Factors Associated with Compliance to Guidelines on the Use of Antibiotics and correlated with Clinical Outcomes of Pregnant Women Admitted in the Department of Obstetrics and Gynecology of a Tertiary Hospital from January 1, 2018 to December 31, 2018

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Abstract

Background: Antimicrobial therapy is an integral part of an acceptable clinical practice in Obstetrics and Gynecology. However, in order for these antimicrobials to deliver the desired clinical outcome, the practice of judicious antibiotic stewardship should be observed. The objective of the study was 1.) To determine the proportion of pregnant women admitted at the Department of Obstetrics and Gynecology who received antibiotics from January 1, 2018 to December 31, 2018, 2.) To determine the proportion of indications for antibiotic administration, 3.) To determine if indications for antimicrobial usage is in accordance with the clinical case, policy guidelines, culture results and antibiogram report, 4.) To determine the percentage of cases not given antimicrobials that should have been started on antimicrobial therapy, 5.) To compare the association of the clinical outcomes among patients given and not given antimicrobials, 6.) To compare the association of the immediate neonatal outcomes among pregnant patients given and not given antimicrobials.

Methods: A retrospective cohort study was done covering a period of 1 year from January to December 2018. The study included all pregnant patients who were admitted and listed based from the master list of the Department of Obstetrics and Gynecology. Included are all the retrieval charts from the records sections whereas gynecologic and those cases with medical records not retrieved were excluded. A total of 3,495 obstetrics patients admitted from January to December 2018 were retrospectively studied. From this group, the complete medical records of 1,092 obstetrics patients were retrieved and included in this study. Detailed clinical information, antibiotics administered, diagnostic and other relevant investigations, and clinical outcomes were recorded from case sheets. After the data were collected from patients' medical records, datas were manually entered into an electronic spreadsheet file, and the data processing and analysis were then carried out using statistical software Stata 13.

Results: There were 1,092 women included in the current study with more than half of them administered or received antibiotics as part of their regimen (n = 663, 60.71%) compared to those not administered antibiotics (n = 429, 39.29%). The results showed that the prevalence of obstetric patients (undelivered, delivered, ectopic pregnancy and abortion) prescribed and given antibiotics was between 57.75 to 63.62 per cent. There was no association between the comparison groups in terms of age (χ^2: 3.62, p: 0.31), marital status (χ^2: 1.29, p: 0.26), body mass index classification (χ^2: 6.88, p: 0.08), hemoglobin level (χ^2: 1.74, p: 0.19), and number of prenatal consults (χ^2: 3.13, p: 0.21. There was a significantly higher proportion of women who delivered abdominally that were administered antibiotics (χ^2: 32.45, p<0.01) as compared to

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women who delivered vaginally (spontaneous or assisted), admitted due to ectopic pregnancy, abortion, and medical management. Cephalosporins are the most widely used antibiotics. Cefazolin (60.48%) followed by Cefuroxime (39.97%) were commonly used for pre-operative prophylaxis and urinary tract infection. Other commonly used antibiotics are Clindamycin (3.62%), Ampicillin (3.47%), Amikacin (2.56%), Ceftriaxone (2.11%) and Doxycycline (1.81%). In 803 of cases (74.15%), reason for administration was not recorded in the chart and stated on working impression and final diagnosis. Majority of the antibiotics were empirically given (99.10%). The irrational use of antibiotics among those administered was observed in 564 cases (52.47%) (95% CI: 49.46-55.47%). Rational use was only observed in 99 cases (19.08%). Among those not given antibiotics, 420 cases (80.92%) with adherence to antibiotic guidelines and 9 cases (52.47%) inappropriately not given antibiotics. It can also be noticed that there was an association between administration (and non-administration) of antibiotics – and having an appropriate indication for such action (χ^2: 718.97, $p<0.01$). Maternal and neonatal outcomes showed that there was no noted association between the administration of antibiotics, and selected outcomes. Additional morbidity appeared to be slightly increased among those who were not given antibiotics than otherwise (z: -1.90, p: 0.60).

Conclusion: The study demonstrated that most of the antibiotic administration from January 1 to December 31, 2018

Keywords: Antimicrobial therapy, Antibiotic Stewardship, Resistance, Clinical Guidelines were found to be not compliant to practice guidelines.

INTRODUCTION

Background of the Study

Antimicrobial therapy is an integral part of an acceptable clinical practice in Obstetrics and Gynecology. However, in order for these antimicrobials to deliver the desired clinical outcome, the practice of judicious antibiotic stewardship should be observed. Strict adherence to policy guidelines, evidence-based recommendations, culture studies and the hospital antibiogram should result to appropriate selection, dosing, route and duration of antimicrobial therapy. The decreased inappropriate use of antimicrobials will also limit undesirable outcomes such as emergence of life-threatening resistance, toxicity, prolonged hospital stay and subsequent increased expenditures and human productivity losses. But despite these updated guidelines and recommendations, reports of prevalence and emergence of hard-to-treat resistant bacterial strains remain. Antimicrobial resistance is more prevalent in health-care associated bacterial infections compared with community agents. In a clinical background of poor prevention and control of infections, inappropriate antibiotic use enhances the development and spread of antibiotic genes resulting to or in association of resistant determinants. Despite this fact, the universal threat of antimicrobial resistance is sometimes underestimated. The challenge now in the emergence and prevalence of resistant bacterial strains, especially in resource-limited settings, is the adherence to recommended and updated policies and guidelines. Factors such as the influence of pharmaceutical companies also affects how clinicians prescribe antimicrobials. Another factor is the prospect of litigation which leads to a defensive over-prescription of antibiotics.

There is a need to investigate on the adherence to antibiotic policy guidelines as an evaluation and regulation tool to antimicrobial usage. The desired urgent impact is the optimization of antibiotic therapy in a sustained manner through conscious efforts in observing appropriate selection, dosage, duration and route of antibiotics. Efforts are oriented towards education, activities that encourage and promote consistent practice of antimicrobial stewardship and constant surveillance of antibiotic administration. Overall, the goal, is to have decreased length of hospital stay, broad-spectrum antimicrobial use, antimicrobial costs, and adverse drug events.

