The Association of Appendectomy, Adhesions, Tubal Pathology, and Female Infertility

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ABSTRACT

Background and Objectives: The aim of the study was to investigate a potential association between previous childhood appendectomy, tube pathology, and female infertility.

Methods: We reviewed patients seeking care at the fertility clinic of our university medical center between 2006 and 2016. The history of previous appendectomy was extracted from hospital documentation and by telephone follow-up. Tubal patency was assessed by diagnostic laparoscopy and chromopertubation.

Results: In our study cohort (N = 237), 24.9% (n = 59) had a history of previous appendectomy. Previous appendectomy, therefore, was about 3-fold more prevalent in women seeking fertility treatment than in the general population. Patients with previous appendectomy had more intra-abdominal adhesions ($P < .001$) and patients with adhesions tended to have compromised tubal patency ($P = .05$). However, there was no direct correlation between a previous appendectomy and tube pathology ($P = .727$).

Conclusion: Because previous appendectomy was associated with intra-abdominal adhesions, and these were in turn associated with tube pathology, but appendectomy was not directly associated with compromised tubal patency, previous appendectomy may indirectly affect female fertility through mechanisms other than direct tubal obstruction. This is one of the largest study analyzing laparoscopic chromopertubation in association with previous childhood appendectomy.

Key Words: Appendicitis, Female infertility, Tube pathology, Adhesions.

INTRODUCTION

Infertility is defined by the World Health Organization (WHO) as the inability to conceive after 1 year of unprotected sexual intercourse.[1] Approximately 50–80 million women are estimated have infertility every year.[2] In general, causes for infertility are equally distributed among women, men, and both partners. Risk factors for infertility can be disorders of the reproductive system, diseases, hormonal imbalances, age, alcohol, immune responses, stress, and chronic diseases.[1]

One of the most common causes for infertility in women is a pathology of the Fallopian tube,[3] particularly compromised patency. Apart from impairments of the reproductive system such as endometriosis or polyps, previous infections[4] or operations may lead to intra-abdominal adhesions and, thus, to dysfunction of the Fallopian tube.[5,6]

Appendicitis is one of the most common reasons for an acute abdomen and has a lifetime prevalence for women ranging from 6.7%[7] to 16.4%.[8] A history of appendicitis combines the possible risk of inflammatory and procedure-associated long-term pelvic and abdominal complications. Because of the anatomic localization of the appendix and its proximity to the adnexa, appendiceal inflammation may, at least in theory, have negative affects on tubal patency or mobility.

A recent meta-analysis[9] attempted to evaluate the effect of previous appendectomy on later tubal infertility. The authors showed that appendicitis was not associated with an increased incidence for infertility in female patients (odds

ratio [OR] 1.03, 95% confidence interval [CI] 0.86–1.24; $P = .710$). However, the heterogeneity of the included studies, their publication dates, and different methodological approaches leave room for interpretation and prompt further exploration. We therefore reviewed the diagnostic laparoscopy findings regarding tubal patency in a larger German female fertility cohort seeking care at a university medical center and correlated these findings with previous appendectomy as a surrogate marker for previous appendicitis and other possible risk factors for infertility.

METHODS

Ethics

This retrospective single-center cohort study was approved by the ethics council of the state medical board (No. 837.251.16) and the data protection officer. Written informed consent of the study participants was obtained.

### Setting, Inclusion Criteria, and Study Design

From January 1, 2006 until December 31, 2016, all female patients who sought care at the fertility clinic of our university medical center qualified in principle to be included in this study. Having undergone diagnostic laparoscopy and chromopertubation were the main inclusion criteria. We therefore excluded patients (1) without a

performed diagnostic laparoscopy and chromopertubation, (2) who were younger than 18 and older than 40 years, and (3) who did not provide consent to participate in the study (**Figure 1**).

Data from the patient records, charts, and questionnaires were extracted during fertility treatment or consultation and included information on previous pregnancies, gynecological history and surgeries, duration of the pregnancy desire, cycle frequency, previous fertility therapy, surgical history, and, in particular, a history of appendectomy in the past.

