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Review Article

Pregnancy-associated mucinous cystic neoplasms of the pancreas - A systematic review

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A B S T R A C T

Introduction: Mucinous cystic neoplasms (MCN) are mucin-producing epithelial cell tumors of pancreas. They consist of an ovarian-type stroma expressing estrogen and progesterone receptors. Pregnancy-associated MCNs are presumed to be larger in size and more aggressive without any concrete evidence.
Objective: and Data Sources: Systematic review of published literature using PubMed and Google Scholar databases. Original articles including case reports and series published between 1970&2021 were included wherein MCN was diagnosed during pregnancy/within one-year post-partum. Thirty-three publications having 36 cases, adding one of our own patient were analyzed in this review.
Result: Median age at presentation was 32 years. Only three (9%) patients were asymptomatic. Mean size of MCN was 135 mm. Ten patients (27%) reported an increase in size during pregnancy. Most tumors involved body and tail of pancreas (60%). Distal pancreatectomy with splenectomy was the most common resection performed (57%). No foetal mortality was reported to date.
Conclusion: Pregnancy may cause a rapid increase in size of MCN. Decision-making is more complex and needs a fine balance between optimal oncological and obstetric outcomes.

1. Introduction

Mucinous cystic neoplasms (MCN) of the pancreas are cyst-forming, mucin-producing tumors characteristically defined by the presence of ovarian-type sub-epithelial stroma. First defined by Compagno et al., in 1978, they combined the previously classified 'cystadenoma' and 'cystadenocarcinoma' into mucin-producing neoplasms.[1] MCNs were identified as a separate entity by WHO in 1996, differentiating them from intraductal papillary mucinous neoplasms (IPMN). These tumors almost exclusively (98% of all MCNs) occur in women. They primarily affect middle-aged females with the mean age at diagnosis being 48 (range 14–95) years.[2] MCNs comprise about 8% of resected cystic lesions of the pancreas. Almost half of the patients are incidentally diagnosed on abdominal imaging with abdominal fullness being the most common symptom.[3] Magnetic Resonance Imaging (MRI) is the investigation of choice; however, computed tomography (CT) scan or endoscopic ultrasonography (EUS) may also be useful in their evaluation.[3,4] Tumor analysis shows presence of a mucin-secreting epithelium with ovarian-like stroma expressing estrogen and progesterone receptors, but this finding is not always seen.[3,5] These tumors have an excellent prognosis with 5-year survival as high as 100%.[3]

Their occurrence in pregnancy was first reported by Smithers et al., in 1986, although the differences in tumor biology and progression during pregnancy was first reported by Ganepola et al., in 1999.[6,7] MCNs, which otherwise predominantly occur in the perimenopausal age, appear at younger ages when associated with pregnancy. With the dynamic hormonal environment during pregnancy, these tumors are presumed to grow rapidly, evident in the larger tumor size at presentation in pregnant women when compared to the general population.

However, pregnancy-associated MCN in itself is a rare entity, with available evidence being limited to occasional case reports or small case series and only a total of 36 cases reported in the English literature to date. It is not possible to establish a cause-effect relationship between pregnancy and the aggressive behaviour of MCN with the available evidence. It is further complicated by the limitations of available modalities of intervention due to the risk of causing undue harm to the developing foetus, making the approach to management of these lesions during pregnancy more complex and debatable.

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Considering the paucity in the data, after a recent experience in the management of a pregnancy-associated MCN, we conducted a systematic review of the available published English literature adding our own case data in an attempt to understand the behavior and association of a rare entity like pregnancy-associated MCN.

2. Materials and methods

We performed a systematic review of the published literature using PubMed and Google Scholar databases using the keywords 'mucinous cystic neoplasm' OR 'mucinous cystadenoma' OR 'mucinous cystadenocarcinoma' AND 'pregnancy' AND 'pancreas. The search was restricted to papers published between 1970 and 2022. Only original case reports in English text were selected. The titles followed by abstracts of the articles were reviewed and only reports wherein MCN of the pancreas was diagnosed and/or treated during pregnancy or within one-year post-partum were included. Any review articles or non-original articles were excluded from the study. Thereafter, a manual search of the articles was conducted to look for any reports that were not found in the database search. A total of 33 papers were finally included in the review (Fig. 1).

The following variables regarding the patients were extracted from the reports wherever available: age, symptoms, parity, pregnancy status, gestation at diagnosis, tumor markers, size of the tumor at presentation, location of the tumor, pre-operative intervention, progression, cyst rupture, gestation at surgery, surgical management, outcome of pregnancy, surgical complications, histopathology, IHC, post-operative chemotherapy, follow-up, recurrence.

A total of 37 cases, along with our own case, were included in the analysis.

2.1. Our case detail

A 33-year-old female, P2, L2 presented to us with complaints of persistent, progressive abdominal fullness and distension three months even after parturition. She also had history suggestive of acute pancreatitis 15 years ago (at the age of 18 years). General physical examination was unremarkable. A firm, 20 × 20 cm lump was palpable in the epigastrium. US showed a cystic lesion in the upper abdomen. A subsequent Contrast-enhanced computed tomography (CECT) of the whole abdomen revealed a well-circumscribed cystic lesion with enhancing septa and mural nodule located in the lesser sac, splaying the body and tail of pancreas, reaching up to splenic hilum (Fig. 2). The main pancreatic duct was not prominent. But, because of the history of acute pancreatitis, we further evaluated the patient with contrast-enhanced MR with cholangio-pancreaticogram (CE-MRI with MRCP) to rule out any ductal communication and the possibility of IPMN (Fig. 1). Pancreatic duct was not dilated and no communication of the cyst with pancreatic duct was seen. Serum CA 19.9, CEA and CA-125 levels were 226.8 U/ml, 3.2 ng/ml, and 39.7 U/ml respectively. In view of her symptoms and suspicious characteristics on imaging, she was planned for distal pancreatectomy and splenectomy. Intra-operatively, a huge mass was seen arising from the body and the tail of the pancreas occupying the lesser sac, displacing the transverse colon into pelvis. The mass was adherent to the mesocolon, spleen, and diaphragm. Distal pancreatectomy and splenectomy was done with excision of the transverse mesocolon with preservation of the marginal arcade to achieve adequate resection margins. The pancreas was divided with linear GI stapler (Ethicon 60 blue cartridge) and the pancreatic stump was reinforced with Prolene 3-0 intermittent mattress suture. The post-operative course was uneventful. Drain was removed on postoperative day 5 and the patient was discharged in a satisfactory condition. Histopathological examination revealed mucinous cystic neoplasm 30x20 × 15 cm in size, with high-grade dysplasia and ovarian-like stroma with stromal cells showing nuclear positivity for Estrogen and progesterone receptors (ER and PR) with all margins free of tumor involvement (Fig. 3).

