Negative appendicectomy rates in adolescent girls compared with boys: the role of ultrasound and serum inflammatory markers

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Background **Adolescent girls are frequently seen with more differentials for abdominal pain than boys. We aim to determine if this infers that a negative appendectomy (NA) is more likely in girls, and if the use of ultrasonography (USS) and inflammatory markers reduce the likelihood of a NA.**

Participants and methods **Over a 17-year period, we reviewed the histology of appendix specimens removed nonincidentally from adolescents aged 12–16 years. Specimens with normal histology were grouped as NAs. The preoperative white cell count, C-reactive protein and USS were analysed.**

Results **Data were available for 430 boys and 273 girls. The overall NA rate was 9.1%, with 7.2 and 12.1% in boys and girls, respectively. This represented an increased odds of a NA in girls [odds ratio (OR): 1.77, 95% confidence interval (95% CI): 1.06–2.96; *P* = 0.030]. When the variance in the preoperative use of USS and inflammatory markers was accounted for, the new odds of a NA in girls compared with boys were now not significantly increased (OR: 2.27, 95% CI: 0.09–60.64; *P* = 0.624). USS did not significantly reduced the odds of a NA (OR: 0.98, 95% CI: 0.48–2.02; *P* = 0.960). There were significantly increased odds of a NA in adolescents with normal white cell count and C-reactive protein (OR: 15.84, 95% CI: 2.12–118.50; *P* = 0.007).**

Conclusion **Adolescent girls are more likely to undergo a NA. When inflammatory markers are elevated, this increased likelihood of a NA is not seen in girls, but rather reduced odds of a NA are seen in both girls and boys. *Ann Pediatr Surg* 14:197–202 © 2018 Annals of Pediatric Surgery.**

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Introduction

Adolescent girls are frequently seen in the emergency department with symptoms of abdominal pain [1,2] and are more often diagnosed with nonspecific abdominal pain, constipation and urinary tract infections when compared with similarly aged boys [2]. Furthermore, adolescent girls have more differential diagnoses for abdominal pain owing to gynaecological conditions like dysmenorrhoea, ovarian cyst rupture and torsion, Mittelschmerz, endometriosis, ectopic pregnancy and pelvic inflammatory disease. It is, therefore, not surprising that a few studies have observed a higher incidence of a nonincidental removal of a normal appendix [negative appendicectomy (NA)] in girls and women of childbearing age who present to hospital with abdominal pain [3–8].

Furthermore, in a recent meta-analysis, ultrasonography (USS) had a sensitivity of 88% and specificity of 94% for diagnosing appendicitis in children [9]. Similarly, in another meta-analysis, C-reactive protein (CRP) had a sensitivity of 57% and specificity of 87% and white cell count (WCC) a sensitivity of 62% and specificity of 75% in detecting appendicitis [10]. However, it remains to be shown that the use of these diagnostic tools translates to lower NA rates.

NAs are associated with unnecessary costs and morbidity [5]. We aim to determine if young adolescent girls, aged 12–16 years, are more likely to undergo a NA when compared with similarly aged boys, and evaluate the usefulness of ultrasonography (USS) and inflammatory markers (WCC and CRP) in reducing NA rates in these young girls and boys.

Participants and methods

This study was carried out at the Children's University Hospital in Dublin, Ireland. Over a 17-year period from January 1995 to December 2012, we retrospectively reviewed the electronically stored data on appendectomies performed in boys and girls, aged 12–16 years, who presented to the emergency department with abdominal pain. The mean age at onset of menarche in Ireland is 12 years [11] and upper age limit for assessing children at our institution is 16 years. Our adolescent age group was thus defined as children between ages 12 and 16 years. The documented histological findings of the appendix specimens and the preoperative data on WCC, CRP and USS were analyzed.