Laparoscopy and Chromopertubation

Diagnostic laparoscopy and chromopertubation were performed by using a standard protocol described elsewhere.[10] The procedure is performed via navel access with the installation of a single-port system. Intraoperative vaginoscopy is performed, and methylene blue is injected through the cervix into the uterine cavity and the Fallopian tubes. The tubal condition was classified intraoperatively by the surgeon as either "promptly patent," "additional pressure needed," or "not patent," depending on exit of methylene blue through the tubes into the abdomen (**Figure 2**). Additional alterations, including adhesions, endometriosis, myomas, cysts, or polyps, and information on possible peritonitis or ascites were noted for later analysis. At the end of the procedure, hysteroscopy
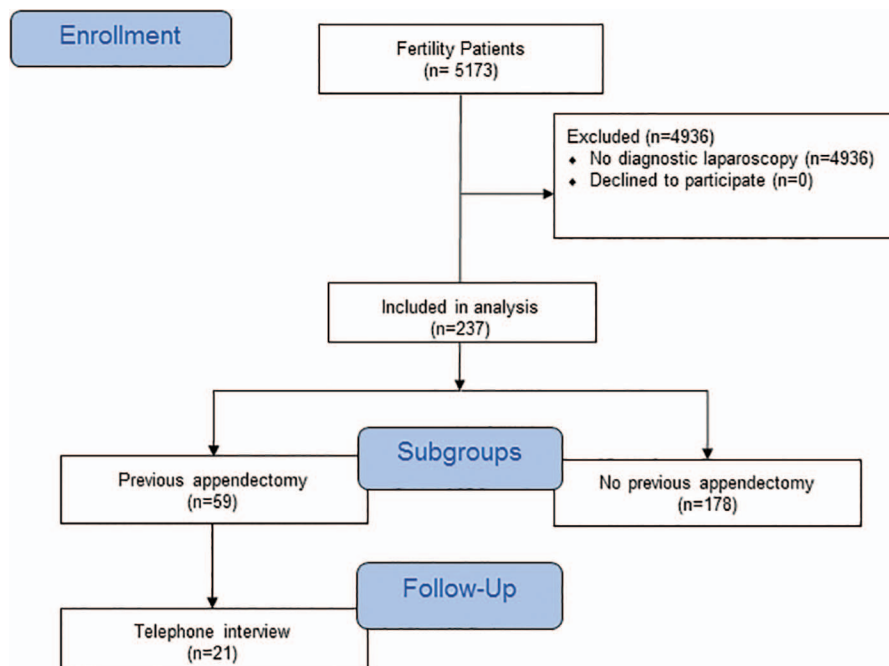
Figure 1. Flowchart of study participants.
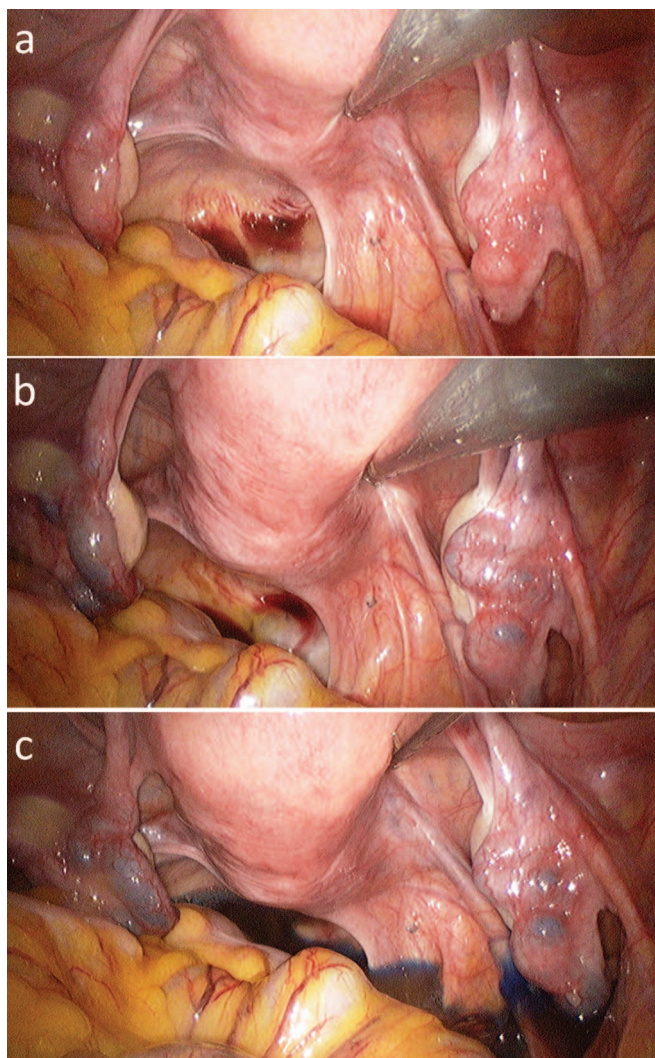
Figure 2. Technique of single-incision laparoscopy and chromopertubation. First, the pelvis is visualized before injection (**a**). The vagina is then injected with methylene blue dye, seen filling the Fallopian tubes from intra-abdominally (**b**). Finally, passage of methylene blue through the Fallopian tubes into the abdominal cavity positively confirms normal patency (**c**).

was performed to determine the status of the hysterotubal orifices.

