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Diagnosis and management of gastric cancer in pregnancy—An evidence-based case report

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ABSTRACT

BACKGROUND: Gastric cancer in pregnancy is a very rare case with an incidence of 0.016% and is mostly detected in a locally advanced or advanced stage due to misinterpretation of non-specific signs and symptoms. Management of gastric cancer in pregnancy should emphasize mother and fetal survival. Currently, there is no diagnostic and management guidance for gastric cancer in pregnancy. The purpose of this study is to ascertain how to diagnose and manage gastric cancer in pregnancy.

METHODS: This study is an evidence-based case report performed in Digestive Division of Department of Surgery in Cipto Mangunkusumo hospital in September–October 2017. Literature search on databases such as *Cochrane*, *PubMed*, *ScienceDirect*, and *Scholar Google* used keywords like “gastric cancer” AND “pregnant” OR “pregnancy” with inclusion criteria which are systematic review, randomized-clinical trial (RCT), cohort study, case report, or case series, performed in human and published in the last 10 years in English language. Critical appraisal is done according to *Oxford Centre For Evidence-Based Medicine 2011*. This work is reported in line with the SCARE criteria.

RESULTS: There are 9 case-report studies and 1 case-control study. Radiology examination includes endoscopy, MRI, and CT scan. Management is given according to cancer stage which is; surgery, surgery with adjuvant therapy, and palliative chemotherapy.

CONCLUSION: Radiology examinations with a lower risk of adverse effects are endoscopy and MRI. CT scan may be performed when the benefits exceed the risk. Surgery and chemoradiation have the lowest rate of adverse effects when done in the second and third trimester.

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1. Introduction

Gastric cancer in pregnancy, with an incidence of 0.016%, can be considered rare. Most of the cases were detected in a locally advanced or even advanced stage due to misinterpretation of signs and symptoms. Early satiety, upper abdominal pain, and weight loss were often diagnosed prematurely by doctors as dyspepsia syndrome which would be belittled by patients. This fact is one of the reasons why lots of gastric cancer were detected a little too late [1,2].

While taking care of mothers, surgeons also have to take fetal survival into account in making the diagnosis, especially with a certain radiologic examination, and thorough management, surgically, or non-surgically. Adverse effects such as hematology disturbance and fetal immunosuppression due to chemotherapy and risk of postoperative miscarriage have to be born in mind, knowing that post laparotomy mortality rate in gastric cancer is 57.1% and 22.7%