Significance

The aim of the study is to provide information on the practice patterns in antibiotic usage and subsequent clinical and neonatal outcomes in the Department of Obstetrics and Gynecology at a tertiary hospital. The clinical and neonatal outcomes are reflective of the appropriateness and effectiveness of antibiotics as to timing, duration, and type of antibiotic regimen.

Knowing the appropriateness and effectiveness of current practices is essential in the improvement of quality patient care. It would motivate clinicians to analyze and alter practice variations that results to morbidity and mortality associated with non-adherence to antibiotic guidelines, culture results and antibiogram reports.

There are no direct benefits but it would intensify surveillance to adherence in recommended policy guidelines. It could lead to implementation of revised protocols designed to address factors that lead to non-adherence to recommendations.

The goal is to optimize and standardize antibiotic use and subsequently reduce rates of antibiotic resistance, hospital expenses, length of hospital stay, avoid adverse drug reactions and toxicity.

Literature Review

The IDSA Guidelines on Institutional Programs to Enhance Antimicrobial Stewardship emphasized the two core strategies that strengthens antimicrobial stewardship. These are prospective audits with direct intervention and feedback between the prescribing clinician and by an infectious specialist and the formulary restriction and preauthorization. Supplements to these two core strategies are education, evidence-based practice guidelines used with correlation with the microbiology and resistance patterns of the hospital, antimicrobial cycling, antimicrobial order

forms, combination therapy, streamlining or de-escalation based on culture results of patients, dose optimization (on the basis of the patient's individual characteristics, causative organisms, site of infection, pharmacokinetics and pharmacodynamic characteristics of the drug), and the parenteral 5oral conversion. The guidelines also emphasized the importance of clinical discretion on the choice of antibiotic therapy and not rely on practice guideline alone.[i]

A study was done by Baysari et al to determine whether the intervention of giving feedback to doctors improves policy adherence. It was concluded that the method did not bring significant change. Issues with policy and the approval process were identified. The study recommended the need for support from senior clinicians, identification of roles and responsibilities in antimicrobial stewardship, and the utilization of technology for antimicrobial approval, monitoring of antibiotic use and compliance. Currently, there is no consensus on which metrics are the most optimal to adequately assess the impact of an antimicrobial stewardship program. Due to the challenges associated with outcomes assessment, most studies to date only focused on measuring the impact of an antimicrobial stewardship program on just one or two metrics, most commonly antimicrobial utilization and costs. The study by Morril et al, provided a detailed assessment of the impact of an antimicrobial stewardship program by measuring and assessing clinical outcomes, antimicrobial utilization, costs, resistance, patient safety, and process metrics. However, this extensive assessment proves to be challenging for some institutions. [iii]

In a prospective study done by Singh et al on the antimicrobial usage in the department of obstetrics and gynecology in a tertiary hospital, a total of 130 out-patient and in-patients were selected in the three-month study. A total of 76.92% of the antimicrobial therapy given were considered rational and in 23.08 % as irrational. The most common obstetrics condition in which antibiotic was prescribed was eclampsia at 23.8%. The other conditions are full term pregnancy in labor, 23%, puerpueral sepsis 14.6%, intrauterine death with previous low transverse cesarean section and diabetes 9.23%, pregnancy-induced hypertension with oligohydramnios 8.43%, 41 weeks with polyhydramnios 7.69%, eight-month amenorrhea with HbsAg carrier with intra-hepatic cholestasis. Beta-lactams were the most commonly prescribed drugs at 47.46% in the following distribution, Ceftriaxone 88%, Cefuroxime 40%, Piperacillin-Tazobactam 22%. Quinolones are the second most commonly prescribed drugs with Levofloxacin at 52% and Ofloxacin at 20%. Amikacin, an aminoglycoside, is the third most commonly prescribed drug at 58%. Metronidazole, a nitroimidazole, came in fourth at 36%. The study only mentioned on the influence of drug companies as one of the factors that influenced the prescribing pattern of clinicians.[iv]

In a study by Shah et al, among 453 patients admitted in the Department of Obstetrics and Gynecology in India, 431 cases were given antimicrobials with an overall incidence of 95.14% which is a very high rate. The high incidence of antimicrobial prescription was due to fear on the part of the clinicians on post-operative infection if antimicrobials were not given. Out of the 431 cases, only 340 cases were able to meet inclusion criteria. And out of the 340 cases, only 42 cases were appropriately given antimicrobials and the remaining cases were inappropriately given. The study noted that ciprofloxacin was the most commonly used antimicrobials (60.90%) followed by ampicillin (54.54%) and metronidazole (39.69%). However, this changes among patients who has to undergo procedures. For patients who underwent low segment cesarean section, it was noted that Metronidazole (92.7%) was the preferred antimicrobial; Ciprofloxacin (97.4%) and Metronidazole (94.8%) in cases of hysterectomy; Ampicillin (66.6%) in cases of normal delivery with episiotomy. It was observed that postoperative infection was 7.6% in cases of hysterectomy and 4.4% in low segment cesarean section. [v]

In another prospective study by Kolasani et al in a rural tertiary care teaching hospital in the south of India, a total of 162 gynecologic in-patients were enrolled. In a duration of one year, an overall total of 1,647 drugs were prescribed. Antimicrobial agents were the most commonly prescribed drugs (35.76%). Metronidazole (oral 17.66%, parenteral 9.68%) was the most commonly prescribed drug followed by Doxicycline (9.68%).[vi]

In a point prevalence surveillance study done by Ylmaz et al, in the Ankara Education and Research Hospital in Turkey, it was noted that out of 422 in-patients included in the study, 153 (36.2%) were given antimicrobials. The reason for admission of the 153 cases given antimicrobials are distributed as follows: elective surgery in 82 cases (53.6%), 44 (28.8%) for medical treatment, and 27 (17.6%) for emergency surgical 7procedures. 64 patients (41.8%) were given antibiotics for treatment and 89 patients (58.2%) were given antibiotics for prophylaxis. Of the 64 patients given antibiotics for treatment, the most frequently used antibiotics were metronidazole (15.5%), third-generation cephalosporins (14.4%) and ampicillin-sulbactam (13.3%). The most frequently used antibiotics for prophylaxis were first-generation cephalosporins (56.9%), ampicillin-sulbactam (11.9%), and ceftriaxone (9.2%). Of the 153 cases given antibiotics, 69 patients (45.7%) were appropriately given antibiotics and 84 patients (54.3%) were inappropriately given. Inappropriate use of antibiotics was more frequent in surgical clinics (62.7%) compared with medical clinics (24.1%). The study noted that the reason for the higher inappropriate use of antibiotics in surgical cases is the lack of infectious disease consultation usually requested in patients admitted in medical clinics. It was also noted that of the 84 cases inappropriately given antibiotics, 75 cases were given treatment or prophylaxis not compatible microbiologically and pharmacologically. And out of the 84 cases not given appropriately, 9 cases were started without an indication. [vii]

