Appendectomy during pregnancy: rates, safety, and outcomes over a five-year period. A hospital-based follow-up study

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Abstract

Objective: To assess the outcome of pregnancy after appendectomy, the mode of surgery used, appendectomy rates and complications. Design: A prospective cohort study of pregnant women undergoing appendectomy. Setting: All appendectomies at South Stockholm General Hospital, December 2015 to February 2021. Population: Pregnant women undergoing appendectomy. Methods: Data on preoperative imaging, surgical method, intraoperative findings, microscopic findings, hospital stay, pregnancy, and 30-day complications were prospectively recorded in a local appendectomy register. Results: During the study period, 50 pregnant women underwent appendectomy of 38 199 women giving birth. During the same period 793 non-pregnant women underwent appendectomy and served as controls. No differences in preterm delivery (4.5% vs. 5.6%), small-for-gestational age (2.3% vs. 6.2%), or mode of delivery (cesarean delivery 18.2% vs. 20.4%) were observed between pregnant women with or without appendectomy. There were no cases of perforated appendix in the second half of pregnancy. However, women with gestational age > 20 weeks more frequently had an innocent appendix compared to those operated < 20 gestational weeks (4/11 vs. 2/39, $p = 0.005$). Laparoscopic surgery was used in 92% of appendectomies < 20 weeks gestation. The appendectomy rate was three times lower during the second half of pregnancy. Conclusion: Appendicitis in pregnancy is not a threat as long as surgery is conducted as soon as possible. Although a low threshold for surgery may increase the risk of finding an innocent appendix, this is outweighed by the lower risk for perforation and serious adverse events such as fetal loss or preterm delivery.

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Conclusion: Appendicitis in pregnancy is not a threat as long as surgery is conducted as soon as possible. Although a low threshold for surgery may increase the risk of finding an innocent appendix, this is outweighed by the lower risk for perforation and serious adverse events such as fetal loss or preterm delivery.

1 | INTRODUCTION

Appendicitis is one of the most common acute abdominal conditions, with a lifetime incidence of 7-9 %. Pregnancy is said to protect against appendicitis [1,2]. Standard treatment for appendicitis is laparoscopic (LapApp) or open appendectomy (OpenApp). Appendicitis during pregnancy requires accurate diagnostics, timely appropriate choice of management, and good communication between obstetrician, anaesthetist, and surgeon. Clinical examination, laboratory testing, and imaging (ultrasound scanning and computer tomography) are routine in non-pregnant women [3]. Computer tomography scan during pregnancy is rarely performed since it exposes the foetus to radiation, making acute appendicitis more difficult to diagnose accurately. Furthermore, in the second half of pregnancy, LapApp is difficult and time-consuming [4].

There are models for predicting the presence and severity of appendicitis in pregnant women [5]. An increased platelet: lymphocyte ratio has been reported in pregnant women with appendicitis [6]. Previous studies have shown that hyponatraemia is a negative predictive factor in appendicitis in children [7]. A Swedish population-based study suggested that pregnancy is protective against appendicitis, with lower risk during pregnancy and an increased risk in the peri- and postpartum periods [2].

The aim of this study was to assess the outcome of pregnancy after appendectomy, mode of surgery, appendectomy rates, and complications associated with appendectomy during pregnancy.

2 | METHODS

2:1 | Data source

At the Department of Surgery, South Stockholm General Hospital, Sweden, information on all patients undergoing appendectomy for acute appendicitis is prospectively recorded in a quality register [8]. South Stockholm General Hospital provides emergency medical care to a catchment area of approximately 700 000

inhabitants. The department of Gynaecology and Obstetrics has approximately 7000 deliveries every year. Data on preoperative imaging, surgical approach, intraoperative findings, microscopic findings, hospital stay, and 30-day complications are recorded prospectively in an appendectomy register. Pregnant women with suspected appendicitis are routinely given priority for surgery (within 6 hours after decision to operate) compared to 24 hours for non-pregnant women without suspicion of peritonitis.