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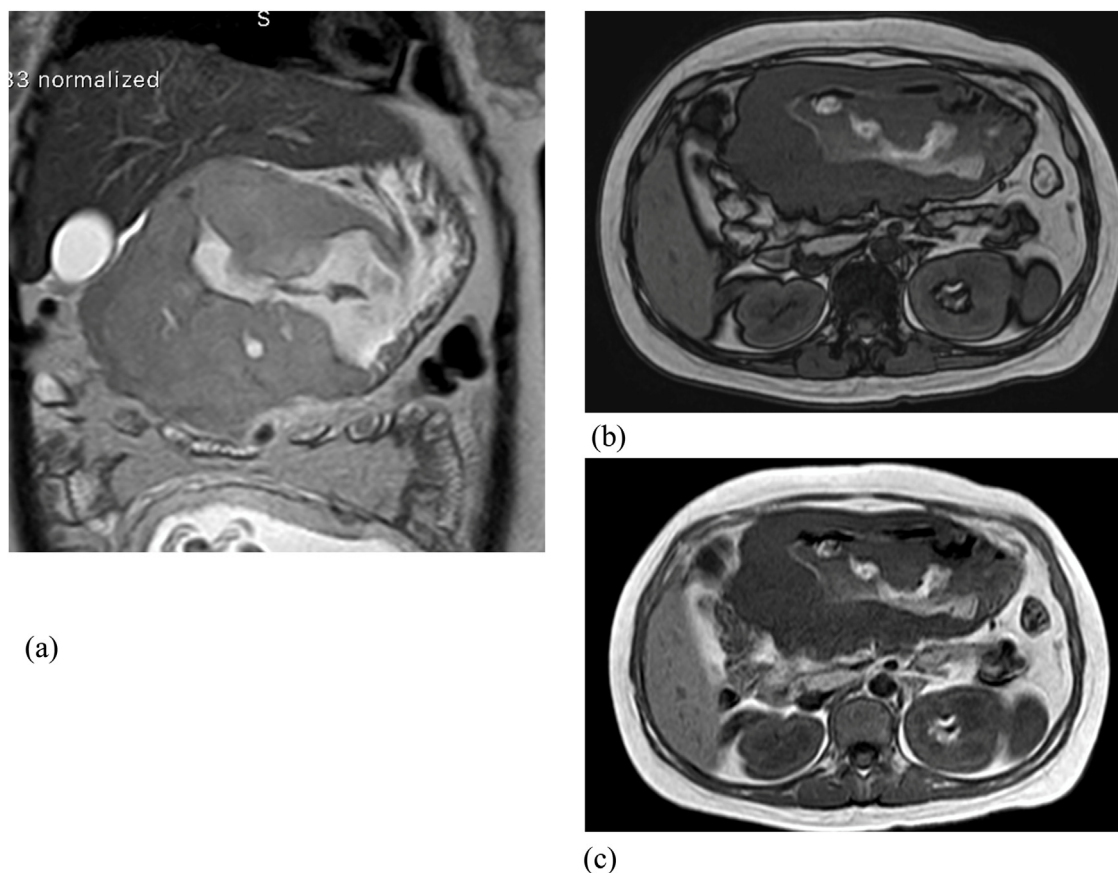
after gastrectomy [3,4]. Due to the rarity and progressivity of the cases, there have never been any guidelines for the diagnosis and standard management for gastric cancer in pregnancy.

2. Case illustration

A 28-year-old, nulliparous woman, with 21-week gestational age, came to emergency care of Cipto Mangunkusumo Hospital with continuous epigastric pain and palpable mass, intractable nausea and vomiting, and history of melena since 12-week gestational age. Due to intractable symptoms, she was performed an MRI which showed a gastric mass (Picture 1). She then referred to us for further management.

On physical examination, we found an alert patient with a prominent abdomen. Her blood pressure was 110/75 mmHg and respiratory rate was 20 times per minute. We encountered palpable upper abdominal mass with a size of 15 × 15 cm. It is mobile, well defined, and non-tender. In the laboratory results, normocytic anemia was detected.

We performed laparotomy in 22–23 weeks of gestational age. We found mass along the antrum until the duodenal bulb. There was small tumor perforation which was walled off by omentum. We



Picture 1. Abdominal MRI.

decided to perform subtotal gastrectomy and Roux-en-Y gastrojejunostomy. She was discharged on 10th postoperative day with unremarkable findings and planned to have chemotherapy after delivery.

3. Methods

This study is an evidence-based case report with the algorithm listed below (Fig. 1). Initially, the research question “How diagnostic procedure and management of locally-advanced gastric cancer on pregnancy were done?” was made and we proceed to PICO components identification. Afterwards, literature searching and selection were done on Cochrane, PubMed, ScienceDirect, and Scholar Google using matched keywords “gastric cancer” AND “pregnant” OR “pregnancy”. Lastly, we completed the SCARE checklist and has been reported in line with SCARE criteria [5].

4. Result

Ten publications were found, comprised of 9 case-reports and 1 case-control study (Table 1). Four case-reports discussed different initial presentations and staging having the same outcome, healthy mother and baby (unrecorded survival time). Different management of each case is also encountered. Three of 4 patients were locally advanced hence performed palliative chemotherapy. Surgical management was only performed in 1 case without adjuvant treatment and achieved 3-disease-free-year. Patients in the rest of the publications were deceased after treatment. There was only 1 publication that reported 1 patient who died untreated due to poor condition.