For the aim of our study, we used the history of appendectomy to investigate the association of an appendectomy in early life and its association with tubal patency. If the patient's records suggested previous appendectomy, patients were contacted by telephone interview to confirm the procedure and inquire about additional details regarding the procedure and illness, including age at appendectomy, duration of symptoms, appen-

dectomy via laparoscopic or open approach, and perioperative complications. We also attempted to differentiate simple (acute) from complex (perforated) appendicitis.

Statistical Analysis

Statistical analysis was performed with SPSS standard package (version 25.0; SPSS Inc, Chicago, IL). A value of $P < .05$ was considered statistically significant. Data are presented as absolute numbers (percentages) or medians with a corresponding interquartile range (IQR; 25th to 75th percentile), and n refers to the number of patients with available data. The χ^2 test and cross tables were used for nominal variables, and Mann-Whitney U tests were used for continuous variables. Subsequently, binary linear regression was performed including odds ratios (ORs) and the matching 95% confidence intervals (CIs).

RESULTS

Study Cohort

During the described study period, a total of 237 patients were included in the study (**Figure 1**). Demographics and baseline characteristics of the study cohort are given in **Table 1**. The patients had a median age of 34 (IQR 29 to 39) years during their diagnostic laparoscopy and had tried to become pregnant for a median of 2 y. About two-thirds were diagnosed with primary infertility, having never conceived a child.

Laparoscopy and Chromopertubation

Nearly half of all patients (46%, 109) had no pathologic findings on laparoscopy or chromopertubation. Tube pathology diagnosed by using the described criteria was noted in 42% (99) of patients. Adhesions were found in 28% (66) of patients. Of these, 38 (16% of the entire study group) patients had both adhesions and tube pathology. Tube pathology was more likely to be found in patients with a previous history of ectopic pregnancy with an OR of 3.6 (95% CI 1.07–12.16; $P = .039$).

Appendectomy

A total of 59 (24.9%) patients reported a history of appendectomy. Of these 59 patients, after successfully contacting 21 patients by phone, information regarding age at appendectomy was available in 54 cases. The median age at the time of surgery was 16 (IQR 11–21) years, and about two-thirds of the patients (34, 60.7%) were under the age

Table 1.
Baseline Characteristics of Study Population

Characteristics	
Age beginning of fertility treatment (n = 237), years (range)	34 (30–37)
Time span of pregnancy desire, years (range)	2 (1.5–4)
Primary infertility (n = 236), n (%)	144 (61.5)
Secondary infertility (n = 236), n (%)	92 (38.5)
Gynecological procedures (n = 18), n (%)	
Ovarian cystectomy	3 (16.6)
Hysteroscopy	1 (5.6)
Polypectomy	1 (5.6)
Others	13 (72.2)
Menstrual cycle (n = 178), days	
Cycle length in days (range)	28 (28–28)
Bleeding interval in days (range)	4 (4–4)
Dysmenorrhea (n = 236), n (%)	34 (14.4)
Adnexitis (n = 236), n (%)	11 (4.7)
AMH value (n = 64), ng/mL (range)	2.5 (1.03–4.83)
Pathological AMH value (n = 64), n (%)	4 (6.3)
Pregnancy rate (n = 234), n (%)	129 (55.1)
Ectopic pregnancy (n = 93), n (%)	16 (17.2)
Cesarean section (n = 92), n (%)	19 (20.7)

AMH, antimullerian hormone; IQR, interquartile range.
Values are presented as median (IQR) or n (%).

of 18 during the time of their appendectomy. Appendectomies in our cohort were performed from 1976 until 2012, with roughly two-thirds (37) performed before 2000.

Information on the type of appendicitis (simple/complex), operative technique, and complications was available from 20 patients. Perforated or complex appendicitis was noted in 8 (40%) of these patients. One patient had a second (revision) operation. Only about one-third of the procedures (6, 29%) were performed laparoscopically.

There was no difference in tube pathology regarding complicated and uncomplicated appendicitis (OR 1.75, 95% CI 0.3–11.2; $P = .554$), and tube pathologies were distributed equally between the right and left Fallopian tubes ($P = .674$). There was no relationship between tube pathology and having had an appendectomy in the past ($P = .73$), nor was there a statistical difference in the incidence of tube pathology after laparoscopic versus open appendectomy ($P = .09$). Finally, previous appendectomy was not found to be a risk factor for later ectopic pregnancy (OR 1.13, 95% CI 0.3–3.9; $P = .85$) or infertility (OR 0.77, 95% CI 0.42–1.41; $P = .40$).