In a multicenter point-prevalence study by Usluer et al on the usage of antimicrobial agents in eighteen tertiary care hospitals, the most frequent reason for hospitalization among 9,471 in-patients was due to medical treatment (42.5%), elective surgery (39.6 %), infectious diseases (17.1 %) and emergency surgical procedures (10.4 %). 2,900 patients were given antimicrobials with the highest frequency among surgical cases (81.6%) and medical (55.2.%). Among the 2,900 cases, 48.8 % of antimicrobials were given for treatment and 44.2 % for prophylactic use. Empirical treatment was high at a rate of 78.4%. The infection ratio in the cases appropriately given antimicrobials was 30.7% compared with a 57.9 % in the inappropriately given group. The study observed that majority of the inappropriately given antimicrobials were due to wrong selection of antimicrobial agents and longer duration than indicated.[viii]

Factors contributing to the inappropriate drug prescription in different healthcare institutions may vary. Example of such factors are as follows: incentives from pharmaceutical companies, persuasive drug promotion, belief that a new drug is better than an older established drug, fear of litigation hence a prescription for every complain of a patient and empiric utilization of broad-spectrum antibiotics. In a prospective observational by Hecker et al, the reasons for unnecessary therapy were identified in a two-week period in an adult ward. Of the 129 patients, 30% were considered given antimicrobials inappropriately. In this study, the antimicrobials were given on extended duration than recommended, antibiotics were given for non-infectious causes and finally colonizing and contaminating agents were treated. 35% of the antimicrobials used inappropriately were anaerobic agents.[ix] In an audit done by Aly et al on the adherence to antibiotic policy guidelines, 25% of the irrational antimicrobial use were secondary to inaccurate diagnosis of cases, poor knowledge of policy recommendations, concerns of litigation, fear of complications and sense of self-assurance on the part of the clinician. Organizational obstacles were also noted such as the lack of systems to audit and review antimicrobial usage, inconsistent antibiotic availability, failure to change a familiar ward-popular antibiotic weak triage system, the lack of senior support for junior staff, and the overall delay associated with implementation of policies.[x] In another retrospective audit by Ahiabu in Ghana, issues that were contributory to high inappropriate use of antimicrobials were secondary to the fee-for-service approach in which higher prescriptions meant higher revenues for the facility. Second is the limited use of diagnostic tools resulting to uncertainty of diagnosis, hence, antibiotics were liberally prescribed to cover for all possible infections. Third is the increase in number of patients gaining access to formal health-care services including free drugs due to insurance. This development led to uninhibited prescribing practices by clinicians due to less consideration on the costs to the patients.[xi]

In the choice of empiric antibiotics, specific guidelines, culture and susceptibility studies, and the antibiogram are very important tools in decision-making. Culture and susceptibility studies contributes to the de-escalation of initial broad-spectrum empiric antibiotic by confirming infection and providing the specific causative pathogen/s. The antibiogram on the other hand is utilized as a basis in deciding the selection of antibiotic for empiric treatment since it could give the hospital's rates and patterns of antibiotic resistance to most commonly isolated organisms. It is an essential component then of the of the clinician's decision-making process.

For preoperative surgical prophylaxis both in obstetrics and gynecology, current evidences encourage not only on administration of antibiotic prophylaxis but on the appropriate time as well of administration. However, administration of antibiotics at the appropriate time still proves to be a challenge resulting to postoperative infections. A retrospective cohort study done by Bratzler among 34, 133 women who underwent abdominal and vaginal hysterectomies showed that 55.7% of women were given antibiotic prophylaxis 1 hour prior to incision; 92.6% were consistent with published guidelines and 40.7% were discontinued 24 hours after surgery. The study concluded that there is stillroom for improvement in the practice of antimicrobial prophylaxis administration. [xi]

In a meta-analysis done by Constantine et al, results showed that antibiotic administration preoperatively resulted to significant reduction in the incidence of postpartum endometritis and wound infection. Further, preoperative administration of antibiotics showed no effect with neonatal infection that needed sepsis work-up. [xii]

A prospective randomized, double-blind, placebo-controlled trial by Sullivan et al, enrolled 357 patients who underwent cesarean section. The patients were classified as to those given Cefazolin 15-60 mins prior to incision and to the controls who were given Cefazolin at the time of cord clamping. Significant reduction in infectious morbidity, and endometritis were noted to those given antibiotic prophylaxis prior to skin incision. Neonatal sepsis, work-ups and the length of stay were not noted to be increased nor affected as well. [xiii]

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The principle is to establish adequate concentrations in the serum, tissue and wound before bacterial inoculation on the basis on an antibiotic half-life. (SGOC, Bratzler) The Society of Obstetricians and Gynecologist of Canada Clinical Practice Guideline recommendation on antibiotic prophylaxis in abdominal surgery is the administration of a first generation cephalosporin 15-60 minutes prior to skin incision. Cephalosporins are the surgical antibiotic prophylaxis commonly studied and used.

Broader spectrum antibiotics are avoided to prevent antibiotic resistance development. The first generation Cefazolin has a half-life of 2 hours making it the preferred antibiotic prophylaxis because of the longer protection it can give. It is also a pregnancy category B drug. It exhibits coverage for gram positive organisms. A single dose of 1 gram Cefazolin is effective unless procedure will exceed > 3 hours and if there is presence of blood loss of > 1500 ml. For patients >80 kgs or with a BMI of >35, Cefazolin is increased to 2 grams to avoid giving suboptimal concentration on serum and tissue.[xvxvi]

Overuse of antimicrobials has contributed to the emergence and dissemination of antimicrobial-resistant nosocomial pathogens. Current data regarding patterns of unnecessary antimicrobial use in adult hospitalized patients with a variety of medical and surgical conditions are needed to identify types of misuse that might be amenable to intervention and improve clinical diagnosis, management and finally outcome.

