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Implications of pregnancy on MCN of the pancreas: A multicentric case-control study

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ABSTRACT

Background: Mucinous cystic neoplasms (MCN) of the pancreas express estrogen and progesterone receptors. Several case reports describe MCN increasing in size during gestation. The aim of this study is to assess if pregnancy is a risk factor for malignant degeneration of MCN.
Methods: All female patients who underwent pancreatic resection of a MCN between 2011 and 2021 were included. MCN resected or diagnosed within 12 months of gestation were defined perigestational. MCN with high grade dysplasia or an invasive component were classified in the high grade (HG) group. The primary outcome was defined as the correlation between exposure to gestation and peri-gestational MCN to development of HG-MCN.
Results: The study includes 176 patients, 25 (14 %) forming the HG group, and 151 (86 %) forming the low grade (LG) group. LG and HG groups had a similar distribution of systemic contraceptives use (26 % vs. 16 %, $p = 0.262$), and perigestational MCN (7 % vs 16 %, $p = 0.108$). At univariate analysis cyst size $\geq$10 cm (OR 5.3, $p < 0.001$) was associated to HG degeneration. Peri gestational MCN positively correlated with cyst size ($R = 0.18$, $p = 0.020$). In the subgroup of 14 perigestational MCN patients 29 % had HG-MCN and 71 % experienced cyst growth during gestation with an average growth of 55.1 $\pm$ 18 mm.
Conclusions: Perigestational MCN are associated to increased cyst diameter, and in the subset of patients affected by MCN during gestation a high rate of growth was observed. Patients with a MCN and pregnancy desire should undergo multidisciplinary counselling.

1. Introduction

Mucinous cystic neoplasms (MCN) of the pancreas are mucin secreting cystic tumors without communication with the ductal system of the gland. These tumors affect predominantly female patients and usually arise in the body-tail of the gland. Histologically MCN are characterized by an inner epithelial layer of mucin-secreting cells and an ovarian-like stroma expressing estrogen and progesterone receptors. MCN are considered borderline tumors with a risk of malignant degeneration between 7 and 15 % reported on cohorts of resected patients.[1-3] Because of their potential for invasive progression and their relatively unknown biology, surgical resection is generally recommended for all MCN by several guidelines.[4,5] Since invasive disease is extremely rare in MCN <40 mm without a solid component[1], a conservative approach in this subset of patients is suggested by the 2018 European evidence-based guidelines on pancreatic cystic tumors[6], but this indication is still debated because the young age of the patients involved demands

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long and expensive follow up with possible progression. It has previously been reported in several case reports and case series of MCN undergoing a rapid increase in size during pregnancy[7], and one hypothesis is that the ovarian-like stroma might interact with hormonal changes occurring during pregnancy or exposure to exogenous hormone contraceptives. Nonetheless, the knowledge on this tumor interaction with sex hormones has thus far been anecdotal and based on educated speculation. The aim of this study is to assess if pregnancy or exogenous hormone exposure is a risk factor for malignant degeneration in pancreatic mucinous cystadenoma.

2. Methods

2.1. Study design

The study involved three high-volume tertiary centers for pancreatic surgery after Institutional Review Board approval was obtained from each respective. A case-control retrospective study was designed and review of surgical MCN database was performed in each single institution, data were eventually merged and analyzed in a single center. Charts of patients resected between January 1, 2010 and July 31, 2022 were reviewed. Including criteria were age $\geq$18, female sex, availability of obstetrical and systemic contraception history, surgical resection, and histological diagnosis of MCN or mucinous cystadenocarcinoma. Exclusion criteria were age $\leq$18, male sex, unavailability of medical history regarding use of systemic contraceptives or gestation, and diagnosis of other pancreatic cystic tumors than MCN (i.e., intraductal papillary cystic neoplasm, serous cystadenoma, solid pseudopapillary neoplasm). Baseline characteristics as age, BMI, tobacco use, and comorbidities were collected. Incidental diagnosis, signs and symptoms related to the cystic tumor were recorded. When obstetrical history and details about use of systemic contraceptives were not available in medical charts patients were contacted via phone interview. Intraoperative data regarding type of resection, surgical approach, spleen preservation, length of surgery and postoperative complications classified with Clavien-Dindo classification were also collected. Relationship with pregnancy was assessed by recording all diagnosis during time of gestation, while MCN resected within 1 year of pregnancy were considered “perigestational MCN”. Peri-gestational cyst growth was calculated from the last measurement before pregnancy (or the first measurement ever, in case of diagnosis during gestation) to the last measurement at time of surgery. The relationship between “perigestational MCN” and cyst size was assessed running a point biserial correlation. Pathology report was used for cyst diameter, presence of macroscopic solid component, mural nodule and to identify malignant MCN defined as tumors with high grade dysplasia or an invasive component (HG-MCN), whereas all tumors with intermediate or low-grade dysplasia were considered benign without distinction (LG-MCN). The primary outcome was the odds ratio of peri gestational MCN and use of systemic contraceptives for high grade degeneration. Secondary outcomes were odds ratio for HG degeneration associated to large cyst size, the relative risk for cyst size of peri gestational MCN and use of systemic contraceptives, and mm of growth during pregnancy.