If the diagnosis was clinically obvious at the time of presentation, children were scheduled for appendicectomy. When the diagnosis was equivocal, children were admitted and prescribed intravenous fluids and analgesia. Twice daily clinical reassessment was performed for a period of 24–48 h, and additional investigations such as abdominal USS and serum inflammatory markers were

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requested. Frequently, serum inflammatory markers had been requested routinely by the emergency department before referral to the surgical team. WCC count and CRP levels greater than 13×10^9/l and 10 mg/l, respectively, were considered abnormally elevated based on our institutional laboratory criteria. Table 1 shows the findings on graded compression abdominal ultrasonography that were used to group patients into four categories: positive, suggestive, inconclusive and negative for appendicitis. Six radiologists performed these ultrasound examinations over the study period, and there were three primary consultant surgeons and up to five senior surgical trainees involved in making the decision to perform an appendicectomy in these children. The appendix specimens, removed nonincidentally, with normal histology were grouped as NAs. In symptomatic children, the following histological features, alone or in combination, of the excised appendices were considered positive: intramural infiltration by acute inflammatory cells, reactive lymphoid hyperplasia, *Enterobius vermicularis* colonization, presence of an obstructing appendicolith, submucosal fibrosis, and a few specimens with chronic inflammatory cell infiltration labelled granulomatous appendicitis.

Table 1 Abdominal ultrasonography findings used to categorize patients into positive, suggestive, inconclusive or negative for appendicitis

	Girls	Boys	Total
Positive or suggestive for appendicitis	$n=50$	$n=42$	$N=92$
Appendix thickened > 6-mm anteroposterior diameter			
Presence of an appendicolith			
Noncompressible appendix			
Periappendiceal fluid or free fluid in RIF			
Echogenic inflammatory fat change in RIF			
Diminished peristalsis in RIF loops of bowel			
Inconclusive for appendicitis	$n=30$	$n=10$	$N=40$
Appendix not visualized			
Cannot exclude appendicitis			
Negative for appendicitis	$n=37$	$n=15$	$N=52$
Normal appendix visualized			
No sonographic evidence of appendicitis			
Presence of ovarian pathology			
Presence of mesenteric lymphadenopathy			
Presence of other alternate diagnosis			

RIF, right iliac fossa.

The exclusion criteria included all interval and incidental appendicectomies and children who had a computed tomography (CT) scan or MRI performed before appendicectomy. Analysis of categorical data and continuous dependent variables utilized Fisher's exact test and Student's *t* test, respectively. The sensitivity and specificity of inflammatory markers and the positive predictive value and negative predictive value of ultrasonography were calculated. Odds ratios (OR) were calculated to analyze the influence of sex and the use of USS and inflammatory markers on NA rates. Significance was set at P less than 0.05.

Results

Over the 17-year study period, 430 boys and 273 girls met the inclusion criteria. The mean age was 13.46 years (boys: 13.48 years and girls: 13.46 years; $P=0.234$). Table 2 shows the NA rates, the positive and negative predictive values [positive predictive value (PPV) and negative predictive value (NPV)] and diagnostic accuracy of USS. Moreover, shown in Table 2 is the sensitivity and specificity of the inflammatory markers, WCC and CRP, when evaluated alone and in combination. Not all children were investigated with USS and inflammatory markers. Table 3 shows how the use of USS and inflammatory markers differed between the adolescent boys' and girls' cohorts. More girls had USS performed ($P<0.0001$). There was no difference between groups in the use of inflammatory markers; however, more girls underwent appendicectomy with a normal WCC ($P=0.0001$), normal CRP ($P=0.0001$) and normal WCC and CRP combined ($P=0.001$).

