, operation time and Apgar scores) were similar between the two groups.[37] In addition, Won *et al* indicated that despite the fact that pregnant women had higher negative appendectomy rates and a lower possibility of undergoing laparoscopic appendectomy, there was no difference in surgical complications that were not related to pregnancy and, while there was an increase in preterm labour risk during surgery, that risk diminished over time.[38] Furthermore, Walker *et al* outlined the lack of strong evidence between laparoscopic and open appendectomy during pregnancy, nevertheless a slight increase in fetal loss rates for those who underwent laparoscopic appendectomy was demonstrated.[39] Preterm labour was the only finding in 2 of 11 pregnant women who underwent laparoscopic appendectomy, as Kocael *et al* described, but no complications in terms of uterine injury, fetal death or maternal mortality were observed.[40] Finally, Park *et al* reported no maternal or fetal mortality or morbidity, no conversion to laparotomy and no uterine injury in eight pregnant women who underwent laparoscopic appendectomy.[41]

Our study presents certain methodological strengths. First of all, our protocol has been registered to the international database PROSPERO. In addition, our study group conducted comprehensive literature search following rigorous and systematic methodology and detailed data extraction with pre-piloted forms. Furthermore, the eligible studies underwent standardised quality assessment using the well-validated ROBINS-I tool, which is indicated for assessing non-randomised trials. In comparison with the previous meta-analysis,[37] in terms of the issue we investigate, our study includes a larger amount of eligible studies, as many studies have been published since 2012 (the year of publication of the previous meta-analysis), while our study presents more outcomes that underwent more extensive analysis, such us sensitivity analysis.

On the other hand, the present paper has some limitations. As with any systematic review and meta-analysis, certain studies did not report on all outcomes of interest and all statistical analyses were performed using available data. The non-randomised nature, as the most studies are retrospective, and the small number of cases of the majority of the included studies constitute another important limitation of our study, because of the possible implementation of certain selection bias in the study design process. However, the possibility of bias for each particular included study has been interpreted by the ROBINS-I tool, which demonstrated low and moderate possibility of bias for the majority of the included studies.

In addition, it was not possible to perform a multivariate analysis to investigate whether the severity of appendicitis or the surgical technique could affect fetal loss rates as independent factors, due to the fact that the present study is a meta-analysis. Finally, the lack of classification of the obstetric and surgical outcomes according to the trimester of pregnancy from the eligible studies meant that we were unable to investigate the correlation between the postoperative outcomes of laparoscopic and open appendectomy with the trimester of pregnancy in which the operation was conducted.

During the past 20 years that laparoscopy has been implemented many surgical procedures, designing and conducting a randomised trial to compare laparoscopic and open appendicitis during pregnancy seemed a difficult issue, because of the emergent nature of acute appendicitis and the high mortality rate that accompanies it during pregnancy.[4] Moreover, conducting a randomised trial is now more difficult, as the findings of recent studies, like ours, demonstrate an increased risk in certain obstetric complications after laparoscopic appendectomy compared with the open procedure, almost double the risk of fetal loss in our study. Nevertheless, all the available outcomes so far have been based on low-quality, non-randomised retrospective studies, so large-scale prospective randomised trials need to be designed and conducted to evaluate which surgical procedure overmatches for managing acute appendicitis in pregnancy. Considering the fact that laparoscopic appendectomy during pregnancy would be an innovative procedure to a novel group of patients, future randomised trials should be programmed according to IDEAL stage 3 framework for surgical innovation, which is the stage of assessment of a novel surgical procedure in a specific patient group.[42]

In addition, there are indications that the outcomes of each procedure, laparoscopic or open appendectomy, depend on the trimester of pregnancy; thus, in future studies need to be stratified into postoperative and obstetric outcomes according to the trimester of pregnancy, in order to conclude in specified guidelines according to the trimester of pregnancy. On the other hand, gynaecologists should inform pregnant women of the risks of appendicitis and raise awareness of recognising symptoms early, as they overlap the symptoms of pregnancy in its early stages, to avoid complicated appendicitis with generalised peritonitis, which is related to increased morbidity and mortality for mother and fetus. Undoubtedly, targeted training of gynaecologists and general surgeons in laparoscopic surgery is a fundamental requirement to improve the postoperative outcomes of laparoscopic appendectomy and its implementation in clinical practice.

Conclusion

Laparoscopic approach for the management of acute appendicitis in pregnancy does not seem to have worse postoperative surgical and obstetric outcomes than open approach, except for a slight increase in the risk of fetal loss at the time of delivery. Consequently, laparoscopic appendectomy in pregnancy seems to be a relatively safe choice, which presents few differences compared with the open procedure when it is indicated, always considering the experience of the surgeon in such procedures. The design and accomplishment of future studies should guide to this direction, in accordance with all the other factors that would outline the superiority of laparoscopic approach.

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