2.2. Statistical analysis

Continuous variables are reported as means ± standard deviation (SD) and are compared using student t-test when normally distributed. Non-normally distributed variables are reported as medians with interquartile ranges (IQR) and are compared with Mann-Whitney U tests. Categorical variables were compared using chi-square test. Univariate and multivariate analysis with logistic regression were used to assess variables independently associated with malignant degeneration. A *p*-value of less than 0.05 is considered to represent statistical significance for all comparisons. Data were analyzed using SPSS software version 28.

3. Results

3.1. Population characteristics

During the study period 176 patients meeting the criteria were included, 25 (14.2 %) HG-MCN constituted the case group and 151 (85.8 %) LG-MCN constituted the control group. The median age was similar [56 (IQR: 44–65) vs. 49 (IQR: 39–58), $p = 0.123$] between HG and LG group. No statistical differences between the two groups were observed in tobacco use (8 % vs. 21 %, p = 0.137) and BMI [24.5 (IQR: 20–28) vs. 24.7 (IQR: 21–30), p = 0.609]. The pattern of incidental diagnosis was similar between the two groups (60 % vs. 70 %, p = 0.343). The cyst size of the HG-MCN was significantly larger both at preoperative imaging (86.2 ± 44.3 SD vs. 58.1 ± 29.3 SD, p < 0.001) and at pathological analysis (87.2 ± 45.2 SD vs. 56 ± 31.6 SD, p < 0.001) compared to LG tumors. The presence of a peripheral cyst wall nodule (20 % vs. 10 %. p = 0.142) or a macroscopic solid component (12 % vs. 5 %, p = 0.200) was more common in the HG-MCN group, but the difference was not statistically significant. In the HG-MCN 11 (44 %) patients had invasive mucinous cystadenocarcinomas; of these 2 (8 %) experienced recurrences and eventually died from disease. In the whole group of resected patients, no invasive MCN had a size $\leq$40 mm without any associated enhancing nodule or macroscopic solid component, though 2 of such patients had HG dysplasia. The data on population characteristics are available on Table 1.

3.2. Exposure to gestation and systemic contraceptives

As shown in Table 2, the HG-MCN group did not differ significantly from the LG-MCN group in terms of patients with a history of gestation (84 % vs. 75 %, p = 0.352), also the number of pregnancies were similarly distributed among the two groups. Despite a larger percentage of peri-gestational MCN (16 % vs. 7 %, p = 0.108) and MCN diagnosed during gestation (12 % vs. 5 %, p = 0.141) in the HG-MCN group, the difference was not significant. The use of systemic contraceptives was not statistically different within the two groups (16 % vs. 26 %, p = 0.262), but higher in the LG-MCN.

At univariate binary logistic regression (Table 3) increasing cyst diameter (OR 1.02, 95%CI 1.01–1.03, p < 0.001) was associated with increased likelihood of HG progression, at the same time cysts with $\geq$10 cm of diameter had 5.3 OR (95%CI 2–13.5, p < 0.001). Tobacco use (OR 0.3, 95%CI 0.1–1.5, p = 0.337), history of gestation (OR 1.7, 95%CI 0.5–5.3, p = 0.356), age (OR 1.03, CI 0.99–1.1, p 0.096), macroscopic solid component (OR 2.4, CI 0.6–9.9, p = 0.213), cyst wall nodule (OR 2.3, 95%CI 0.7–6.9, p = 0.151) and incidental diagnosis (OR 0.7, 95%CI 0.3–1.6, p = 0.345) were not significantly associated with HG degeneration. Perigestational MCN had a 2.7 OR (95%CI 0.8–9.3, p = 0.120) and systemic contraceptive use had a 0.5 OR (95%CI 0.2–1.6, p = 0.268), both did not reach statistical significance in prediction of HG-MCN degeneration. These results are visually represented on the Forrest plot in Fig. 1.