The role of sex in negative appendicectomy rates

The overall NA rate was 9.1%, with 7.2% in boys and 12.1% in girls (Table 2). This finding translates to a statistically significant increased odds of a NA in adolescent girls compared with boys (OR: 1.77, 95% confidence interval (95% CI): 1.06–2.96; $P=0.030$; Table 4). However, as both groups differed in the use of USS and in the proportion of adolescents in each group that underwent appendicectomy with normal inflammatory markers (Table 3), the effects of these confounding variables were evaluated. First, we observed nonsignificant reduced odds of a NA in boys

Table 2 Negative appendectomy rates, positive and negative predictive value of ultrasound and sensitivity/specificity of inflammatory markers in adolescent boys and girls

	Boys with USS[a]	Boys no USS	Total boys	Girls with USS[a]	Girls no USS	Total girls	Overall total
Appendectomies	67	363	430	117	156	273	703
Normal appendix	9	22	31	15	18	33	64
Negative appendectomy rate (%)	13.4	6	7.2	12.8	11.5	12.1	9.1
Positive predictive value USS (%)[b]	95.2	–	–	92	–	–	93.5
Negative predictive value USS (%)[c]	40	–	–	21.6	–	–	26.9
Diagnostic accuracy USS (%)	80	–	–	62	–	–	69.4
Sensitivity/specificity white cell count when performed (%) ($n=503$)	–	–	60.3/90.5	–	–	40.5/94	53/92.3
Sensitivity/specificity C-reactive protein when performed (%) ($n=373$)	–	–	68.7/93.3	–	–	44.8/80	59.5/88
Sensitivity/specificity white cell count and C-reactive protein when performed (%) ($n=367$)	–	–	47.1/100	–	–	28.4/90	39.8/96

USS, ultrasonography.
[a]Ultrasonography that was positive, suggestive, inconclusive or negative for appendicitis.
[b]Positive predictive value was calculated using positive and suggestive USS only.
[c]Negative predictive value was calculated using negative USS only.

Table 3 Differences between groups in the use of USS, CRP, and WCC and the differences in the proportion with normal WCC and CRP

	Girls (total = 273)	Boys (total = 430)	Total	P^a
Adolescents with USS performed irrespective of findings	117	67	184	< 0.0001
Adolescents with WCC performed	190	313	503	0.391
adolescents with normal WCC	119	135	254	*0.0001*
Adolescents with CRP performed	144	229	373	0.938
Adolescents with normal CRP	82	81	163	*0.0001*
Adolescents with CRP and WCC performed	144	223	367	0.877
Adolescents with normal CRP and WCC	105	125	230	*0.001*

CRP, C-reactive protein; USS, ultrasonography; WCC, white cell count.
[a]Fisher's exact test.
Italic values indicates significance $P < 0.05$.

Table 4 Odds of a negative appendicectomy in girls versus boys

	Odds ratio	95% Confidence interval	*P*
Overall odds of an adolescent girl having a NA compared with adolescent boys	1.77	1.06–2.96	0.030
Odds of NA in girls with a positive, suggestive or inconclusive USS compared with boys with similar USS	1.57	0.39–6.35	0.530
Odds of NA in girls with elevated WCC compared with boys with elevated WCC	1.26	0.11–14.09	0.853
Odds of NA in girls with elevated CRP compared with boys with elevated CRP	4.90	0.44–55.06	0.198
Odds of a NA in girls with elevated CRP + WCC compared with boys with elevated CRP + WCC	7.68	0.31–192.54	0.215
Odds of NA in girls with a positive, suggestive or inconclusive USS and elevated WCC + CRP compared with boys with similar USS and elevated WCC + CRP	2.27	0.09–60.64	0.624

CRP, C-reactive protein; NA, negative appendicectomy; USS, ultrasonography; WCC, white cell count.

Table 5 Odds of a negative appendicectomy in boys and girls when USS performed compared with no USS performed preoperatively

	Odds ratio	95% Confidence interval	*P* value
Odds of a NA with a positive, suggestive, inconclusive or negative USS compared with no USS in girls and boys	1.80	1.05–3.07	0.033
Odds of NA with a positive, suggestive or inconclusive USS compared with no USS in boys	0.95	0.27–3.29	0.934
Odds of NA with a positive, suggestive or inconclusive USS compared with no USS in girls	0.74	0.29–1.84	0.511
Odds of NA with a positive, suggestive or inconclusive USS compared with no USS in girls and boys	0.98	0.48–2.02	0.960
Odds of a NA with a positive and suggestive USS only compared with no USS in girls and boys	0.70	0.29–1.68	0.419

CRP, C-reactive protein; NA, negative appendicectomy; USS, ultrasonography; WCC, white cell count.

