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Risk of Acute Appendicitis in and Around Pregnancy

A Population-based Cohort Study From England

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Objective: To determine the absolute and relative risk of acute appendicitis during the antepartum and postpartum periods compared with the time outside pregnancy among women of childbearing age.

Background: Acute appendicitis is the most common nonobstetric surgical emergency during pregnancy. Estimates of the incidence of acute appendicitis in pregnancy remain imprecise and inconsistent.

Methods: All potential fertile women aged 15 to 44 years registered within Clinical Practice Research Datalink with linkages to the Hospital Episodes Statistics between 1997 and 2012 were identified. Absolute rates of acute appendicitis were calculated during the antepartum and postpartum periods and were compared with the time outside pregnancy in terms of incidence rate ratio (IRR) using a Poisson regression model.

Results: Among 1,624,804 women, there were 362,219 pregnancies resulting in live or stillbirths. Compared with the time outside pregnancy, the rate of acute appendicitis was 35% lower during the antepartum period [IRR, 0.65; 95% confidence interval (CI), 0.55–0.76], with the lowest rate reported during the third trimester (IRR, 0.47; 95% CI, 0.35–0.64) for all ages; no increased risk of acute appendicitis was observed in the postpartum period compared with the time outside pregnancy among women aged 15 to 34 years but an 84% increased risk for women older than 35 years (IRR, 1.84; 95% CI, 1.18–2.86). The highest and lowest rates of negative appendectomy were encountered in the second and the third trimesters, respectively.

Conclusions: Pregnant women are less likely to be diagnosed with acute appendicitis than nonpregnant women, with the lowest risk reported during the third trimester.

Keywords: acute appendicitis, antepartum, incidence, postpartum, pregnancy

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Acute appendicitis is the most common nonobstetric surgical emergency during pregnancy.[1,2] Maternal mortality associated with acute appendicitis declined from 24% in 1908[3] to 0.5% in 1977[4] and rarely occurs today; however, there remains a high risk of morbidity for both the mother and the fetus,[5] after appendectomy. Among the complications encountered are wound infection, intestinal obstruction, respiratory complications, preterm labor, and fetal mortality.[5,6] Furthermore, these risks can occur after a negative appendectomy, and the rates of negative appendectomy may be greater in pregnant than in nonpregnant women due to diagnostic difficulty.[7] Current estimates of the incidence of acute appendicitis in pregnancy are inconsistent and vary widely ranging from 1.8 to 41 per 10,000 pregnancies.[8–18] In particular, the trimester of pregnancy during which a woman is at highest risk of acute appendicitis and the extent to which age affects these risks are poorly understood.[8–18] In addition, there is no population-based study to date reporting the incidence rates of acute appendicitis during the postpartum period. Finally, the reported negative appendectomy rate in pregnancy varies considerably among studies from 5% to 50%.[8–20]

A better understanding of the risk of acute appendicitis in and around pregnancy will aid clinicians in assessing the risk of acute appendicitis within each period. Therefore, we have carried out a large, population-based cohort study to determine the rate of acute appendicitis in the antepartum and postpartum periods and compared it with the rate outside pregnancy among women of childbearing age.

METHODS

Study Population

The Clinical Practice Research Datalink (CPRD)[21] is a computerized primary health care database containing demographic, medical prescription, and lifestyle-related information of anonymized patients across the United Kingdom. Around 99% of the UK population is registered to a general practitioner who is responsible for the entirety of the patient's medical care.[22] Several studies have reported high validity of CPRD data according to the quality and completeness of the recorded data.[23] The Hospital Episode Statistics (HES) data set[24] contains details of all hospital admissions to National Health Service hospitals in England. It contains demographic data along with information on discharge diagnoses and procedures codes using *International classification of diseases* (*ICD*) version 10 and Operation and Procedure Coding Supplement (OPCS) version 4, respectively. The HES maternity data are a subset of the HES, which contains details of each delivery taking place in a National Health Service hospital and it is the primary source of maternity statistics in England, which is externally validated.[25] The CPRD and HES patients have been linked using National Health Service number, date of birth, and sex.[26] Because HES contains information only on English hospital admissions, practices from Wales, Scotland, and Northern Ireland were excluded. All potentially fertile women (15–44 years of age) registered within the CPRD-HES linked data set were identified. Women with a history of appendectomy or acute appendicitis were excluded.

