

■ Original Article

Is antibiotic therapy necessary after emergency laparoscopic cholecystectomy for acute calculous cholecystitis?

Akut taşlı kolesistitte acil laparoskopik kolesistektomi sonrası antibiyotik tedavisi gerekli mi?

Alpaslan Sahin*¹ , Kemal Arslan² 

¹Department of Surgery, University of Health Science Konya City Hospital

²Department of Surgery, University of Health Science Konya City Hospital

ABSTRACT

Aim: While preoperative antibiotic therapy is standard to prevent surgical site infections in acute calculous cholecystitis, prescribing antibiotics after discharge is controversial. This study aimed to investigate the effect of antibiotic administration in discharge prescription on surgical site infections.

Material and Methods: Data from patients who underwent emergency laparoscopic cholecystectomy for acute calculous cholecystitis between January 2018 and February 2020 were retrospectively reviewed. Those with a decompensated systemic disease, those who were converted to open cholecystectomy, those with stage 3 disease, and those who underwent open cholecystectomy and cholecystostomy were excluded. Ampicillin-sulbactam 1 g was administered parenterally three times a day before and after surgery.

The patients were divided into two groups according to their discharge prescriptions: those who were given antibiotics (AB group) and those who were not given antibiotics (NA group). The primary outcome was the development of surgical site infections.

Results: 107 patients in the AB group and 109 in the NA group. Surgical site infection developed in 29 (13.4%) patients, 11 (10.3%) in the AB group, and 18 (16.5%) in the NA group. No significant difference was found between the two groups regarding surgical site infection rate ($p>0.05$). In logistic regression analysis, obesity was a risk factor for surgical site infections.

Conclusions: Failure to prescribe ampicillin-sulbactam to acute calculous cholecystitis patients discharged after laparoscopic surgery does not increase surgical site infections. However, prescribing ampicillin-sulbactam to obese patients may reduce surgical site infections.

Keywords: Surgical site infections; Acute calculous cholecystitis; Emergency laparoscopic cholecystectomy; Obesity

Corresponding Author*: Alpaslan Sahin, Department of Surgery, University of Health Science Konya City Hospital, 42020 Konya, Türkiye

E-mail: drasahin@gmail.com

ORCID: 0000-0001-5707-1203

DOI: 10.18663/tjcl.1131853

Received: 16.06.2022 Accepted: 02.09.2022

ÖZ

Amaç: Akut taşlı kolesistitte cerrahi alan enfeksiyonlarını önlemek için preoperatif antibiyotik tedavisi standart iken, taburcu olduktan sonra antibiyotik reçete edilmesi tartışmalıdır. Bu çalışmada taburculuk reçetesinde antibiyotik uygulamasının cerrahi alan enfeksiyonlarına etkisinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Ocak 2018 ile Şubat 2020 arasında akut taşlı kolesistit nedeniyle acil laparoskopik kolesistektomi yapılan hastaların verileri geriye dönük olarak gözden geçirildi. Dekompense sistemik hastalığı olanlar, açık kolesistektomiye dönülen vakalar, evre 3 hastalığı olanlar, açık kolesistektomi ve kolesistostomi yapılan hastalar çalışmaya dahil edilmedi. Ampisilin-sulbaktam 1 gr, ameliyattan önce ve sonra günde üç kez parenteral olarak uygulandı.

Hastalar taburculuk reçetelerine göre antibiyotik verilenler (AB grubu) ve antibiyotik verilmeyenler (NA grubu) olmak üzere iki gruba ayrıldı. Birincil sonuç, cerrahi alan enfeksiyonlarının gelişmesiydi.

Bulgular: AB grubunda 107, NA grubunda 109 hasta vardı. Toplam 29 (%13,4) hasta olmak üzere, AB grubunda 11 (%10,3) ve NA grubunda 18 (%16,5) hastada cerrahi alan enfeksiyonu gelişti. Cerrahi alan enfeksiyon oranı açısından iki grup arasında anlamlı fark bulunmadı ($p>0.05$). Lojistik regresyon analizinde obezite cerrahi alan enfeksiyonları için bir risk faktörüydü.