Table 6 Odds of a negative appendicectomy when inflammatory markers are normal compared with when elevated

	Odds ratio	95% Confidence interval	*P* value
Odds of NA in boys and girls when WCC is normal	13.54	4.11–44.59	< 0.0001
Odds of NA in girls when WCC is normal	11.67	1.52–89.69	0.018
Odds of NA in boys when WCC is normal	14.41	3.30–63.05	0.0004
Odds of NA in boys and girls when CRP is normal	10.77	3.16–36.65	0.0001
Odds of NA in girls when CRP is normal	3.24	0.66–15.85	0.145
Odds of NA in boys when CRP is normal	30.72	3.96–238.43	0.001
Odds of NA in boys and girls when CRP and WCC are normal	15.84	2.12–118.50	0.007
Odds of NA in girls when CRP and WCC are normal	3.56	0.44–29.09	0.236
Odds of NA in boys when CRP and WCC are normal	27.63	1.63–467.92	0.022

CRP, C-reactive protein; NA, negative appendicectomy; USS, ultrasonography; WCC, white cell count.

and girls individually, and combined, when USS was positive, suggestive or inconclusive for appendicitis, compared with no USS performed (Table 5). Second, we observed in each cohort individually, and combined, that when the inflammatory markers were normal there were increased odds of a NA. As shown in Table 6, these odds were significant in most scenarios (OR: 15.84, 95% CI: 2.12–118.50; $P = 0.007$ for normal WCC and CRP compared with elevated WCC and CRP in both cohorts combined). Adjusting for this variance in USS use and the variance between cohorts in the proportion of children with normal and elevated inflammatory markers, the new odds of a NA in girls compared with boys were now not statistically significantly increased (OR: 2.27, 95% CI: 0.09–60.64; $P = 0.624$; Table 4). In summary, when both groups had similar USS findings and elevated inflammatory markers, the increased odds of a NA in the girls compared with the boys were not statistically significant.

Role of inflammatory markers

As shown in Table 2, the specificity of WCC, CRP and both tests combined was much higher than the sensitivity in both cohorts individually and overall. A specificity of 96% was observed in boys and girls when both tests were combined. As shown in Table 6, this high specificity was evident as significantly increased odds of a NA when WCC and CRP combined were normal in boys and girls (OR: 15.84, 95% CI: 2.12–118.50; $P = 0.007$).

Role of ultrasonography

Children who had USS performed, irrespective of the findings (positive, suggestive, inconclusive and negative), had higher NA rates compared with children with no USS performed. Overall rates were 13% in USS group versus 7.7% in no USS group (OR: 1.80, 95% CI: 1.05–3.07; $P = 0.033$) (Table 5). This observation was significant in boys (USS vs. no USS: 13.4 vs. 6%; $P = 0.040$), but nonsignificant in girls (USS vs. no USS: 12.8 vs. 11.5%; $P = 0.851$). However, as shown in Table 5, when USS was positive, suggestive or inconclusive for appendicitis (negative USS excluded), the odds of a NA were still not significantly reduced. This was evident in both cohorts individually, and overall, when compared with not having an USS performed: (OR: 0.98, 95% CI: 0.48–2.02; $P = 0.960$; boys and girls combined; Table 5). Furthermore, if appendicectomies had been performed with only a positive and suggestive USS (which has a PPV of 93.5% in both cohorts combined), the odds of a NA were still not significantly reduced when compared

with not having USS performed (OR: 0.70, 95% CI: 0.29–1.68; $P = 0.419$; Table 5). The group with no USS performed likely had more clinically obvious appendicitis compared with the equivocal cases in the USS group. USS was found to be more useful in diagnosing an inflamed appendix than a normal appendix in both cohorts, as shown by the PPV and NPV (Table 2). Finally, USS had a lower PPV and NPV and thus lower overall accuracy in girls compared with boys (Table 2).

