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REPORTE DE CASO

Pancreatic adenocarcinoma during pregnancy. Case report

Adenocarcinoma pancreático durante el embarazo. Reporte de caso

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Conflict of interest
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ABSTRACT
Pancreatic ductal adenocarcinoma during pregnancy is extremely rare. Overall, including our case, only 19 cases confirmed antepartum have been reported to date. We report the case of a 37 year-old woman at 24 weeks of pregnancy in whom a pancreatic adenocarcinoma was identified during investigation of a suspected acute pancreatitis. Surgery was postponed until fetal maturity. However, chemotherapy was not tolerated, clinical condition of the mother worsened after cesarean section, and surgical findings revealed an unresectable disease. Patient died due to septic shock and multiple organ failure, but her child is in very good health. Pancreatic ductal adenocarcinoma during pregnancy carries the same poor prognosis of the general population. A pregnant with severe epigastric pain radiating to the back, in the presence of jaundice and weight loss, should rule out a pancreatic neoplasm. In case a malignancy is identified, the histology diagnosis is required, and decisions should be taken as a consensus between the mother and a multidisciplinary team in a referal center.
Keywords: *Adenocarcinoma; Diagnosis; Pancreas; Pregnancy (source: MeSH NLM).*

RESUMEN
El adenocarcinoma ductal pancreático durante el embarazo es extremadamente raro. En total, incluyendo nuestro caso, se han reportado hasta la fecha solo 19 casos confirmados anteparto. Se presenta el caso de una mujer de 37 años, a las 24 semanas de embarazo, fue diagnosticada con un adenocarcinoma durante la investigación de una sospecha de pancreatitis aguda. La cirugía se pospuso hasta la madurez fetal. Sin embargo, la quimioterapia no fue tolerada, la condición clínica de la madre empeoró tras la cesárea y los hallazgos quirúrgicos revelaron una enfermedad irresecable. La paciente falleció debido a shock séptico y falla multiorgánica, pero su hijo se encuentra en muy buen estado de salud. El adenocarcinoma ductal pancreático durante el embarazo tiene el mismo mal pronóstico que en la población general. Una mujer embarazada con dolor epigástrico severo que irradia hacia la espalda, en presencia de ictericia y pérdida de peso, debe descartar una neoplasia pancreática. En caso de identificarse una malignidad, se requiere un diagnóstico histológico, y las decisiones deben tomarse de manera consensuada entre la madre y un equipo multidisciplinario en un centro de referencia.
Palabras clave: *Adenocarcinoma; Diagnóstico; Páncreas; Embarazo (fuente: DeCS Bireme).*

INTRODUCTION

Cancer in pregnancy comprises malignancies diagnosed during pregnancy or within 1 year after delivery [(1)]. Pancreatic neoplasms during pregnancy can be cystic or solid lesions. Pancreatic cystic neoplasms, either the mucinous or the solid pseudopappilary lesions, and neuroendocrine tumors, especially the insulinomas, are more common and have a better prognosis [(2-4)]. On the other hand, pancreatic ductal adenocarcinoma is extremely rare and carries a poor prognosis. There have been a few cases of pancreatic adenocarcinoma reported during pregnancy, and only 18 of them were confirmed antepartum [(5-22)].

Herein, we describe a new case, and review all the few cases of pancreatic adenocarcinoma diagnosed antepartum during pregnancy.

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CASE REPORT

A 37 year-old pregnant woman at 24 weeks of gestation was admitted to the Obstetric Department of the Divina Providencia Hospital with a history of epigastric pain radiating to the back, vomiting, choluria, and jaundice. Previous obstetric history revealed a normal term delivery three years earlier, and routine prenatal evaluations and obstetric ultrasounds were normal.

Remarkable laboratory data on admission showed high serum levels of alanine aminotransferase (330 U/L), aspartate aminotransferase (144 U/L), total bilirubin (6.4 mg/dL), direct bilirubin (5.8 mg/dL), alkaline phosphatase (442 U/L), gamma-glutamyl-transpeptidase (348 U/L), and amylase (442 U/L). An abdominal ultrasound demonstrated a previous cholecystectomy, no residual gallstones in the biliary tract, and an ill-defined mass at the pancreatic head with dilatation of the common bile duct.

