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Editorial Board Member of *World Journal of Gastroenterology*, Maria Gazouli, PhD, Professor, Basice Medical Sciences, Athens Medical School, Athens 11527, Greece. mgazouli@med.uoa.gr

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Primary hyperparathyroidism-induced acute pancreatitis in pregnancy: A systematic review with a diagnostic-treatment algorithm

Goran Augustin, Quirino Lai, Maja Cigrovski Berkovic

Goran Augustin, Department of Surgery, University Hospital Centre Zagreb and School of Medicine University of Zagreb, Zagreb 10000, Croatia

Quirino Lai, General Surgery and Organ Transplantation Unit, Department of Surgery, Sapienza University of Rome, Rome 00018, Italy

Maja Cigrovski Berkovic, Department for Sport and Exercise Medicine, Faculty of Kinesiology, University of Zagreb, Zagreb 10000, Croatia

Corresponding author: Goran Augustin, MD, Associate Professor, Department of Surgery, University Hospital Centre Zagreb and School of Medicine University of Zagreb, Kišpatićeva 12, Zagreb 10000, Croatia. augustin.goran@gmail.com

Abstract

BACKGROUND
Primary hyperparathyroidism (PHPT)-induced acute pancreatitis (AP) during pregnancy has rarely been described. Due to this rarity, there are no diagnostic or treatment algorithms for pregnant patients.

AIM
To determine appropriate diagnostic methods, therapeutic options, and factors related to maternal and fetal outcomes for PHPT-induced AP in pregnancy.

METHODS
A literature search of articles in English, Japanese, German, Spanish, and Italian was performed using PubMed (1946-2023), PubMed Central (1900-2023), and Google Scholar. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) protocol was followed. The search terms included "pancreatite acuta," "iperparatiroidismo primario," "gravidanza," "travaglio," "puerperio," "postpartum," "akute pankreatitis," "primärer hyperpara-thyreoidismus," "Schwangerschaft," "Wehen," "Wochenbett," "pancreatitis aguda," "hiperparatiroidismo primario," "embarazo," "parto," "puerperio," "posparto," "acute pancreatitis," "primary hyperparathyroidism," "pregnancy," "labor," "puerperium," and "postpartum." Additional studies were identified by reviewing the reference lists of retrieved studies. Demographic, imaging, surgical, obstetric, and outcome data were obtained.

RESULTS

Fifty-four cases were collected from the 51 studies. The median maternal age was 29 years. PHPT-induced AP starts at the 20th gestational week; higher gestational weeks were seen in mothers who died (mean gestational week 28). Median values of amylase (1399, Q1-Q3 = 519-2072), lipase (2072, Q1-Q3 = 893-2804), serum calcium (3.5, Q1-Q3 = 3.1-3.9), and parathormone (PTH) (384, Q1-Q3 = 123-910) were reported. In 46 cases, adenoma was the cause of PHPT, followed by 2 cases of carcinoma and 1 case of hyperplasia. In the remaining 5 cases, the diagnosis was not reported. Neck ultrasound was positive in 34 cases, whereas sestamibi was performed in 3 cases, and neck computed tomography or magnetic resonance imaging was performed in 9 cases (the enlarged parathyroid gland was not localized in 3 cases). Surgery was the preferred treatment during pregnancy in 33 cases (median week of gestation 25, Q1-Q3 = 20-30) and postpartum in 12 cases. The timing was not reported in the remaining 9 cases, or surgery was not performed. AP was managed surgically in 11 cases and conservatively in 43 (79.6%) cases. Maternal and fetal mortality was 9.3% (5 cases). Surgery was more common in deceased mothers (60.0% *vs* 16.3%; *P* = 0.052), and PTH values tended to be higher in this group (910 pg/mL *vs* 302 pg/mL; *P* = 0.059). Maternal mortality was higher with higher serum lipase levels and earlier delivery week. Higher calcium (4.1 mmol/L *vs* 3.3 mmol/L; *P* = 0.009) and PTH (1914 pg/mL *vs* 302 pg/mL; *P* = 0.003) values increased fetal/child mortality, as well as abortions (40.0% *vs* 0.0%; *P* = 0.007) and complex deliveries (60.0% *vs* 8.2%; *P* = 0.01).

CONCLUSION

If serum calcium is not tested during admission, definitive diagnosis of PHPT-induced AP in pregnancy is delayed, while early diagnosis and immediate intervention lead to excellent maternal and fetal outcomes.

Key Words: Primary hyperparathyroidism; Acute pancreatitis; Pregnancy; Diagnosis; Maternal mortality; Fetal mortality; Algorithm

Core Tip: Primary hyperparathyroidism (PHPT)-induced acute pancreatitis (AP) in pregnancy is extremely rare. Definitive diagnosis of PHPT-induced AP in pregnancy is delayed if serum calcium is not tested during admission. PHPT-induced AP starts at the 20th gestational week. Maternal and fetal mortality was 9.3%. Maternal mortality was higher with higher serum lipase levels and earlier delivery week. Higher calcium and PTH values increased fetal/child mortality, abortions, and complex deliveries Early diagnosis and immediate intervention lead to excellent maternal and fetal outcomes.