Discussion

NA rates in the literature vary widely from 1.1 to more than 36% [2,3]. The rates depend on the definition of a NA [12], presence of obesity [13], age group [3,5,7], and the use of imaging [14] and laparoscopy [8]. Interestingly, sex differences have been shown to be an important variable when reporting NA rates [2–8,13]. Women of child-bearing age (15–45 years) have NA rates higher than men [5,8,15] and even other females [16], and this can be as high as 44% in some published studies [17]. This finding has been largely attributed to gynaecological conditions like pelvic inflammatory disease and ovarian cysts that can masquerade as appendicitis [15,16]. Similarly, young girls from the age of 10 years, and particularly teenage girls, have also been observed to have higher NA rates than boys [2,5–7] and gynaecological conditions are not entirely responsible for this [2]. Nonspecific abdominal pain, constipation and urinary tract infections are more frequently diagnosed in adolescent girls [2]. Some studies have even suggested that female sex is associated with slower colonic transit times that predispose them to constipation [18]. Furthermore, adolescent girls may be more susceptible to stress [1] and have poorer eating habits which may be responsible for their higher incidence of irritable bowel syndrome [19,20]. The findings of these aforementioned studies may partly explain why adolescent girls present to emergency departments more frequently with abdominal pain [1,2]. Furthermore, girls have a lower incidence of appendicitis than boys [21]. Therefore, the more frequent emergency department presentations, lower incidence of appendicitis and more common gynaecological and nongynaecological causes of abdominal pain [2] predisposes girls to being misdiagnosed with appendicitis. Our results initially corroborated this hypothesis. Over the 17-year study period, girls aged 12–16 years had higher NA rates and increased odds of a NA compared with boys. Several variables in the boys and girls cohorts can influence the NA rates and these include their sex, use of USS [3], differences in the serum levels of WCC and CRP [22], the variable severity of appendicitis (suppurative, gangrenous and perforated; the latter being more obvious clinically [23]), presence of obesity [13] and fever [23], period of observation before appendicectomy, and the clinical expertise of the attending surgeon. When the variability of USS use and serum inflammatory markers was accounted for, we did not observe significantly increased odds of a NA in the girls compared with boys.

Ultrasonography has arguably been shown to be a useful aid when evaluating children and adults for appendicitis [3,16,24–27]. It avoids the cost and the risk from radiation exposure associated with CT [28]. However, the specificity and sensitivity is not quite on par with CT scanning [9,24,26,27]. USS is operator dependent and is affected by body habitus and overlying bowel gas particularly when the appendix is retrocecal [29]. The PPV range from 81.3 to 94%, NPV 23.9 to 98% and accuracy 43.4 to 92% depending on the study design and studied age groups [24–27]. In our series, the overall PPV, NPV and diagnostic accuracy were 93.5, 26.9 and 69.4%, respectively; these values were slightly higher in boys, and significantly more girls had USS performed. These findings suggest that USS is more useful in confirming the presence of appendicitis rather than its absence. The low NPV (high false negative) of USS in our series may be owing to comments often used in USS reports such as 'no sonographic evidence of appendicitis', which was more commonly used than the more definitive comment of 'normal appendix visualized'. Several reports have highlighted the difficulty in visualizing a normal appendix with USS [29]. As shown in Table 1, diagnosing another pathology such as enlarged mesenteric lymph nodes or ovarian pathology along with the comment 'no sonographic evidence of appendicitis' was more confidently categorized as a negative USS, whereas the comment 'cannot exclude appendicitis' was categorized as inconclusive USS. Furthermore, we postulate that appendiceal pathology such as *E. vermicularis* colonization, submucosal fibrosis and lymphoid hyperplasia (all of which can cause appendix-mediated symptoms without gross appendiceal inflammation [30–33]) may not always have met the USS diagnostic criteria required for appendicitis [29] thus also responsible for the high false negative (low NPV) of USS. These children who proceeded to appendicectomy despite having a negative USS were owing to their clinical signs becoming more suggestive for appendicitis while under observation. The USS group overall had a higher NA rate and so increased odds of a NA compared with the no USS group. This was owing to USS being performed in patients (mostly girls) who presented a diagnostic challenge clinically. When negative and inconclusive USS reports were excluded, the odds of a NA when USS was positive or suggestive were still not significantly reduced compared with not having an USS performed in boys and girls. The clinical expertise of the attending surgeons in the no-USS group was most of the time sufficient to accurately diagnose appendicitis without the use of USS. These limitations of USS present a role for CT and MRI to further reduce NA rates in equivocal cases. CT with a sensitivity of 94% and specificity of 95% [14] has been shown to reduce NA rates in girls older than 10 years but is not as valuable in boys older than 5 years who already have low NA rates independent of cross-sectional imaging [3]. CT presents a risk from radiation exposure [28], thus the use of MRI, reported to have a 100% sensitivity and 98% specificity, has been evaluated for reducing NA rates particularly in the obese. Because of the higher costs and limited availability, its routine use in suspected appendicitis is not yet recommended by many researchers [14].