There was 1 prognostic case-control study published by Song et al. [2016] comparing 20 cases of gastric cancer in pregnancy (group A) with 39 in the general population (group B), collected from 1991–2012. Seventy percent of group A presented with advanced stage (distant metastasis) and 10% locally-advanced stage (stage III). Forty percent of group A underwent palliative treatment, 20% operation followed by adjuvant chemotherapy, and 10% underwent only surgical treatment. No published data on radiology examination performed and gestational age was not included as a prognostic factor.

Critical appraisal was done based on guidelines published by Oxford Centre for Evidence-based Medicine in 2011. Based on the checklist, there are 3 aspects reviewed in critical appraisal, which are validity, importance, and applicability. Out of 10 journals found, there were 9 case-report studies and 1 case-control study.

The characteristics of 9 case-reports were mostly similar in the validity aspect. Only 1 difference was found in one case-report by Unek et al, which had no recorded long and complete follow-up on the patient. One case-control study by Song et al. had the same treatment between groups, statistically analyzed, complete and long period of follow-up, and objective valuation of outcomes. In the importance aspect, all publications collected were compared to each other in discussion. In the applicability aspect, all publications have the same studies' samples, benefit outweighed the risk, appropriate with the subject's preference and value, and applicable in a local hospital.

5. Discussion

Most of the gastric cancer patients had unspecific symptoms similar to dyspepsia syndromes such as epigastric pain, nausea, and

Table 1
Summary of supporting publications.

No	Author	Method	Year	Pt's Age (y.o)	Gestational Age	Symptoms	Radiology Tools	Tumor Characteristics	PA Result	Abortion	Treatment	Deceased	LoE
1.	Unek et al. [6]	Case report	2007	22	7 weeks	Anorexia Early satiety Lower abdominal pain	Endoscopy Abdominal CT Scan	<i>Unresectable:</i> invasion to pancreas and spleen	<i>Signet-ring cell</i>	Yes	Chemotherapy	No	4
2.	Yoshida et al. [7]	Case report	2009	32	29 weeks	Epigastric pain Nauseous Pale and Melena	USG MRI	Tumor on minor curvature Borrmann 3	Poor- differentiated tubular ade- nocarcinoma with signet-ring cell morphology <i>Signet-ring cell</i>	No	C-section on 30 weeks + <i>pyloric-preserving gastrectomy</i> + lymph node dissection	No	4
3.	Terzi et al. [8]	Case report	2010	37	6 months	Anorexia Early satiety Vomiting	Endoscopy USG	Subserosal tumor, size 5x6 cm (corpus and antrum)	<i>Signet-ring cell</i>	No	Total gastrectomy + Roux-en-Y esophagojejunostomy Patient rejected chemotherapy	Yes	4
4.	Mohamed et al. [9]	Case-series report	2011	33	28 weeks	Preeclampsia Abdominal pain Edema Ascites	EGD Abdominal CT Scan	Carcinomatosis	Poor- differentiated adenocarci- noma	No (c-section on 32 wks)	None	Yes	4
				32	31 weeks	Upper abdominal pain Vomiting Weight loss	USG EGD	Invasion to pancreas and spleen with liver metastasis	Poor- differentiated adenocarci- noma with signet-ring cell morphology <i>Signet-ring cell</i>	No (c-section on 32 weeks)	None	Yes	
5.	Cift et al. [10]	Case report	2011	26	20 weeks	Severe abdominal pain Nauseous Vomiting Ascites	USG Gastroduodenoscopy MRI	Lung metastasis	<i>Signet-ring cell</i>	No	Chemotherapy (5-FU + Leucovorin)	Yes	4
6.	Chen et al. [11]	Case report	2014	35	34 weeks	Nauseous Epigastric pain Coagulopathy	Gastroendoscopy Abdominal CT Scan	<i>Linitis plastica</i> with metastasis to the placenta	Moderate- differentiated adenocarci- noma	No (c-section on 34 weeks)	Chemotherapy	No	4

Table 1 (Continued)

