Acute pancreatitis in pregnancy: meta-analysis of maternal and fetal outcomes

D. Ll. Hughes1,2,*, A. Hughes3, P. B. White4 and M. A. Silva2

1Department of Oncology, University of Oxford, Oxford, UK
2Department of Hepatobiliary and Pancreatic Surgery, Oxford University Hospitals NHS, Oxford, UK
3Cardiff University Medical School, Cardiff, UK
4Department of Obstetrics and Gynaecology, University Hospital of Wales, Cardiff, UK

*Correspondence to: Department of Oncology, University of Oxford, Old Road Campus Research Building, Old Road Campus, Off Roosevelt Drive, Headington, Oxford OX3 7DQ, UK (e-mail: hughesdaniel32@yahoo.com)

Introduction
Acute pancreatitis in pregnancy is uncommon, with an estimated incidence rate of between 1 in 1000 and 1 in 10 000 pregnancies1,2. One aspect that remains unclear is the impact of acute pancreatitis in pregnancy on maternal and fetal outcomes. Historical case series reported very poor outcomes, with maternal mortality rates of 20 per cent and fetal loss of 50 per cent3,4. However, these studies are of an era that is not representative of current clinical practice. There is a clear need to define recent outcomes of acute pancreatitis in pregnancy to create risk stratification criteria with which to identify patients most at risk of adverse outcomes. This meta-analysis aimed to quantify maternal and fetal outcomes in acute pancreatitis in pregnancy.

Methods
The systematic review and meta-analysis were conducted according to PRISMA guidance5. A search of four online databases (PubMed, Web of Science, MEDLINE, and Embase) was undertaken. The following search criteria were used to identify the patient-specific cohort: pancreatitis (combined with acute, mild, moderate and severe) and pregnancy.

Two authors independently screened titles and abstracts from the final search against predefined inclusion criteria. The inclusion criteria consisted of studies that described the clinical features of acute pancreatitis in pregnancy. Studies were required to include specific (fetal and/or maternal) outcome measures following acute pancreatitis in pregnancy.

Exclusion criteria comprised case series with less than five patients and non-English language articles. Articles published before 2010 were excluded to determine mortality trends based on studies reflective of current clinical practice.

Data extraction was performed independently by three authors using a predesigned data collection tool. Disagreements were resolved following discussion until consensus was achieved.

Outcomes of interest
The primary outcome of this meta-analysis was the prevalence of maternal and fetal mortality following acute pancreatitis in pregnancy. The secondary outcome measure aimed to investigate the impact of the timing of onset of pancreatitis in relation to the trimesters of pregnancy on maternal and fetal outcomes.

Statistical analysis
All statistical analysis was performed using R software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Each article was assessed formally for methodological quality and risk of bias according to the methodological index for non-randomized studies (MINORS) criteria6.

A meta-analysis of outcomes was carried out using a random-effects model incorporating the DerSimonian–Laird method. Results were visualized through forest plots. I² values were calculated to assess the degree of heterogeneity among the included studies.

Results
A total of 8995 patients with acute pancreatitis in pregnancy across 23 studies were included in the meta-analysis (Table S1). Included articles were of low methodological quality based on the MINORS criteria (Table S2). The mean age at onset of acute pancreatitis in pregnancy was 28.5 years. Pancreatitis predominantly presented in the third trimester of pregnancy (548 patients, 64.9 per cent). Pancreatitis secondary to cholelithiasis was the most frequent cause of pancreatitis, followed by hypertriglyceridaemia (Table S3). The severity of the pancreatitis was noted; of 823 patients, over half (467 patients) developed a mild episode of acute pancreatitis. Approximately one-third of patients (249) developed severe pancreatitis (Table S4).

Maternal and fetal mortality rates for acute pancreatitis in pregnancy are shown in Fig. 1 and Table S5. Meta-analyses of pooled study data demonstrated that the maternal mortality rate following acute pancreatitis in pregnancy was 2.8 (95 per cent c.i. 1.5 to 5.1) per cent (Fig. 1a). The pooled fetal mortality rate...
secondary to acute pancreatitis in pregnancy was 12.3 (5.7 to 24.7) per cent (Fig. 1b). Survival trends over time showed an improvement in maternal outcome (mortality rate 2.4 per cent in 2010–2015, reduced from 3.3 per cent in 2010–2015). For fetal outcomes, a much smaller reduction in the mortality rate was observed (12.6 from 13.0 per cent).
Patients were stratified by trimester of onset of acute pancreatitis to determine the impact of acute pancreatitis and gestational age on maternal and fetal outcomes. The timing of onset of acute pancreatitis and mortality outcomes were recorded for 696 patients. Meta-analysis of proportions showed that the pooled rate for maternal death was highest during the first trimester at 12.7 per cent, compared with 7.9 and 6.4 per cent in the second and third trimesters respectively (Table 1). Fetal death mirrored this trend; the highest rate of death was in the first trimester (20.9 per cent). Intrauterine fetal death occurred most frequently during the third trimester (8.8 per cent), whereas stillbirth rates were highest during the second trimester (6.2 per cent).