2:2 | Patient population

We identified all pregnant women who underwent appendectomy at South Stockholm General Hospital between December 2015 and February 2021. As a reference group to be able to compare pregnancy outcome, we identified women giving birth without appendectomy giving birth during the same time-period. Appendicitis rates were determined based on all pregnant and non-pregnant women with appendectomy in the Stockholm region. For comparisons of times and complication rates, we also identified a control group of non-pregnant fertile women, aged 18 – 45 years undergoing appendectomy.

2:3 | Routines and complications

There are standard routines for antibiotic administration at South Stockholm General Hospital, and these apply to both pregnant and non-pregnant women. Routine antibiotic treatment is based on the degree of inflammation of the appendix at surgery. When no inflammation is suspected, no antibiotics are given. If the appendix is phlegmonous, one dose of 1.5 gm metronidazole iv is given, and for gangrenous appendix, 3 doses of Piperacillin Tazobactam iv are given. In cases of perforated appendix, Piperacillin Tazobactam i.v. 3 times daily is given until bowel function is restored, and thereafter Ciprofloxacin 500 mg x 2 and metronidazole 400 mg x3 by mouth.

At South Stockholm General Hospital, it is standard for pregnant women to be operated within 6 hours and non-pregnant within 24 hours after appendicitis has been diagnosed or is suspected. Thromboembolic prophylaxis is recommended for one week after surgery during pregnancy according to the Swedish algorithm for pregnant women [9].

To assess risk factors for adverse outcomes due to appendectomy within 30 days after surgery, including surgical or medical complications, readmission, and need for surgical reintervention, we reviewed data obtained from the electronic medical records, TakeCare (CompuGroup Medical, Helsinki, Finland) and Obstetrics (Cerner Sverige AB, Stockholm, Sweden) registers. Data concerning surgical procedures and background variables were transferred automatically from the Surgical Department's planning software (Orbit 5, TietoEvry, Kristianstad, Sweden).

Initial sodium levels, CRP, white blood cell count, and ultrasound were investigated for their possible predictive value in the diagnosis of appendicitis during pregnancy.

2:4 Statistical analysis

We present results as number (percentages), mean (±standard deviation) or median (interquartile range). We used Fischer-Freeman-Halton exact test to compare proportions and Mann Whitney U test to compare means and medians between the groups. Comparisons were made in SPSS version 28. To calculate incidence rates (IR) for appendectomy for the years 2016-2020 we used numerators from the quality register [8] and denominator from statistics Sweden. Estimates and confidence intervals for the IR were done in open Epi version 3.01. A p -value < 0.05 was considered as a significant difference.

3 | Results

During the study period 50 pregnant women were appendectomized and 38 155 who gave birth without appendectomy. During the same period 793 non-pregnant fertile women underwent appendectomy for suspected acute appendicitis (control group). Of the pregnant women, 39 (78%) were operated during the first half and 11 (22%) during the second half of pregnancy (54% were in the first trimester, 36% in the second, and 10% in the third trimester). The pregnant women were 32 +5-years-of-age, and the non-pregnant control group 31 + 8 years.

Details of pregnancy, outcome, and complications among women with and without appendectomy are presented in Table 1. There was one case of legal abortion after appendectomy, one extrauterine pregnancy, one spontaneous miscarriage (4^{th} gestational week), and two cases with abortus imminens (foetal death before surgery). One woman was a tourist in Sweden and was delivered in her home country. There were no differences in birth or pregnancy complications between the two groups.

Table 2 shows grade of appendicitis, type of surgery, complications, and prophylactic treatment among pregnant and non-pregnant women with appendectomy. LapApp was used in 39 of 50 (78%) pregnant women and in 770 of 793 (97%) non-pregnant women ($p < 0.001$). OpenApp was used in 11 pregnant women (8 of these > 20 weeks of gestation), and in 7 non-pregnant women. Twelve per cent (n = 6) of pregnant women operated had an innocent appendix, 4 (36%) > 20 weeks gestation and 2 (4%) < 20 weeks). The corresponding figure in the non-pregnant control group was 2.1% ($p = 0.03$).