A non-contrast magnetic resonance imaging (MRI) was performed, revealing a 4-cm solid lesion at the pancreatic head, dilating biliary (18 mm) and pancreatic (4 mm) ducts, without evidence of large blood vessels involvement (Figure 1).

Serum levels of carbohydrate antigen (CA 19-9) were elevated (2.474 U/mL). A plastic biliay stent was placed by endoscopic retrograde cholangiopancreatography to relieve the jaundice. A lead shield was in place to minimize radiation exposure to the fetus. After a few days, patient was submitted to an endoscopic ultrasound evaluation with biopsy of the mass (Figure 2).

A pathologist was on site to guarantee a quick and definitive diagnosis, and the histopathology confirmed a ductal adenocarcinoma (Figure 3).

At this moment, with a pancreatic carcinoma at clinical stage IB (cT2N0M0), a collaborative decision between a multidisciplinary team and the family was to begin neoadjuvant chemotherapy during pregnancy, guaranteeing the fetal maturity and postponing surgery.

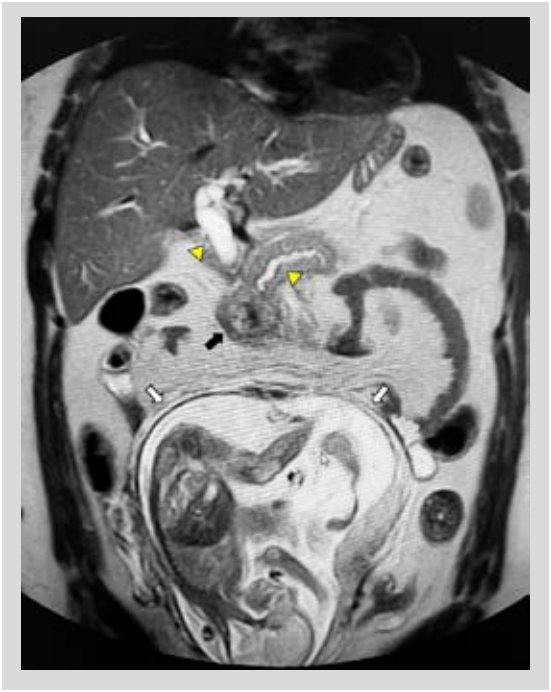

Figure 1. Non-contrast abdomino-pelvic T2-weighted coronal MRI demonstrating a 4-cm solid mass at the pancreatic head (black arrow) with marked dilatation of the common bile duct and the main pancreatic duct (yellow arrowheads). A 24-week gravid uterus with a normal fetus can also be seen (withe arrows).

Chemotherapy with folinic acid, fluorouracil, irinotecan, and oxaliplatin (Folfirinox) was administered on an inpatient basis for a close monitoring of the mother and fetus. After 2 cycles, patient developed an afebrile neutropenia, and chemotherapy had to be interrupted. The delivery was delayed until 34 weeks of gestation, two weeks after interruption of the chemotherapy to allow the recovery of maternal bone marrow, and 2 doses of betamethasone were given at 30 weeks to promote the fetal lung maturation.