OBJECTIVES

General Objective:

This study aims to review antibiotic practice patterns and the association with clinical outcomes among pregnant women admitted at the Department of Obstetrics and Gynecology in a Tertiary Hospital from January 1, 2018 to December 31, 2018 and evaluate if such patterns are indicated by the clinical case, policy guidelines, culture results and the 2018 antibiogram report.

Specific Objectives:

1. To determine the proportion of pregnant women admitted at the Department of Obstetrics and Gynecology who received antibiotics from January 1, 2018 to December 31, 2018.
2. To determine the proportion of indications for antibiotic administration among women admitted at the Department of Obstetrics and Gynecology who received antibiotics from January 1, 2018 to December 31, 2018.
3. To determine if indications for antimicrobial usage is in accordance with the clinical case, policy guidelines, culture results and antibiogram report.
4. To determine the percentage of cases not given antimicrobials that should have been started on antimicrobial therapy in accordance with the clinical case, policy guidelines, culture results, and antibiogram reports?
5. To compare the association of the clinical outcomes among patients given and not given antimicrobials.
6. To compare the association of the immediate neonatal outcomes among pregnant patients given and not given antimicrobials.

METHODOLOGY

Study Design:

A retrospective cohort study whose duration would span from January to December 2018 and would include all pregnant patients who were admitted and listed based from the master list of the Department of Obstetrics and Gynecology will be used for the initial listing of patients. Clinical Information and screening results will be recorded from case sheets.

Sampling Plan

The study will include all service (charity) patients admitted at Philippine General Hospital who were pregnant between the said study period, and without the exclusion criteria (i.e. not pregnant during the period of data collection) needed for the study.

Based on the review of the annual reports submitted to the department annually, about 3,495 obstetrics patients were admitted just last year, making the Philippine General Hospital, Department of Obstetrics and Gynecology a big tertiary hospital with diverse infectious and non-infectious cases utilizing antimicrobial agents for varied indications. Thus, it is an excellent study site for evaluating antimicrobial usage pattern. Being a training hospital involved in research and utilization of evidence-based guidelines, it is an institution as well that is familiar with the importance of antimicrobial stewardship programs.

Despite the large number of women for inclusion, there are limited cases for the outcomes and no reliable, regular data about these outcomes – as such all eligible pregnant participants will be included in the study.

Sample Size

As previously mentioned, the study population was estimated to be around 3,495 women based on average census of the OB-Admitting Section in 2018. However, the minimum sample size was computed based on a power of 20%, a level of confidence set at 95%, with a hypothesized proportion of women who had received inappropriate antibiotics at 23.08% based on the study by Singh, et al (2017), and an estimated design effect at 3.0 considering for multi-level stratification based on their management during gravidity. The computed sample size was a need for at least 952 women in the current study - but an additional oversampling of 15% was included to account for incomplete data. An additional oversampling of 15% was included to account for incomplete data – resulting to a minimum sample of at least 1,120 women – 840 who delivered vaginally or abdominally, 140 women who were

managed for ectopic pregnancy; and 140 women who were managed in the institution while still pregnant.

Data Collection and Processing Plan

Initial listing based from the master list of the Department of Obstetrics and Gynecology will be done. A research assistant will collect data. The department of Obstetrics and Gynecology will give authority for access to medical records. Without the exclusion criteria, the study will include all service (charity) patients admitted at the Philippine General Hospital who were pregnant between the said study period. Only clinical information required for answering the research questions will be taken. Identifying data will be removed before usage and analysis. Data gathered will be coded. Data collected will be seen by the researchers and members of the regulatory board only. Clinical information and screening results will be recorded from case sheets. Data collected will be manually entered into an electronic spreadsheet file, and the data processing and analysis will be carried out using Statistical Software Stata 13.

Data Analysis Plan

In order to provide an overview of the study population, descriptive statistics such as mean, standard deviation, median and range will be used for numerical data variables, while frequency or percentage will be used for categorical variables.

A z-test of proportions and a Chi-square test of association, or Fisher's exact test, whichever is applicable, will be used to determine if differences in the proportions of women who were given or not given antibiotics; and those who were appropriately or inappropriately given antibiotic for certain disease conditions.

Proportion per categories of the qualitative variables such as those given antibiotics – and those who were given antimicrobials appropriately or otherwise; delivered vaginally or abdominally – will also be described. Point and interval estimates of these proportions for those who have the outcomes will also be determined.

The level of significance for all sets of analysis was set at a p-value less than 0.05 using two-tailed comparisons. Significance levels will be adjusted for multiple comparisons performed, if necessary.

Inclusion Criteria:
All retrieval charts from the records sections admitted at the department from January 1, 2018 to December 31, 2018

Exclusion Criteria
Non-pregnant
Incomplete charts (without OB sheet, etc)

Operational Terms

Antimicrobial Stewardship - Selection of antimicrobials with the least collateral damage to improve the quality of patient care, Clinical outcomes and stabilize rates of resistance through proper selection of drugs, dosing, duration, frequency and route.

Appropriate Use of antimicrobial therapy - When the selection, dose, route of administration, frequency and duration of antibiotic prescribed is according to the clinical case, policy guidelines, microbiological culture and sensitivity and antibiogram results.

Inappropriate Use of antimicrobial therapy - When the selection, dose, route of administration, frequency and duration antibiotic prescribed is not according to the clinical case, policy guidelines, microbiological culture and sensitivity and antibiogram results.

Antibiogram - refers to a cumulative summary of in vitro antimicrobial susceptibility test results obtained with bacteria and/or fungi recovered from patients with infection over a defined period of time in a given healthcare setting.

Improved - resolution of signs and symptoms leading to discharge from hospital.

Morbidity - presence of complications and worsening of condition.

Mortality - death.