In pregnant women, the rate of perforated appendicitis was 12% (6/50), where no perforation was seen in the second half of pregnancy. In the non-pregnant control group, the rate was 19% ($p = 0.03$). Three pregnancy complications were noted: one case of early foetal loss (4^{th} week), one case of contractions, and one newborn with flaccid moderate hypoxic ischaemic encephalopathy (HIE = 2). Early neonatal lumbal puncture showed signs of meningitis, but cultures were negative. There was no sign of acute asphyxia. However, the patient had been admitted to another hospital for suspected appendicitis 3 months earlier. Ultrasound indicated appendicitis, but the decision was taken to refrain from surgery.

In the pregnant appendectomy group, there were 3 (6%) surgical complications and in the non-pregnant control group 31 (3.9%) (p= 0.001). Intra-abdominal abscess and paralytic ileus were the dominant surgical complications (Table 2). No reoperation occurred within 30 days in the pregnant women group, but in 2 of the non-pregnant group. Two pregnant women (4%) were readmitted within 30 days, one for contractions that needed cerclage and one with a postoperative abscess. In the non-pregnant group, 14 (1.6 %) were readmitted within 30 days ($p = 0.4$). No death occurred within 30 days.

Histopathology examination of the appendix was performed in 88 % of pregnant cases (n = 44) and in 84.9 % (n = 673) in the non-pregnant control group. Of these 2.1 % had an innocent appendix, 0.6 % a tumour (n = 5), and "other diagnosis" in 0.6 %.

Seventy-four per cent (37/50) of appendectomy cases during pregnancy were treated with low molecular weight heparin after surgery, in most cases for 7 days. No case of postoperative venous thromboembolic event (VTE) was registered.

Diagnostic laboratory test results are presented in Table 3. All 6 pregnant women with perforated appendicitis had a low S-Na (< 136 mmol/L). White blood cell count was> 16 x 10^9/L in 36% (18/50) of appendectomy cases. CRP was > 20 mg/L in 60% (30/50) of cases and < 10 mg/L in 15% (6/50). Ultrasound diagnosis of appendicitis showed 100% specificity and 66% sensitivity (33/50) giving a high positive predictive value (PPV = 100%), while the negative predictive value was lower.

Times associated with appendectomy are presented in Table 4. There was a highly significant longer time-to-surgery in the non-pregnant control group compared to both early- and late pregnancy groups ($p = 0.001$ and $p = <0.001$, respectively). There were no significant differences in operation times or total time-in-surgery between the groups. Total in-hospital stay was significantly longer in the late pregnancy group compared to the non-pregnant control group ($p = 0.02$).

The mean annual incidence rate (IR) of appendectomy in Stockholm County for females ages 20 to 44 years was 132/100,000 women/year (95% CI 123-141), decreasing from IR = 137 (95% CI 115-164) for women aged 20 to 24 to IR = 89 (95% CI 73-107) for those aged 40 to 44. The rate of appendectomy among delivering women was 115/100 000 (1/870) and the rate of appendicitis 99.6/100 000 (1/1004). Of these 33/44 (75%) occurred in early pregnancy (< 20 weeks) and 11/44 (25%) after 20 weeks of gestation. Thus, the odds of late pregnancy appendectomy were 3 times less in late pregnancy. Since, 7/11 late appendectomies had appendicitis, the true odds of appendicitis were even lower in late pregnancy.

4 | DISCUSSION

Main Findings

The present study on appendectomy (both definite and suspected cases) in pregnant women at a hospital normally carrying out surgery in pregnancy, showed a low risk for pregnancy and other surgical postoperative complications. Immediate surgery (within 6 hours) seems to significantly reduce the risk for appendix perforation, but at the cost of a high rate of surgery for an innocent appendix, as reported in a previous paper [10]. The low risk for preterm delivery and foetal loss seen in this study is in contrast to previously reported increased risk for fetal loss, preterm delivery, low birth weight, and foetal growth restriction [10, 11]. Indeed, we were unable to show any increase in risk beyond those normally seen in pregnancy. However, for one of the newborns in this study we could not rule out rule out persistent low-grade appendicitis with haematogenous spread leading to meningitis.

