STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN:

LAPAROSCOPIC TREATMENT FOR APPENDICITIS DURING PREGNANCY: RETROSPECTIVE COHORT STUDY

Database construction and analysis and study protocol were authorized by the Institutional Evaluation Committee under N° B20-010 and P20-070

30/01/2021

Introduction:

Acute abdomen in pregnancy (AAP) represents a diagnostic and therapeutic challenge due to its multiple obstetric and non-obstetric causes, as well as the anatomical and physiological changes that occur during pregnancy, alterations in usual laboratory parameters and the reluctance to use diagnostic modalities such as radiography and tomography[i] [ii].

Accurate and timely diagnosis and treatment decrease maternal and foetal morbidity and mortality[iii].

Acute appendicitis is the most frequent non-obstetric surgical emergency during pregnancy, with an incidence between 0.04% - 0.2%[iv] [v]. Although it can occur at any time during pregnancy, the incidence is higher in the second trimester. It is the most common cause of non-obstetric surgical procedures performed during pregnancy, representing 25%[vi].

Other non-obstetric causes of AAP include cholecystitis, ovarian torsion, splenic disorders, symptomatic hernias, complications of inflammatory bowel diseases, acute pancreatitis, intestinal obstruction, and trauma[vii].

In the past, laparoscopy was contraindicated due to the risk of uterine injury with surgical instruments, greater technical difficulty due to a reduced working space because of the uterus, the concern for foetal acidosis secondary to insufflation with carbon dioxide and the decrease in maternal venous return owing to intra-abdominal pressure increase because of pneumoperitoneum. Currently, numerous studies have presented laparoscopy as a feasible, safe and effective therapeutic option throughout pregnancy[viii] [ix] [x].

The benefits of laparoscopy during pregnancy include less uterine manipulation, less postoperative ileus, decrease in foetal respiratory depression due to lower narcotic requirements for pain management, lower incidence of wound complications and thromboembolic events, shorter hospital length-of-stay and a prompt return to normal activity[xi] [xii] [xiii]. Nonetheless, complications can occur, and these can affect both the mother and/or the foetus.

General Objectives: Describe the results of the laparoscopic treatment of acute appendicitis in pregnant women at our institution.

Specific Objectives:

1- Determine postoperative maternal complications in pregnant women operated on for acute appendicitis

2- Evaluate fetal and perinatological obstetric complications in this group of patients

3- Determine if there is a difference between the time from the onset of symptoms to surgical resolution and postoperative complications between trimesters of pregnancy.
4- Determine if there is a difference in the clinical presentation of appendicitis between trimesters of pregnancy
5-Determine if there is a difference in postsurgical morbidity between trimesters of pregnancy

Design:

Retrospective observational study

Included population

All pregnant patients with a pre-surgical diagnosis of acute appendicitis operated on at the Austral University Hospital between September / 2005 and July / 2020 will be included.

Participants. Inclusion and exclusion criteria

Database authorized by the Institutional Evaluation Committee under No. B20-010 will be used. Included patiets will be those who, prior to their hospitalization, have signed the informed consent for hospitalization, in which they give their consent for the use of their health information for research purposes.

Inclusion criteria:

• Age greater than or equal to 18 years
• Pregnant with a preoperative diagnosis of acute appendicitis.

Exclusion criteria:

• Patients referred to the Austral Hospital after being operated, to continue the postoperative follow-up at our institution.
• Under 18 years of age.

Data management:

Data will be obtained from computerized medical records (PECTRA System). Those involved in the preparation of the database will access the medical records using a personal, individual, non-

transferable password, in search only of the information necessary for this study. The lead investigator will be able to access with his personal password to audit and control the quality of the data load.

Epidemiological, clinical and laboratory patient data, characteristics of the procedure performed and intraoperative findings, postoperative evolution, and maternal-foetal morbidity and mortality will be obtained within 30 days of surgery and until the end of pregnancy (described in detail in variable description section). The gathered information is part of the usual care and surgical practices of the pathology under study. The research protocol will not involve any additional procedure on the patients included in it.

The collected data will be entered into a template made in Excel. Patients will be coded according to their clinical history number, and will be anonymized prior to data analysis.

The data reported will protect the identity of its owner and will be treated with absolute confidentiality.

Variables, data source and measurements

Data will be obtained from the computerized medical records of the PECTRA system.

The categorical variables will be entered into the Excel template according to a pre-established code (see Table below). Continuous variables will be entered with up to 1 decimal place.

Primary event on which we will analyze the results: surgical morbidity (including intraoperative and postoperative complications up to 30 days after surgery).