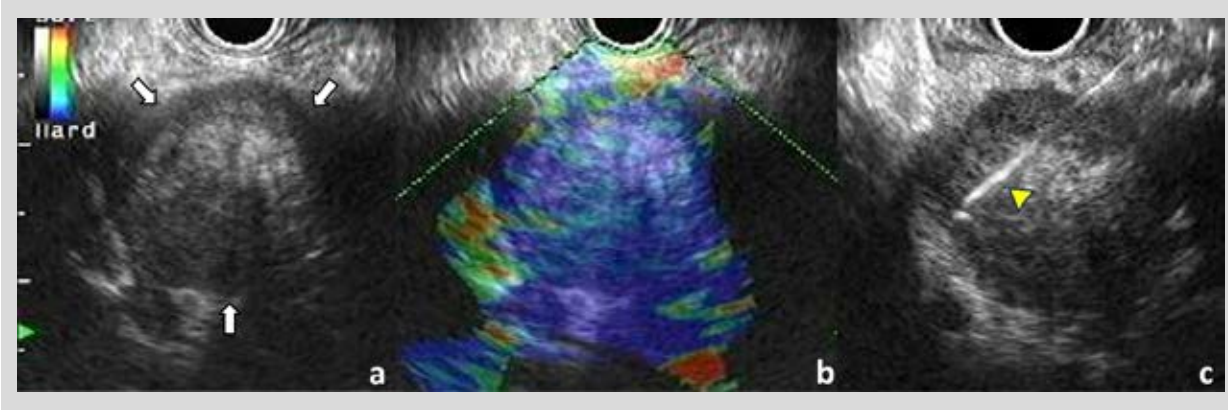

Figure 2. Linear-array endossonography. **a)** A hypoechogenic heterogeneous mass with ill-defined borders at the pancreatic head (withe arrows). **b)** EUS elastography of the pancreatic lesion demonstrating the solid nature of the mass (blue color area). **c)** EUS-guided core-needle biopsy (yellow arrowhead).

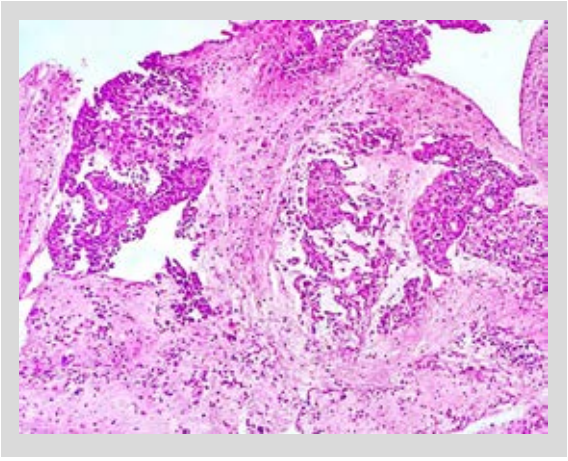

Figure 3. Histopathology findings of core-needle biopsies of the pancreatic mass demonstrating a poorly-differentiated ductal adenocarcinoma (cell block; hematoxylin and eosin; x100).

A cesarean section was performed and a baby girl was delivered weighing 3.230 g with Apgar scores 8 and 9 at 1 and 5 min. Nevertheless, four days after delivery, the clinical condition of the mother worsened criticaly.

Patient developed fever and severe abdominal pain. An Enterobacter sepsis was confirmed, and it was managed with antibiotics (meropenem, vancomycin, and cefepime). A few days later, the patient started vomiting profusely. Digestive endoscopy revealed tumor infiltration of the duodenum wall with severe stricture of the lumen, and a nasoenteral tube was required to ensure nutritional support.

A gadolinium-based contrast MRI was performed 2 weeks after delivery to evaluate the neoplasm. Pancreatic carcinoma had enlarged to 7 cm, common bile duct was more dilated (20 mm), medial wall of the second and third segments of duodenum were invaded by the tumor, and two 3-cm celiac lymph nodes were detected; vascular findings were encasement of the left gastric artery, invasion of the gastroduodenal artery, and abutment of superior mesenteric vein < 180°. The imaging findings classified the neoplasm as a borderline disease with a clinical stage IIB (cT3N1M0).

Four weeks postpartum, patient was submitted to a pancreaticoduodenectomy. Surgical findings revealed an unresectable neoplasm with massive infiltration of the mesentery and retroperitoneal space, as well as small liver metastases. Only palliative surgical procedures were performed, including a decompressive gastrostomy, a feeding jejunostomy, and a biliary bypass. Patient died 6 days after surgical intervention, 5 weeks postpartum, due to septic shock and multiple organ failure. Her child is in very good health and developing normally.