The risk for appendicitis is reported to be lower in pregnancy [2,12,13]. In this large sample of non-pregnant control women the IR was 132/100 000. We found a strong age-dependency for appendicitis with the maximum IR being 137/100 000 between 20 and 24-years-of-age, declining to 89 between 40 and 44 years. The rate of appendectomy among women giving birth was 115/100 000, i.e., 1/870 women giving birth. This is close to a prior large (n = 778) Swedish study during 1973 to 1981, one in 936 [12]. In that study 23% of early appendectomies were innocent as compared to 4% in our material ($p < 0.001$) [19]. In late pregnancy the percentage of innocent appendix was, however, similar as the present 36% [12].

Clearly, a lower time to surgery in pregnancy will lower the risk of outcome regarding perforated appendicitis with its complications. The decision to operate would be further improved by better diagnostic tools to indicate whether or not appendicitis is present, to avoid perforation. When positive, ultrasound gave correct diagnosis in 2/3 of the cases. MRI is excellent in diagnosing appendicitis in pregnancy and recommended in current international guidelines [14]. Thus, although we did not have access to MRI, it would presumably have improved pre-operative diagnostics and decrease the number of innocent appendices in late pregnancy. Furthermore, LapApp used as first choice during the first half of pregnancy, may have lowered the threshold for surgery as it provides diagnostic information on other pathological conditions present. Another Swedish study assessing appendectomies 1973 to 2013 with 5.8% LapApp, showed a low incidence in late pregnancy appendectomies and a high rate during peripartum period [2]. The high peripartum rate is supposedly due to a high rate of combination Cesarean section and appendectomy close to delivery, but appendectomy *en passant* cannot be excluded [2].

Laboratory biomarkers also aid decision-making in the pregnant patient with signs of appendicitis. All pregnant women with perforated and half of non-perforated appendicitis in the present cohort had low plasma sodium levels (< 136 mmol/L), which is in-line with prior reports [7,15]. Most pregnant women (60%) had increased CRP (> 20 mg/L), but 15% had CRP < 10 mg/L at the time of diagnosis.

The risk for a thromboembolic event is increased about 10 times during pregnancy, and a further 5 times after surgery. The recommendation to give thromboprophylaxis for one week was followed in 74% of cases [16,17]. No postoperative thrombotic event was seen in our cohort.

Strengths and limitations

We interpret our results in the light of the inherent limitations of the retrospective design of the study, but comparisons have been made with comparable cohorts both with respect to pregnant women without appendicitis and non-pregnant women with appendicitis. The IR are subject to substantial fluctuations, and clinically important complications are rare. However, due to the devastating consequences of late pregnancy foetal complications, the present results contribute to an updated perspective on the risks and complications of appendectomy during pregnancy. Although not included in our local management guidelines, we could not exclude non-operative antibiotic treatment for appendicitis in pregnancy, especially close to delivery [15,18].

In conclusion, appendectomy during pregnancy requires extra care to avoid complications for both mother and the unborn child. An active approach with a low threshold for surgery increases the risk of negative

findings, but this a low price for avoiding a perforated appendix and an increased risk of fetal loss and preterm delivery.

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Disclosure of interests

The authors declare no conflict of interest.

Contributions to Authorship

LB, GS, HP, and PL contributed to study design, data analysis, data interpretation and manuscript. MD contributed to manuscript and critical manuscript revision. All authors approve the final version

Ethics approval

This study was approved by the Regional Ethics Committee, Uppsala University Dnr 2019-05976 and Dnr 2020-03849. Use of registers was approved by the South Stockholm General Hospital Ethics Board.