Many studies have evaluated the role of CRP and WCC in diagnosing appendicitis. They have been shown useful in scoring systems for appendicitis, [22] and the role of other inflammatory markers such as procalcitonin [10]

and granulocyte colony stimulating factor [34] in diagnosing appendicitis has been evaluated. The published sensitivities and specificities of CRP and WCC vary widely, and a meta-analysis on the subject has shown higher specificities than sensitivities for both markers [10]. Furthermore, in a meta-analysis by Andersson [35], the combination of elevated WCC and CRP had a higher predictive power for appendicitis than either marker alone. In our cohort of young adolescent boys and girls, we observed significantly increased odds of a NA when CRP and WCC were normal, when evaluated alone or in combination. This finding was more marked in boys particularly, as CRP alone and when combined with WCC had a higher sensitivity and specificity in boys compared with girls (Table 2). More studies are necessary to evaluate if the rise in serum levels of inflammatory markers in appendicitis are sex related, just as obesity in children may cause CRP to be a less reliable marker of appendiceal inflammation [36]; for instance, the females may have a delayed rise in these inflammatory markers making appendicitis more likely with initially normal markers. Similar to other published findings, the specificities of these markers (alone or combined) were consistently higher than the sensitivities in both groups [10] and appendicitis was less likely when both inflammatory markers were normal [23,25,35]. Therefore, when appendicitis is confirmed, these markers may not always have been raised (lower sensitivity owing to higher false negative rate); however, when these markers are raised in suspected appendicitis, the likelihood of appendicitis is much higher (higher specificity due to lower false positive rate). Finally, inflammatory markers, particularly CRP, are also useful in predicting the pathological severity of appendicitis [37].

Apart from retrospective nature of this study and the modest numbers, particularly in the USS group, the other limitations include the unaccounted aforementioned variables like obesity, period of observation before surgery, the surgeon's clinical expertise and the stage of appendicitis (perforated or not) that may have differed in the boys and girls cohorts. Similarly, the numerous radiologists who performed these USS scans in equivocal cases were a limiting factor. This study did not evaluate the well-published role of scoring systems, CT scanning and MRI [14].

Conclusion

Adolescent girls aged 12–16 are more likely to have an unnecessary surgery for appendicitis when compared to their counterpart boys. When the inflammatory markers, WBC count and CRP, are utilized and found to be elevated, this increased likelihood of a NA is not observed in girls but rather reduced odds of a NA are seen in both girls and boys. Ultrasonography in equivocal cases is a helpful assessment tool, but it does not significantly reduce the odds of a NA and is thus not superior to clinical assessment alone. Therefore, in difficult cases, a period of observation and re-examination is warranted prior to early appendicectomy or premature discharge which predisposes to appendiceal perforation and subsequent litigation [38].