Ethical considerations

Ethical approval for the report of this case was obtained from our Institutional Review Board (6.872.165).

DISCUSSION

Pancreatic adenocarcinoma during pregnancy is extremely rare. Including our report, only 19 cases have been confirmed antepartum to date. Previous reported cases are shown in Table 1 [5-22]. The median maternal age at presentation was 36 years-old (range: 25-40), and the median gestational age was 22 weeks (range: 3-30). The main site of the lesion was the pancreatic head (14 cases), and the median size was 4 cm, ranging from 2.5 to 8 cm. In our case, a 37 year-old woman at 24 weeks of pregnancy identified a pancreatic neoplasm antepartum during investigation of a suspected acute pancreatitis, and a ductal adenocarcinoma was confirmed by endoscopic ultrasound-guided tissue acquisition.

Patients with pancreatic adenocarcinoma during pregnancy present multiple symptoms. The most common complaint was upper abdominal pain or back pain for all but one of these 19 cases. Disabling nausea and vomiting, and obstructive jaundice were manifested in 11 and 6 cases, respectively. Weight loss was experienced by 6 cases. Our patient presented epigastric pain radiating to the back, vomiting, choluria, acholia and jaundice. In the presence of clinical and laboratorial findings of acute pancreatitis, as was the initial presentation of our case and for other 4 cases, at least an abdominal ultrasound should be required to evaluate the pancreas and the presence of biliary lithiasis. In the absence of stones, a high index of suspicion for a neoplasm is mandatory.

Once confirmed a pancreatic neoplasm, serum levels of tumor marker CA 19-9 can define a pancreatic malignancy as the most likely lesion [23]. The CA 19-9 level was 2.474 U/mL for our patient. Serum levels of CA 19-9 were requested for 11 of 19 cases antepartum, and the mean value was 1.506 U/mL, ranging from 1 to 4.309 U/mL.

The prompt management of pancreatic adenocarcinoma requires histological diagnosis [23]. With the inclusion of our case, 5 of 19 cases were confirmed antepartum by endoscopic ultrasound-guided tissue acquisition [14-16,21]. Other 6 cases were confirmed by ultrasound or tomography-guided biopsies of the pancreatic mass (3) [6,17,19] or liver metastasis (3) [9,13,18]. Three cases with invasion of duodenal wall were confirmed by endoscopic biopsies [10,12,22]. A single case was confirmed after excision of a metastatic supraclavicular lymph node [20], and another case was confirmed by intraoperative biopsy of the mass at 17 weeks of gestation [7]. Three additional pancreatic neoplasms had been detected before the delivery, but were sampled and confirmed as adenocarcinomas during postpartum exploratory laparotomy [5,8,11].

The deliveries for these patients were as follows: 11 cesarean and 3 vaginal deliveries were performed. Two pregnancies were interrupted at 3 and 24 weeks, and 2 intrauterine fetal deaths were confirmed at 16 and 19 weeks. Another case was at 29 weeks of gestation until publication of the report after surgical removal of the mass during pregnancy. Median gestational ages for cesarean and normal deliveries were, respectively, 31

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Table 1. Reported cases of pancreatic adenocarcinoma during pregnancy with antepartum diagnosis §