No	Author	Method	Year	Pt's Age (y.o)	Gestational Age	Symptoms	Radiology Tools	Tumor Characteristics	PA Result	Abortion	Treatment	Deceased	LoE
7.	Pacheco et al. [12]	Case-series report	2016	27	12 weeks	Epigastric pain Weight loss	EGD MRI	Whole gaster cT3N3M1	Poor-differentiated adenocarcinoma with signet-ring cell morphology	No	Palliative chemotherapy (5FU + Cisplatin)	Yes	4
				33	15 weeks	Epigastric pain Weight loss	EGD Abdominal CT Scan	Whole gaster T4aN3M0	Poor-differentiated adenocarcinoma with signet-ring cell morphology	No	Neoadjuvant chemotherapy (FOLFOX 4) on 18 weeks, total gastrectomy + D2 dissection, adjuvant chemoradiation (5-FU + Leucovorin and radiation 45 Gy)	Yes	
				29	6 weeks	Epigastric pain	EGD Abdominal CT Scan	Distal stomach T3N3M0	Adenocarcinoma with signet-ring cell morphology	No	Subtotal gastrectomy + D2 dissection on 14 weeks, adjuvant chemoradiation	No	
8.	Barbosa et al. [3]	Case report	2015	25	29 weeks	Asthenia Vomiting Weight loss Alopecia	Endoscopy	Peritoneal metastasis	Signet-ring cell	No (spontaneous delivery on 34 weeks)	Explorative laparotomy + chemotherapy (cisplatin + capecitabine)	No	4
9.	Zeng et al. [13]	Case-series report and mini-review	2015	29	26 weeks	Nauseous Vomiting Melena	No data	Borrmann 3	Moderate-differentiated adenocarcinoma	No data	Pancreaticoduodenectomy	Yes	4
				31	24 weeks	Abdominal distension Nauseous Vomiting	No data	Borrmann 4	Poor-differentiated adenocarcinoma	No data	None	Yes	
				36	post-partum	Abdominal pain Nauseous Vomiting Weight loss	No data	Borrmann 3	Poor-differentiated adenocarcinoma	No data	Subtotal gastrectomy	Yes	
10.	Song et al. [14]	Case-control	2016	23–39	No data	No data	No data	Stage 1-4	50% Poor-differentiated adenocarcinoma 50% signet-ring cell	35% Yes	40% Palliative 20% Surgery + adjuvant chemotherapy 10% Surgery only	80% Yes	3b

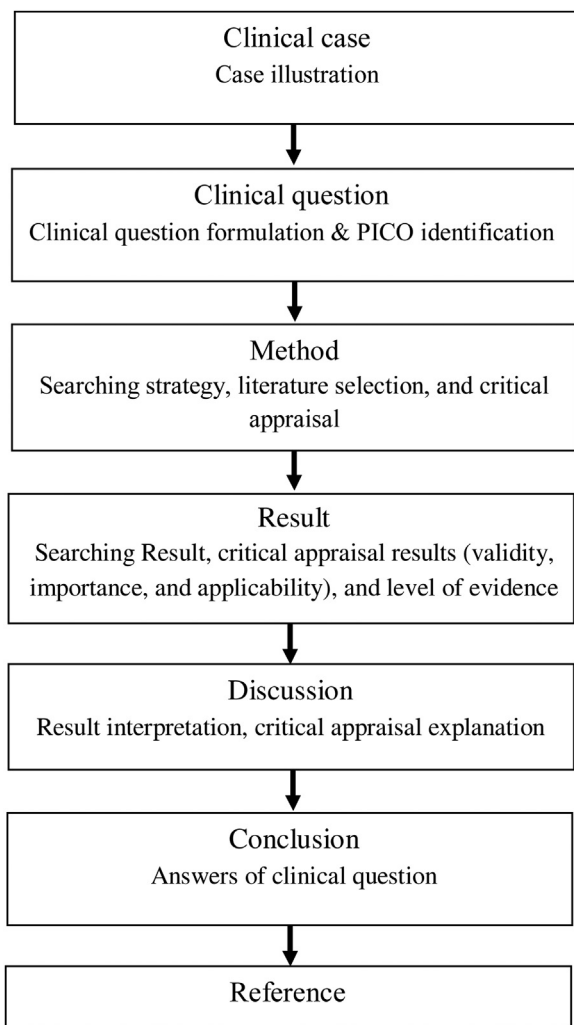


Fig. 1. Evidence-based case report structure algorithm.

vomiting which lower the surgeons' guard towards the possibility of malignancy who considered those symptoms commonly happened in pregnancy. Patients with such complaints were treated with over-the-counter drugs which were nugatory.