Sonuç: Laparoskopik cerrahi sonrası taburcu edilen akut taşlı kolesistit hastalarına ampisilin-sulbaktam verilmemesi cerrahi alan enfeksiyonlarını artırmaz. Ancak obez hastalara ampisilin-sulbaktam verilmesi cerrahi alan enfeksiyonlarını azaltabilir.

Anahtar Kelimeler: Cerrahi alan enfeksiyonu; Akut taşlı kolesistit; Acil laparoskopik kolesistektomi; Obezite

Introduction

Cholelithiasis is one of the most common diseases of the digestive system and occurs in 10-20% of adults, and its incidence increases with age (1, 2). More than 70% of patients with cholelithiasis have asymptomatic, and the annual rate of symptomatic patients is 5% (3).

The reported mortality of acute cholecystitis, a common serious complication of gallstones, is approximately 3%, but the rate increases with patient age or comorbidity. Acute cholecystitis typically presents with acute right upper quadrant pain after eating, fever, nausea, and right upper quadrant tenderness on physical examination (4,5). If appropriate treatment is delayed, the prognosis may worsen, and complications may develop. The current standard of treatment in acute calculous cholecystitis is early laparoscopic cholecystectomy with appropriate fluid-electrolyte replacement and antibiotics. On the other hand, percutaneous gallbladder drainage can be performed as an alternative for those with the severity of the disease and high operational risk (6-8).

In the United States alone, 300,000 cases of surgical site infection have been reported, and the annual cost is \$10 billion (9,10). Post-discharge antibiotic prescription to prevent surgical site infections in acute calculous cholecystitis is controversial (11, 12). Therefore, this study aimed to investigate the effect of antibiotic administration in discharge prescription on surgical site infections.

Material and Methods

This retrospective study was conducted in the General Surgery Clinic of a tertiary reference hospital between January 2018 and February 2020 and was approved by the University of Health Sciences Hamidiye Scientific Research Ethics Committee (Decision number 2022/16). Written consent was obtained from all patients. This study protocol was created in accordance with the STROBE guidelines. The study is in accordance with the principles of the Declaration of Helsinki. Patients who underwent emergency laparoscopic cholecystectomy for acute calculous cholecystitis were included in the study. Pre-diagnostic criteria for acute cholecystitis were right upper quadrant pain for >4 hours, fever >38°C, right upper quadrant tenderness, mass or Murphy's sign, and leukocytosis (>12,000 cells/mm³). A definitive diagnosis was made with the following ultrasound findings, presence of posterior acoustic shadow stone, gallbladder wall thickness >4 mm, and presence of pericholecystic fluid. The patients were staged according to the Tokyo Guidelines 2013 (TG13) criteria (13). TG13 criteria are presented in Table 1. Patients who did not accept emergency cholecystectomy, those with a decompensated systemic disease, patients who had undergone open cholecystectomy for various reasons such as previous abdominal surgery, those who were converted to open surgery for various reasons such as difficult dissection, and those who underwent cholecystostomy were excluded. Data of 216 patients, 107 in the AB group and 109 in the NA group, were analyzed.

Table 1. Tokyo guidelines severity criteria for acute cholecystitis

Grade I
Acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in gallbladder
Grade II
Acute cholecystitis associated with one of the following conditions: 1. Elevated white blood cell count (>18,000/mm ³) 2. Palpable tender mass in the right upper abdominal quadrant 3. Complaint duration >72 h 4. Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, biliary peritonitis, emphysematous cholecystitis)
Grade III
Acute cholecystitis associated with failure of anyone of the following organs/systems: cardiovascular, neurological, respiratory, renal, hepatic or hematological dysfunction.

The patient's demographic characteristics, body mass index (BMI), American Society of Anesthesiologists (ASA) score, and acute calculous cholecystitis stages according to TG13 criteria and other data were recorded. Obesity was defined as >30 kg/m². Laparoscopic cholecystectomy was performed 12-72 hours after hospitalization. Culture or antibiotic susceptibility test data were unavailable as bile samples were not collected during surgery. According to the 2018 Tokyo guidelines recommendation, Ampicillin-sulbactam 1 g was administered parenterally three times daily before and after surgery. Ampicillin/sulbactam has been recommended as first-line antibiotic therapy in acute cholecystitis (14).