Cross-sectional imaging was repeated after one year of follow-up which showed no evidence of recurrence and she is currently doing well.

2.2. Results of the systematic review

Median age at presentation of 37 patients with pregnancy-associated MCN was 32 (range 20–41) years. Twenty-nine patients presented during pregnancy in various trimesters and eight patients presented within one year after the completion of pregnancy. The patients presented with varying symptom complexes, with abdominal pain being the most common complaint (50%) followed by abdominal distension and abdominal lump (24% and 18% respectively). Two patients each presented with acute pancreatitis and upper GI bleeding requiring blood transfusions. Three (9%) patients were diagnosed incidentally on routine antenatal US. A diagnostic MRI was done in nearly all patients during pregnancy and a CT for those in post-partum. The mean size at diagnosis was 135 (range 15–210) mm. Thirteen patients had a reported increase in size of the tumour during the course of evaluation to management.

The tumour was in the pancreatic tail in 13 (35%) patients, body in five (14%), head in two (5%), and was involving both body and tail in 15 (40%). Eighteen (49%) patients underwent the surgery for the MCN during pregnancy. Among these Ten patients were operated in their second trimester and four each were operated in first and third trimesters. Nineteen (51%) patients underwent surgery after index pregnancy, including our case. Majority of the patients underwent radical resections in the form of Distal pancreatectomy (88%), Pancreaticoduodenectomy (3%) and subtotal pancreatectomy (3%). Parenchyma preserving pancreatic resections like central pancreatectomy (3%) and cystectomy or enucleation (8%) were also reported. Cyst rupture was reported either pre-operatively or during laparotomy in four (10.8%) patients. One patient developed prolonged post-operative pancreatic fistula (POPF), but no operative or post-operative mortality was reported in any of these patients.

Thirty-five (95%) patients had completed the pregnancy successfully. Two (5%) patients underwent abortion during the first trimester due to an imminent need for surgery. Among the patients who had completed their pregnancy, four (11%; 4/35) were reported to have a preterm delivery, while the remaining delivered after the completion of the term. There is only one (3%) reported case with intra-uterine growth retardation. However, there were no foetal or maternal mortalities reported till date.

All patients reported presence of ovarian-type stroma but with variable expression of ER (58%) and PR(73%). Low-grade and high-grade

Fig. 1. Schematic representation of the systematic review of MCN in pregnancy.

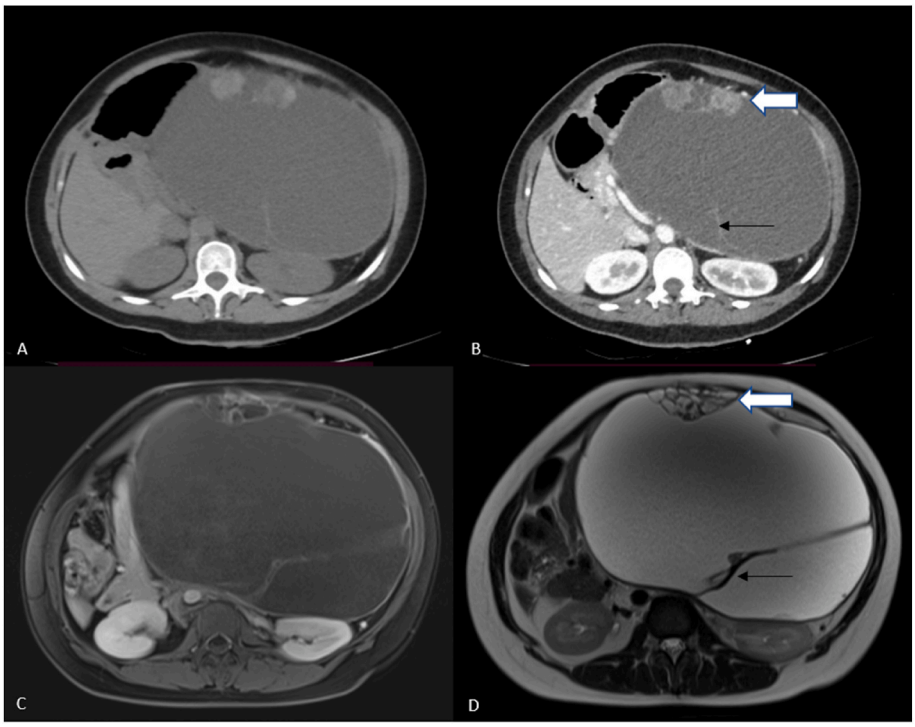

Fig. 2. A) NCCT Abdomen showing a large cyst in the abdominal cavity with septations (black arrow) and solid content within (mural nodule, white arrow) B) The mural nodule and septations are seen to enhance on contrast enhanced images C) Contrast enhanced T1w MRI of the same patient showing hypointense fluid within cyst cavity with hyperintense mural nodules D) Hyperintense fluid within the cyst on T2w MRI with hypointense mural nodules.