A statistically significant positive correlation was identified between peri-gestational MCN and cyst diameter (R = 0.18, p = 0.020), the data are presented on the scatter plot of Fig. 2. On the contrary, the use of systemic contraceptives did not correlate with cyst diameter (R = −0.11, p 0.140).

Table 1
Patient demographics.

	TOT N = 176	Low grade N = 151	High grade N = 25	P value
Age, mean (IQR)	49.5 (40–58)	49 (39–58)	56 (44–65)	0.123
BMI, mean (IQR)	24.7 (21–29)	24.7 (21–30)	24.5 (20–28)	0.609
Tobacco use, pts (%)	33 (19)	31 (21)	2 [8]	0.137
Incidental diagnosis (%)	120 (68)	105 (70)	15 (60)	0.343
Symptoms (%)				
Abdominal pain	74 (42)	61 (40)	13 (52)	0.276
Acute pancreatitis	22 [13]	20 [13]	2 [8]	0.463
Weight loss	10 [6]	9 [6]	1 [4]	0.695
Jaundice	2 [1]	0	2 [8]	**<0.001**
Type of surgery (%)				0.262
Pancreaticoduodenectomy	9 [5]	7 [5]	2 [8]	
Distal pancreatectomy	165 (94)	143 (95)	22 (88)	
Total pancreatectomy	2 [1]	1 [1]	1 [4]	
Spleen preserving (%)	27 (15)	25 (17)	2 [8]	0.272
Minimally invasive approach (%)	86 (49)	77 (51)	9 (36)	0.221
Days of hospitalization, mean ± SD	9.6 ± 7.8	9.5 ± 8.1	10.1 ± 5.9	0.364
Radiological cyst size, mm, mean ± SD	62.1 ± 33.2	58.1 ± 29.3	86.2 ± 44.3	**<0.001**
Pathological cyst size, mm, mean ± SD	60.4 ± 35.4	56 ± 31.6	87.2 ± 45.2	**<0.001**
Peripheral nodule (%)	20 [11]	15 [10]	5 (20)	0.142
Macroscopic solid component (%)	11 [6]	8 [5]	3 [12]	0.200
Grade of dysplasia (%)				**<0.001**
Low grade	146 (83)	146 (97)	0	
Intermediate	5 [3]	5 [3]	0	
High grade	14 [8]	0	14 (56)	
Invasive	11 [6]	0	11 (44)	
Relapse (%)	2 [1]	0	2 [8]	**<0.001**
Death due to tumor (%)	2 [1]	0	2 [8]	**<0.001**

TOT = total, IQR = interquartile range, BMI = body mass index, SD = standard deviation, pts = patients.

Table 2
Exposure to gestation and systemic contraceptives.

	TOT N = 176	Low grade N = 151	High grade N = 25	P value
History of gestation (%)	135 (77)	114 (75)	21 (84)	0.352
Number of pregnancies (%)				0.181
1	36 (20)	31 (21)	5 (20)	
2	60 (34)	47 (31)	13 (52)	
≥3	39 (22)	36 (24)	3 [12]	
Perigestational MCN (%)	14 [8]	10 [7]	4 (16)	0.108
Diagnosed during gestation (%)	10 [6]	7 [5]	3 [12]	0.141
Growth during gestation (%)	10 [6]	8 [5]	2 [8]	0.589
Surgery during gestation (%)	2 [1]	2 [1]	0	0.563
First trimester	0	0	0	
Second trimester	2 [1]	2 [1]	0	
Third trimester	0	0	0	
Use of systemic contraceptives (%)	44 (25)	40 (26)	4 (16)	0.262
Estrogen/progesterone combination	16 [9]	15 [10]	1 [4]	
Progesterone only	12 [7]	12 [8]	0	
Unspecified contraceptive	16 [9]	13 [9]	3 [12]	
Mean contraceptive use time ± SD, yrs	8.9 ± 7.7	8.7 ± 7.8	11.7 ± 7.6	0.265
History of gynecological diseases (%)				
Ovarian cyst	14 [8]	12 [8]	2 [8]	0.993
Endometrial polyp	5 [3]	4 [3]	1 [4]	0.706
Uterine Leiomyoma	14 [8]	14 [9]	0	0.113
PCOS	3 [2]	2 [1]	1 [4]	0.338
Endometriosis	3 [2]	2 [1]	1 [4]	0.338
Previous gynecological surgery (%)				0.038
Hysterosalpingectomy	3 [2]	3 [2]	0	
Salpingectomy	1 [1]	0	1 [4]	