The patients were divided into two groups according to their discharge prescriptions: those who were given antibiotics (AB group) and those who were not given antibiotics (NA group). The prescription of the AB group included ampicillin/sulbactam 1g (7 days). Surgical site infection was defined as superficial and deep/organ site surgical site infections according to the Centers for Disease Control and Prevention (CDC) recommendations (10). The diagnosis of surgical site infection was based on the definition of CDC: (a) purulent drainage from the superficial incision with or without laboratory approval, (b) organisms isolated from the liquid culture aseptically obtained from the superficial incision, (c) the presence of at least one of the following signs of infection: pain, localized swelling, redness, or increased heat. Data including the demographic characteristics and clinical outcomes of the patients were obtained from the hospital medical software, patient follow-up forms, and hospitalization file.

The primary outcome measure was the development of surgical site infection in the operative field or other parts of the body

in the first month post-operatively. Complications other than surgical site infections were considered secondary outcomes. In case of surgical site infection detected by clinical examination and other diagnostic methods (laboratory, ultrasound and tomography), antibiotic treatment in the AB group was changed to cefixime, a third-generation cephalosporin. Superficial and deep surgical site infections were drained locally, while organ site surgical site infections were drained under the guidance of ultrasonography or tomography.

Statistical Analysis

Kolmogorov-Smirnov normality test was performed to test for normality. If normality was not met, the Mann-Whitney U test, a nonparametric test, was used to compare the variables between the two groups. For categorical variables, chi-square and Fisher's exact tests were used to analyze the relationship or difference between the groups. Univariate logistic regression analysis was performed to determine the factors thought to cause surgical site infections. Descriptive statistics were expressed as number (percentage) for qualitative variables and mean \pm standard deviation and median (minimum-maximum) for quantitative variables. Statistical package for the social sciences (SPSS), version 17.0 (SPSS Inc., Chicago, IL, USA) program was used for statistical analysis. A p value <0.05 was accepted as statistically significant.

Results

There were 283 patients with acute calculous cholecystitis; 14 patients who refused emergency laparoscopic cholecystectomy surgery, 5 patients with decompensated systemic disease, 7 patients who underwent open cholecystectomy, 8 patients who were converted to open surgery due to difficult dissection, 8 patients with stage 3 acute calculous cholecystitis and 3 patients who underwent cholecystectomy, were excluded. Therefore, 238 patients with Grade I and Grade II acute calculous cholecystitis who were scheduled for emergency laparoscopic cholecystectomy were included in the study. Fourteen patients refused to follow-up process; thus, 224 patients were included. The patients were divided into two groups according to their discharge prescriptions: those who were given antibiotics (AB group) and those who were not given antibiotics (NA group); however, 5 patients from the AB group and 3 patients from the NA group were excluded during follow-up, due to non-compliance to the treatment process. Thus, 107 (49.5%) patients from the AB group and 109 (50.5%) patients from the NA group were analyzed.

The median age of these 216 patients was 63 years (range, 24-

84 years), and 148 (68.5%) of the patients were females. Baseline characteristics, including demographics and BMI, obesity, ASA score, presence of diabetes mellitus, smoking, duration of surgery, and length of hospital stay. The demographic characteristics of the patients are shown in Table 2.

Table 2. Demographic characteristics

Items	AB Group (n=107)	NA Group (n=109)	P
Age, year	60.83 ± 11.96	62.61 ± 10.93	0.243
Sex (female/male)	74/33	74/35	0.841
BMI	25.74 ± 3.97	25.91 ± 4.24	0.786
Obesity	10 (9.3)	14 (12.8)	0.414
ASA class			
I	5 (4.7)	3 (2.8)	0.605
II	37 (34.6)	36 (33.0)	
III	65 (60.7)	70 (64.2)	
Diabetes Mellitus	18 (16.8)	16 (14.7)	0.666
Smoking	19 (17.8)	17 (15.6)	0.671
Duration of surgery, min	84.02 (24.6)	81.95 (22.12)	0.761
Length of hospital stay, day	2.05 (0.52)	2.06 (0.54)	0.494

Data are presented as mean ± standard deviation or number (%), where appropriate.