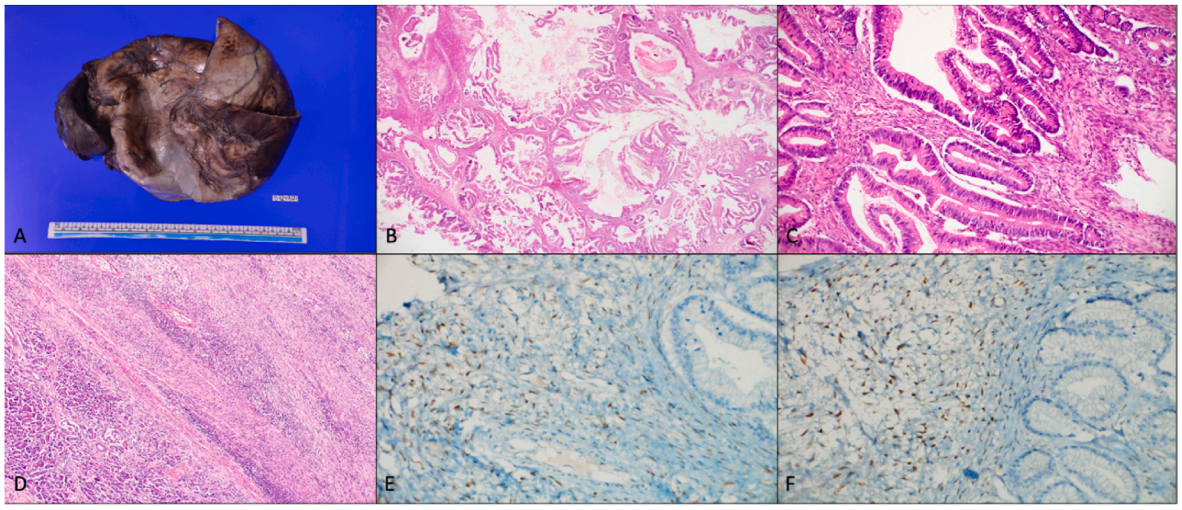

Fig. 3. A) Gross photograph of the resected cyst with attached spleen. B) Thickened areas of the cyst wall showing complex architectural papillae lined by mucinous epithelium (H & E, 100x). C) Lining cells show features of high-grade dysplasia in the form of nuclear stratification, hyperchromasia, and loss of polarity, and intervening stroma is cellular having spindle shaped cells reminiscent of ovarian-like stroma (H & E, 400x). D) The adjacent pancreatic parenchyma shows features of chronic pancreatitis in the form of loss of acinar tissue, and lymph-mononuclear cell infiltrate (H & E, 200x). The stromal cells demonstrate nuclear positivity for ER (E) and PR (F) (DAB chromogen, haematoxylin counterstain, 400x).

MCN were reported in twenty (54%) and eight (22%) patients respectively, while mucinous cystadenocarcinoma was reported in nine (24%). Two patients with mucinous cystadenocarcinoma were administered adjuvant Gemcitabine chemotherapy. The median duration of follow-up was 18 months. Of the 9 patients with mucinous cystadenocarcinoma, two patients developed recurrence.

Description of the demographics, presentation, biochemical and radiological investigations, management, histopathology and outcome of pregnancy of all the 37 patients, including our own is summarised in Tables 1–3.

3. Discussion

Mucinous cystic neoplasms (MCN) of the pancreas have been known as a separate entity for a long time since their first description by Compagno and Oertel in 1978.[1] They have been characterised as mucin-producing, cystic lesions with a well-defined cyst wall without connection to the pancreatic duct or its branches.[4] However, it was not until the late 1900's when Ganepola suspected a difference in the tumor biology and behaviour among pregnant women.[6] Although a large number of cases of MCN have been reported in the literature, their

Table 1
LOW-GRADE MCN.

S. No	Author	Patient Demographics		Clinical History						Progression (Increase in size)	Management					Histopathology			Follow-up	
		Age	OF	Presentation	POG at Diagnosis[e]	Size at Diagnosis[b]	Pregnancy Complications	CEA[a]	CA-19-9[d]		POG at Surgery[e]	Size at Surgery[b]	Location	Surgery	Complications	OS	ER	PR	Duration[c]	Recurrence
1.	Asciutti et al.[29]	31	G2P1	Acute Pancreatitis	Immediate pre-pregnancy	15	Pre-term LSCS due to pancreatitis	NA	213.7	4x in 6 months	PP	NA	Tail	Lap. DP + S	None	+	NA	NA	NA	–
2.	Wiseman et al.[30]	32	G5P2	Abdominal pain, vomiting	11	150	Viable till Follow-up	NA	NA	NA	15 + 5	NA	Tail	SP[j]	None	+	NA	NA	Till 26 wks POG	None
3.	Kato et al.[31]	33	G2P1	NA	15	NA	None	NA	NA	1.4x in 1 month	23	220	Body	DP + S	None	+	+	+	NA	NA
4.	Ikuta et al.[32]	30	NA	Abdominal distension and pain	10	180	Abortion at 10 wks	NA	NA	–	10	NA	NA	DP	None	+	+	+	12	None
5.	Kosumi et al.[33]	33	NA	Back pain	4th month	60	None	NA	92	NA	PP (2 wks)	NA	NA	DP	None	+	+	+	NA	NA
6.	Ishikawa et al.[34]	33	G2P1	Abdominal lump	17	120	None	NA	NA	1.5x in 7 months	PP (2 months)	180	Body and Tail	DP + S	None	+	–	–	7	None
7.	Tica et al.[35]	27	G1P1	Incidental	29	116	None	WNL	WNL	1.2x in 4 months	PP (2 months)	140	Body and Tail	DP	None	+	–	–	6	None
8.	Fernandez et al.[36]	26	G1P1	Abdominal pain, vomiting	20	140	None	NA	NA	–	20	150	Tail	DP	None	+	NA	NA	48	None
9.	Martins Filho et al.[37]	20	NA	Abdominal pain and distension	20	150	None	NA	NA	–	22	NA	Tail	DP + S	None	+	NA	NA	NA	–
10.	Kitagawa et al.[38]	25	P1	Abdominal lump	PP (10 months)	150	None	NA	3090	NA	PP (11 months)	NA	Body	DP	None	+	NA	+	NA	–
11.	Urabe et al.[39]	34	G2P1	Abdominal pain	16	160	None	WNL	18.5	1.03x in 8 wks	PP (1 month)	NA	Body	DP + S	Persistent POPF	+	NA	NA	NA	–
12.	Urabe et al.[39]	40	G3P2	Acute Pancreatitis	33	NA	Pre-term LSCS due to pancreatitis	WNL	26	NA	PP (1 month)	120	Tail	DP + S	Pre-op cyst rupture	+	+	–	48	None
13.	Shirakawa et al.[40]	31	G1P1	Abdominal distension	26	190	None	WNL	WNL	Nil	PP (3 months)	190	Body and Tail	DP	None	+	+	+	NA	–
14.	Olsen et al.[41]	25	NA	NA	5	50	None	NA	NA	Nil	18	50	Tail	DP	None	+	NA	NA	NA	–
15.	Ganepola et al.[6]	37	G2P1	Abdominal pain	4	55	None	NA	NA	2.2x in 4 months	23	120	Tail	DP + S	None	+	–	+	60	None
16.	Coral et al.[42]	26	G2P1	Incidental	3	120	Pre-term LSCS for severe Pre-eclampsia	NA	NA	2.42x in 5 months	PP (1 month)	230	Body and Tail	Cystectomy + S	None	+	–	+	6	None
17.	Komatsu et al.[43]	31	P2	Abdominal distension	PP (6 months)	150	None	NA	NA	–	PP (6 months)	150	Tail	DP + S	None	+	+	+	NA	–
18.	Carvalho et al.[44]	32	NA	Incidental	31	210	IUGR	WNL	WNL	1.43x in 11 weeks	PP (5 weeks)	300	Tail	DP	None	+	NA	NA	12	None
19.	Berevoescu et al.[45]	30	NA	Abdominal pain, distension and vomiting	PP (8 months)	160	None	WNL	WNL	NA	NA	180	Body	Central Pancreatectomy without ductal reconstruction	None	+	NA	NA	24	None
20.	Lee et al.[46]	35	G2P1	Abdominal pain	26	150	Fetal distress	NA	2	–	26	150	Body and Tail	DP + S	None	+	+	+	12	None