There are several factors causing nausea and vomiting of pregnancy (NVP). One of which is the hormonal factor. NVP often begins within weeks of missing menses then peaks between 10 and 16-week gestation and resolves after 20 weeks, but up 10% of women can be symptomatic beyond 22 weeks. The peak period of NVP happens simultaneously with the peak of hCG production, 12–14 weeks. Another hormone related to NVP is prostaglandin E2 (PGE2) which affects gastric smooth muscle. The highest level of PGE2 in pregnancy is within 9–12 weeks [15].

Six of 9 case reports showed that patients have been complaining at least 1 trimester before admission. There was 1 patient who already sought doctor's treatment 3 times since 18-week gestational age but had the endoscopy in 29-week gestational age [7]. In a case-control study by Song, 25% of patients had abdominal pain, 20% nausea and vomiting, and the rest had bleeding and metastatic related symptoms [14]. Until recently, there are still some difficulties in detecting gastric malignancy in pregnancy, probably due to the rarity of cases in young women and also a misinterpretation of signs and symptoms. Cift et al. recommended a radiology examination in pregnant women who complained of epigastric pain, nausea, and vomiting which are intractable and go on more than 16-week gestational age [10]. There is no known publication about the best

time to perform endoscopy for pregnant women with NVP in their first trimester where the level of hCG and PGE2 peak. Screening indication for gastric malignancy in a pregnant woman is similar to the general population, which is a first degree family with gastric cancer. Gastric cancer in the general population mostly happens in men on their 7th decade and screening indication is not limited only for patients with *Helicobacter pylori* [16].

Radiologic examinations for diagnosing gastric malignancy are endoscopy, MRI, and MDCT with the latter as the gold standard. Endoscopy combined with ultrasonography is only recommended for the early stage of gastric cancer. MRI is not recommended for staging and evaluation of invasion to adhered structure, especially the involvement of vascular and only used for patients with contraindication to MDCT. Endoscopy has roles as both screening and diagnostic tools to detect premalignancy lesions and cancer as early as possible. Several publications stated that a better prognosis is related to earlier diagnosis [14,17].

Borrmann classified lesions according to types of growth patterns which can be identified by endoscopy. Other advantages of endoscopy are recognizing the exact location of mass to plan surgical technique and identifying *linitis plastica* which is difficult to notice in other radiology tools. Doctors can also determine the histopathology and immunohistochemistry of cancer by performing a biopsy per endoscopy [1,18].

In 4 case-reports, an abdominal CT scan was performed to identify extension and invasion of gastric malignancy to the surrounding area. Two of 4 performed it after delivery, 1 unknowingly of the pregnancy (week 6 and week 15), and others had no clear data. In 3 publications, abdominal MRI was performed after biopsy per endoscopy (week 12, 20, and 29).

Abdominal CT Scan exposure can reach 10–50 mGy with fetal exposure 1,3–35 mGy. A 10–20 mGy fetal exposure can increase the risk of leukemia by a factor of 1,5–2,0. CT scan should be performed as clinically indicated as long as benefits outweigh the calculated risk and are subject to the patient's consent [19]. In non-emergency cases, MRI is recommended as a safer alternative to CT scan for evaluation of tumor extension as well as malignant invasion of the gaster [18–20]. Sohn et al. also stated there is no significant difference in the accuracy of gastric cancer stage assessment between fast MRI and helical CT scan [20].