INTRODUCTION

Acute pancreatitis (AP) during pregnancy is uncommon but can lead to severe maternal and fetal adverse outcomes. The most prominent causes of AP, due to the increasing parturition age, rising overweight/obesity rates, and dietary fat content, include cholelithiasis and dyslipidemia-hypertriglyceridemia[1]. Primary hyperparathyroidism (PHPT) in pregnancy is rare, with a reported incidence of 1.4%[2]. Maternal and fetal/neonatal complications occur in 67% and 80% of untreated cases, respectively[3]. Maternal complications include nephrolithiasis, AP, hyperemesis gravidarum, preeclampsia, and hypercalcemic crises. Fetal complications include intrauterine growth restriction, preterm delivery, and a 3-fold to 5-fold increased risk of miscarriage. There is a direct relationship between the degree of hypercalcemia and miscarriage risk, with miscarriage being more common in patients with serum calcium greater than 2.85 mmol/L[3,4].

PHPT during pregnancy is often overseen because specific signs and symptoms related to hypercalcemia, especially if not severe, can be mistaken for normal pregnancy. Hyperemesis gravidarum is the most common symptom, and nephrolithiasis and AP are important hypercalcemia-related complications. Diagnosis of PHPT requires elevated serum calcium values (serum ionized calcium or calcium adjusted for albumin) and parathormone (PTH), either elevated or non-suppressed for the level of calcemia[3]. The management of PHPT-induced AP, due to lack of strong evidence, is still elusive and further complicates decision-making on the best approach to AP during pregnancy and puerperium.

Although four "systematic" reviews collecting 15 to 26 cases were published, there are still no recommendations and guidelines for this condition during pregnancy. This is the largest systematic review of PHPT-induced AP in pregnancy (54 cases) of literature published over 55 years. The core of this review is summarized using knowledge on the topic, focusing on the diagnostic approach, type, and timing of interventions, and a proposed diagnostic-treatment algorithm.

MATERIALS AND METHODS

Study selection

Following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology guidelines[5], we performed a systematic review of articles in English, Japanese, German, Spanish, and Italian using PubMed, PubMed Central, and Google Scholar (Figure 1). The search items included "pancreatite acuta," "iperparatiroidismo primario," "gravidanza," "travaglio," "puerperio," "postpartum," "akute pankreatitis," "primärer hyperparathyreoidismus," "Schwangerschaft," "Wehen," "Wochenbett," "Wochenbett," "pancreatitis aguda," "hiperparatiroidismo primario," "embarazo," "parto," "puerperio," "posparto," "acute pancreatitis," "primary hyperparathyroidism," "pregnancy," "labor," "puerperium," and "postpartum." Additional studies were identified by reviewing the reference lists of retrieved studies. Articles in languages other than English were translated using the websites deepl.com and Google Translate.

We included all cases and case series identified as having a PHPT-induced AP during pregnancy or puerperium (Supplementary material). Exclusion criteria were: (1) AP of other causes; (2) Patients not fulfilling the definition of pregnancy or puerperium; and (3) Incomplete data or unavailable full-text articles. The primary outcome was to identify associations of demographic data (age), obstetric data (trimester of pregnancy, parity), maternal risk factors (*e.g.*, previous pancreatitis episodes, miscarriage), serum calcium and PTH levels, and pancreatitis severity, diagnostic tools for diagnosing AP (ultrasound, abdominal computed tomography [CT], abdominal magnetic resonance imaging [MRI]/ magnetic resonance cholangiopancreatography) and PHPT (neck ultrasound, 99 mTc-sestamibi scintigraphy, neck CT/ MRI), therapeutic intervention related to AP and PHPT (surgical, pharmacological), timing of surgery with maternal and fetal outcomes. The study is exempt from ethics approval because the data was procured from previously published studies.

Data extraction

A data extraction form was prepared and piloted to determine if changes were required before extracting data from the full review. Two authors (Augustin G and Cigrovski Berkovic M) independently performed data extraction following the PRISMA guidelines for data extraction and quality assessment. In addition, the examiners assessed the studies' methodologies according to the tool for evaluating the methodological quality of case reports and case series described by Murad *et al*[6].

The data extracted were as follows: Publication year, maternal age, obstetric history (parity, the number of prior Cesarean sections), gestational age at presentation or postpartum day at presentation, symptoms, diagnostic modalities, treatment approaches, gestation age at delivery and delivery type, and maternal/fetal outcome. The data collected were available from the included studies. However, several characteristics were missing from more than half of the data.

Statistical analyses

Categorical data are reported as absolute numbers with percentages, and continuous data as medians with first-third quartile (Q1-Q3) ranges. Data were pooled, and descriptive statistics were produced from the dataset. A pseudo-individual participant data meta-analysis (pseudo-Individual Participant Data Meta-Analysis [IPDMA]) was conducted to synthesize clinical study evidence. IPDMA represents a specific type of systematic review in which, rather than extracting aggregate data from study publications, the original research data are obtained directly from the researchers responsible for each study. These data can then be re-analyzed centrally and combined in meta-analyses. Overall, pseudo-IPDMA analyses can improve the quality of data and the type of analyses that can produce more reliable results. For this reason, this method is considered the 'gold standard' of systematic review. In this specific setting, as all variables of interest were available from the articles, a pseudo-IPDMA was created. In other terms, the authors of the original articles were not directly recontacted, but all the information available from the papers was adequate for creating a pseudo-individual baseline and outcomes dataset. Categorical variables were compared with the χ^2 or Fischer's exact test, and the continuous variables with the Mann-Whitney test. Multivariable logistic regression analyses were also realized. Odds ratios (OR) and 95% confidence interval (95%CI) were reported. $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS 27.0 (SPSS Inc., Chicago, IL, United States).