Defining the Study's Time Periods

Information on pregnant status was retrieved using the HES maternity data. Overall, the person-time for each woman in this study was divided into antepartum (time between the expected date of

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conception and date of delivery), postpartum (up to 12 weeks after childbirth), and the time outside pregnancy, details of which are summarized elsewhere.[27] The antepartum period was further divided into individual trimesters whereas the postpartum period was divided into early (first 6 weeks after childbirth) and late postpartum (second 6 weeks after childbirth).

Defining Acute Appendicitis Events

Acute appendicitis events were extracted using primary and secondary care medical records. Women were considered as having acute appendicitis if they had an *ICD-10* code that unequivocally suggested acute appendicitis (K350, K351, K359, K36, K37), or an appendectomy code from secondary care (H011, H012, H018, H019, H028, H029, H031, H032, H038, H039). Women were also considered as having acute appendicitis if they had a nonspecific *ICD-10* code for appendicitis (K388, K389), or a Read code for appendicitis if accompanied by surgical codes (appendectomy or laparoscopy/laparotomy procedures) recorded within 7 days of the event. For women with more than 1 source of diagnosis (diagnostic and surgical codes), the earliest date of acute appendicitis recording was used as the date of diagnosis. We also defined a stricter definition that included only acute appendicitis events defined by surgical codes using the date of surgery as the date of diagnosis. Finally, women were defined as having negative appendectomy if there was any evidence of a normal appendix in the primary or secondary care record postappendectomy.

Statistical Analysis

Absolute rates of acute appendicitis per 10,000 person-years were calculated during the antepartum and postpartum periods and the time outside pregnancy. Incidence rates ratios (IRRs) were calculated by comparing the rate of acute appendicitis during the antepartum and postpartum periods with the time outside pregnancy, using a Poisson regression model. Similarly, IRRs were also calculated by comparing the rate of acute appendicitis in each trimester and postpartum period with the time outside pregnancy. Given that the overall incidence of acute appendicitis is influenced by both age and calendar year,[28,29] we assessed the potential for confounding by these variables by treating them (age and calendar year) as time-varying covariates, which were categorized as 3 (15–24, 25–34, and 35–44 years) and 4 (1997–2000, 2001–2004, 2005–2008, and 2009–2012) level categories, respectively. All our IRRs were adjusted for calendar year and age, when not stratified by them. Finally, frequencies of negative appendectomies were calculated by dividing the number of negative appendectomies that occurred in each antepartum and postpartum period by the total number of acute appendicitis events defined by surgery codes (including negative appendectomies) recorded during the same period. This study has been approved by the Independent Scientific Advisory Committee (reference number 10-193R). The Independent Scientific Advisory Committee is a nonstatutory expert advisory body that provides advice on research-related requests to access data from the CPRD.

RESULTS

Study Population

The study population consisted of 1,624,804 women, of which 274,116 (16.9%) experienced at least 1 pregnancy during the study period. There were a total of 362,219 pregnancies during the study period, of which 99.4% and 0.6% resulted in live births and stillbirths, respectively (Table 1). The median follow-up of the study was 3.1 years (interquartile range, 1.3–6.5 years). The study had a total follow-up time of 7,190,548 person-years, of which 247,755 and 80,775 person-years took place during the antepartum and postpartum periods, respectively (Table 1).

TABLE 1. Characteristics of the Study Population and Study Parameters

Variables	Number
Number of women during fertility period	1,624,804
Pregnancies	362,219
Live births (%)	360,016 (99.4)
Stillbirths (%)	2,203 (0.6)
Total person-years follow-up time	7,190,548
During antepartum	247,755
During postpartum	80,775
During the time outside pregnancy	6,862,018
Median follow-up of the study (IQR)	3.1 (1.3–6.5)

IQR indicates interquartile range.

Acute Appendicitis During the Antepartum and Postpartum Periods

The absolute rate of acute appendicitis during the antepartum and postpartum periods was calculated to be 6.3 and 9.9 per 10,000 person-years, respectively. During the antepartum period, the rate of acute appendicitis was 35% lower [IRR, 0.65; 95% confidence interval (CI), 0.55–0.76] than the time outside pregnancy after adjusting for age and calendar year (Table 2). During the postpartum period, the rate of acute appendicitis was similar to that of outside pregnancy (IRR, 1.01; 95% CI, 0.81–1.26). These rate ratios remained roughly similar for women aged 15 to 34 years. For older women (older than 35 years), we observed an 84% (IRR, 1.84; 95% CI, 1.18–2.86) increased risk of acute appendicitis during the overall postpartum period (Table 2).