Prolonged Hospital Stay - admission date to time of discharge is more than 5 days.
Adverse Drug Reactions - presence of rashes, jaundice, anemia, decreased white cell count etc as a result of drug administration.

Antibiotic Prophylaxis - prevent infection; intended for elective procedures when the incision will be closed in the operating room.

Anemia - Hemoglobin <11.0 g/dl on the first and 3rd Trimester. Hemoglobin < 10.5 g/dl on 2nd trimester.

Sepsis – clinical syndrome that has physiologic, biologic, and biochemical abnormalities caused by dysregulated inflammatory response to infection. Sepsis and the inflammatory response that ensues can lead to multiple organ dysfunction syndrome and death.

Urinary Tract Infection

Asymptomatic Bacteriuria - It is defined as two consecutive voided urine specimens with isolation of the same bacterial strain in quantitative counts >100,000 cfu/ml. A single catheterized urine specimen with one bacterial species isolated in a quantitative count >100 cfu/ml identifies bacteriuria. Significant pyuria (>10 wbc/hpf) or a positive gram stain of unspun urine (>2 microorganisms/oif) in two consecutive midstream urine samples can be used to screen for asymptomatic bacteriuria in facilities where urine culture and sensitivity is not available.

Acute Uncomplicated Cystitis - It is characterized by urinary frequency, urgency, dysuria and bacteriuria without fever and costovertebral angle tenderness. Gross hematuria may also be present. Diagnosed using urine culture and sensitivity tests of a midstream clean-catch urine specimen. In the absence of urine culture, laboratory criteria for the diagnosis of acute cystitis are as follows: presence of significant pyuria on urinalysis defined as, >8 pus cells/mm3 of uncentrifuged urine, or >5 pus cells/hpf of centrifuged urine, a positive leukocyte esterase and nitrite test on dipstick.

Acute Uncomplicated Pyelonephritis - The presence of classic syndrome of fever (T >38 C), chills, flank pain, costovertebral angle tenderness, nausea and vomiting, with or without signs and symptoms of lower urinary tract infection.

Complicated UTI - It is defined as significant bacteriuria plus clinical signs and symptoms which occur in the setting of functional or anatomic abnormalities of the urinary tract or kidneys, presence of an underlying disease that interferes with host defense mechanisms, any condition that increases the risk of acquiring persistent infection and/or treatment failure such as obstructive uropathy due to carcinoma, bladder outlet obstruction urethral or ureteric strictures, tumor, calculi etc. The cut-off for significant bacteriuria is 100,000 18 cfu/ml. And in catheterized patients, low-level bacteriuria or counts <100,000 cfu/ml maybe significant.

Community Acquired Pneumonia - Clinical diagnosis includes new lung infiltrate plus clinical evidence that the infiltrate is of infectious in origin, new onset fever, purulent sputum, leukocytosis, decline in oxygenation.

PID - Clinical and diagnostic criteria include the following minimum criteria: cervical motion tenderness, uterine tenderness, and adnexal tenderness.

Additional criteria which supports the diagnosis of pelvic inflammatory disease include, oral temperature higher than 101 fahrenheit/38.3 degrees celsius, abnormal vaginal or cervical discharge, white blood cells on saline (>10 polymorphonuclear leukocytes per high-power field), elevated erythrocyte sedimentation rate (>15 mm/h), elevated C-reactive protein, elevated white blood cell count >10,000 cells/ml, and laboratory evidence of Neisseria gonorrhea or chlamydia trachomatis.

Definitive criteria which confirm the diagnosis of pelvic inflammatory disease includes a histopathologic evidence of endometritis, imaging showing thickened, fluid-filled tubes, with or without pelvic free fluid or tubo-ovarian complex, doppler studies suggesting pelvic infection, intra-abdominal findings consistent with pelvic inflammatory disease on laparoscopy.

Intraamnionic Infection - Any pregnancy at the age of viability with fever 38 C lasting at least one hour, or one episode of fever greater than or equal to 38.3 C with a history of at least one of the following: Ruptured bag of waters, prolonged labor, multiple internal examinations plus at least 2 of the following criteria: Uterine pain, offensive-smelling vaginal discharge, maternal tachycardia (>100/min), fetal tachycardia (>160/min), maternal leukocytosis, uterine fundal tenderness, inflammation of the placenta, membranes or umbilical cord (funisitis) upon histopathologic exam.

Endometritis – refers to the infection of the decidua which may extend to the myometrium and parametria; common cause of postpartum febrile morbidity (oral temperature of>38 C on any of the first 10 days postpartum, exclusive of the first 24 hours.

Surgical Site Infection – infection occurring within 30 days operatively in one of 3 locations: superficial at the incision site; deep at the incision site or in other organs or spaces opened or manipulated during an operation.

Septic Abortion - spontaneous or induced, complicated by infection ranging from focal involvement of the endometrial cavity or its contents or both, with or without the involvement of the uterus and its appendages.

Ethical Considerations

The information that we will collect from this research will be kept confidential as per mandate of the RA 10173, Data Privacy Act of 2012. The two important ethical issues related to chart reviews are informed consent, patient privacy and data confidentiality.

The nature of the study and the questions would cause minimal harm should confidentiality or anonymity be breached. Unless required by law, confidentiality of information will be practiced at all times. Only clinical information will be used for the analysis. Specific information linking to individuals shall not be released. Only information required for answering the research questions will be taken to avoid risk of release of information or possibility of misuse that can expose patients to possible harm or social stigma. Identifying data will be removed before usage and analysis. Data gathered will be coded. Data collected will be seen by the researchers and members of the regulatory board only. Such steps will be instructed to research assistants as well. In case of breach of privacy, it will be reported to the PGH Data Privacy Officer.

Since data collected and stored in medical records were not done with the explicit intention of further use in research, there is no a-priori informed consent for the use of data in chart reviews. Due to the retrospective nature of the study, informed consent is considered as unnecessary since it cannot be carried out, absence of patient interaction, history-taking and physical examination. Confidentiality and anonymity of individuals and their data will be observed. In accordance with the National Ethical Guidelines of Health and Health Related Research 2017, a waiver of informed consent will be requested from the UPMREB panel because the study presents only with minimal risk which does not adversely affects the rights and welfare of those included in the study. The study has no conflict of interest to declare.