RESULTS

Systematic search and study quality assessment

This study included 54 cases from 51 studies published between 1968 and 2023. All of the studies are case reports or small case series.

Mother's outcomes

All reported cases had PHPT-induced AP during pregnancy or immediately after delivery. The median maternal age was 29 (Q1-Q3 = 26-32) years. Median values of amylase (1399 IU/L, Q1-Q3 = 519-2072 IU/L), lipase (2072 IU/L, Q1-Q3 = 893-2804 IU/L), serum calcium (3.5 mmol/L, Q1-Q3 = 3.1-3.9), and PTH (384 pg/mL, Q1-Q3 = 123-910 pg/mL) were reported.

In 41 cases, imaging for identifying the cause of hyperparathyroidism was reported. Neck ultrasounds identified the cause of PHPT in 34 cases (82.9%), rarely by 99 mTc-sestamibi scintigraphy (n = 3) and CT/MRI (n = 1). In 3 cases, the
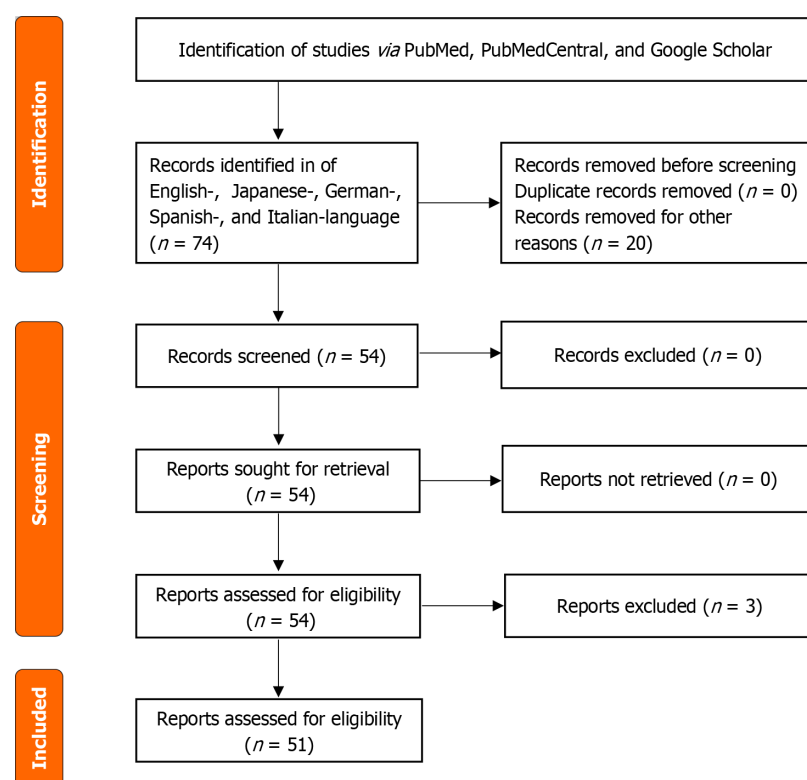
Figure 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses 2009 diagram.

imaging was negative. Neck surgery was performed during pregnancy in 33 cases (median gestational week = 25, Q1-Q3 = 20-30). In 12 cases, surgery was performed after delivery. The timing was not reported in the remaining 9 cases, or surgery was not performed. In 46 cases, an adenoma was identified, followed by 2 cases of carcinoma and 1 of hyperplasia. In the remaining 5 cases, no histological characteristics of the cause of hyperparathyroidism were specified, nor surgery was performed. In 5 (9.3%) cases, maternal death was reported. Two groups were compared according to the maternal outcome (Table 1). No statistical differences were found between the groups regarding the mother's age, number of previous pregnancies, number of previous deliveries, and pregnancy week in which AP was diagnosed.

Although not statistically significant, the indication to manage AP surgically merged the statistical significance with a greater number of patients requiring surgery in the group of mothers experiencing death (60.0% *vs* 16.3%; $P = 0.052$). No differences between the groups were reported regarding serum calcium, phosphorus, amylase, and lipase levels reported at the time of AP. PTH values were higher in the group with maternal death, although only merging statistical relevance (910 pg/mL *vs* 302 pg/mL; $P = 0.059$). No differences were observed in terms of the number of abortions, complex deliveries, and fetal/child deaths. Delivery tended to be during earlier gestation in cases of maternal death, but the difference did not reach statistical significance ($P = 0.09$).