Acute Appendicitis by Trimester and in Early and Later Postpartum

The rates of acute appendicitis were similar during the first and second trimesters (7.4 and 7.3 per 10,000 person-years, respectively) and lower during the third trimester (4.6 per 10,000 person-years) (Fig. 1). The rate of acute appendicitis in the last trimester was 53% lower than the rate during the time outside pregnancy (IRR, 0.47; 95% CI, 0.35–0.64) after adjusting for age and calendar year (Table 3). When the analysis was stratified by age, we observed a significantly lower risk of acute appendicitis during the second and third trimesters in women aged 15 to 24 years, the third trimester in women aged 25 to 34 years, and the first trimester in women older than 35, compared with the time outside pregnancy (Table 3).

The overall rates of acute appendicitis during the early and later postpartum periods were observed to be 10.2 and 9.3 per 10,000 person-years, respectively, similar to the rate in the time outside pregnancy (9.6 per 10,000 person-years) for all ages (Table 4 and Fig. 1). However, although women aged 15 to 34 years had a similar risk of acute appendicitis during both the early and later postpartum periods to the time outside pregnancy, we found a significantly higher risk of acute appendicitis during the later postpartum than the time outside pregnancy in women older than 35 years (IRR, 2.38; 95% CI, 1.38–4.11) (Table 4). When we repeated the aforementioned analysis using only acute appendicitis events defined by surgery codes, we found similar results (Table 5).

Incidence Rates of Negative Appendectomy

We found 1397 (17.4%) women who underwent appendectomy and whose outcome was eventually coded as a normal

TABLE 2. Overall and Age-specific Absolute and Relative Rates of Acute Appendicitis During Antepartum and Postpartum Period, Compared With the Time Outside Pregnancy

Time Period	Person-years	Number of AA Events	Incidence Rate* (95% CI)	Crude IRR (95% CI)	Adjusted IRR† (95% CI)
All ages					
Time outside pregnancy	6,862,018	6,560	9.6 (9.3–9.8)	1	1
Antepartum overall	247,755	156	6.3 (5.4–7.4)	0.66 (0.56–0.77)	0.65 (0.55–0.76)
Postpartum overall	80,775	79	9.9 (7.8–12.2)	1.02 (0.82–1.3)	1.01 (0.81–1.26)
15–24 yr					
Time outside pregnancy	1,933,797	2,947	15.2 (14.7–15.8)	1	1
Antepartum	58,964	58	9.8 (7.6–12.7)	0.64 (0.49–0.83)	0.65 (0.49–0.84)
Postpartum	17,730	23	12.9 (8.6–19.5)	0.85 (0.56–1.28)	0.85 (0.56–1.3)
25–34 yr					
Time outside pregnancy	2,281,737	1,951	8.6 (8.2–8.9)	1	1
Antepartum	142,239	79	5.5 (4.4–6.9)	0.64 (0.51–0.8)	0.65 (0.51–0.81)
Postpartum	46,072	36	7.8 (5.6–10.8)	0.9 (0.66–1.27)	0.9 (0.65–1.26)
35–44 yr					
Time outside pregnancy	2,646,484	1,662	6.3 (5.9–6.6)	1	1
Antepartum	46,552	19	4.1 (2.6–6.4)	0.65 (0.41–1.02)	0.64 (0.4–1)
Postpartum	16,973	20	11.8 (7.6–18.3)	1.87 (1.21–2.91)	1.84 (1.18–2.86)

*Per 10,000 person-years.
†Adjusted for calendar year and age (when not stratified).
AA indicates acute appendicitis.

