Malignant disease as a risk factor for surgical site infection

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Summary

Introduction and objective: Postoperative infections are a great constituent of surgical complications. The most common one is surgical site infection (SSI), as well as vaginal and/or urinary tract infections, infections affecting distant organs and systems and systemic circulation leading to sepsis and septic shock. Our aim was to emphasize the effect of malignant disease on postoperative infection and to establish malignant disease as a risk factor for SSI, per se. *Material and Method:* We designed a retrospective study in which 538 women who underwent surgery in the Gynecology and Obstetrics Clinical Center of Serbia during a six-month period in 2009 were analyzed. We collected relevant data regarding SSI incidence (CDC definitions), malignant disease (primary site, type and stage) and other potential risk factors for SSI. We used descriptive statistics, chi-square and Student's t test for comparison of variables with statistical significance at $p < 0.05$. We also used univariate, multivariate logistic regression and ROC analysis. *Results:* Surgical site infection was present in 40 patients (7.5%). Univariate analysis revealed that the following factors were significantly related to SSI: age, malignant disease, stage of malignant disease, surgery longer than 120 min, postmenopause, diabetes mellitus, positive preoperative vaginal culture, ASA score and intraoperative blood loss. Multivariate analysis showed that the most important risk factors that contribute to SSI with RR of 4 and 5 are, respectively, FIGO II and FIGO III/IV stage of malignant disease (FIGO II $p < 0.05$ RR= 4.097; FIGO III/IV < 0.01 RR = 5.061). *Conclusion:* In our study malignant disease erupted as the most important risk factor for SSI. This brings us to question the pathophysiological mechanisms and systemic effects associated with malignant disease. There are few studies discussing the issue of malignancy as an isolated risk factor that 4-5 fold increases the risk of SSIs. It is of utmost interest to define protocols of antimicrobial prophylaxis for gynecological malignancy surgery as are suggested for some other malignancies.

Key words: Surgical site infection; Malignant disease.

Introduction

Postoperative infections are a great constituent of surgical complications. The most common one is surgical site infection (SSI), as well as vaginal and/or urinary tract infections, infections affecting distant organs and systems and systemic circulation leading to sepsis and septic shock. Postoperative infections result in higher morbidity and mortality, increased financial costs and prolonged hospital stay [1, 2]. In the 1990s, patients who developed SSI had longer and costlier hospitalizations than patients who did not develop such infections. They are twice as likely to die, 60% more likely to spend time in an ICU, and more than five times more likely to be readmitted to the hospital [3].

Our aim was to emphasize the effect of malignant disease on postoperative infection and to establish malignant disease as a risk factor for SSI, per se. In a wider sense, we investigated the incidence and other potential risk factors for SSI and tried to contribute to defining a relationship between different factors, especially malignancy, and SSI after surgical therapy of genital tract disease.

Material and Method

We designed retrospective study in which 538 women who underwent surgery in The Clinic for Gynecology and Obstetrics, Clinical Center of Serbia during six months period in 2009 were analyzed. Laparoscopy was performed in another specialized unit and was not included in the study. We used medical records to collect patient demographics and medical status.

For statistical analyses we used descriptive statistics for distribution of variables. Incidence of SSI was compared among groups of patients depending on certain analyzed variables and potential risk factors using inferential statistics: categorical variables were compared using the chi-square test and continuous variables were compared using Student's t-test; statistical significance was defined as $p < 0.05$. Predictors of SSI, overall morbidity, and mortality were analyzed by univariate and multivariate logistic regression with relative risk (RR) and confidence interval (CI) 95%. We also used ROC analysis for evaluation of surgery duration as a potential risk factor, defining cut-off value and calculating sensitivity and specificity.

Results

Average age of this group of 538 women patients was 50 years (SD = 14.01). Indications for surgery were cervical cancer in 9.5%, uterine corporal cancer 4.3%, vulvar cancer 2.6%, ovarian cancer 10.8%, uterine prolapse and other pelvic organ prolapse 12.2%, uterine leiomyoma 24%, benign adnexal tumors 27.7%, premalignant cervical lesions 7.8% and other organ malignancies 0.4%. Pathohistological analysis showed malignant disease FIGO Stage I or border-line in 84 (15.6%) patients, 18 (3.3%) FIGO Stage II, 40 (7.4%) FIGO III and three (0.6%) FIGO IV, while in 347 cases postoperative pathohystology analysis showed benign disease. Premalignant lesions of the cervix and vulva were found in 36 (6.7%), while for ten (1.9%) there were no available data of postoperative pathohistology diagnosis.