Fetal/child outcomes

A total of 53 children were born: Twins in 1 case and abortion in 2. There were 21 vaginal deliveries and 21 cesarean sections (unknown type of delivery for additional cases). A higher number of vaginal deliveries compared to cesarean sections was observed before 2000 (38.1% *vs* 19.0%). The median child gestational age at delivery was 36 (Q1-Q3 = 36-38). The child's sex was reported in 30 cases: 20 females and 10 males. The child's weight was reported in 30 cases, with a median weight of 2583 gr (Q1-Q3 = 2083-3010 gr). The Apgar score at birth was reported in 22 cases with a median of 8 (Q1-Q3 = 6-9).

Fetal mortality was 9.3% (5 cases): Two miscarriages and three child deaths after the delivery. Two groups were compared according to the outcome of the fetus/child (Table 2). No statistical differences were observed in the two groups regarding the mother's age, number of previous pregnancies, and number of previous deliveries. The pregnancy week in which the AP was diagnosed was earlier for the group with fetal/child death, although not statistically significant (16 weeks *vs* 28 weeks; $P = 0.08$). The need to manage AP surgically did not correlate with the risk of fetal/child death.

No differences between the groups were reported regarding serum phosphorus, amylase, and lipase levels at the time of AP. Calcium (4.1 mmol/L *vs* 3.3 mmol/L; $P = 0.009$) and PTH (1914 pg/mL *vs* 302 pg/mL; $P = 0.003$) values were statistically higher in the group with fetal/child death. Miscarriages (40.0% *vs* 0.0%; $P = 0.007$) and complex deliveries (60.0% *vs* 8.2%; $P = 0.01$) increased fetal/child mortality. A delivery week and the mother's death did not influence fetal mortality. In detail, only 1 case of contemporary death of the mother and the fetal abortion was reported. In the other 4 cases of the mother's death, the child survived.

Table 1 Comparison of the characteristics between the survived and deceased mothers due to maternal primary hyperparathyroidism-induced acute pancreatitis during pregnancy

Variables	Entire cohort, *n* = 54, 100.0%	Mother alive, *n* = 49, 90.7%	Mother died, *n* = 5, 9.3%	*P* value
Age in years	29 (26-32)	29 (27-32)	26 (24-33)	0.25
Previous pregnancies	2 (1-2)	2 (1-2)	2 (1-2)	0.56
Previous deliveries	1 (0-1)	1 (0-1)	1 (1-2)	0.35
Pancreatitis occurrence in gestational week	27 (20-33)	26 (20-33)	28 (21-40)	0.38
Pancreatitis postpartum	4 (7.4)	3 (6.1)	1 (20.0)	0.33
Surgical management	11 (20.4)	8 (16.3)	3 (60.0)	0.052
Amylase in IU/L	1399 (519-2072)	1415 (510-2006)	1200 (642-3091)	0.66
Lipase in IU/L	2072 (893-2804)	2072 (869-2521)	3320 (855-6997)	0.31
Calcium in mmol/L	3.5 (3.1-3.9)	3.5 (3.1-3.8)	3.1 (2.5-4.7)	0.73
Phosphorus in mmol/L	0.7 (0.7-0.7)	0.7 (0.7-0.7)	0.7 (0.7-0.8)	0.50
PTH in pg/mL	384 (123-910)	302 (122-910)	910 (541-5665)	0.059
Abortion	2 (3.7)	1 (2.0)	1 (20.0)	0.18
Complex delivery	7 (13.0)	6 (12.2)	1 (20.0)	0.52
Delivery occurrence week	36 (36-38)	36 (36-39)	36 (23-37)	0.09
Fetal/child death	5 (9.3)	4 (8.2)	1 (20.0)	0.40

Data are *n* (%) or median (Q1-Q3). PHT: Parathormone.

Table 2 Comparison of the characteristics between the group of fetal/child survival or death due to maternal primary hyperparathyroidism-induced acute pancreatitis during pregnancy

Variables	Entire cohort, *n* = 54, 100.0%	Child alive, *n* = 49, 90.7%	Fetal/child death, *n* = 5, 9.3%	*P* value
Age in years	29 (26-32)	29 (26-32)	28 (28-36)	0.77
Previous pregnancies	2 (1-2)	2 (1-2)	2 (1-7)	0.98
Previous deliveries	1 (0-1)	1 (0-1)	1 (1-5)	0.52
Pancreatitis occurrence week	27 (20-33)	28 (22-33)	16 (13-26)	0.08
Pancreatitis post-partum	4 (7.4)	4 (8.2)	0 (-)	1.00
Surgical management	11 (20.4)	10 (20.4)	1 (20.0)	0.73
Amylase in IU/L	1399 (519-2072)	1500 (510-2072)	1113 (752-2004)	0.89
Lipase in IU/L	2072 (893-2804)	2072 (869-2808)	1415 (751-5664)	0.95
Calcium in mmol/L	3.5 (3.1-3.9)	3.3 (3.1-3.8)	4.1 (3.8-4.7)	0.009
Phosphorus in mmol/L	0.7 (0.7-0.7)	0.7 (0.7-0.7)	0.7 (0.5-0.8)	0.89
PTH in pg/mL	384 (123-910)	302 (122-910)	1914 (910-3330)	0.003
Abortion	2 (3.7)	0 (-)	2 (40.0)	0.007
Complex delivery	7 (13.0)	4 (8.2)	3 (60.0)	0.01
Delivery week	36 (36-38)	36 (36-39)	34 (19-39)	0.12
Mother death	5 (9.3)	4 (8.2)	1 (20.0)	0.40

Data are *n* (%) or median (Q1-Q3). PHT: Parathormone.