Conflicts of interest

There are no conflicts of interest.

References

1 Vila M, Kramer T, Obiols JE, Garralda ME. Abdominal pain in British young people: associations, impairment and health care use. *J Psychosom Res* 2012; **73**:437–442.
2 Buddingh KT, Wieselmann E, Heineman E, Broens PM. Constipation and nonspecific abdominal pain in teenage girls referred for emergency surgical consultation. *J Pediatr Gastroenterol Nutr* 2012; **54**:672–676.
3 Bachur RG, Hennelly K, Callahan MJ, Chen C, Monuteaux MC. Diagnostic imaging and negative appendectomy rates in children: effects of age and gender. *Pediatrics* 2012; **129**:877–884.
4 Ponsky TA, Huang ZJ, Kittle K, Eichelberger MR, Gilbert JC, Brody F, *et al.* Hospital- and patient-level characteristics and the risk of appendiceal rupture and negative appendectomy in children. *JAMA* 2004; **292**:1977–1982.
5 Flum DR, Koepsell T. The clinical and economic correlates of misdiagnosed appendicitis: nationwide analysis. *Arch Surg* 2002; **137**:799–804.
6 Pearl RH, Hale DA, Molloy M, Schutt DC, Jaques DP. Pediatric appendectomy. *J Pediatr Surg* 1995; **30**:173–178.
7 Oyetunji TA, Ong'uti SK, Bolorunduro OB, Cornwell EE, Nwomeh BC. Pediatric negative appendectomy rate: trend, predictors, and differentials. *J Surg Res* 2012; **173**:16–20.
8 Flum DR, Morris A, Koepsell T, Dellinger EP. Has misdiagnosis of appendicitis decreased over time? A population-based analysis. *JAMA* 2001; **286**:1748–1753.
9 Doria AS, Moineddin R, Kellenberger CJ, Epelman M, Beyene J, Schuh S, *et al.* US or CT for diagnosis of appendicitis in children and adults? A meta-analysis. *Radiology* 2006; **241**:83–94.
10 Yu CW, Juan LI, Wu MH, Shen CJ, Wu JY, Lee CC. Systematic review and meta-analysis of the diagnostic accuracy of procalcitonin, C-reactive protein and white blood cell count for suspected acute appendicitis. *Br J Surg* 2013; **100**:322–329.
11 O'connell A, Gavin A, Kelly C, Molcho M, Nic Gabhainn S. The mean age at menarche of Irish girls in 2006. *Ir Med J* 2009; **102**:76–79.
12 Mariadason JG, Wang WN, Wallack MK, Belmonte A, Matari H. Negative appendicectomy rate as a quality metric in the management of appendicitis: impact of computed tomography, Alvarado score and the definition of negative appendicectomy. *Ann R Coll Surg Engl* 2012; **94**:395–401.
13 Kutasy B, Hunziker M, Laxamanadass G, Puri P. Increased incidence of negative appendectomy in childhood obesity. *Pediatr Surg Int* 2010; **26**:959–962.
14 Cole MA, Maldonado N. Evidence-based management of suspected appendicitis in the emergency department. *Emerg Med Pract* 2011; **13**:1–29.
15 Seetahal SA, Bolorunduro OB, Sookdeo TC, Oyetunji TA, Greene WR, Frederick W, *et al.* Negative appendectomy: a 10-year review of a nationally representative sample. *Am J Surg* 2011; **201**:433–437.
16 Ma KW, Chia NH, Yeung HW, Cheung MT. If not appendicitis, then what else can it be? A retrospective review of 1492 appendectomies. *Hong Kong Med J* 2010; **16**:12–17.
17 Laine S, Rantala A, Gullichsen R, Ovaska J. Laparoscopic appendectomy-is it worthwhile? A prospective, randomized study in young women. *Surg Endosc* 1997; **11**:95–97.
18 Meier R, Beglinger C, Dederding JP, Meyer-Wyss B, Fumagalli M, Rowedder A, *et al.* Influence of age, gender, hormonal status and smoking habits on colonic transit time. *Neurogastroenterol Motil* 1995; **7**:235–238.
19 Reshetnikov OV, Kurilovich SA, Denisova DV, Zav'ialova LG, Svetlova IO, Tereshonok IN, *et al.* Prevalence and risk factors of the development of irritable bowel syndrome in adolescents: a population study. *Ter Arkh* 2001; **73**:24–29.
20 Rajindrajith S, Devanarayana NM. Subtypes and symptomatology of irritable bowel syndrome in children and adolescents: a school-based survey using Rome III criteria. *J Neurogastroenterol Motil* 2012; **18**:298–304.
21 Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol* 1990; **132**:910–925.
22 Andersson M, Andersson RE. The appendicitis inflammatory response score: a tool for the diagnosis of acute appendicitis that outperforms the Alvarado score. *World J Surg* 2008; **32**:1843–1849.
23 Bundy DG, Byerley JS, Liles EA, Perrin EM, Katznelson J, Rice HE. Does this child have appendicitis? *JAMA* 2007; **298**:438–451.
24 Parks NA, Schroeppel TJ. Update on imaging for acute appendicitis. *Surg Clin North Am* 2011; **91**:141–154.
25 Lee SL, Walsh AJ, Ho HS. Computed tomography and ultrasonography do not improve and may delay the diagnosis and treatment of acute appendicitis. *Arch Surg* 2001; **136**:556–562.
26 Kaiser S, Frenckner B, Jorulf HK. Suspected appendicitis in children: US and CT–a prospective randomized study. *Radiology* 2002; **223**:633–638.
27 Rosendahl K, Aukland SM, Fosse K. Imaging strategies in children with suspected appendicitis. *Eur Radiol* 2004; **14** (**Suppl 4**):138–145.