References

1. Addiss DG, Shaffer N, Fowler BS, et al. The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol 1990;132:910-25. 10.1093/oxfordjournals.aje.a115734

2. Moltubak E, Landerholm K, Blomberg M, et al. Major Variation in the Incidence of Appendicitis Before, During and After Pregnancy: A Population-Based Cohort Study. World J Surg 2020;44:2601-8. 10.1007/s00268-020-05524-z

3. Augustin G, di Saverio S. MRI is Mandatory for the Assignment into Antibiotic Treatment or Appendectomy Group of Patients During Pregnancy. Am J Med 2020;133:e208. 10.1016/j.amjmed.2019.06.043

4. Lee SH, Lee JY, Choi YY, et al. Laparoscopic appendectomy versus open appendectomy for suspected appendicitis during pregnancy: a systematic review and updated meta-analysis. BMC Surg 2019;19:41. 10.1186/s12893-019-0505-9

5. Mantoglu B, Gonullu E, Akdeniz Y, et al. Which appendicitis scoring system is most suitable for pregnant patients? A comparison of nine different systems. World journal of emergency surgery : WJES 2020;15:34. 10.1186/s13017-020-00310-7

6. Liu L, Shao Z, Yu H, et al. Is the platelet to lymphocyte ratio a promising biomarker to distinguish acute appendicitis? Evidence from a systematic review with meta-analysis. PLoS ONE 2020;15:e0233470. 10.1371/journal.pone.0233470

7. Giannis D, Matenoglou E, Moris D. Hyponatremia as a marker of complicated appendicitis: A systematic review. The surgeon : journal of the Royal Colleges of Surgeons of Edinburgh and Ireland 2020;18:295-304. 10.1016/j.surge.2020.01.002

8. Dahlberg MJA, Pieniowski EHA, Bostrom LAS. Trends in the Management of Acute Appendicitis in a Single-Center Quality Register Cohort of 5,614 Patients. Digestive surgery 2018;35:144-54. 10.1159/000477269

9. HemArg. Hemostasrubbningar inom obstetrik och gynekologi, Rapport nr 79; 2018.

10. Aggenbach L, Zeeman GG, Cantineau AE, Gordijn SJ, Hofker HS. Impact of appendicitis during pregnancy: no delay in accurate diagnosis and treatment. Int J Surg. 2015 Mar;15:84-9

11. Reedy MB, Kallen B, Kuehl TJ. Laparoscopy during pregnancy: a study of five fetal outcome parameters with use of the Swedish Health Registry. Am J Obstet Gynecol 1997;177:673-9. 10.1016/s0002-9378(97)70163-7

12. Mazze RI, Kallen B. Appendectomy during pregnancy: a Swedish registry study of 778 cases. Obstet Gynecol 1991;77:835-40.

13. Andersson RE, Lambe M. Incidence of appendicitis during pregnancy. Int J Epidemiol 2001;30:1281-5. 10.1093/ije/30.6.1281

14. Kave M, Parooie F, Salarzaei M. Pregnancy and appendicitis: a systematic review and meta-analysis on the clinical use of MRI in diagnosis of appendicitis in pregnant women. World J Emerg Surg. 2019 Jul 22;14:37

15. Nakashima M, Takeuchi M, Kawakami K. Clinical Outcomes of Acute Appendicitis During Pregnancy: Conservative Management and Appendectomy. World J Surg. 2021 Jun;45(6):1717-1724

16. Lindqvist PG, Dahlback B, Marsal K. Thrombotic risk during pregnancy: a population study. Obstet Gynecol 1999;94:595-9. 10.1016/s0029-7844(99)00308-7

17. Lindqvist PG, Hellgren M. Obstetric thromboprophylaxis: the Swedish guidelines. Advances in hematology 2011;2011:157483. 10.1155/2011/157483

18. Joo JI, Park HC, Kim MJ, Lee BH. Outcomes of Antibiotic Therapy for Uncomplicated Appendicitis in Pregnancy. Am J Med. 2017 Dec;130(12):1467-1469

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