Risk factors for maternal and fetal mortality

A multivariable logistic regression model analyzed the risk of maternal mortality according to the pseudo-IPDMA data (Table 3). The value of serum lipase at the time of AP (OR = 1.001, 95%CI: 1.00-1.001; *P* = 0.03) and the delivery week (OR = 0.81, 95%CI: 0.66-0.99; *P* = 0.04) were the only independent parameters. The number of previous pregnancies and deliveries only merged the statistical relevance (*P* = 0.051 for both). A plot correlating maternal mortality to the values of serum lipase and delivery week is presented in Figure 2.

The complex delivery was the only independent risk factor for fetal/child mortality or miscarriage (OR = 11.31, 95%CI: 2.07-17.67; *P* = 0.02). Only gestational week of AP occurrence merged statistical relevance (OR = 0.78, 95%CI: 0.61-1.00; *P* = 0.05) (Table 3). A plot correlating fetal/child death to the pregnancy week at the time of AP diagnosis is presented in Figure 3.

DISCUSSION

PHPT arises from the overproductive parathyroid adenoma or, less often, parathyroid hyperplasia, or carcinoma, characterized by signs and symptoms of hypercalcemia[7]. It occurs mainly sporadic in women over 50 years and is usually asymptomatic. In 3%-5%, it occurs at a younger age as a part of multiple endocrine neoplasia syndromes[8,9]. Hence, although PHPT in pregnant women should prompt investigation of syndromic hypercalcemia and genetic testing, it is rarely done in clinical practice. Most nonpregnant PHPT patients have serum calcium from 1 to 1.5 mg/dL (0.25 to 0.375 mmol/L) above the upper normal limit, accompanied by an elevated or inappropriately normal (nonsupressed) PTH level. By contrast, calcium levels in pregnant women with PHPT are reportedly much higher, and those greater than 2.85 mmol/L correlate with a higher probability of maternal and fetal complications[3,10,11]. The clinical manifestations of PHPT are diverse and include hypercalcemia-related gastrointestinal, neuromuscular, renal, and psychological signs and symptoms, which can be overseen during pregnancy and, therefore, postpone the correct diagnosis or calcium level determination[12]. Due to its rarity, PHPT-induced AP during pregnancy is a diagnostic and therapeutic challenge[1].

Hence, a case series of PHPT during pregnancy reported from a single center between 2000 and 2015 suggested calcemia < 2.85 mmol/L could be managed conservatively in the absence of AP or other hypercalcemia-related symptoms [9]. According to the guidelines for PHPT management in the nonpregnant population, surgery is the preferred treatment for: (1) Symptomatic disease; (2) Calcium levels > 0.25 mmol/L (> 1 mg/dL) above the upper limit; or (3) Complications such as nephrolithiasis, osteoporosis or AP[8]. Due to the lack of randomized controlled trials, there are no clear recommendations for the management of PHPT during pregnancy or PHPT-induced AP. Currently, the main practice is to operate PHPT during pregnancy in case of persistent hypercalcemia above 2.75 mmol/L or symptomatic hypercalcemia. However, some advocate surgery in the second trimester regardless of serum calcium levels[13-18]. Conservative treatment options are limited and lack clear guidance. They rely on intravenous fluids and forced diuresis with furosemide, calcitonin subcutaneous (limited use due to tachyphylaxis), and cinacalcet (lacking long-term safety data). By contrast, intravenous bisphosphonate use is debatable due to potentially negative effects on fetal bone development[14].

A further issue is the assessment of AP severity during pregnancy and its relation to treatment decisions. Different scoring systems in nonpregnant populations rely on imaging, such as CT, commonly avoided during pregnancy. Several recent articles described the case of PHPT-induced AP in pregnancy and made a "review of the literature." Unfortunately, all four reviews have less than half of the cases we collected. In 2014, Lee *et al*[19] collected 15 cases with a small number of analyzed parameters. There were no conclusions that help in dealing with this pathology except that it is rare, and clinicians should have a high level of suspicion. Liu *et al*[20] have "literature review" in their title but without a formal systematic or any type of review. It is not even a "narrative" review because many statements do not have references for statement confirmation. The best review was by Kongmalai[21] in 2021, but it had significant limitations. The first was that it collected only 23 cases. The second is a limited number of analyzed parameters with a minimal number of conclusions. In the most recent (2023) review, Zhou *et al*[22] collected 26 cases, while there were only 16 cases from 2000 onwards in the supplementary online material. Again, only several parameters were analyzed. The authors did a narrative review without the data/percentages from their collection of cases of pregnancy. For example, we do not know which imaging method has the best accuracy, sensitivity, and specificity for diagnosing PHPT in pregnancy. A similar goes to the treatment with a single conclusion based on 2 (carcinoma) cases. In conclusion, neither of these four reviews made a detailed analysis of laboratory, diagnostic, or therapeutic parameters. The most important drawback is the lack of diagnostic, treatment, or diagnostic-treatment algorithms. Therefore, within this review, it is presently the largest systematic review of PHPT-induced AP in pregnancy and postpartum. It proposes optimal diagnostic workups and treatment strategies, all of which are summarized in the diagnostic treatment algorithm.