28 Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, *et al*. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet* 2012; **380**:499–505.
29 Estey A, Poonai N, Lim R. Appendix not seen: the predictive value of secondary inflammatory sonographic signs. *Pediatr Emerg Care* 2013; **29**:435–439.
30 Aydin O. Incidental parasitic infestations in surgically removed appendices: a retrospective analysis. *Diagn Pathol* 2007; **2**:16.
31 Arca MJ, Gates RL, Groner JI, Hammond S, Caniano DA. Clinical manifestations of appendiceal pinworms in children: an institutional experience and a review of the literature. *Pediatr Surg Int* 2004; **20**:372–375.
32 Smith TA. Lymphoid hyperplasia of the appendix in children; its relation to recurrent appendicitis. *Ann Surg* 1924; **79**:871–878.
33 Grüssner R, Pistor G, Engelskirchen R, Hofmann-von Kap-herr S. Appendicitis in childhood. *Monatsschr Kinderheilkd* 1985; **133**:158–166.
34 Allister L, Bachur R, Glickman J, Horwitz B. Serum markers in acute appendicitis. *J Surg Res* 2011; **168**:70–75.
35 Andersson RE. Meta-analysis of the clinical and laboratory diagnosis of appendicitis. *Br J Surg* 2004; **91**:28–37.
36 Kutasy B, Laxamanadass G, Puri P. Is C-reactive protein a reliable test for suspected appendicitis in extremely obese children? *Pediatr Surg Int* 2010; **26**:123–125.
37 Shindoh J, Niwa H, Kawai K, Ohata K, Ishihara Y, Takabayashi N, *et al*. Diagnostic power of inflammatory markers in predicting severity of appendicitis. *Hepatogastroenterology* 2011; **58**:2003–2006.
38 Selbst SM, Friedman MJ, Singh SB. Epidemiology and etiology of malpractice lawsuits involving children in US emergency departments and urgent care centers. *Pediatr Emerg Care* 2005; **21**:165–169.