A total of 29 patients (13.4%) developed surgical site infections in the postoperative period; 11 patients (10.3%) in the AB group and 18 patients (16.5%) in the NA group. The average time until the development of surgical site infection is 9 days (range, 3-21 days). There were 14 (6.5%) infectious complications other than surgical site infections; 6 in the AB group and 8 in the NA group. The rates of surgical site infections and infectious complications other than surgical site infections were similar in both groups (p>0.05). Superficial surgical site infections were treated with local drainage and antibiotic treatment selected according to the study group. Three patients who developed organ/ space infections in the gallbladder were hospitalized and treated with ultrasound-guided percutaneous drainage without any surgery, and they were all discharged on the fourth day. Antibiotics were administered parenterally to these patients as long as they were hospitalized and continued orally after discharge. Percutaneous drains were removed on the tenth day.

The rate of non-infectious complications were also similar in the two groups; 3 in the AB and 4 in the NA group, (p>0.05). There were no adverse events related to antibiotic treatment. There were no deaths. Table 3 shows the infectious and non-infectious complications in the study groups. Hemostasis was performed in 2 patients with bleeding at the incision site. Acute

erosive gastritis was detected in a patient who applied with upper gastrointestinal bleeding after discharge and healed with conservative treatment. Two patients who developed deep vein thrombosis were treated with medical treatment at the outpatient clinic, and one patient who developed pulmonary embolism was hospitalized in the Chest Diseases department.

Table 3. Postoperative complications

Items	AB Group n=107 n (%)	NA Group n=109 n (%)	P
Infectious complications			
Superficial incisional infections	5 (4.7)	12 (11.0)	0.085
Deep incisional infections	4 (3.7)	5 (4.6)	0.755
Organ/space infections	2 (1.9)	1 (0.9)	0.551
Pneumonia	3 (2.8)	2 (1.8)	0.637
Urinary tract infections	3 (2.8)	6 (5.5)	0.322
Non-infectious complications			
Postoperative hemorrhage	1 (0.9)	1 (0.9)	0.990
Deep venous thrombosis	1 (0.9)	2 (1.8)	0.573
Pulmonary embolism	0 (0)	1 (0.9)	0.322
Gastrointestinal hemorrhage	1 (0.9)	0 (0)	0.313

Table 4. Univariate logistic regression analysis related to the risk factors affecting superficial surgical site infections

Risk factors	OR [95% CI]	p
Not using antibiotics	2.394 [0.776-7.382]	0.129
Sex	0.535 [0.138-2.077]	0.366
Obesity	5.026 [1.600-15.786]	0.006
High ASA (ASA 3-4)	0.792 [0.268-2.344]	0.674
Smoking	1.149 [0.285-4.636]	0.845

OR, Odds ratio; CI, Confidence interval

In univariate logistic regression analysis carried out for risk factors that were thought to affect surgical site infection, obesity was found to be a statistically significant risk factor for superficial surgical site infections (p=0.006).

Discussion

Acute cholecystitis is primarily an inflammatory process, but secondary infection of the gallbladder can occur as a result of cystic duct obstruction and bile stasis (15, 16). The rate of gallbladder empyema and a pericholecystic abscess is overall low, but patients can easily develop life-threatening sepsis. Thus, antibiotics are commonly administered prophylactically to protect against wound infection and sepsis. Infectious Diseases Society of America and Tokyo guidelines recommend antibiotic treatment after early cholecystectomy for acute calculous cholecystitis to eliminate infectious microorganisms, prevent the spread of infection to other systems, and improve infection symptoms (17, 18). Therefore,

antibiotics have become a standard part of the management of acute calculous cholecystitis in most centers. However, the duration of antibiotic therapy after emergency laparoscopic cholecystectomy is questionable (15, 16, 19).