TOT = total, MCN = mucinous cystic neoplasm, SD = standard deviation, yrs = years.

Table 3
Univariate binary logistic regression for variables associated to HG degeneration.

	Odds ratio **(95%CI)**	P value
Tobacco use	0.3 (0.1–1.5)	0.337
Age	1.03 (0.99–1.1)	0.096
Radiological cyst size ≥10 cm	5.3 (2–13.5)	**<0.001**
Macroscopic solid component	2.4 (0.6–9.9)	0.213
Cyst wall nodule	2.3 (0.7–6.9)	0.151
History of gestation	1.7 (0.5–5.3)	0.356
Perigestational MCN	2.7 (0.8–9.3)	0.120
Systemic contraceptive use	0.5 (0.2–1.6)	0.268
Incidental diagnosis	0.7 (0.3–1.6)	0.345

MCN = mucinous cystic neoplasm.

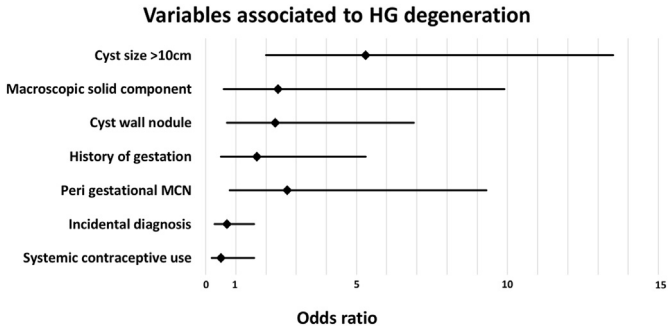

Fig. 1. Forrest Plot for variables associated to high grade degeneration of IPMN.

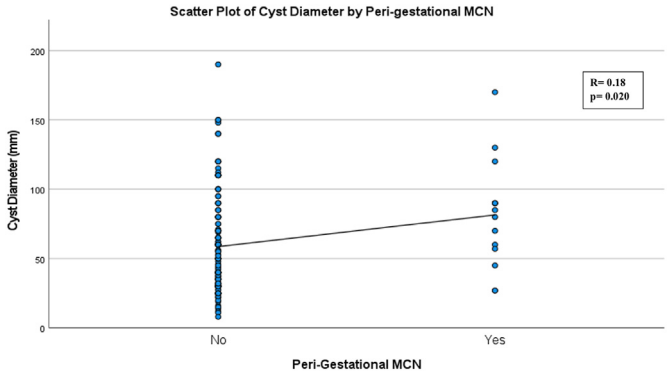

Fig. 2. Scatter plot of cyst diameter by peri-gestational MCN status.

3.3. Perigestational MCN

The patients who were treated for an MCN within 1 year of pregnancy were a subgroup of 14 (8 %) patients (Table 4). In this subgroup average age and BMI were 36.5 ± 6.2 SD and 23.1 ± 5.3 SD, respectively. Ten (71 %) of these patients were diagnosed during gestation, and half of them had an incidental diagnosis. The most common presenting symptom was abdominal pain affecting 7 patients (50 %), while acute pancreatitis was observed in 2 (14 %) patients. Ten (71 %) patients in this subgroup experienced cyst growth during pregnancy, in these patients the average growth was 55.1 ± 18 SD mm. The average cyst diameter of the subgroup was 83.1 ± 35.4 SD mm. Only two (14 %) patients were surgically treated during pregnancy, both of them because of a rapid increase in cyst size and symptoms. Both of the surgeries happened during the second trimester of pregnancy. Four (29 %) perigestational MCN had HG degeneration and 3 (21 %) of them had an invasive malignant component. One (7 %) of these patients died because of the disease. If we consider the group of 162 patients that did not have a perigestational MCN only 21 (13 %) had a HG tumor, p = 0.108. All of the four HG-MCN in the peri-gestational subgroup had worrisome radiological features: one was 60 mm in cyst diameter with a wall nodule, one was 120 mm in diameter, another one was 45 mm in diameter with a macroscopic solid component and enhancing nodule, and the last one was 79 mm in diameter with an enhancing wall. In the remaining 10 LG perigestational MCN no patient had nodules of macroscopic solid components, but the diameter of the cyst ranged from 40 mm to 170 mm.