OF- Obstetric Formula.
PP- Post-Partum.

DP- Distal Pancreatectomy.
SP- Subtotal Pancreatectomy.
S- Splenectomy.
c-months.
j- Subtotal pancreatectomy.
[a] ng/ml.
[b] Maximum dimension (mm).
[d] IU/ml.
[e] weeks.

Table 2
HIGH-GRADE MCN.

S. No	Author	Patient Demographics		Clinical History						Progression (Increase in size)	Management					Histopathology			Follow-up	
		Age	OF	Presentation	POG at Diagnosis[e]	Size at Diagnosis[b]	Pregnancy Complications	CEA[a]	CA-19-9[d]		POG at Surgery[e]	Size at Surgery[b]	Location	Surgery	Complications	OS	ER	PR	Duration[c]	Recurrence
1.	Brown et al.[47]	38	NA	Occult UGI Bleed	8	–	None	NA	NA	–	8	100	Body and Tail	DP + S + PG[f]	None	+	NA	NA	60	None
2.	Herring et al.[23]	34	G2P1	Abdominal lump	3	190	None	NA	NA	1.05x in 14 wks	17	200	Tail	DP + S	None	+	+	+	3	None
3.	Tsuda et al.[48]	28	G2P1	NA	Pre-pregnancy	NA	None	NA	10	1.07x in 9 wks	18 + 3	150	Body and Tail	DP + S	None	+	+	+	8	None
4.	Revoredo et al.[49]	38	G3P2	Abdominal pain	18	200	None	0.91	10.7	None	29	200	Body and Tail	DP + S	Pre-op cyst rupture	+	–	+	96	None
5.	Boyd et al.[24]	21	G2P1	Abdominal distension	11	172	None	NA	NA	None	20	170	Body and Tail	DP	None	+	NA	NA	12	None
6.	Kleef et al.[50]	41	G1P1	Abdominal pain	PP (3 months)	70	None	NA	NA	1.75x in 3 yrs	PP (3 months)	NA	Body	DP + S	None	+	+	+	NA	–
7.	Takashima et al.[51]	28	G3P2	Abdominal lump	12	90	None	1.3	73	1.4x in 6 months	PP (1 month)	130	Head	Cystectomy + Cholecystectomy	None	+	+	+	30	None
8.	Current case	33	P2	Abdominal distension	PP (6 months)	200	None	3.2	226.8	1.26x in 1 month	PP (7 months)	250	Body and Tail	DP + S	None	+	+	+	12	None

Table 3
MCN carcinoma.

S. No	Author	Patient Demographics		Clinical History						Progression (Increase in size)	Management					Histopathology				Follow-up	
		Age	OF	Presentation	POG at Diagnosis[e]	Size at Diagnosis[b]	Pregnancy Complications	CEA[a]	CA-19-9[d]		POG at Surgery[e]	Size at Surgery[b]	Location	Surgery	Complications	OS	ER	PR	Invasion	Duration[c]	Recurrence
1.	Ozden et al.[52]	32	G2P1	Acute Abdomen[g]	36	150	Pre-term LSCS due to Fetal distress	NA	NA	–	36	150	Tail	En-masse cyst excision	Pre-op cyst rupture	+	–	–	No LVSI	12	None
2.	Hakamada et al.[53]	38	G2P1	UGI Bleed	2 yrs Pre-preg	100	None	NA	NA	1.4x in 2 yrs	T2	140	Tail	DP + S + PG[f]	None	+	NA	+	No LVSI	48	Yes
3.	Smithers et al.[7]	33	NA	Acute Abdomen	7	100	Elective MTP at 8 wks POG	NA	NA	–	8	100	Body and Tail	DP + S	Pre-op cyst rupture	+	NA	NA	NA	NA	NA
4.	Berindoague et al.[54]	31	NA	Abdominal pain and lump	PP (2 months)	–	None	WNL	WNL	–	PP (2 months)	120	Body and Tail	DP + S	None	+	–	–	No LVSI	NA	NA
5.	Revoredo et al.[49]	30	G1P1	Abdominal pain	17	118	None	4.1	51.9	–	17	150	Body and Tail	DP + S	None	+	+	+	NA	60	None
6.	Baiocchi et al.[55]	29	NA	Abdominal pain and lump	T3	100	None	NA	NA	–	PP	100	Tail	DP + S	None	+	NA	NA	Stromal invasion +	24	None
7.	Iusco et al.[56]	28	P2	Abdominal discomfort	PP	160	None	NA	64.4	–	PP	160	Body and Tail	DP + S	None	+	+	+	No LVSI	6	None
8.	Naganuma et al.[57]	32	G1P1	Acute Abdomen	34	NA	Pre-term LSCS	WNL	4750	NA	34	110	Head	PD[i]	None	+	–	+	No LVSI	36	Yes
9.	Shirakawa et al.[40]	36	P2	Abdominal pain	PP (3 wks)	150	None	WNL	WNL	1.06x in 10 days	PP (1 month)	160	Body and Tail	DP	None	+	–	–	NA	132	None

f- Partial Gastrectomy.
g- Acute abdominal pain warranting immediate intervention.
h- Pre-term labour.
i- Pancreaticoduodenectomy.

occurrence among pregnant women has been rare. We could find only a total of 33 case reports/series published in English literature reporting 36 cases till date.