Adhesions

Patients with tube pathology tended to be diagnosed with adhesions more often than did patients without tube pathology (37 [38.1%] vs no tube pathology 29 [21.3%]; $P = .050$). Also, adhesions were more often diagnosed in patients with a history of appendectomy (27 [46.6%] vs no appendectomy 39 [22%]; $P < .001$). Patients with secondary infertility showed more adhesions than did patients with primary infertility ($P = .015$), and the OR for having a secondary infertility in patients with adhesions was 2.0 (95% CI 1.1–3.6; $P = .016$). Adhesiolysis was performed intraoperatively in 14% (35) of patients with adhesions. There was no difference in subsequent pregnancy rate in the patients who did or did not undergo adhesiolysis ($P = .857$).

DISCUSSION

Although a recent systematic review of studies[9] published between 1971 and 2001 suggests that previous appendectomy increases the risk for ectopic pregnancy without compromising fertility, the mechanisms behind this observation are poorly understood. Interestingly, there is a striking lack of studies published on this topic in the new millennium, although surgical technique, antibiotic availability and treatment algorithms have evolved.

Laparoscopic chromopertubation is generally considered the gold standard to evaluate for tubal patency against all other methods are compared.[11,12] We have been performing a standard technique for >2 decades on women with infertility with extremely low morbidity and excellent predictive value. Although more invasive than radiographic or sonographic hysterosalpingography, its advantages are that it requires no ionizing radiation and that, in selected cases, tubal patency can be reestablished intraoperatively.[13]

We empirically perceived a higher incidence of previous childhood and adolescent appendectomy in women seen at our fertility clinic. This observation prompted us to investigate a possible association between infertility and previous appendectomy, along with any potential under-

lying causative factors. Because the standard workup of women with infertility suggestive of an adnexal etiology includes diagnostic laparoscopy and chromopertubation, tubal patency and adhesion formation were primary investigative targets.

Depending on geography and country, the reported lifetime prevalence of appendicitis for females ranges from 6.7% in the United States[7] to 16.3% in South Korea.[8] In Germany, it has been calculated at around 1 case per 1000 patient years,[14] translating into a lifetime incidence of about 12%. Due to the close proximity of the appendix to the internal female reproductive organs in the pelvis, it is at least theoretically conceivable that the inflammation associated with appendicitis could have negative effects on later fertility. Considering the overall prevalence of appendicitis among females in the general population, it is surprising that almost a quarter of women seen at our fertility clinic gave a history of previous appendectomy, suggesting a possible association between the two. In fact, other studies also found an increased appendectomy rate in women seeking care at a fertility clinic, ranging from 20%[15] to 29%.[16]

In our study, appendectomy was not directly associated with impaired tube patency on chromopertubation. However, structural patency is only one factor influencing normal adnexal function, the others being ciliary movement and secretion of tubular fluid.[17] Chromopertubation, or other tubal patency examinations such as hysterosalpingography, are less sensitive to detect anomalies other than obstruction. Since we only reviewed macroscopic and functional factors during the diagnostic laparoscopy, we could not evaluate the transport function of the fallopian tube and some studies discuss the relevance of pH-levels or oxygen consumption on the implantation process.[18]

Some other studies reviewed the fertility rate after an appendectomy. Wei et al[19] showed an elevated fertility rate after appendectomy. In our study, 60.3% of patients with a previous appendectomy and 55.3% of all patients were able to conceive, but this was not statistically significant. The authors hypothesized that a possible explanation for the elevated rate could be the removal of the lymphoid organ and, therefore, fewer subclinical or chronic inflammation.[19]

On the other hand, there are studies that consider inflammatory factors such as cytokines, growth factors, or transcription factors and prostaglandin relevant for the implantation process.[20,21] Both pathway mechanisms might be possible because the amount of inflammation may be either beneficial or damaging to the reproductive system. Inflammation may correspondingly lead to adhesions and, again, to mechanical sterility. These highly complex interactions are not verifiable from our study but definitively warrant further exploration.

Laparoscopic chromopertubation is considered the best standard to evaluate tubal patency[22] and has the additional advantage that adhesions can be diagnosed simultaneously.

Adhesions were significantly more common in those patients who had undergone appendectomy. There are 2 factors that may explain these findings. First, inflammation resulting from presumed appendicitis may have resulted in adhesions. Second, the operation itself may have caused some adhesions, particularly because most of the operations were still performed in an open surgical fashion. Our study also showed that adhesions tended to be associated with tube pathology, indicating that previous inflammation or the intervention somehow negatively affected later tubal patency. However, in this study, we were unable to find a direct relationship between previous appendectomy and tube pathology. Interestingly, tube pathology was indeed correlated with secondary infertility in our cohort.