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Surgical site infection was present in 40 patients (7.5% of total number of women). In abdominal procedures alone (409 cases), the incidence was 6.1%. Microorganisms as causative agents were isolated from 7.1% cultures of wounds. Most frequent was *Enterococcus spp*. in 2.2% of the total number of wounds. We also isolated methicillin-resistant *Staphylococcus aureus* in five cases and *Acinetobacter* (biggest challenge for antibiotic therapy in our hospital) in three patient cultures. Wound dehiscence was present in seven patients, and other complications found were enterocutaneous fistula, anterior abdominal wall hematoma and three patients were diagnosed with pulmonary embolus. Outcomes were such that out of 538 patients 530 were discharged home from hospital, six underwent repeated surgery in a short postoperative period, and two were diagnosed with pulmonary embolisms and transferred to a clinic for pulmonary disease for further treatment.

In the group of patients with malignant disease, 26 (17.8%) had diagnosed SSI compared to 14 (3.6%) in the group of patients with non-malignant disease - which presented a highly statistical significant difference (x^2 = 30.407, $p < 0.0001$). Distribution of incidence of SSI in benign and different stages of malignant disease of women's genital tract is shown in Table 1. Besides the difference between groups of patients with malignant and non-malignant gynecological disease, a highly statistically significant difference was present among groups of patients in different stages of malignant disease, between the group who had benign/premalignant/FIGO I and those with FIGO II, FIGO III/IV (x^2 = 75,870 $p < 0.0001$). This was regardless of the organ with malignant alteration.

We also recognized a high statistical significance in distribution of SSI between groups of postmenopausal women and those that were not (x^2 = 31.226, $p < 0.0001$). In women who had diagnosed diabetes mellitus postoperative SSI was present in 26.3% and in those without diabetes mellitus in 6.9% which was also highly statistically significant (x^2 = 9.985, $p < 0.01$); there was also a statistically significant difference in those whose preoperative vaginal cultures were positive compared to the ones with no isolates (x^2 = 4.012, $p < 0.05$). Increasing ASA score showed a statistically significant increased occurrence of SSIs in ASA scores 1 through 5, respectively, four (2.4%), 12 (6.5%), seven (8.3%), ten (18.2%), six (28.6%) (x^2= 28.244, $p < 0.0001$).

The average length of surgery in patients without SSI was 84.87 min, while in patients with SSI it was 133.21 min which was a high statistically significant difference (t = 6.184, $p < 0.0001$). Based on ROC analysis (area-0.745, SE = 046, $p < 0.0001$), the chosen cut-off value for the length of surgery was 120 min with sensitivity = 61.5%, specificity = 81.6%.

Results of univariate logistical regression analysis – which we used for determination of predictors of incidence of SSI – are shown in Table 2. The most important predictors were calculated using multivariate analysis including determined predictors of incidence of SSI (Table 2) are shown in Table 3.

Table 1. — *Distribution of surgical site infection (SSI) based on the FIGO stage of malignant disease.*

	NO SSI	SSI
Benign/premalignant lesion		
FIGO Stage I	442 (96.1%)	18 (3.9%)
FIGO Stage II	13 (72.2%)	5 (27.8%)
FIGO Stage III/IV	26 (61.9%)	16 (38.1%)
Total	481 (92.5%)	39 (7.5%)

Table 2. — *Determination of predictors of incidence of SSI.*

Variables	*p*	RR	CI 95%
Age	< 0.0001	1.061	1.035-1.088
Malignant disease	< 0.0001	5.726	2.896-11.321
FIGO Stage II	< 0.0001	9.444	3.093-29.353
FIGO Stage III/IV	< 0.0001	15.111	6.920-32.997
Surgery length > 120 min	< 0.0001	7.442	3.763-14.720
Postmenopause	< 0.0001	7.909	3.428-18.244
Diabetes mellitus	< 0.01	4.837	1.647-14.204
Positive preoperative vaginal culture	< 0.05	2.231	0.999-4.980
ASA score	< 0.0001	1.912	1.462-2.501
Intraoperative blood loss	< 0.001	3.140	1.634-6.036

RR: relative risk; CI: confidence interval.

Table 3. — *Most important predictors of SSI occurrence.*

Risk factor	*p*	RR
FIGO Stage II	< 0.05	4.097
FIGO Stage III/IV	< 0.01	5.061
Postmenopause	< 0.05	3.168
Surgery length > 120 min	< 0.05	2.808
Positive preoperative vaginal culture	< 0.05	2.521

RR: relative risk.