Incidence

PHPT-induced AP in pregnancy is exceedingly rare. We collected 54 cases, the highest collection of this pathology in pregnancy. The overall incidence of AP in pregnancy is estimated to be approximately 1 in 1000-10000 pregnancies[1,23]. The incidence of PHPT-induced AP cannot be determined due to the extreme rarity and unknown data on other causes of AP in pregnancy in these periods and countries.

Pathophysiology

Most AP cases result from parathyroid adenoma. The symptomatology starts after 20 weeks of gestation, similar to other, more frequent causes of AP (gallstones, hypertriglyceridemia)[1]. Physiologically, PTH during pregnancy falls to a low-

Table 3 Multivariable models for the identification of the risk factors for maternal or fetal mortality during pregnancy and postpartum

Variables	Beta	SE	Wald	OR	Lower	Upper	*P* value
Mother death							
Lipase in IU/L	0.001	< 0.001	4.63	1.001	1.00	1.001	0.03
Delivery week	-0.21	0.10	4.46	0.81	0.66	0.99	0.04
Previous pregnancies	-2.61	1.34	3.80	0.07	0.01	1.01	0.051
Previous deliveries	3.22	1.65	3.80	25.12	0.98	64.68	0.051
Constant	4.15	3.29	1.59	63.37	-	-	0.21
Fetal/child death							
Complex delivery	5.25	2.31	5.18	11.31	2.07	17.67	0.02
Pancreatitis occurrence in pregnancy week	-0.25	0.13	3.84	0.78	0.61	1.00	0.05
Constant	1.32	1.81	0.53	3.73	-	-	0.47

Variables initially introduced in the model's construction: Patient age, previous pregnancies, previous deliveries, pregnancy week in which the pancreatitis was diagnosed, serum calcium, serum phosphorous, parathormone, amylase, lipase, surgical management of acute pancreatitis, aborted fetus, complex delivery, delivery week. OR: Odds ratio.
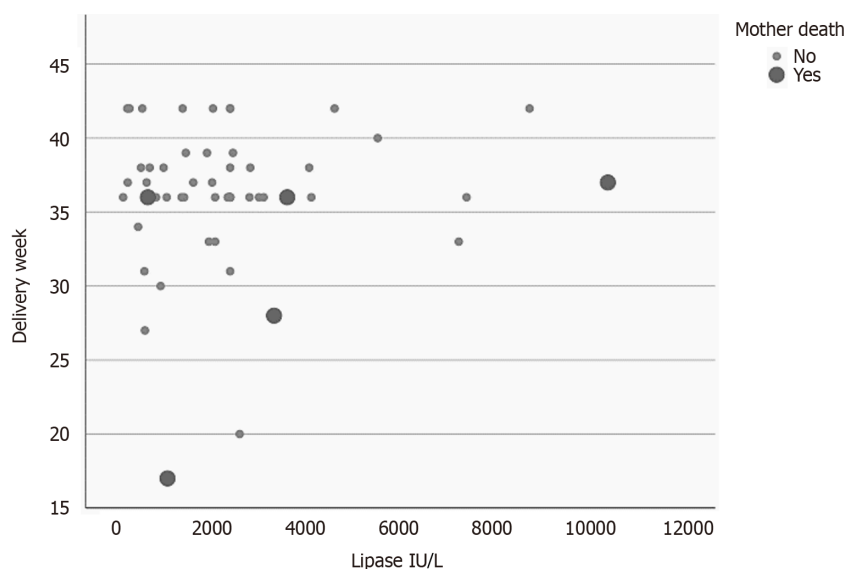
Figure 2 Correlation between lipase value at the time of acute pancreatitis and delivery week for the risk of mother's death.

normal range during the first trimester and rises to a mid-normal range by term. This follows the findings that AP occurs after 20 weeks, although adenoma PTH secretion is probably completely independent. Increasing intra-abdominal pressure as the pregnancy advances probably does not increase the probability of AP as in biliary AP due to biliary compression.

Clinical presentation
Clinical presentation of PHPT-induced AP included a spectrum of symptoms ranging from nausea, vomiting, hyperemesis gravidarum, acute abdomen, preeclampsia, hypertension, and behavioral changes to loss of consciousness. Confirmed PHPT before conception was described in 2 cases, while possible, undiagnosed PHPT presenting as AP, hypercalcemia and/or nephrolithiasis, all suggestive of undiagnosed PHPT, emerged in four and seven reported pregnancies, respectively.