RESULTS AND DISCUSSION

There were 1,092 women included in the current study with more than half of them administered or received antibiotics as part of their regimen (n = 663, 60.71%) compared to those not administered antibiotics (n = 429, 39.29%) as shown in Table 1. The results showed that the prevalence of obstetric patients (undelivered, delivered, ectopic pregnancy and abortion) prescribed and given antibiotics was between 57.75 to 63.62 per cent. The highest proportions of obstetrics cases administered with antibiotics are the following: age group of 18-30 years (n=418, 63%), single (n=426, 64.25%), gravida 1-3 (n=534, 80.54%), high school level (n=376, 56.71%), overweight (n=232, 34.99%), length of hospital stay 4-6 days (n=342, 51.58%), underwent cesarean delivery (n=312, 47.06%), normal hemoglobin levels (n=624, 94.12%), with 4-6 prenatal visits (n=309, 46.96%) at a local health center (n=356, 54.35%). There was no association between the comparison groups in terms of age (χ^2: 3.62, p: 0.31), marital status (χ^2: 1.29, p: 0.26), body mass index classification (χ^2: 6.88, p: 0.08), hemoglobin level (χ^2: 1.74, p: 0.19), and number of prenatal consults (χ^2: 3.13, p: 0.21. It can be observed that patients who reached elementary level significantly has a higher proportion of women who were not given antibiotics (χ^2: 7.10, p: 0.03). There was a slightly higher proportion of women who were not given antibiotics among those who have shorter and longer duration of hospital stay, as compared to those who were admitted within four to six days (χ^2: 7.43, p: 0.02). There was a significantly higher proportion of women who delivered abdominally that were administered antibiotics (χ^2: 32.45, p<0.01) as compared to women who delivered vaginally (spontaneous or assisted), admitted due to ectopic pregnancy, abortion, and medical management. There was a noted association between administration of antibiotics among those women who were seen at the health center and in the hospital (χ^2: 10.71, p<0.01), but there was no noted difference among those with prenatal consultations from the lying-in clinics.

Table 1. Socio-demographic Characteristics of the Study Population

Variables	Overall	Received Antibiotics	Did not Receive	p-value
Number (%)		663 (60.71%)	429 (39.29%)	
Age in years				
15-17 years	62 (5.68%)	33 (4.98%)	33 (4.98%)	
18-30 years	668 (61.17%)	418 (63.05%)	250 (58.28%)	0.31
30-45 years	355 (32.51%)	207 (31.22%)	148 (34.50%)	
46-50 years	7 (0.64%)	5 (0.75%)	2 (0.47%)	
Marital Status				
Single	716 (65.57%)	426 (64.25%)	290 (67.60%)	0.26
Married	376 (34.43%)	237 (35.75%)	139 (32.40%)	
Gravidity				
G1-3	865 (79.21%)	534 (80.54%)	331 (77.16%)	
G4-6	197 (18.04%)	116 (17.50%)	81 (18.88%)	0.11
G7 and up	30 (2.75%)	13 (1.96%)	17 (3.96%)	
Educational Level				
Elementary	113 (10.35%)	58 (8.75%)	55 (12.82%)	
High school	627 (57.42%)	376 (56.71%)	251 (58.51%)	0.03*
Vocational/College	352 (32.23%)	229 (34.54%)	123 (28.67%)	
BMI Category				
Normal	368 (33.76%)	212 (31.98%)	156 (36.53%)	
Underweight	140 (12.84%)	81 (12.22%)	59 (13.82%)	0.08
Overweight	380 (34.86%)	232 (34.99%)	148 (34.66%)	
Obese	202 (18.53%)	138 (20.81%)	64 (14.99%)	
Duration of Confinement				
1-3 days	402 (36.81%)	232 (34.99%)	170 (39.63%)	
4-6 days	528 (48.35%)	342 (51.58%)	186 (43.36%)	0.02*
7 or more days	162 (14.84%)	89 (13.42%)	73 (17.02%)	
Mode of Delivery				
Spontaneous vaginal	530 (48.53%)	288 (43.44%)	242 (56.41%)	
Caesarean section	442 (40.48%)	312 (47.06%)	130 (30.30%)	<0.01*
Vacuum-assisted	89 (8.15%)	50 (7.54%)	39 (9.09%)	
Others	31 (2.84%)	13 (1.96%)	18 (4.20%)	
Hemoglobin Level				
Normal	1019 (93.32%)	624 (94.12%)	395 (92.07%)	0.19
Anemic	73 (6.68%)	39 (5.88%)	34 (7.93%)	
Number of Prenatal Visits				
1-3 visits	158 (14.56%)	100 (15.20%)	58 (13.58%)	
4-6 visits	533 (49.12%)	309 (46.96%)	224 (52.46%)	0.21
7 or more visits	394 (36.31%)	249 (37.84%)	145 (33.96%)	
Health Care Facility				
Health center	627 (57.95%)	356 (54.35%)	271 (63.47%)	<0.01*
Lying-in clinic	198 (18.30%)	123 (18.78%)	75 (17.56%)	
Hospital	257 (23.75%)	176 (26.87%)	81 (18.97%)	

Table 2 showed that Cephalosporins are the most widely used antibiotics by the Department of Obstetrics and Gynecology. Cefazolin (60.48%) followed by Cefuroxime (39.97%) were commonly used for pre-operative prophylaxis and urinary tract infection (based on pyuria or bacteriuria in urinalysis) respectively. Other commonly used antibiotics are Clindamycin (3.62%), Ampicillin (3.47%), Amikacin (2.56%), Ceftriaxone (2.11%) and Doxycycline (1.81%). Majority of the antibiotics were administered as monotherapy (80.39%) through intravenous route (54.15%) vs oral route (45.85%).

Table 2 also showed that administration of antibiotic were commonly given for pre-operative prophylaxis (69.98%) and asymptomatic urinary tract infection diagnosed through pyuria and bacteriuria in urinalysis collected at the admitting section. Other reasons for antibiotic administration were for suspected intra-amnionic infection (3.02%), abortion (0.75%), endometritis (0.60%), ectopic pregnancy (1.51%). In 803 of cases (74.15%), reason for administration was not recorded in the chart and stated on working impression and final diagnosis. Majority of the antibiotics were empirically given (99.10%).