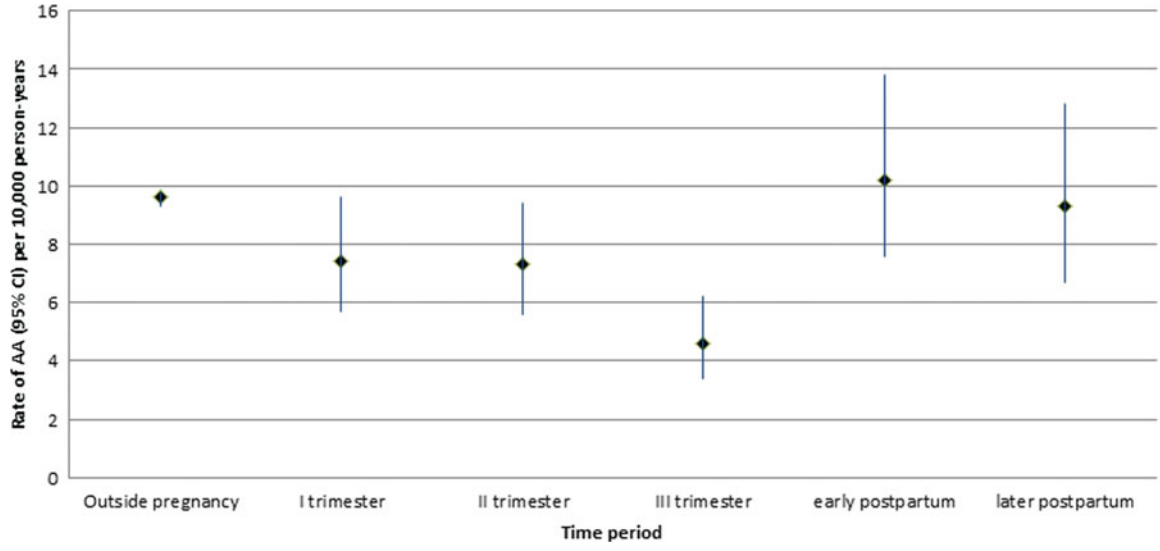

FIGURE 1. Absolute rates of acute appendicitis per 10,000 person-years by trimesters and early and later postpartum period. AA indicates acute appendicitis.

appendix. Among pregnant women, the highest percentage of negative appendectomy was found in the second trimester, where among 80 appendectomies made, 21 (26.2%) resulted in negative appendectomies. Conversely, the lowest percentage was found in the third trimester, where, among 42 appendectomies, only 3 (7.1%) resulted in negative appendectomies (Table 6).

DISCUSSION

Main Findings

In this large, nationally representative cohort of almost 1.6 million childbearing women, we have shown that pregnant women during the antepartum period were 35% less likely to be diagnosed with acute appendicitis than the time outside pregnancy, with the lowest risk reported during the third trimester. These results were not materially changed after adjusting for age and calendar year. Furthermore, we found no increased risk of acute appendicitis in the postpartum period compared with the time outside pregnancy among women aged 15 and 34 years. However, the risk increased by almost 2-fold in older women during the later postpartum. Finally, we found that the highest and the lowest rate of negative appendectomies were in the second and third trimesters, respectively.

Strengths and Limitations

This is the largest population-based study to date to estimate the incidence rate of acute appendicitis among childbearing women. Our study, therefore, provides both contemporary and reasonably

TABLE 3. Overall and Age-specific Absolute and Relative Rates of Acute Appendicitis by Trimester, Compared With the Time Outside Pregnancy

Time Period	Person-years	Number of AA Events	Incidence Rate* (95% CI)	Crude IRR (95% CI)	Adjusted IRR† (95% CI)
All ages					
Time outside pregnancy	6,862,018	6,560	9.6 (9.3–9.8)	1	1
I trimester	74,648	55	7.4 (5.7–9.6)	0.77 (0.59–1)	0.75 (0.58–0.98)
II trimester	81,259	59	7.3 (5.6–9.4)	0.76 (0.59–0.99)	0.74 (0.57–0.96)
III trimester	91,849	42	4.6 (3.4–6.2)	0.48 (0.35–0.65)	0.47 (0.35–0.64)
15–24 yr					
Time outside pregnancy				1	1
I trimester	18,150	26	14.3 (9.7–21)	0.94 (0.63–1.39)	0.94 (0.64–1.4)
II trimester	19,426	17	8.7 (5.4–14.1)	0.57 (0.35–0.92)	0.6 (0.35–0.93)
III trimester	21,389	15	7 (4.2–11.6)	0.46 (0.27–0.76)	0.46 (0.27–0.76)
25–34 yr					
Time outside pregnancy				1	1
I trimester	43,073	27	6.3 (4.3–9.1)	0.73 (0.5–1.07)	0.73 (0.5–1.06)
II trimester	46,640	31	6.6 (4.7–9.4)	0.77 (0.54–1.1)	0.77 (0.54–1.1)
III trimester	52,526	21	4 (2.6–6.1)	0.47 (0.3–0.7)	0.46 (0.3–0.71)
35–44 yr					
Time outside pregnancy				1	1
I trimester	13,425	2	1.5 (0.4–5.9)	0.24 (0.06–0.94)	0.23 (0.05–0.94)
II trimester	15,193	11	7.2 (4–13.1)	1.15 (0.63–2.08)	1.13 (0.62–2.06)
III trimester	17,934	6	3.3 (1.5–7.4)	0.53 (0.23–1.18)	0.52 (0.23–1.17)