4. Discussion

This multicenter study on MCN includes a large cohort of resected patients, considering the overall relatively rare prevalence of the disease. The demographics and rate of malignant degeneration observed in the study are in line with current literature[1-3], and this confirms the validity of the cohort.

Perigestational MCN constituted 8 % of the whole population of resected MCN, reflecting that this is a rare though not negligible occurrence when facing this disease. A recent survey of Iacopi et al.[8] suggested that 1 pancreatic surgeon out of 2 is expected to care for patients with perigestational MCN at least once in their career. Moreover, the diagnosis of a potentially malignant pancreatic tumor during gestation is a delicate situation for both the patient and the team of physicians as it involves the health of both the mother and the fetus, and it is a clinical scenario that crosses medical specialties.

The results obtained by this study confirm[9] that in MCN the size of the cyst is the most important predictor of malignant degeneration. Indeed, cyst size was the only variable significantly associated with HG degeneration, and the presence of a MCN >10 cm resulted in a 5.3 high odds ratio. We did not observe any invasive component in MCN less than 4 cm, but two patients with an MCN size of 32 mm and 33 mm had a high-grade component. Thus, the current European guidelines might induce to keep under surveillance some high grade MCN.[9] The arbitrary 10 cm measure observed in this series of resected MCN cannot be interpreted as “guideline cutoff”. However, straightforward surgical resection could be complicated in patients who receive a MCN diagnosis during pregnancy, and the association of MCN size and HG degeneration could be a useful indicator in the process of deciding whether it is safe to delay the resection post-partum.

The primary aim of the study was to assess the relevance of gestation and use of systemic contraceptives in the malignant degeneration of MCN. These cystic tumors are currently thought to arise from ovarian embryologic remnants and are characterized histologically by the presence of an ovarian-like stroma expressing estrogen and progesterone receptors. If this hypothesis was true, that would require MCN tissue, including ovarian type stroma, to be present at birth and then evolve during life after being possibly exposed to a number of environmental factors. Despite a small number of cases, perigestational MCN showed a positive correlation with cyst diameter, suggesting that when a MCN is present during pregnancy, rapid cyst growth is likely, and these patients need very close observation and multidisciplinary care. Patients with peri-gestational disease showed odds of having an HG-MCN 2.7 times higher than patients without peri-gestational MCN. This result was not statistically significant, but this may be a function of the small sample size. Another relevant issue is represented by those women diagnosed with MCN who desire to be pregnant. In this specific subset of individuals appropriate counselling is extremely important and needed. Strict follow-up during and after gestation seems appropriate for a tailored approach based on patient's age and MCN specific risk of malignancy.

The observational data presented in Table 4 aligns with

Table 4
Diagnosed during gestation subgroup.

Peri-gestational MCN N = 14	
Age, yrs, mean ± SD	36.5 ± 6.2
BMI, mean ± SD	23.1 ± 5.3
Diagnosed during gestation (%)	10 (71)
Incidental diagnosis (%)	7 (50)
Symptoms (%)	
Abdominal pain	7 (50)
Acute pancreatitis	2 (14)
Weight loss	1 [7]
Jaundice	0
Peripheral nodule (%)	1 [7]
Macroscopic solid component (%)	1 [7]
Radiologic cyst size, mm, mean ± SD	83.1 ± 35.4
Cyst growth during gestation (%)	10 (71)
Mean growth during gestation[a], mm, ±SD)	55.1 ± 18
Surgery during gestation (%)	2 (14)
Minimally invasive approach (%)	9 (64)
Grade of dysplasia (%)	
Low grade	8 (57)
Intermediate grade	2 (14)
High Grade	1 [7]
Invasive	3 (21)
HG-MCN (%)	4 (29)
Death due to tumor (%)	1 [7]