Author	Year	Age (yr)	Gestation (weeks)	Symptoms and signs	Size	Location	CA 19-9 U/mL	Metastases	Mode of Delivery	Delivery (weeks)	Newborn situation	CHT	Timing of CHT	Surgery	Timing of surgery	Maternal Death post-delivery (weeks)
Present case	2024	37	24	Abdominal pain, vomiting jaundice, choluria, acholia, pancreatitis	37	Head	2,474	Yes *	Cesarean	34	alive	Yes	GA at 30 wks	Paliation	GA at 38 wks	5
Gamberdella *et al.* [5]	1984	37	24	Abdominal pain, weight loss	40	Head	NR	Yes #	Cesarean	32	alive / twins	No		Paliation	PD	12
Simchuk *et al.* [6]	1995	39	16	Abdominal pain	NR	Head	NR	No	Cesarean	28	alive	No		Paliation	GA at 20 wks	4
Blackbourne *et al.* [7]	1997	32	14	Back pain, vomiting, jaundice, choluria	25	Head	NR	No	Ongoing pregnancy	29	alive fetus	No		Resection	GA at 17 wks	Alive until publi-cation
Gojnic *et al.* [8]	2005	37	2nd trim	Abdominal pain, diarrhea	NR	NR	High	No	Cesarean	NR	alive	No		Resection	NR	Alive until publi-cation
Su *et al.* [9]	2006	37	22	Abdominal pain, jaundice	50	Head	NR	Yes #	Voluntary termination	24	dead	Yes	PD	None		4
Marinoni *et al.* [10]	2006	38	27	Abdominal pain, back pain, vomiting, jaundice, pancreatitis	40	Head	240	Yes #	Cesarean	30	alive	No		None		7
Somoye *et al.* [11]	2008	34	30	Abdominal pain, vomiting, jaundice, choluria, acholia	30	Head	NR	Yes *	Cesarean	32	alive	Yes	PS	Paliation	PD	12
Kakoza *et al.* [12]	2009	40	24	Abdominal pain, vomiting, pancreatitis, choluria, acholia, weight loss	35	Head	4,309	No	Cesarean	28	alive	Yes	PS	Resection	GA at 30 wks	28
Perera *et al.* [13]	2011	25	20	Abdominal pain, vomiting, pancreatitis	NR	NR	NR	Yes #	Cesarean	30	alive	No		None		2
Lubner *et al.* [14]	2011	37	16	Back pain, vomiting, choluria, acholia	32	Head	200	Yes *	Vaginal	35	alive	Yes	GA at 24 wks	Resection	GA at 18 wks	33
Papoutsis *et al.* [15]	2012	33	16	Weight loss, anemia, weakness	NR	NR	2,750	Yes #	Intrauterine death	19	dead	NR		NR		NR
Boyd *et al.* [16] - case 3	2012	37	17	Back pain, vomiting, choluria, acholia	42	Head	NR	Yes *	Vaginal	34	alive	Yes	GA at 24 wks	Resection	GA at 19 wks	37
Khatsiev *et al.* [17]	2014	29	3	Abdominal pain	47	Head	NR	No	Voluntary termination	3	dead	No		Resection		NR
Labarca-Acosta *et al.* [18]	2015	35	16	Abdominal pain, vomiting, weight loss	40	Tail	2,750	Yes #	Intrauterine death	16	dead	No		None		4
Lui *et al.* [19]	2015	35	22	Back pain, weight loss	80	Body	40	Yes *	Vaginal	30	alive	Yes	PD	None		20
Aker *et al.* [20]	2016	27	28	Abdominal pain, vomiting	NR	Head	2,064	Yes #	Cesarean	28	dead	No		None		2
Davis *et al.* [21]	2016	34	26	Abdominal pain, pancreatitis, weight loss	38	Head	1	Yes #	Cesarean	32	alive	No		None		16
Aynioglu *et al.* [22]	2017	36	28	Abdominal pain, back pain, vomiting, jaundice	70	Head	232	No	Cesarean	32	alive	Yes	PD	Resection	GA at 32 wks	NR

§ Carcinomas arising from mucinous cystic neoplasms or intraductal papillary mucinous neoplasms were not included.
GA: Gestational Age (weeks); CHT: Chemotherapy; DIC: disseminated intravascular coagulation; HELLP: hemolysis, elevated liver enzymes, low platelet syndrome;
PD: Post-delivery; PS: Post-surgery; NR: not reported
metastases confirmed in the diagnosis of pancreatic neoplasia, * metastases detected postpartum or surgery.

weeks (range: 28-34) and 34 weeks (range: 30-35). The postpartum period was uneventful for 11 babies delivered by cesarean sections (there was a twin pregnancy), and one 28-week baby died due to sepsis. The three babies delivered by vaginal deliveries left the hospital in good health. Corticotherapy with betamethasone was given to 6 of 19 pregnant women, including our case [10,12,19,20,22]. Five but one [20] of these patients delivered healthy babies. As we noticed, the fetal outcome was highly favourable, as was the situation in our case.