Fuks et al. (15) suggested that all patients with acute cholecystitis should be routinely administered an antibiotic before surgery, but whether antibiotic therapy should be continued after emergency cholecystectomy should be confirmed in a randomized study. According to our results, surgical site infection or other complications were not increased in patients who did not use antibiotics after discharge. The rate of surgical site infections, the length of hospital stay, and the duration of antibiotic use during hospitalization were similar in the two groups. In this study, the mean operation time was 83.05 minutes, and the mean length of hospital stay after the operation was 2.06 days. These results are consistent with the outcomes observed in the previous studies (20).

Regimbeau et al. (11) conducted a randomized study on patients who underwent early cholecystectomy for acute calculous cholecystitis. All patients received an amoxicillin regimen at the time of surgery, and the patients who were randomized to the non-treatment group received no antibiotics. In contrast, those randomized to the treatment group received the same antibiotic regimen thrice daily for five days after surgery. Patients were discharged within five days of surgery and completed oral antibiotic treatment at home. Postoperative infection rates were 17% in the non-treatment group and 15% in the antibiotic group. They reported that the absence of postoperative antibiotic treatment was not associated with a higher incidence of postoperative infectious complications (11). In 2014, Jaafar et al. (21) conducted a retrospective study to assess the effect of antibiotic prophylaxis on postoperative infections in acute cholecystectomy and found no significant benefit. The present study supports these findings in patients with grade 1 and 2 acute calculous cholecystitis.

In our study, obesity was an independent risk factor for surgical site infections in the logistic regression analysis. In other studies, risk analysis for surgical site infection was not performed in emergency laparoscopic cholecystectomy for grade 1 and 2 acute calculous cholecystitis. Obesity is associated with comorbidities, anatomical factors, and adipose tissue, increasing the risk of surgical site infection (22). Adipose tissue regulates various hormones, chemokines, cytokines, inflammation, and oxidative stress (23). In a study by Alanis et al. (24), an increase in surgical site infections was observed in obese pregnant women as BMI increases.

The limitations of our study were that the patients were hospitalized for at least one day and a maximum of postoperative 3 days and used ampicillin-sulbactam parenterally during their hospital stay. In addition, patients who used antibiotics for one day / three days were divided into two groups according to their discharge prescriptions. Therefore, the duration of antibiotic use of the patients was slightly different. Another limitation is the lack of bile sampling; therefore, no culture or antibiotic susceptibility tests could be performed. In addition, the retrospective design of the study was a limitation.

Conclusions

Failure to prescribe ampicillin-sulbactam after discharge in patients who underwent emergency laparoscopic cholecystectomy for grade I and II acute calculous cholecystitis does not cause an increase in the incidence of surgical site infections. However, not using ampicillin-sulbactam after discharge may lead to surgical site infections in obese patients.

Ethics approval

This retrospective study has been approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki (2000).

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

Dr. K. Arslan and Dr. A. Şahin designed the study, Dr. K. Arslan and Dr. A. Şahin acquired the data and wrote the article, Dr. K. Arslan and Dr. A. Şahin reviewed the article. All authors analyzed the data and approved the final version for publication.

Acknowledgments

None

References

1. Fischer JE, ed. *Mastery of surgery*. 5 ed. Philadelphia: Lippincott Williams & Wilkins 2007.
2. Duncan CB, Riall TS. Evidence-based current surgical practice: calculous gallbladder disease. *J Gastrointest Surg* 2012;16: 2011–25.
3. Portincasa P, Moschetta A, Petruzzelli M, Palasciano G, Di Ciaula A, Pezzolla A. Gallstone disease: symptoms and Diagnosis of gallbladder stones. *Best Pract Res Clin Gastroenterol*. 2006;20: 1017–29.