*Per 10,000 person-years.
†Adjusted for calendar year and age (when not stratified).
AA indicates acute appendicitis.

TABLE 4. Overall and Age-specific Absolute and Relative Rates of Acute Appendicitis in Early and Later Postpartum Compared With the Time Outside Pregnancy

Time Period	Person-years	Number of AA Events	Incidence Rate* (95% CI)	Crude IRR (95% CI)	Adjusted IRR† (95% CI)
All ages					
Time outside pregnancy				1	1
Early postpartum	41,010	42	10.2 (7.6–13.8)	1.07 (0.79–1.45)	1.06 (0.78–1.44)
Later postpartum	39,765	37	9.3 (6.7–12.8)	0.97 (0.7–1.34)	0.97 (0.7–1.34)
15–24 yr					
Time outside pregnancy				1	1
Early postpartum	9,188	11	11.9 (6.6–21.6)	0.78 (0.43–1.4)	0.78 (0.43–1.41)
Later postpartum	8,542	12	14 (7.9–24.7)	0.92 (0.52–1.62)	0.91 (0.52–1.61)
25–34 yr					
Time outside pregnancy				1	1
Early postpartum	23,370	24	10.3 (6.8–15.3)	1.2 (0.8–1.8)	1.19 (0.79–1.78)
Later postpartum	22,702	12	5.3 (3–9.3)	0.6 (0.35–1.09)	0.61 (0.34–1.08)
35–44 yr					
Time outside pregnancy				1	1
Early postpartum	8,452	7	8.2 (3.9–17.4)	1.31 (0.62–2.8)	1.29 (0.61–2.72)
Later postpartum	8,521	13	15.2 (8.8–26.3)	2.4 (1.4–4.2)	2.38 (1.38–4.11)

*Per 10,000 person-years.
†Adjusted for calendar year and age (when not stratified).
AA indicates acute appendicitis.

precise estimates. We used an open cohort approach to analysis that used person-time as the denominator to calculate the incidence of acute appendicitis during the antepartum period, postpartum period, and the time outside pregnancy rather than the traditional approach adopted in the previous studies (ie, calculation of incidence by taking number of pregnancies or births as denominator). In this way, we were able to adjust for differences in the duration in the antepartum and postpartum periods and to compare with the time outside pregnancy.

A potential limitation of this study was the lack of a previous validated definition of acute appendicitis using these data sets. The outcome definition we have used may have led to an overestimation of the incidence rate in the overall period if, for example, it was too sensitive. To account for this possible overestimation, we carried out a sensitivity analysis using a stricter (more specific) definition of acute appendicitis events that showed similar results. Moreover, we found that around 84% of the acute appendicitis events included in our overall analysis had been identified by specific *ICD-10* codes that

TABLE 5. Sensitivity Analysis of the Outcome Definition Using Acute Appendicitis Events Defined by Surgical Procedures

Time Period	Person-years	Number of AA Events	Incidence Rate* (95% CI)	Crude IRR (95% CI)	Adjusted IRR† (95% CI)
Time outside pregnancy	6,862,602	6,391	9.3 (9–9.5)	1	1
I trimester	74,659	51	6.8 (5.1–8.9)	0.73 (0.55–0.97)	0.72 (0.54–0.94)
II trimester	81,270	59	7.2 (5.6–9.3)	0.77 (0.6–1.01)	0.76 (0.59–0.99)
III trimester	91,861	39	4.2 (3.1–5.8)	0.45 (0.33–0.62)	0.45 (0.33–0.61)
Early postpartum	41,015	42	9.7 (7.1–13.3)	1.07 (0.79–1.46)	1.09 (0.81–1.48)
Later postpartum	39,771	34	8.8 (6.3–12.2)	0.92 (0.66–1.29)	0.92 (0.65–1.28)

*Per 10,000 person-years.
†Adjusted for calendar year and age.
AA indicates acute appendicitis (defined by surgery codes).