The median age at presentation for MCN in the general population is 45 years.[8] However, according to our review, they seem to present at younger age groups in pregnant women than the general population (median age at presentation 32 years).

More than half of the patients with MCN in the general population are detected incidentally as reported by Yamao et al. in a multi-institutional study, with abdominal fullness (60–90%) and abdominal lump being the most common among the symptomatic patients.[3,9] Contrary to this evidence, only 9% patients among the pregnancy associated MCN in this review were incidentally detected. Abdominal pain (44%) and disproportionate abdominal distension (24%) to the stage of pregnancy were the common symptoms reported in this subset of population. MCNs also harbour the potential of causing acute pancreatitis, secondary to compression of the pancreatic duct as seen in 9% of the general population.[8] In our current review, 14% patients had a documented episode of pancreatitis in the past, and 6% patients presented with features suggestive of acute pancreatitis.

Although complaints of abdominal pain, fullness or vomiting can be a normal physiological phenomenon in pregnancy, any new onset and/or worsening symptom during pregnancy should not be ignored and must be thoroughly investigated for its cause. Since a myriad of diseases can be attributed to the cause of such symptoms, this mandates an US of the whole abdomen instead of just a focused obstetric US to rule out the common non-obstetric complications in pregnancy such as acute appendicitis, acute cholecystitis or pancreatitis. Ultrasonography being a cost-effective modality and easily available in most obstetric setups can be an important tool to screen for other rare pathologies which have the potential to grow rapidly during pregnancy.

Ultrasonography of abdomen is usually the first abdominal imaging done. It can detect presence of a cyst in the pancreas, comment on its vascularity and/or presence of any solid components. The sensitivity of abdominal US to detect cystic lesions of the pancreas is low (70%), which falls further to 27% for lesions in pancreatic tail,[10] with the accuracy to detect MCN being below 50%.[11] Therefore, US abdomen, although being a cheap and accessible investigation does little to guide the management of these lesions.

The investigation of choice for MCN is MRI which shows a multi/unilocular macrocyst with hyperintense appearing mucin on T1w images that lacks communication with the pancreatic duct. It is highly accurate (88%) to distinguish malignant pancreatic lesions.[12] Features such as large size (≥3 cm), presence of mural nodules, eggshell calcification on MRI are predictors for malignant transformation. An EUS-FNA with raised fluid CEA (>194 ng/ml) and low amylase is typical of MCN.[13,14] Even so, pregnancy poses a great limitation to most of the modalities of investigation. MRIs, especially those that need contrast enhancement, have safety concerns during pregnancy and should be performed if benefits outweigh the risk regardless of the period of gestation of pregnancy.[15] EUS often involves administration of a sedative or short-term anaesthesia may pose safety concerns for the developing foetus.[16]

Techniques such as microforceps biopsy (EUS-MFB) provide some hope for a definitive pre-operative diagnosis of MCN in the future, but it's utility and efficacy is still under evaluation and surgical resection currently remains the only method of definitive diagnosis of these lesions.[17,18]

The role of tumor markers is less reliable for detecting MCN of the pancreas. An elevated serum CEA level has a sensitivity of only 17%. If two out of the three serum tumor markers (CEA, Ca 19-9 and Ca 125) of pancreatic malignancy are raised, it is highly suggestive of a MCN (specificity 100%) but the sensitivity drops further down to 13%.[11,19]

MCNs are predominantly benign although they harbour a risk of malignant transformation. They have been defined as small, slow-growing tumors (5 mm/year),[20] with large size and/or rapid growth suggestive of malignant transformation.[4] This, however cannot be generalised, as evident from our review wherein the mean size of MCN in pregnant patients was double (13.5 cm) that of the general population (6 cm [4]). Also, this review suggests that growth of the tumor cannot be necessarily related to malignant transformation in pregnant patients. Only two out of ten patients with MCN in this review, with recorded increase in size during the evaluation period had shown adenocarcinoma while the remaining had carcinoma-in-situ or adenomas. However, it must also be noted that most of our review compared size of tumors on the first imaging to the size during surgery and/or another imaging with a time interval. Since most of the patients underwent an US which is subjective and has high interobserver variation, no conclusive interpretation on the growth of the lesions can be made until prospective trials with set protocols are conducted in the future.

Since most of the tumors are located within the body and/or the tail of the pancreas their management consists of a distal pancreatectomy (90–95% patients with pancreatic MCN) with or without splenectomy. Even, parenchyma preserving resections in the form of enucleation/excision or parenchyma preserving surgeries (middle pancreatectomy) were also reported, for smaller and superficial lesions without any high-risk features on cross-sectional imaging.[11,21]

Management of MCN during pregnancy poses a complex challenge. As it needs a fine balance between the treatment of a complex pancreatic tumour and minimising the impact of tumour, its treatment on the outcome of pregnancy. Watchful waiting can be considered in some patients with small, asymptomatic and slow growing tumors. However, complete surgical excision is the definitive management of MCN. Hence, the difficult questions to be answered would be the timing of pancreatic surgery in pregnancy and the potential impact of surgery on the outcome of pregnancy.