Variable	Definition	Type of variable	Data Report
Age	Age at the time of surgery	Continuous	years
Gestational Age	According to the date of the last menstruation	Continuous	Days
Trimester	<13 weeks: first trimester 13-26,6 weeks: second trimester 27 or more weeks: third trimester	Categorical	1= first trimester 2= second trimester 3= third trimester
Prior abdominal surgery	Abdominal surgery with cavity entry, performed at any time prior to the current consultation, whether open or laparoscopic.	Categorical	0=No 1=yes
white blood cell count	White blood cell count in the laboratory performed on admission.	Continuous	Cells/mm3

Urinary sediment analysis	Performing urinary sediment as a complementary study at the time of admission.	Categorical	0=No 1=yes
Murphy Chronology	Abdominal pain of onset in the epigastrium and posterior migration to the right iliac fossa	Categorical	0=No 1=yes
Rebound tenderness	Presence of pain on abdominal decompression in the physical examination performed on admission.	Categorical	0=No 1=yes
Symptom time	Time from symptom onset to the start of surgery	Continuous	hours
Abdominal Ultrasound	Carrying out the study as a complementary method of diagnosis upon admission	Categorical	0=No 1=yes
transvaginal ultrasound	Carrying out the study as a complementary method of diagnosis upon admission	Categorical	0=No 1=yes
ASA	According to the American Society of Anesthesiology classification	Categorical	1= ASA 1 2= ASA 2 3= ASA 3 4= ASA 4
Surgery	Type of surgery carried out	Categorical	0= lexploratory laparoscopy 1= Appendectomy 2= Colectomy
Intraoperative diagnosis	Macroscopic characteristics of the appendix evidenced during surgical exploration.	Categorical	0= Normal 1= Phlegmonous 2= Gangrenous 3= appendicular plastron
Peritonitis	Presence of purulent fluid in abdominal cavity evidenced during surgical exploration	Categorical	0=No 1=yes
Conversion	Modification of the initial laparoscopic approach towards the open technique, whatever the incision chosen to perform it.	Categorical	0=No 1=Si
Date of surgery	Date in which the surgery was performed	Continuous	day/month/year
Surgical time	Time from initial skin incision to completion of surgery and skin closure.	Continuous	minutes
Tocolytics	Use of tocolytics in the perioperative period	Categorical	0=No 1=yes
Intraoperative complications	All unexpected intraoperative events, excluding conversion to conventional surgery, which were analyzed as an independent event.	Categorical	0=No 1=yes
Uterine injury	Injury to the gravid uterus, fallopian tubes or ovaries during the surgical procedure.	Categorical	0=No 1=yes
Postoperative complications	Any deviation from the usual postoperative period that occurred within 30 days of surgery.	Categorical	0=No 1=yes
Hospitalization days	Time elapsed from surgery to hospital discharge.	Continuous	Days
Re-addmission	Need for re-admission of the patient to the hospital for diagnosis or treatment, whatever the cause that motivated her re-admission.	Categorical	0=No 1=yes
Obstetric Complication	Complication arising from the appendectomy to the end of the pregnancy, including foetal death and excluding preterm delivery.	Categorical	0=No 1=yes

Foetal demise	Including spontaneous or generated abortion or foetal death, at any time from hospital admission for surgery until the end of the pregnancy.	Categorical	0=No 1=yes
maternal death	Patient surgical procedure-related death	Categorical	0=No 1=yes
Preterm labor	Delivery or cesarean section before the 37th week of pregnancy	Categorical	0=No 1=yes
Newborn weight	Newborn weight at delivery or cesarean section	Categorical	grams
Apgar	At the minute and at 5 minutes	Categorical	According to Apgar Scale
Complete follow-up	Follow-up from the initial surgery to the end of the pregnancy, either by birth (delivery or cesarean section) or by fetal or maternal death	Categorical	0=No 1=yes

Statistical Analysis plan

For continuous variables, mean, standard deviation and / or minimum and maximum, or median and interquartile interval (IQR) will be used, according to distribution. For categorical variables, the number and corresponding percentages will be reported. Continuous parameter comparisons will be made using the t-test for independent samples or Wilcoxon-rank test; and when there are more than two groups, Anova or Kruskal Wallis will be used. For the comparison of categorical variables, the chi-square test or Fisher's exact test will be used, as appropriate. A $p < 0.05$ will be considered statistically significant. Likewise, a multivariate analysis will be performed for the presence of postoperative complications and obstetric complications.

The statistical analysis will be performed with STATA version 14.2 (StataCorp 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Biases:

Due to the retrospective nature of the study, we are limited in the information available in the medical records. However, we do not believe that the data we wish to obtain is lacking, in particular clinical, surgical and complication data, since it is standardized information that is always included in the medical record. A complete follow-up of the pregnancy could not be fulfilled beyond 30 days after surgery if the patients were cared for outside the HUA, losing information on possible obstetric or perinatological complications. We believe that this bias will not be of sufficient magnitude to compromise the feasibility of the study.

Sample size:

Knowing that we have 63 pregnant women with a pre-surgical diagnosis of acute appendicitis, assuming a relationship between surgery within 48 hours of the onset of symptoms and surgery after 48 hours of the onset of symptoms of 3: 1, we have an 80% power of find a difference in postoperative morbidity between groups of 30% with a type I error of 0.05.

Funding: none

Data Confidentiality and Participant Identity protection:

Only the doctors involved in this study will have access to the database, and only the doctors assigned to load the data will be able to modify it. The lead investigator will also be able to access the database to audit the data load.

Data will be collected in a coded database according to the medical record number. Prior to the analysis, data will be anonymized in such a way that the subjects cannot be related to the data.

The lead investigator may relate the data to the subjects, committing to maintain the highest confidentiality and privacy in their handling and not to share them with those who are not authorized.

At the time of publication of the results, the identity of the individuals and the confidentiality of their data will be protected, in accordance with the Good Practice Guidelines.

Conflicts of interest: none

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