4. Attili AF, Carulli N, Roda E, Barbara B, Capocaccia L, Menotti A, Okoliksanyi L, Ricci G, Capocaccia R, Festi D, et al. Epidemiology of gallstone disease in Italy: prevalence data of the Multicenter Italian Study on Cholelithiasis (M.I.COL.). *Am J Epidemiol.* 1995;141: 158–65.
5. Halldestam I, Enell EL, Kullman E, Borch K. Development of symptoms and complications in individuals with asymptomatic gallstones. *Br J Surg* 2004; 91: 734–738.
6. Haisley KR, Hunter JG. Gallbladder and the Extrahepatic Biliary System. Brunicaardi FC, Andersen DK, Billiar TR, editors. *Schwartz's Principles of Surgery.* Eleventh Edition. New York: Mc Graw Hill;2019. pp. 1405-36.
7. Hunter JG. Acute cholecystitis revisited: get it while it's hot. *Ann Surg.* 1998;227(4):468-469.
8. Ansaloni L, Pisano M, Coccolini F, et al. 2016 WSES guidelines on acute calculous cholecystitis. *World J Emerg Surg.* 2016; 11:25.
9. Anderson DJ, Podgorny K, Berríos-Torres SI, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol.* 2014;35(6):605-627. doi:10.1086/676022
10. Mangram AJ, Horan TC, Pearson ML, et al. (1999) Guideline for Prevention of Surgical Site Infection. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. *Am J Infect Control.* 27(2): 97-132.
11. Regimbeau JM, Fuks D, Pautrat K, Mauvais F, Haccart V, Msika S, et al. Effect of postoperative antibiotic administration on postoperative infection following cholecystectomy for acute calculous cholecystitis: a randomized clinical trial. *JAMA.* 2014;312:145–54.
12. Loozen CS, Kortram K, Kornmann VN, van Ramshorst B, Vlamincx B, Knibbe CA, et al. Randomized clinical trial of extended versus single-dose perioperative antibiotic prophylaxis for acute calculous cholecystitis. *Br J Surg.* 2017;104: 151–7.
13. Yokoe M, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Gomi H, et al. TG13 diagnostic criteria and severity grading of acute cholecystitis (with videos). *J Hepatobiliary Pancreat Sci* 2013; 20: 35–46. DOI: 10.1007/s00534-012-0568-9.
14. Gomi H, Solomkin JS, Schlossberg D, Okamoto K, Takada T, Strasberg SM, et al. Tokyo Guidelines 2018: antimicrobial therapy for acute cholangitis and cholecystitis. *J Hepatobiliary Pancreat Sci* 2018; 25:3–16. DOI: 10.1002/jhbp.518. Epub 2018 Jan 9.
15. Fuks D, Cosse C, Regimbeau JM. Antibiotic therapy in acute calculous cholecystitis. *J Visc Surg* 2013; Feb;150(1):3-8. doi: 10.1016/j.jvisc.2013.01.004.
16. Strasberg SM. Clinical practice. Acute calculous cholecystitis. *N Engl J Med* 2008; 358: 2804.
17. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Surg Infect (Larchmt).* 2010 Feb;11(1):79-109. DOI: 10.1089/sur.2009.9930.
18. Hirota M, Takada T, Kawarada Y, et al. Diagnostic criteria and severity assessment of acute cholecystitis: Tokyo Guidelines. *J Hepatobiliary Pancreat Surg.* 2007;14(1):78-82.
19. Mazeh H, Mizrahi I, Dior U, et al. Role of antibiotic therapy in mild acute calculous cholecystitis: a prospective randomized controlled trial. *World J Surg* 2012; 36:1750-59.
20. Gurusamy K, Samraj K, Gluud C, Wilson E, Davidson BR. Meta-analysis of randomized controlled trials on the safety and effectiveness of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. *Br J Surg.* 2010;97(2):141-150.
21. Jaafar G, Persson G, Svenblad B, Sandblom G. Outcomes of antibiotic prophylaxis in acute cholecystectomy in a population-based gallstone surgery registry. *Br J Surg* 2014;101:69-73. DOI: 10.1002/bjs.9369.
22. Pierpont YN, Dinh TP, Salas RE, et al. Obesity and surgical wound healing: a current review. *ISRN Obes.* 2014; Feb 20;2014:638936. doi: 10.1155/2014/638936.
23. Eming SA, Martin P, Tomic-Canic M. Wound repair and regeneration: mechanisms, signaling, and translation. *Sci Transl Med.* 2014; 6(265):265sr6.
24. Alanis MC, Villers MS, Law TL, Steadman EM, Robinson CJ. Complications of cesarean delivery in the massively obese parturient. *Am J Obstet Gynecol.* 2010;203(3): 271.e1-271.e7.