In the current day scenario, even though there are no contraindications for abdominal surgery during the first trimester, the tendency to avoid surgery due to the safety concerns of the foetus makes close monitoring a chosen option by many experts.[22] However, surgery cannot be deferred in patients with rapidly growing tumors or when there is a high suspicion of malignancy on clinical or radiological grounds. In such a scenario the possibility or the need for the termination of the pregnancy has to be decided after a discussion with the patient, her family and the obstetrician. If MCN is detected in the second trimester of the pregnancy, the proclivity was more towards the resection of the tumour. This is reiterated by the fact ten out of 18 patients were in their second trimester who were operated during the pregnancy in this review. Many clinicians believe that this potentially alleviates the chance of foetal complications like IUGR and preterm deliveries due to the pressure effects of the large MCN on the growing uterus, especially when allowed into the third trimester. This is Evident in two patients (28%) in the current review who were allowed to continue into their third trimester without intervening for MCN had complications like IUGR, Foetal distress and preterm delivery. No such complications were reported among the patients who had underwent the surgery in the second trimester till date. Patients in whom the MCN is detected in the 3rd trimester surgery can be postponed to the post-partum period, although the risk of foetal complications is high. In our review, 4 patients (67%) developed some form of foetal complication although no foetal mortality was reported.[23–25]

However, we should also understand that pancreatic resections are associated with a high risk of post-operative complications and morbidity. Most worrisome complication of all is the development of POPF which is reported up to 30% patients following distal pancreatectomy, which is the most commonly performed resection for MCN as noted in this review.[26] Even though in our review only a single patient was reported to have developed a post-operative morbidity, the potential deleterious effects of POPF on the maternal as well as foetal outcomes cannot be overlooked. Hence every effort should be made to reduce the post pancreatectomy complications. This can be achieved by the resections being undertaken in a high-volume centres with a

multidisciplinary team comprising of experienced pancreatic surgeon, obstetrician, Neonatologist, Radiologist and intensivist.

MCNs have two very distinct histological layers, first the outer epithelial layer consisting of mucin-producing cells and the inner layer of dense cellular ovarian stroma. It is this stromal layer that distinguishes MCN from serous cystic neoplasm (SCN) and IPMN. The origin of the stromal layer is under debate with some claiming it to be an ectopic ovarian stroma incorporated during embryogenesis that gets activated during hormonal imbalance; others claim its origin to differentiation of persistent foetal periductal mesenchyme. However, both these hypotheses have their own fallacies and none has been universally accepted.[4,27,28]

WHO has divided these tumors into 3 major histologic categories - low-grade MCN/mucinous cystadenoma (combining the previous 'MCN with low-grade dysplasia' and 'MCN with intermediate-grade dysplasia'), high-grade MCN/carcinoma-in-situ and MCN with associated invasive carcinoma/mucinous cystadenocarcinoma. Different series report the prevalence of carcinoma ranging from 7 to 36%. In gross distribution, about 70–75% of all MCNs are cystadenomas with the rest being carcinoma-in-situ.[5,8,9,13,28] Our review is consistent with this distribution suggesting that even though the growth of tumors is high during pregnancy, the aggressiveness in terms of malignant transformation is not increased.

The epithelium varies in the degrees of dysplasia among different patients as well as within the same tumour at different sites suggesting presence of a definitive sequence of benign to malignant transformation in these tumors. The characteristic temporal association of malignant transformation along with presence of benign-looking regions within the same malignant cysts also suggests the gradual accumulation of mutations for malignant conversion much similar to that described for colorectal cancer (CRC) although a proper adenoma-carcinoma sequence has yet not elucidated among these tumors.

The expression of ER and PR in MCNs of pancreas is not universal. Estrogen receptor is expressed in 78% patients and progesterone receptor in 88% patients.[3] Despite MCNs portraying a similar receptor expression pattern in pregnant patients as seen in our review, they are seen to grow at a much faster pace compared to that of the general population. Also, there exists no definitive relation between the growth of tumour and expression of estrogen or progesterone receptor according to our review. This might suggest a complex interplay of other unknown factors which might also influence the difference in tumor biology in this subset of patients. However, any further comment on the tumor behaviour requires large-scale prospective studies and/or molecular analysis regarding the same.

Pregnancy-associated MCN being a rare condition, the data available is very limited to draw any conclusion in terms of the association of the pregnancy and the aggressive behaviour of the Mucinous cystic neoplasms. However, this review sheds light on potential problems like the effect of pregnancy on tumour growth and vice versa. The cumulative data in this review reiterates the potential of MCN to attain very large sizes causing compression over the growing uterus with a theoretical possibility of growth retardation in the foetus along with the risk of preterm deliveries affecting the outcome of pregnancy. Even though the complication rate after pancreatic surgery in this review was very low, the morbidity and mortality associated with pancreatic resections are very high and well known. This in turn may have a negative impact on the outcomes of pregnancy. As there are no set guidelines for the management in this specific subset of patients, owing to the paucity of data, the review reiterates the need to develop robust database which would aid the formulation of future guidelines, multidisciplinary discussions involving the surgeon, obstetrician, radiologist, patient, and her family in order to improve not only the oncological outcomes but also optimize the maternal and the foetal safety.