Diagnosis
PHPT-related AP was mostly diagnosed during pregnancy, beginning with 20 weeks of gestation. In 4 cases, previous pregnancies were complicated by AP, leading to multiple miscarriages. Mean calcium levels were 3.5 mmol/L, and the mean PTH was 384 pg/mL. Data on vitamin D (25-OH-D) were reported in 13 cases, and an average value was 52.81 nmol/L. A neck ultrasound was the first imaging method, and it detected parathyroid pathology in 34 patients (62.96%).
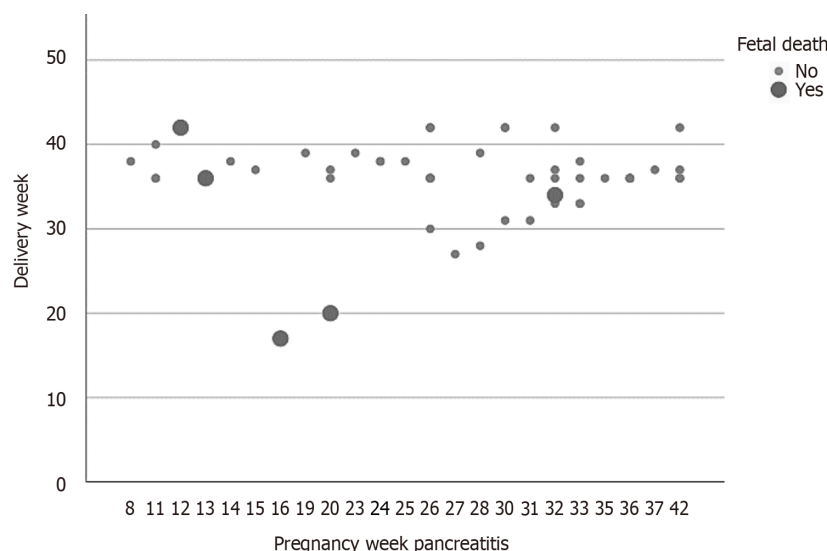
Figure 3 Correlation between pregnancy week in which the acute pancreatitis was diagnosed and delivery week for the risk of fetal/child death.

Other imaging methods were 99 mTc-sestamibi scintigraphy (positive in 8/10 cases) and neck CT/MRI (positive in 8/10 cases). Ultrasound-negative but 99 mTc-sestamibi scintigraphy-positive finding was reported in 3 (5.55%) and ultrasound-negative but CT/MRI-positive finding of overactive parathyroid gland in 1 (1.85%) patients, respectively. In 3 patients, no imaging modality was useful in detecting the overactive parathyroid gland.

Histopathology confirmed parathyroid adenoma in 46 cases, followed by 2 cases of carcinoma and 1 case of hyperplasia. In the remaining 5 cases, no histological characteristics of the cause of hyperparathyroidism were specified, nor was surgery performed. Six studies reported AP severity (according to Glasgow, Ranson, or Balthazar criteria). Twenty-five cases involved abdominal ultrasound, while in 16 studies, abdominal CT and MRI/MRCP were performed. Workup for multiple endocrine neoplasia was done in 3 cases and reported negative.

Treatment

While there is no clear international consensus on the management of PHPT in pregnancy, a historical consensus is a parathyroidectomy in the second trimester for patients whose calcium persists above 2.75 mmol/L[24-26]. However, this approach is not evidence-based, and many of the complications and risks of severe hypercalcemia may occur in the first trimester, such as hyperemesis gravidarum, renal calculi, AP, and hypercalcemic crisis[13,14,27]. Moreover, prolonged hypercalcemia increases the risk of renal calculi, renal insufficiency, and osteoporosis. Neck surgery was performed during pregnancy in 33 cases (median week = 25, Q1-Q3 = 20-30). In 12 cases, surgery was performed after delivery. The timing was not reported in the remaining 9 cases, or surgery was not performed. Conservative treatment with a eucalcemic diet and aggressive hydration often fails[28]. Moreover, guidelines on pharmacotherapy are still lacking. However, calcitonin, cinecalcet, and intravenous bisphosphonates (zolendronate) have been used. Still, the results are either modest due to tachyphylaxis (calcitonin) or insufficient long-term safety data (cinacalcet and intravenous bisphos-phonates). Therefore, symptomatic cases (AP) and patients with calcium levels above 2.75 mmol/L should undergo parathyroidectomy (Figure 4). The treatment of AP should not differ from other causes of AP and should not be influenced by pregnancy.

Obstetric management

A total of 53 children were born. In 1 case, a delivery of twins was reported, while 2 cases of miscarriages were described. The type of delivery was described in 42 cases: 21 vaginal deliveries and 21 cesarean sections. A major number of vaginal deliveries *vs* cesarean sections was observed before the year 2000 (38.1% *vs* 19.0%). The median child gestational age at delivery was 36 weeks (Q1-Q3 = 36-38). The child's sex was reported in 30 cases: 20 females and 10 males. The child's weight was reported in 30 cases, with a median weight of 2583 gr (Q1-Q3 = 2083-3010 gr). The Apgar score at birth was reported in 22 cases: The median value was 8 (Q1-Q3 = 6-9). Regarding children's complications, the most reported was transient hypocalcemia. In short, the earlier treatment of PHPT and resolution of AP, the higher proportion of term pregnancies delivered vaginally.