The treatment for the pancreatic adenocarcinoma is the surgical resection [23]. However, less than 20% of patients present a resectable disease, and the 5-year survival for such cases reaches 11% in high-volume reference centers [24]. Regarding the treatment of pancreatic adenocarcinoma during pregnancy, as the literature has only scarce case reports about pancreatic cancer during pregnancy, there are not enough data to define the best treatment. In an attempt to protect the fetus and the mother as much as possible, multidisciplinary consultations are the cornerstone to define strategies about delivery, chemotherapy, and surgical intervention.

The most suitable moment to perform an abdominal surgery in pregnant women is the second trimester of gestation [1]. As the majority of pancreatic tumors were diagnosed during this moment, immediate surgery should have been a possible therapeutic approach for most of such cases. However, as pancreatic adenocarcinoma is one of the most aggressive malignancies of the digestive tract, unresectable disease (stage IV) was present in 12 of 19 cases. Only 5 cases submitted to surgery were amenable to curative resection [7,8,12,17,22], and their outcomes were very disappointing regardless of their better tumoral staging. One patient was alive after distal pancreatectomy until publication of that report, but there was no information on the precise time of follow-up [8], and other case at 29 weeks of an ongoing pregnancy was alive 12 weeks after pancreaticoduodenectomy [7]. The other 3 patients died after pancreatoduodenectomy [12,17,22]. Liver metastases were detected during delivery in 2 other patients previously defined as resectable disease, and only palliative surgeries were performed [14,16].

As a rule, for malignant neoplasms, distant metastases define a disease as incurable [23,24]. Metastases were detected in 13 of 19 (68%) patients, 8 cases in the moment of the diagnosis, and other 5 cases immediately postpartum or during surgery, as was our case.

In regard to chemotherapy, there is nothing defined on its value for the management of pancreatic adenocarcinoma during pregnancy. So far, including our case, 8 patients received either gencitabine or Folfirinox [9,11,12,14,16,19,22], but only 3 of such cases during pregnancy, between 24 and 30 weeks of gestation, with no prejudice to the fetus [14,16]. Whereas, 5 cases were treated after delivery or surgery. Our patient with a potentially resectable clinical stage IB disease started chemotherapy during pregnancy, and surgery was postponed until delivery. Nonetheless, the chemotherapy regimen could not be accomplished because of a drug-induced neutropenia, and the treatment had to be interrupted shortly after the second cycle.

The outcome of pregnant women with pancreatic adenocarcinoma is devastating. As a whole, mean survival was 13.2 +/- 11.9 weeks. Fourteen patients died between 2 and 37 weeks postpartum (11 of such cases died within five months after delivery), one patient was at 29 weeks of an ongoing pregnancy [7], other patient was alive until publication of that report [9], and another case was alive 4 years after surgical resection of a clear cell adenocarcinoma with low-grade differentiation [17]. The outcome was not available for other 2 patients. Median survival for 11 patients exclusively submitted to palliative care was only 5 weeks (range: 2-20). Our patient received only palliative surgical procedures. She died due to septic shock and multiple organ failure. Eventually, whether an initially resectable disease of our patient became an unresectable disease as a consequence of its more aggressive biologic behaviour or a surgical delay of 2 months cannot be clarified at this moment.

A pregnant woman with severe epigastric pain radiating to the back, especially in the presence of jaundice, should have ruled out a pancreatic neoplasm. In case a malignancy is identified, the histology diagnosis is required. In case a pancreatic adenocarcinoma is confirmed, the treatment should be taken as a consensus between the mother and a multidisciplinary team in a referal center, pursuing the best outcome for both mother and fetus.

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