4. Conclusion

Pregnancy-associated MCN is a rare entity. Pregnancy may cause a rapid increase in size of MCN. However, it may not alter the underlying biology of the tumour. Decision-making in the management of MCN when associated with pregnancy is more complex as it needs a fine balance between optimal oncological and obstetric outcomes. The study emphasizes the need for strict reporting of this entity to enable better understanding and formulate management guidelines in the future.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Compagno J, Oertel JE. Mucinous cystic neoplasms of the pancreas with overt and latent malignancy (cystadenocarcinoma and cystadenoma): a clinicopathologic study of 41 cases. *Am J Clin Pathol*. 1978;69:573–580.
2. Klöppel G, Solcia E, Longnecker DS, Capella C, Sobin LH, Organization WH. *Histological Typing of Tumours of the Exocrine Pancreas* [Internet]. Springer-Verlag; 1996 [cited 2022 Jul 29]. Available from: https://apps.who.int/iris/handle/10665/37470.
3. Yamao K, Yanagisawa A, Takahashi K, Kimura W, Doi R, Fukushima N, et al. Clinicopathological features and prognosis of mucinous cystic neoplasm with ovarian-type stroma: a multi-institutional study of the Japan pancreas society. *Pancreas*. 2011;40:67–71.
4. Board WC of TE. Digestive system tumours [Internet]. [cited 2022 Feb 8]. Available from: https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Digestive-System-Tumours-2019.
5. Goh BKP, Tan YM, Chung YFA, Chow PKH, Cheow PC, Wong WK, et al. A review of mucinous cystic neoplasms of the pancreas defined by ovarian-type stroma: clinicopathological features of 344 patients. *World J Surg*. 2006;30:2236–2245.
6. Ganepola GA, Gritsman AY, Asimakopulos N, Yiengpruksawan A. Are pancreatic tumors hormone dependent?: a case report of unusual, rapidly growing pancreatic tumor during pregnancy, its possible relationship to female sex hormones, and review of the literature. *Am Surg*. 1999;65:105–111.
7. Smithers BM, Welch C, Goodall P. Cystadenocarcinoma of the pancreas presenting in pregnancy. *Br J Surg*. 1986;73:591.
8. Fernández-del Castillo C. Mucinous cystic neoplasms. *J Gastrointest Surg*. 2008;12:411–413.
9. Testini M, Gurrado A, Lissidini G, Venezia P, Greco L, Piccinni G. Management of mucinous cystic neoplasms of the pancreas. *World J Gastroenterol WJG*. 2010;16:5682–5692.
10. Ashida R, Tanaka S, Yamanaka H, Okagaki S, Nakao K, Fukuda J, et al. The role of transabdominal ultrasound in the diagnosis of early stage pancreatic cancer: review and single-center experience. *Diagnostics*. 2018;9:2.
11. Naveed S, Qari H, Banday T, Altaf A, Para M. Mucinous cystic neoplasms of pancreas. *Gastroenterol Res*. 2014;7:44–50.
12. Sahani DV, Kambadakone A, Macari M, Takahashi N, Chari S, Castillo CF del. Diagnosis and management of cystic pancreatic lesions. *Am J Roentgenol*. 2013;200:343–354.
13. Nilsson LN, Keane MG, Shamali A, Millastre Bocos J, Marijinissen van Zanten M, Antila A, et al. Nature and management of pancreatic mucinous cystic neoplasm (MCN): a systematic review of the literature. *Pancreatology*. 2016;16:1028–1036.
14. Morana G, Ciet P, Venturini S. Cystic pancreatic lesions: MR imaging findings and management. *Insights Imaging*. 2021;12:115.
15. Guidelines for diagnostic imaging during pregnancy and lactation [Internet]. [cited 2022 Jul 30]. Available from: https://www.acog.org/en/clinical/clinical-guidance/committee-opinion/articles/2017/10/guidelines-for-diagnostic-imaging-during-pregnancy-and-lactation.
16. Friedel D, Stavropoulos S, Iqbal S, Cappell MS. Gastrointestinal endoscopy in the pregnant woman. *World J Gastrointest Endosc*. 2014;6:156–167.
17. Cho SH, Song TJ, Seo DW, Oh D, Park DH, Lee SS, et al. Efficacy and safety of EUS-guided through-the-needle microforceps biopsy sampling in categorizing the type of pancreatic cystic lesions. *Gastrointest Endosc*. 2022;95:299–309.
18. Orr J, Lockwood R, Salaria S, Gamboa A, Yachimski P. Mucinous cystic neoplasm diagnosed by EUS-guided microforceps biopsy. *Endosc Int Open*. 2018;6:E1379–E1381.
19. Wang H, Chen S, Shu X, Liu Z, Liu P, Zhu Y, et al. The value of serum tumor markers and blood inflammation markers in differentiating pancreatic serous cystic neoplasms and pancreatic mucinous cystic neoplasms [Internet] *Front Oncol*; 2022 [cited 2022 Jul 26];12. Available from: https://www.frontiersin.org/articles/10.3389/fonc.2022.831355.
20. Chalian H, Töre HG, Rezai P, Bentrem DJ, Yaghmai V. MDCT evaluation of the growth kinetics of serous and benign mucinous cystic neoplasms of the pancreas. *Cancer Imag*. 2011;11:116–122.
21. Pancreas TESG on CT of the. European evidence-based guidelines on pancreatic cystic neoplasms. *Gut*. 2018;67:789–804.