Surgery procedure for gastric cancer in pregnancy is a dilemma in which should have a curative purpose if performed as early as possible, while this quickness can increase the risk of fetal death. Gastric cancer detected in gestational age more than 28 weeks is recommended to be treated by curative surgery after caesarean with or without chemotherapy afterward [9,21]. Management of gastric cancer in less than 27-week pregnancy is controversial, especially, nowadays, where there are more studies about advanced perinatal care for a very premature baby [21].

Song et al. revealed that 35% of pregnant women underwent termination of pregnancy or abortion with a gestational age range of 7–23 weeks [14]. In contrast to nine case reports collected, only one had an abortion (6-week gestational age). In Indonesia, termination of pregnancy at any gestational age is a criminal offense. In this case report, the patient underwent surgical action aimed at curative without termination of pregnancy at 22–23-week gestation.

In three of nine case reports collected, gastric cancer in pregnant women was treated with surgery alone. Therapy in two other case study studies was a surgical procedure followed by adjuvant systemic chemotherapy. The rest are given palliative systemic chemotherapy. In a case-control study by Song et al., most of the management provided was palliative-intention, with only 20% taking surgery followed by adjuvant chemotherapy and 10% of surgery alone. Non-obstetric surgical measures were performed on low-risk pregnant women during the use of modern surgery and

anesthesia techniques. Besides, surgery and general anesthesia do not increase the risk of spontaneous abortion and major malformations [22].

Of the nine case reports collected, only one locally advanced patient performed neoadjuvant chemotherapy followed by adjuvant surgery and chemotherapy. The reason for the neoadjuvant chemotherapy was the patient's rejection of curative surgery at 15 weeks' gestation, thus being given preoperative chemotherapy at 18 weeks of gestation to slow the progression of the tumor while increasing the resectability.

In this study, we decided to perform subtotal gastrectomy and Roux-en-Y esophagojejunostomy in resectable gastric cancer following MRI images previously done several weeks before admission. Unfortunately, a clear surgical margin was not achieved intraoperatively due to the wide extension of lesion up to the proximal duodenum and posterior adhesion which were not detected in MRI. We planned chemotherapy after delivery.

Perioperative chemotherapy may be given to unresectable and distant metastatic gastric cancer to improve resectability and increase disease-free survival and overall survival [23]. Chemotherapy given in the first trimester, when organogenesis occurs, increase the risk for spontaneous abortion, major malformations, and fetal death [24]. While administration in the second and third trimesters has no significant risk to the fetus.

Only one case study report from Chile which included radiation therapy as an adjuvant treatment for minimal T2 and unresectable cancer. The severity of radiation adverse effects on the fetus depends on the age of the pregnancy and the dose of radiation. The most significant risk of side effects is in the first trimester of organogenesis, then reduced in the second trimester, and lowest in the third trimester. The radiation dose threshold which can cause malformations is more than 100–200 mGy, but 100 mGy dose is not even achieved with 3 times pelvic CT scan or 20 times plain ordinary photos.

6. Conclusion

1. No high level of evidence in previous publication
2. Delay of diagnosis happens due to misinterpretation of signs and symptoms
3. We should suspect a possibility of gastric cancer when complaints of epigastric/abdominal pain, nauseous, vomiting happen progressively, intractably, and continuously until the 2nd trimester.
4. Radiology tools in pregnancy: endoscopy, abdominal MRI, and contrast abdominal CT scan.
5. Abdominal MRI is recommended for staging evaluation despite low accuracy for resectability. Contrast abdominal CT scan can be done in pregnancy with consent.
6. Surgery and chemotherapy are relatively safe in the 2nd and 3rd trimester for their lower risk of malformation and abortion.

Conclusions are supported by 1 case-control study (LoE 3) and 9 case-reports (LoE 4).

Declaration of Competing Interest

The authors report no declarations of interest.

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None.

Ethical approval

Our institution exempt this study from ethical approval because all actions, examination, and procedure were done according to hospital's standard of procedure and policy.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Vania Myralda Giamour Marbun: study concept, data collection, data analysis & interpretation, writing the papers.

Agi Satria Putranto: study concept, data collection, data analysis & interpretation.

Registration of research studies

N/A.

Guarantor

Vania Myralda Giamour.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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