In an unpublished study by Angelo et al on the practice of antibiotic prophylaxis in the same institution, a total of 855 cases who underwent cesarean were reviewed. Cefazolin 1 to 2 grams IV was the prophylactic antibiotic used in 98.71% of cases but only 26.76% of cases were appropriate timing of administration was done. The same findings were noted in this study wherein majority of the pre-operative prophylaxis where given after cutting of incision. Ideally, pre-operative prophylaxis should be given 15-60 minutes prior to skin incision.

Clindamycin, Amikacin and Ampicillin were commonly used for suspected intra-amnionic infection and few cases of endometritis. Irrational use were commonly due to lack of basis for the suspected intraamnionic infection and continuation of antibiotics for more than 48 hours with oral step-down antibiotics to complete 7 days despite having clinical improvement and not culture-guided. In an unpublished study by Taladtad et al in the same institution as this study, 203 cases of intraamnionic infection from January 31, 2018 were reviewed. Fever which remains to be the cardinal manifestation of IAI was not apparent. Only 75 cases (55.15%) presented with fever. Recent recommendations no longer included uterine tenderness as a clinical criterion but in this study, it was noted that this was the most common symptom present as basis for the diagnosis of IAI. Thirteen percent were diagnosed with closed cervix and intact membranes. And of the 74 cases (54.41%) with biopsy of the placenta, only 29 cases (39.2%) were noted to have histopathologic findings consistent with chorioamnionitis and funisitis.

Majority of obstetrics cases who delivered either vaginally or abdominally were given home medications of Cefuroxime 500 mgs BID x 7 days for pyuria and bacteriuria in urinalysis collected at the admitting section. Patients were asymptomatic and no gram stain or culture studies were requested and noted in charts. The reason was not stated on records and on working impression and final diagnosis.

There were however, cases of third degree to fourth degree perineal lacerations who were not given the recommended antibiotic regimens for such cases.

All cases of ectopic pregnancy were administered pre-operatively with Ceftriaxone 2 grams as a single dose and given oral Doxicycline 100 mgs BID for two weeks. There are no guidelines for antibiotic prophylaxis for ectopic pregnancy but not all cases are due to PID.

Table 2. Distribution of Administration of Antibiotics Across Disease Conditions

Variables	Frequency	Percentage
Type of Antibiotics		
Amikacin	17	2.56
Ampicillin	23	3.47
Ampicillin-sulbactam	5	0.75
Amoxicillin	7	1.06
Azithromycin	3	0.45
Doxycycline	12	1.81
Cefuroxime	265	39.97
Cefazolin	401	60.48
Ceftriaxone	14	2.11
Cefoxitin	9	1.36
Clindamycin	24	3.62
Co-amoxiclav	2	0.30
Erythromycin	8	1.21
Gentamycin	10	1.51
Levofloxacin	2	0.30
Metronidazole	7	1.06
Penicillin G	4	0.60

Variables	Frequency	Percentage
Number of Agents		
Single	533	80.39
Multiple	130	19.61
Two-agents	110	16.59
Three-agents	20	3.02
Route of Antibiotics		
Oral route	304	45.85
Intravenous only	359	54.15
Reason Provided		
Yes	280	25.85
No	803	74.15
Indications		
Prophylaxis	464	69.98
Urinary tract infection	253	38.16
Intra-amniotic infection	20	3.02
Endometritis	4	0.60
Abortion	5	0.75
Ectopic pregnancy	10	1.51
Empirical	657	99.10
Targeted	6	0.90

Table 3 showed that the irrational use of antibiotics among those administered was observed in 564 cases (52.47%) (95% CI: 49.46-55.47%) – which is higher than the estimate by Singh, et al (2017). Rational use was only observed in 99 cases (19.08%). Among those not given antibiotics, 420 cases (80.92%) with adherence to antibiotic guidelines and 9 cases (52.47%) inappropriately not given antibiotics. It can also be noticed that there was an association between administration (and non-administration) of antibiotics – and having an appropriate indication for such action (χ^2: 718.97, p<0.01).

Table 3. Distribution of Rationality of Antibiotic Use

Given Antibiotics	Overall	Rational	Irrational
Yes	663 (60.71%)	99 (19.08%)	564 (98.43%)
No	429 (39.29%)	420 (80.92%)	9 (1.57%)
Total		519 (47.53%)	573 (52.47%)

Table 4 showed that there were 2 cases (0.30%) of adverse drug reaction among those administered with antibiotics. It can be noted that additional morbidity appeared to be slightly increased among those who were not given antibiotics than otherwise (z: -1.90, p: 0.60) (Table 4). The highest proportions among neonates whose mothers were administered with antibiotics are the following: Birthweight of 2501-3000 grams (n=259, 40.475%), term (n=471, 73.71%), appropriate for gestational age pediatric aging (n=589, 92.18%), good 1st minute APGAR (n=593, 93.09%), good 5th minute APGAR (n=626, 98.27%), direct room-in (n=496, 77.99%), neonatal pneumonia (n=50, 7.86%). The summary of the maternal and neonatal outcomes (Table 4) showed that there was no noted association between the administration of antibiotics, and selected outcomes. These outcomes specifically are: birth weight (χ^2: 1.47, p: 0.83), gestational age (χ^2: 0.64, p: 0.73), pediatric aging category (χ^2: 2.03, p: 0.36), 1st minute Apgar score (χ^2: 1.19, p: 0.28), 5th minute Apgar score (χ^2: 0.38, p: 0.54), neonatal disposition (χ^2: 1.21, p: 0.55), neonatal sepsis (z: -0.43, p: 0.67), pneumonia (z: 0.99, p: 0.32); and mortality (χ^2: 1.49, p: 0.22).