22. Iacopi S, Lombardo C, Menonna F, Mazzeo S, Caramella D, Amorese G, et al. Management of pregnancy-associated pancreatic cystic tumors: review of the literature and results of a Pancreas Club Inc. *Survey*. *Pancreatology*. 2018;18:905–912.
23. Herring AA, Graubard MB, Gan SI, Schwaitzberg SD. Mucinous cystadenocarcinoma of the pancreas during pregnancy. *Pancreas*. 2007;34:470–473.
24. Boyd CA, Benarroch-Gampel J, Kilic G, Kruse EJ, Weber SM, Riall TS. Pancreatic neoplasms in pregnancy: diagnosis, complications, and management. *J Gastrointest Surg*. 2012;16:1064–1071.
25. Nonobstetric surgery during pregnancy [Internet]. [cited 2022 Jul 27]. Available from: https://www.acog.org/en/clinical/clinical-guidance/committee-opinion/articles/2019/04/nonobstetric-surgery-during-pregnancy.
26. Malleo G, Vollmer CM. Postpancreatectomy complications and management. *Surg Clin North Am*. 2016;96:1313–1336.
27. Babiker HM, Hoilat GJ, Recio-Boiles A. Mucinous cystic pancreatic neoplasms [Internet]. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2022 [cited 2022 Mar 3]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK448105/.
28. Reddy RP, Smyrk TC, Zapiach M, Levy MJ, Pearson RK, Clain JE, et al. Pancreatic mucinous cystic neoplasm defined by ovarian stroma: demographics, clinical features, and prevalence of cancer. *Clin Gastroenterol Hepatol*. 2004;2:1026–1031.
29. Asciutti S, Kanninen TT, Clerici G, Nardi E, Castellani D, Renzo GCD, et al. Acute pancreatitis with a mucinous cystoadenoma of the pancreas in pregnancy. *Anticancer Res*. 2010;30:1025–1028.
30. Wiseman JES. Cystic pancreatic neoplasm in pregnancy: a case report and review of the literature. *Arch Surg*. 2008;143:84.
31. Kato M, Kubota K, Kita J, Shimoda M, Rokkaku K, Inaba N, et al. Huge mucinous cystadenoma of the pancreas developing during pregnancy: a case report. *Pancreas*. 2005;30:186–188.
32. Ikuta S ichi, Aihara T, Yasui C, Iida H, Yanagi H, Mitsunobu M, et al. Large mucinous cystic neoplasm of the pancreas associated with pregnancy. *World J Gastroenterol WJG*. 2008;14:7252–7255.
33. Kosumi K, Takamori H, Hashimoto D, Tanaka H, Abe S, Nakahara O, et al. Mucinous cystic neoplasm of the pancreas activated during pregnancy. *Surg Case Rep*. 2015;1:13.
34. Ishikawa K, Hirashita T, Kinoshita H, Kitano M, Matsuo S, Matsumata T, et al. Large mucinous cystadenoma of the pancreas during pregnancy: report of a case. *Surg Today*. 2007;37:1013–1017.
35. Tica AA, Tica OS, Saftoiu A, Camen D. Tica VI. Large pancreatic mucinous cystic neoplasm during pregnancy: what should Be done? *Gynecol Obstet Invest*. 2013;75:132–138.
36. Fernández EMLT, Malagón AM, Gonzalez IA, Montes JRM, Luis HD, Hermoso FG, et al. Mucinous cystic neoplasm of the pancreas during pregnancy: the importance of proper management. *J Hepatobiliary Pancreat Surg*. 2005;12:494–497.
37. Martins Filho ED, Lima T, Jaques RPM, Guerra GV, Adeodato L, Kreimer F. Neoplasia cística mucinosa do pâncreas durante a gestação: Relato de Caso. *Rev Bras Saúde Materno Infant*. 2011;11:187–190.
38. Kitagawa H, Okabayashi T, Nishimori I, Kobayashi M, Sugimoto T, Akimori T, et al. Rapid growth of mucinous cystic adenoma of the pancreas following pregnancy. *Int J Gastrointest Cancer*. 2006;37:45–48.
39. Urabe K, Murakami Y, Uemura K, Sudo T, Hashimoto Y, Kondo N, Nakagawa N, Sasaki H, Ohge H, Sueda T. Clinicopathological features of 11 resected cases of mucinous cystic neoplasms of the pancreas. *Suizo*. 2014;29:721–728.
40. Shirakawa S, Matsumoto I, Nakayama S, Mukubo H, Toyama H, Shinzeki M, et al. [Mucinous cystic neoplasm of the pancreas associated with pregnancy: report of two cases]. *Nihon Shokakibyo Gakkai Zasshi Jpn J Gastro-Enterol*. 2010;107:1828–1834.
41. M O. Pancreatic mucinous cystadenoma during pregnancy. *Am J Gynecol Health*. 1993;4:27–30.
42. Coral RP, Coral RV, De Bacco FW, Rinaldi N, Zettler CG. Cistoadenoma mucinoso de pâncreas durante a gravidez. *Rev AMRIGS*. 2010:328–330.
43. yoshino komatsu et al. The Japanese Journal of Gastroenterological Surgery Online Journal: Abstract: Vol.40 No.1 74-79 [Internet]. [cited 2022 Jan 28]. Available from: https://www.jsgs.or.jp/journal/abstract/040010074_e.html.
44. Carvalho L, Ferreira T, Frutuoso L, Matos L, Castro T, Rodrigues D, et al. Large mucinous cystic neoplasm of the pancreas during pregnancy: a case report. *J Surg Case Rep*. 2020;2020. rjaa085.
45. Berevoescu N, Scăunașu R, Berevoescu M, Croitoru A. Mucinous cystadenoma of the pancreas associated with pregnancy. Case report and review of the literature. *J Clin Investig Surg*. 2018;3:88–94.
46. Lee YJ, Kim SW, Kim Y. Ovarian mass combined with pancreatic neoplasm in pregnancy: a rare case report and literature review. *J Obstet Gynaecol Res*. 2022;48:244–250.
47. Brown TH, Menon VS, Richards DG, Griffiths AP. Gastrointestinal bleeding in a pregnant woman: mucinous cystic neoplasm of pancreas mimicking gastrointestinal stromal tumor of stomach. *J Hepatobiliary Pancreat Surg*. 2009;16:681–683.
48. Tsuda H, Kotani T, Sumigama S, Mano Y, Shimoyama Y, Kikkawa F. Mucinous cystic neoplasm of the pancreas with severe dysplasia during pregnancy: case report and review of the literature. *Taiwan J Obstet Gynecol*. 2012;51:635–638.
49. Revoredo F, de Vinatea J, Reaño G, Villanueva L, Kometter F, Arenas J, et al. Mucinous cystic neoplasms of the pancreas associated with pregnancy. *Medicine (Baltim)*. 2020;99, e21471.
50. kleef DB. *Progression of a Cystic Pancreatic Lesion during Pregnancy*. vol. 4. 2015.
51. Takashima S, Wato M, Inaba T, Mizukawa S, Izumikawa K, Ishikawa S, et al. A case of pancreatic mucinous cystic neoplasm that enlarged during pregnancy and was resected after childbirth. *Nippon Shokakibyo Gakkai Zasshi Jpn J Gastro-Enterol*. 2014;111:1789–1797.
52. Ozden S, Haliloglu B, Ilter E, Akin FT, Kebudi A, Peker O. An extremely rare cause of acute abdomen in pregnancy: Ruptured pancreatic mucinous cystadenocarcinoma. *Pancreas*. 2007;34:474–476.
53. Hakamada K, Miura T, Kimura A, Nara M, Toyoki Y, Narumi S, et al. Anaplastic carcinoma associated with a mucinous cystic neoplasm of the pancreas during pregnancy: report of a case and a review of the literature. *World J Gastroenterol WJG*. 2008;14:132–135.
54. Berindoague R, Targarona E, Savelli A, Pernas J, Lloreta J. Mucinous cystadenocarcinoma of the pancreas diagnosed in postpartum. *Langenbeck's Arch Surg*. 2007;392:493–496.
55. Baiocchi C, Landonio G, Majno M, Minola E, Scanzi F, Ghislandi E. Pancreatic cystadenocarcinoma and pregnancy: a case report. *Tumori J*. 1990;76:294–295.
56. Iusco DR, Navarra G, Bonomi S, Grassi A, Vicari S, Virzì S. Pancreatic large mucinous cystoadenoma with invasive ductal carcinoma in pregnancy. *Case report. Il G Chir*. 2012;33:163–167.
57. Naganuma S, Honda K, Noriki S, Kimura S, Murakami M, Koneri K, et al. Ruptured mucinous cystic neoplasm with an associated invasive carcinoma of pancreatic head in a pregnant woman: report of a case and review of literature: Ruptured pancreatic MCN in pregnancy. *Pathol Int*. 2011;61:28–33.