Outcome

Maternal outcome: Maternal mortality due to PHPT-induced AP is 9.3%, while maternal mortality from other causes of AP during pregnancy dropped to 2.8%[23,29,30]. PHPT is a single-cause condition resulting in AP. With the cause elimination, the AP resolves. AP resolution decreases the risk of maternal mortality. This is confirmed by the fact that the value of serum lipase at the time of AP (OR = 1.001, 95%CI: 1.00-1.001; *P* = 0.03) and the delivery week (OR = 0.81, 95%CI: 0.66-0.99; *P* = 0.04) were the only independent parameters increasing maternal mortality. As for post-parathyroidectomy
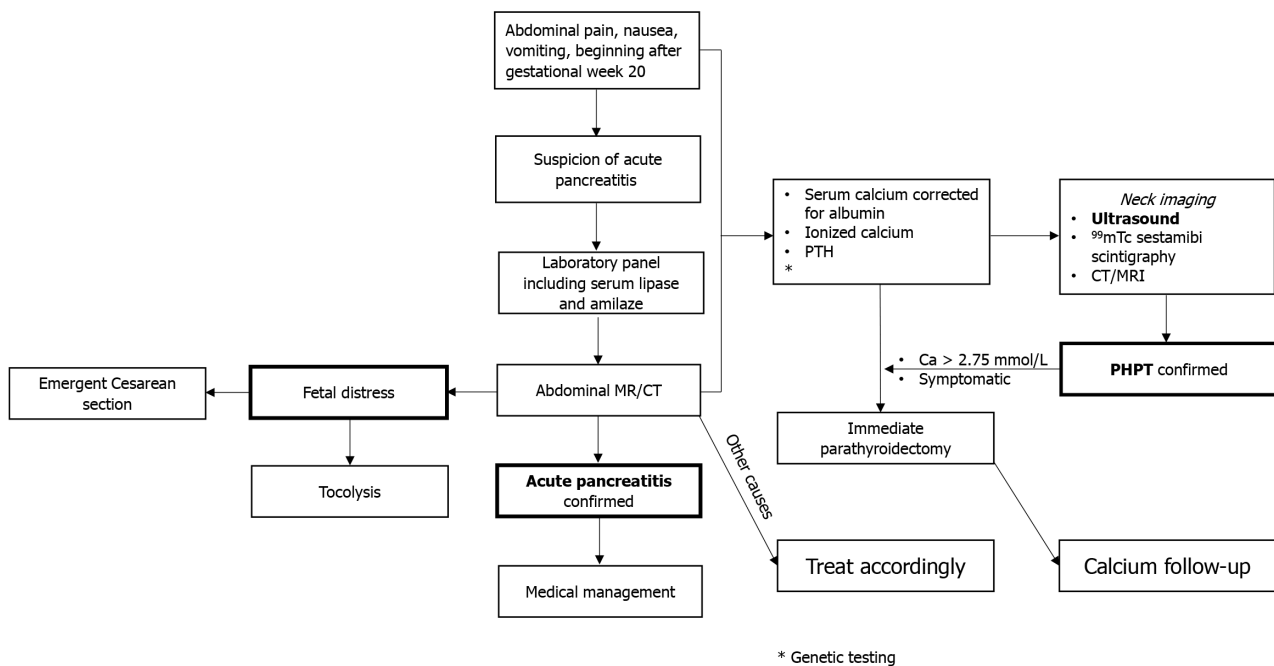
Figure 4 Diagnostic-therapeutic algorithm for primary hyperparathyroidism-induced acute pancreatitis in pregnancy. CT: Computed tomography; MR: Magnetic resonance; MRI: Magnetic resonance imaging; PHPT: Primary hyperparathyroidism; PTH: Parathormone.

complications, hungry bone syndrome was described in 3 and transient hypocalcemia in 2 cases.

Neonatal outcome: Neonatal survival is excellent, with 9.3% mortality. Outcomes of other causes of AP are improving but are still 12.3%[1,28-30]. The median weight was 2583 gr (Q1-Q3 = 2083-3010 gr), and the median Apgar score at birth was 8 (Q1-Q3 = 6-9). PHPT is a single-cause condition of hypercalcemia resulting in AP. The AP and hypercalcemia were resolved by eliminating the cause (PHPT treatment). AP resolution decreases the risk of fetal mortality. This is confirmed by the fact that higher calcium (4.1 mmol/L *vs* 3.3 mmol/L; *P* = 0.009) and PTH (1914 pg/mL *vs* 302 pg/mL; *P* = 0.003) values increase fetal mortality. Transient hypocalcemia might occur; therefore, calcium serum levels should be monitored.

Limitations of the study: Despite the highest number of cases collected, these were published over 55 years. Older studies have limited value today, primarily in diagnostic and partly management aspects. PTH essays differ significantly over 55 years. Older essays also measured inactive PTH units, so false values could be presented. Conservative treatment is of limited use, with no randomized controlled trials and long-term safety data and no reliable comparison between the outcomes related to treatment options: Conservative *vs* operative.

CONCLUSION

PHPT-induced AP patients have serum calcium levels above 3.5 mmol/L. Symptomatic PHPT cases and patients with calcium levels above 2.75 mmol/L should undergo semi-urgent parathyroidectomy. PHPT-induced AP starts at the 20th gestational week. Parathyroidectomy immediately normalizes serum calcium values, leading to AP resolution. Maternal and fetal survival is excellent with AP caused by PHPT, although transient hypocalcemia (maternal and fetal) can be expected.

FOOTNOTES

Country of origin: Croatia

ORCID number: Goran Augustin 0000-0002-0202-3324; Quirino Lai 0000-0003-1487-3235; Maja Cigrovski Berkovic 0000-0003-0750-9785.

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