Table 4. Distribution of Clinical Outcomes across Administration of Antibiotics

	Received Antibiotics	Did not Receive	p-value
Maternal Outcomes			
Adverse drug reaction	2 (0.30%)	-	-
Additional morbidity	1 (0.16%)	4 (1%)	0.06
Birth weight			
1500-2000 g	54 (8.44%)	36 (8.93%)	
2001-2500 g	86 (13.44%)	63 (15.63%)	
2501-3000 g	259 (40.47%)	156 (38.71%)	0.83
3001-3500 g	182 (28.44%)	108 (26.80%)	
>3500 g	59 (9.22%)	40 (9.93%)	
Birthweight Category			
Normal	500 (78.13%)	304 (75.43%)	0.31
Low birthweight	140 (21.88%)	99 (24.57%)	
Age of Gestation			
Term	471 (73.71%)	296 (73.45%)	
Pre-term	110 (17.21%)	65 (16.13%)	0.73
Post-term	58 (9.08%)	42 (10.42%)	
Pediatric Aging Category			
SGA	32 (5.01%)	16 (3.97%)	
AGA	589 (92.18%)	370 (91.81%)	0.36
LGA	18 (2.82%)	17 (4.22%)	
1st minute Apgar			
Good	593 (93.09%)	381 (94.78%)	0.28
Poor	44 (6.91%)	21 (5.22%)	
5th minute Apgar			
Good	626 (98.27%)	397 (98.76%)	0.54
Poor	11 (1.73%)	5 (1.24%)	
Neonatal Disposition			
Direct Rooming-in	496 (77.99%)	317 (78.86%)	
High Risk - DRI	33 (5.19%)	15 (3.73%)	0.55
Neonatal ICU	107 (16.82%)	70 (17.41%)	
Neonatal Outcomes			
Sepsis	43 (6.76%)	30 (7.46%)	0.67
Pneumonia	50 (7.86%)	25 (6.22%)	0.32
Mortality	8 (1.26%)	2 (0.50%)	0.22

Table 5 showed that the highest proportions among neonates whose mothers were irrationally administered with antibiotics are the following: Normal birthweight (n=428, 77.40%), term (n=404, 73.19%), appropriate for gestational age pediatric aging (n=507, 92.85%), good 1st minute APGAR (n=514, 93.45%), good 5th minute APGAR (n=541, 98.36%), direct room-in (n=422, 76.87%), neonatal pneumonia (n=40, 6.98%).

Table 5. Distribution of Clinical Outcomes across Administration of Antibiotics

	Irrational	Rational	p-value
Maternal Outcomes			
Adverse drug reaction	2 (0.35%)	-	0.18
Additional morbidity	4 (0.70%)	1 (0.36%)	0.76
Birthweight Category			
Normal	428 (77.40%)	376 (76.73%)	0.80
Low birthweight	125 (22.60%)	114 (23.27%)	
Age of Gestation			
Term	404 (73.19%)	363 (74.08%)	
Pre-term	97 (17.57%)	78 (15.92%)	0.74
Post-term	51 (9.24%)	49 (10%)	
Pediatric Aging Category			
SGA	30 (3.67%)	18 (3.67%)	
AGA	507 (91.85%)	452 (92.24%)	0.20
LGA	15 (2.72%)	20 (4.08%)	
1st minute Apgar			
Good	514 (93.45%)	460 (94.07%)	0.68
Poor	36 (6.55%)	29 (5.93%)	
5th minute Apgar			
Good	541 (98.36%)	482 (98.57%)	0.79
Poor	9 (1.64%)	7 (1.43%)	
Neonatal Disposition			
Direct Rooming-in	422 (76.87%)	391 (79.96%)	
High Risk - DRI	30 (5.46%)	18 (3.68%)	0.31
Neonatal ICU	97 (17.67%)	80 (16.36%)	
Neonatal Outcomes			
Sepsis	37 (6.46%)	36 (6.94%)	0.75
Pneumonia	40 (6.98%)	35 (6.74%)	0.87
Mortality	7 (1.22%)	3 (0.58%)	0.26

CONCLUSION

More than half of obstetrics patients admitted from January 1, 2018 to December 31, 2018 were administered with antibiotics. Most of the obstetrics patients administered with antibiotics were 18-30 years old, single, gravida 1-3, high school educational attainment, overweight, stayed at the hospital for 4-6 days, underwent cesarean delivery, with normal hemoglobin levels, had 4-6 prenatal consultations at a local health center. There was no association between the comparison groups in terms of age, marital status, body mass index, hemoglobin levels, and number of prenatal consultations. Significantly, a high proportion of obstetrics patients who reached only elementary level were not given antibiotics. It was also observed significantly that antibiotic administration has a higher proportion among those admitted and underwent cesarean section as compared to being admitted for vaginal delivery, ectopic pregnancy, abortion and medical management. And significant association was also noted between administration of antibiotics among women who were seen at the health center and in the hospital. There was no noted difference among those with prenatal consultations from the lying-in clinics. Cephalosporins, specifically, Cefazolin and Cefuroxime, were the antibiotics commonly used in the Department of Obstetrics and Gynecology for pre-operative prophylaxis and urinary tract infection respectively. Majority of antibiotics administered were empirically given through the IV route and as monotherapy. Reasons and indications for administration were commonly not in records. The study concluded that majority of antibiotic usage was irrational. Maternal and neonatal outcomes showed that there was no noted association between the administration of antibiotics and the selected outcomes.

LIMITATIONS

Because the study is a retrospective design, it will be limited by the information gathered only on the patient's records. These records may not be recorded reliably, incomplete with patient's data, diagnostics and radiologic results. Reasons for administration and failure to receive antimicrobial therapy may not be stated and postoperative complications such as surgical site infections, postpartum endometritis, etc. that occurred days after discharge may not be included.

RECOMMENDATIONS

We highly recommend that the same study be done prospectively either on a combined or separate obstetrics and gynecologic admissions, and to include all patients classified as morbidity and mortality. A separate prospective study among those given antibiotic prophylaxis with out-patient follow-up is highly recommended. A prospective study on all ectopic pregnancy and prevalence of

gonococcal infection is also recommended. The judicious follow-up on the gram stain and culture results should be observed. Updated antibiotic guidelines should be placed on the different sections of the Department of Obstetrics and Gynecology (admitting section, labor room, delivery room, operating room, out-patient and at the wards). An updated manual for guidelines on antibiotic usage and case protocols in the setting of the institution should also be done. Continuation of antibiotic audit weekly by the infectious team should also be constant.

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