TABLE 6. Frequency of Negative Appendectomy During the Time in and Around Pregnancy and the Time Outside Pregnancy

	Total Appendectomies*	Negative Appendectomies	% of Negative Appendectomies
Time outside pregnancy	7743	1352	17.5
I trimester	60	9	15
II trimester	80	21	26.2
III trimester	42	3	7.1
Early postpartum	49	7	14.3
Later postpartum	39	5	12.8

*Acute Appendicitis Events defined by surgery codes (including negative appendectomies).

were supplemented by appendectomy. Misclassification of negative appendectomies may have also occurred, as we did not have direct access to patients' histological reports. Therefore, it is possible that we might have missed some negative appendectomies if these were incorrectly recorded. Bhangu et al[30] recently analyzed the accuracy of clinical coding in identifying negative appendectomies in a British district general hospital, describing that 14% of patients were incorrectly coded as having had appendicitis, when, in fact, they had a histopathologically normal appendix (153/1107). Although this may have led to an underestimation of the overall negative appendectomy rate, we think that it is unlikely that this would be differential with respect to trimester of pregnancy.

Comparison With Previous Studies

Most previous cross-sectional studies have attempted to identify clinical features and postoperative maternal and fetal outcomes and/or described the best diagnostic tools and surgical treatments for acute appendicitis, using data collected on few patients from single centers,[8–15,19,20] with only 3 previous studies using national registers.[16–18] The rate of acute appendicitis reported during the antepartum period in our study (6.3 per 10,000 person-years) was between that reported in 2 prior population-based studies (2.4 and 9.25 per 10,000 person-years).[16,17] Both these studies reported the highest risk of acute appendicitis during the second trimester and a percentage of negative appendectomy of 36% and 50%, respectively, which were higher than that observed in our study during pregnancy (33/182, 18.1%). A study from Taiwan[18] reported 908 acute appendicitis diagnoses among 218,776 pregnancies ending in live births during 1 year (2005), reporting the rate of acute appendicitis of 55.3 per 10,000 person-years, which was around 9 times higher than the incidence reported in our study. The differences between our studies and the previous reports[16–18] could be due to changes over time, differences in terms of geographical location, or due to methodological differences between the studies, particularly the outcome definition. Our results are very consistent with a 2001 Swedish case-control study,[31] which showed that pregnant women were less likely to have appendectomy for acute appendicitis particularly in the third trimester and a lower risk of negative appendectomy in the third trimester. Moreover, the authors[31] reported that the postpartum period was not associated with an increased risk of appendectomy, which is the same as our finding (except for older women).

We found that there is a lower risk of acute appendicitis throughout pregnancy and particularly in the third trimester than that in nonpregnancy, which could be due either to biological or behavioral reasons. For example, pregnancy is accompanied by major immunological changes characterized by a very high T-helper-2:T-helper-1 cytokine ratio.[31–33] These changes may cause an exacerbation of diseases, such as asthma[34] and an improvement of other ones, such as inflammatory bowel diseases[35] during pregnancy. Because acute appendicitis is an inflammatory process of the appendiceal wall,[36] the inverse relationship between pregnancy and acute appendicitis could suggest that a TH1-mediated inflammatory response is partly at work. Moreover, cigarette smoking has a proinflammatory effect[37] and is reported to be associated with an increased risk of acute appendicitis.[38] Because pregnancy may motivate women to quit smoking,[39,40] this could also partially contribute to the lower risk of acute appendicitis we observed during pregnancy. On the contrary, surgeons may be averse to operating unduly upon pregnant women in view of the increased risk of fetal and maternal complications after surgery.[5] Thus, the decreased percentage of negative appendectomy we observed, in particular, during the third trimester, might be a consequence of the higher level of evidence needed to motivate the surgeon to operate on pregnant women who are thought to have appendicitis after clinical assessment.

CONCLUSIONS

We have shown that pregnant women are less likely to be diagnosed with acute appendicitis than nonpregnant women, with

the lowest risk reported during the third trimester. Moreover, older women may be at increased risk of appendicitis in the postpartum period, suggesting that clinicians of all specialties should remain alert to the risk of acute appendicitis among postpartum older women presenting with lower abdominal pain.

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