Discussion

The mortality rate for pregnant women with acute pancreatitis in pregnancy is comparable to the rate described in the general patient population with acute pancreatitis; pregnant women are not at a higher risk of death during the disease course. Patients should be counselled regarding the rates of fetal death per trimester and the increased risk of stillbirth with advancing gestational age.

This meta-analysis has demonstrated improvement in maternal and fetal mortality rates following acute pancreatitis in pregnancy compared with historical data. The overall maternal mortality rate associated with acute pancreatitis during pregnancy was comparable to that of the general population. Fu and colleagues reviewed 2248 patients with pancreatitis and calculated a 3.8 per cent overall mortality rate. In the present analysis, the fetal mortality rate was highest in the first trimester (20.9 per cent). A possible reason for this is that fetal viability is currently defined at 24 weeks’ gestation. Acute pancreatitis in pregnancy in the first trimester requires a greater time period of growth/survival for fetuses to achieve the viable age, making them vulnerable to an adverse outcome. However, caution is required in interpreting these data. Although the mortality rate may appear high, it is important to highlight that miscarriage in general in the first trimester is common. Current evidence suggests that the present miscarriage rate is induction of labour. In such circumstances, a subgroup analysis of fetal death by medical termination was not possible. Acute pancreatitis in pregnancy is uncommon and the included studies contained relatively small cohorts of patients. Missing data and a lack of individual-patient data precluded subgroup analyses, such as the incidence of severe acute pancreatitis per trimester.

Disclosure. The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at BJS online.

References

1. Ramin KD, Ramin SM, Richey SD, Cunningham FG. Acute pancreatitis in pregnancy. Am J Obstet Gynecol 1995;173:187–191
2. Pitchumoni CS, Yegneswaran B. Acute pancreatitis in pregnancy. World J Gastroenterol 2009;15:5641–5646
3. Corlett RC Jr, Mitchell DR Jr. Pancreatitis in pregnancy. Am J Obstet Gynecol 1972;113:281–290
4. Wilkinson EJ. Acute pancreatitis in pregnancy: a review of 98 cases and a report of 8 new cases. Obstet Gynecol Surv 1973;28:281–303
5. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006–1012
6. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 2003;73:712–716
7. National Institute for Health and Care Excellence. Pancreatitis NICE guideline [NG104]. https://www.nice.org.uk/guidance/ng104 (accessed 29 October 2020)
8. Fu CY, Yeh CN, Hsu JT, Jan YY, Hwang TL. Timing of mortality in severe acute pancreatitis: experience from 643 patients. World J Gastroenterol 2007;13:1956–1969
9. Seaton SE, King S, Manktelow BN, Draper ES, Field DJ. Babies born at the threshold of viability: changes in survival and workload over 20 years. Arch Dis Child Fetal Neonatal Ed 2013;98:F15–F20
10. Sagli H, Divers M. Modern management of miscarriage. The Obstetrician & Gynaecologist 2007;9:102–108
11. National Institute for Health and Care Excellence. Ectopic Pregnancy and Miscarriage: Diagnosis and Initial Management [CG154]. https://www.nice.org.uk/guidance/CG154 (accessed 29 October 2020)
12. Royal College of Obstetricians and Gynaecologists. Late Intrauterine Fetal Death and Stillbirth (Green-top Guideline No. 55). https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_55.pdf (accessed 29 October 2020)
13. Masood A, Saleh S, Shaheen A, Fakhry T, Shawky M, Badr H. Maternal and fetal outcome in pregnant women with acute appendicitis: a three year observational study. Obstet Gynecol Int J 2016;5:000173
14. Jelin EB, Smink DS, Vernon AH, Brooks DC. Management of biliary tract disease during pregnancy: a decision analysis. Surg Endosc 2008;22:54–60
15. Webster PJ, Bailey MA, Wilson J, Burke DA. Small bowel obstruction in pregnancy is a complex surgical problem with a high risk of fetal loss. Ann R Coll Surg Engl 2015;97:339–344

Table 1 Maternal and fetal outcomes stratified by trimester of onset of acute pancreatitis

|                  | 1st trimester | 2nd trimester | 3rd trimester |
|------------------|---------------|---------------|---------------|
| Maternal death (%) | 12.7 (5.6, 26.1) | 7.9 (3.1, 18.8) | 6.4 (3.7, 10.8) |
| Fetal death (%)   | 20.9 (8.0, 44.7) | 12.4 (4.4, 30.2) | 12.0 (7.0, 19.9) |
| Intrauterine death (%) | – | 7.7 (3.1, 17.8) | 8.8 (4.8, 15.5) |
| Stillbirth (%)    | –             | 6.2 (2.9, 12.9) | 4.4 (2.4, 7.9) |

Values in parentheses are 95 per cent confidence intervals.