Discussion

Observed surgical site infection (7.5%) was higher than that reported in surveillance studies from developed countries of Western Europe, e.g., the United Kingdom (3.1%) and the Netherlands (4.3%) [5, 6]. Serbia is a country in transition with a significantly lower budget dedicated to public health. Also, our health system is in constant reform and adjustment with systems in developed countries and current medical protocols. The Clinic for Gynecology and Obstetrics, a tertiary level institution is the largest such hospital in Serbia. Nevertheless our data are not easy to compare, since for a period our clinic did not have uniform protocols for prophylactic antimicrobial therapy in accordance with different recommendations that have been used in developed countries for decades [7, 8]. Although, the incidence of SSI that our data show when it comes to gynecologic malignancy was similar to the one reported in the work of Latrakis *et al*. [9].

Univariate analysis revealed that the following factors were significantly related to SSI: age, malignant disease, stage of malignant disease, surgery longer than 120 min, postmenopause, diabetes mellitus, positive preoperative vaginal culture, ASA score, and intraoperative blood loss which are similar to those identified in different studies. Multivariate analysis showed that most important risk factors that contribute to SSI with RR of 4 and 5 were respectively, FIGO II and FIGO III/IV stage of malignant disease. This brings us to a question of immunologic abnormalities associated with malignancy, which have been widely observed through decades [10, 11]. In many instances, it is hard to ascertain whether the immune defect was an early event that led to failure of immune response, including tumor surveillance, or if it arose later, as a paraneoplastic process.

Diminished skin and in vitro T cell activity have been associated with decreased peripheral T lymphocyte counts which may be progressive with malignancy spread. Such observations were made in a variety of tumors originating in the head and neck, skin, breast, colon and pelvis [12, 13]. B cell numbers and antibody responses are relatively spared in most cancers [10].

Several other patient-related characteristics have consistently been identified as risk factors for SSI in well designed studies [14]. These risk factors include: diabetes, obesity, cigarette smoking, systemic corticosteroids or treatment with other immunosuppressive drugs, malnutrition, preoperative nasal carriage or colonization at other sites with *S. aureus,* the presence of a remote focus of infection, duration of preoperative hospitalization and preoperative severity of illness of the patient. There are few studies discussing the issue of malignancy as an isolated risk factor that 4-5 fold increases the risk of SSIs [15]. Many of these patient-related factors such as malignant disease and its stage cannot be altered preoperatively, therefore aiming to strengthen prevention and early detection of malignant tumors contributes to decreasing morbidity and mortality including surgical complications such as SSIs and others. This becomes much more than a standard medical doctrine phrase, keeping in mind the fact that Serbia is the country with the highest incidence of cervical cancer in Europe with 27.2 newly diagnosed patients per 100,000 women per year in central Serbia, compared to 8.1 in the European Union and 15 globally.

The efficacy of antibiotic prophylaxis for reducing surgical SSI has been clearly established. Nevertheless, errors are common, such as shown in the study of 34,133 patients undergoing surgery in centers around the United States, where an antimicrobial was administered within one hour before incision to only 56% of patients, and antimicrobials were discontinued within 24 hours of surgery in only 41% of patients [16]. The 2009 American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin recommends antibiotic prophylaxis prior to the following gynecologic operations or procedures (7): hysterectomy, urogynecology procedures, including those involving mesh, hysterosalpingogram or chromopertubation (only if the patient has a history of pelvic inflammatory disease or the procedure demonstrates dilated fallopian tubes), surgical abortion. Randomized trials have consistently demonstrated the efficacy of antibiotic prophylaxis for vaginal hysterectomy. There is a smaller, but significant, reduction in infectious complications for abdominal hysterectomy [17, 18].

In some recommendations for preparation for gynecologic surgery, malignancy is recognized as a risk factor per se and general recommendations are adjusted for patients with malignant disease. The risk of venous thromboembolism is particularly high in women undergoing surgery for gynecologic cancers, especially ovarian cancer. Combined mechanical and pharmacologic prophylaxis may be necessary for these patients [19, 20]. Our conclusion is that it is of utmost interest to define protocols of antimicrobial prophylaxis for gynecological malignancy surgery as suggested for some other malignancies [21]. Some randomized controlled studies need to be conducted in the future.

The following factors did not show any significant correlation: anemia, positive preoperative cervical culture, emergent surgery and length of preoperative hospital stay.

Limitations of this retrospective study are based on the fact that only data from medical records were available; therefore because of lack of definitions and data we could not analyze factors that in different studies are mentioned as risk factors for SSIs such as obesity [14], malnutrition, protocols of preoperative shaving [7] or class of surgical site, etc. For the same reason, further follow-up data were unavailable for the survey.

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