According to Lash et al,[23] tube pathology is diagnosed more commonly in those with secondary infertility. Our findings indicate that patients with adhesions were at higher risk of having tube pathology. In our fertility clinic, tubal obstruction, particularly bilateral, is one of the most reliable predictors of female infertility. These findings are corroborated by other studies: Chanu et al[24] evaluated adhesions in fertility clinic patients and showed a comparable adhesion rate to ours (Chanu et al 21.2% vs present-study 28.1%). Nonsurgical interventions to reestablish patency often are not successful. Bosteels et al[25] reviewed the use of an antiadhesion therapy (including different forms of antiadhesion therapy such as hormonal treatment or barrier gels) in a Cochrane analysis and could not show any advantage to the placebo group, which, again, corresponds to our findings.

The relationship of appendectomy and tube pathology has been investigated in previous trials with conflicting results. Trimbos-Kemper et al[26] showed a significant difference in tube pathologies for patients with complicated appendicitis. Lalos[15] reviewed risk factors for tube pathologies and compared 2 groups of patients with tubal infertility and a control group, without showing a difference in the appendectomy rate ($P = .499$). However, they considered the surgically trauma and the perioperative serosal

reaction with adhesions a possible cause for the development of tube pathologies. Thus, the authors recommended an atraumatic laparoscopic approach. Puri et al[27] included female patients who underwent appendectomy under the age of 13 y and performed a follow-up regarding the "fertility status," showing no significant difference regarding the tube pathology rate. In our study, we showed similar data for children under the age of 13 ($P = .884$), which had a comparable tube pathology rate to all included patients with a previous appendectomy (children 36.0% vs total 41.7%).

Mueller et al[28] divided patients into primary and secondary infertility and reviewed their tube pathology rate. For perforated appendicitis, the relative risk was elevated for both primary (RR 4.8 [95% CI 1.5–4.9]; $P < .050$) and secondary (RR 3.2 ([95% CI 1.1–9.6]; $P < .050$) infertility, concluding that a rapid therapy for appendicitis before perforation could have a positive effect on female fertility and that the impact on the fertility would depend on the degree of inflammation. Urbach and Cohen[29] and Urbach et al[30] published a study and a meta-analysis regarding primary infertility and could not show an elevated OR (1.4, 95% CI 0.30–6.20; $P = .66$) in patients with primary infertility and appendicitis for a tube pathology. Summarizing all studies and findings, there is no definite answer regarding the association between an appendectomy and tube pathology.

Our study has several limitations. Due to the retrospective nature of our study and using appendectomy as a surrogate marker for appendicitis, there are intrinsic confounders that may hamper the interpretability of our findings regarding the effect of appendicitis on later fertility. First, the symptoms that led to the removal of the appendix may have been due to other entities such as pelvic inflammatory disease or inflammatory bowel disease. A negative appendectomy rate between 8% and 15% was generally considered acceptable at the time when most of the women in our cohort were operated on.[31] In general, small patient numbers preclude broad generalization but do indicate that larger prospective studies may be warranted.

However, because previous appendectomy was directly correlated in our study with adhesions but not with tubal patency and because appendectomy itself was more common in patients seeking care at our fertility clinic, it is conceivable that other factors play a role in the pathogenesis of infertility. The fimbriae of the Fallopian tubes may be compromised by local inflammation after appendicitis. Fibrosis in and around the ovarian capsule may also play a role. Future studies are needed to delineate the mechanisms involved in detail. In the meantime, decreasing surgical trauma by performing appendectomies using minimally invasive means and early antibiotic treatment of perforated appendicitis may decrease tissue trauma and sequela resulting from the local inflammatory response in the female pelvis.

CONCLUSION

As pediatric surgeons, we often ask ourselves how management affects the later life of our patients. During the course of the past decades, treatment algorithms have changed. Perforated appendicitis with an inflammatory mass in the right lower quadrant is generally treated with broad-spectrum antibiotics followed by possible later interval appendectomy rather than an upfront operation. Currently, protocols using nonoperative antibiotic treatment for simple, acute appendicitis are being compared with the standard operative approach. Our study adds to the ample body of evidence that appendicitis has an impact on adhesion formation and, thus, on female fertility. Therefore, trials evaluating new treatment options for simple or complex appendicitis in children should not only focus on perioperative complications and recurrence rate but also take into account long-term effects on female fertility.

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