[a] Calculated in subset of patients with growth during gestation. BMI = body mass index, SD = standard deviation, HG-MCN = high grade mucinous cystic neoplasm.

previously published literature reviews on the topic.[7,8] Peri-gestational MCN in our population have an average cyst size of 83 mm, and 71 % of these patients had a rapid cyst growth during pregnancy with an average growth of 55 mm (In Fig. 3 is shown an example of large peri-gestational MCN after resection). The percentage of invasive MCN in this subgroup of patients was 21 %, which is higher when compared to the rest of the cohort (5 %) and the results reported in other large cohorts of resected patients (7–15 %).[1-3] Similar observations could be made by considering all HG and Invasive MCN in the same category, which represent 29 % of the perigestational MCN while only 13 % of the MCN diagnosed remote from gestation are HG. The most common symptom reported was a non-specific abdominal pain, though this symptom is challenging to evaluate during pregnancy. A rare occurrence observed in some of the available case reports[10,11] is the rupture of the MCN, this was not observed in our cohort. Two patients needed surgical resection during gestation, both because of the rapid growth of the cyst and during the second trimester of pregnancy.

In the event of MCN diagnosis during pregnancy or of a patient in fertile age with a known MCN in follow up we can propose some recommendations from this retrospective study. First, a patient in fertile age, with childbearing desire, and with a known MCN in follow up should be warned of the increased risk of cyst growth during gestation and that a correlation between exposure to gestation and malignant degeneration cannot currently be excluded. These patients should be offered the possibility of pre-emptive resection before trying to conceive, perhaps even if smaller than the current threshold of 4 cm. Second, in case of a MCN diagnosis occurring during pregnancy, a discussion about surgical resection is a complex matter. European guidelines indicate resection in case of cyst diameter ≥40 mm[6], but no data is available on the safety of postponing a MCN resection. Considering that all of the peri-gestational HG-MCN observed in our population had either an enhancing nodule, a macroscopic solid component, or a large cyst (120 mm), immediate surgical treatment should be offered during the course of pregnancy for all those MCN possessing those features. Patients whose MCN do not present a nodule, solid component, or have a diameter <4 cm are still candidates for resection but can be closely monitored during gestation and an early post-partum pancreatic resection can be scheduled, especially if the diagnosis occurs during the third trimester of pregnancy.

The retrospective design of this study, the rare prevalence of the disease and particularly of the subgroup of interest constitute intrinsic limitations that decrease the magnitude of our recommendations. Nonetheless, this is the only study addressing peri-gestational MCN in a multicenter cohort of resected patients, providing useful insights on a non-negligible clinical scenario in pancreatic surgery.

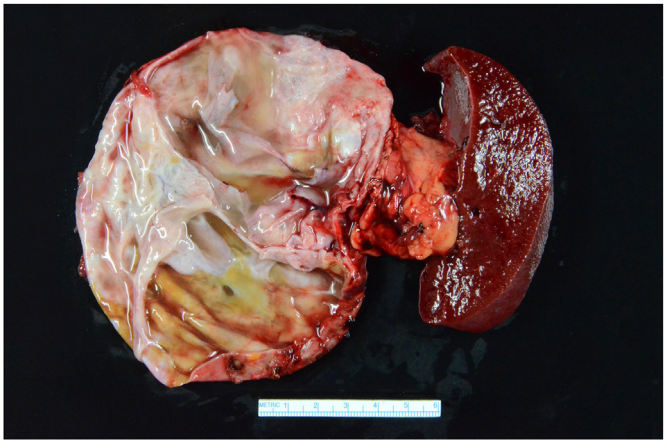

Fig. 3. A large 148 mm pancreatic tail mucinous cystadenoma.

5. Conclusion

History of previous gestation and use of systemic contraceptive do not to correlate with a higher chance of HG degeneration of MCN. Perigestational MCN are associated to increased cyst diameter and in this small subgroup of patients we observed a 71 % chance of cyst growth and a 29 % chance of HG development. Patients with desire of procreation and a known MCN in follow up should be warned of the potential risk of cyst growth and should offered resection before trying to conceive. Patients diagnosed during gestation should receive close follow up and should be offered immediate resection if an enhancing nodule, macroscopic solid component or a >10 cm cyst diameter characterizes their MCN because of the potential risk of invasive carcinoma.

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