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Gastric cancer during pregnancy: A report on 13 cases and review of the literature with focus on chemotherapy during pregnancy

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Abstract

Introduction: Gastric cancer during pregnancy is extremely rare and data on optimal treatment and possible chemotherapeutic regimens are scarce. The aim of this study is to describe the obstetric and maternal outcome of women with gastric cancer during pregnancy and review the literature on antenatal chemotherapy for gastric cancer.

Material and methods: Treatment and outcome of patients registered in the International Network on Cancer, Infertility and Pregnancy database with gastric cancer diagnosed during pregnancy were analyzed.

Abbreviations: 5-FU, 5-fluorouracil; ER, estrogen receptors; FOLFOX, 5-fluorouracil, leucovorin and oxaliplatin; INCIP, International Network on Cancer, Infertility and Pregnancy; SGA, small for gestational age.

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Results: In total, 13 women with gastric cancer during pregnancy were registered between 2002 and 2018. Median gestational age at diagnosis was 22 weeks (range 6-30 weeks). Twelve women were diagnosed with advanced disease and died within 2 years after pregnancy, most within 6 months. In total, eight out of 10 live births ended in a preterm delivery because of preeclampsia, maternal deterioration, or therapy planning. Two out of six women who initiated chemotherapy during pregnancy delivered at term. Two neonates prenatally exposed to chemotherapy were growth restricted and one of them developed a systemic infection with brain abscess after preterm delivery for preeclampsia 2 weeks after chemotherapy. No malformations were reported.

Conclusions: The prognosis of gastric cancer during pregnancy is poor, mainly due to advanced disease at diagnosis, emphasizing the need for early diagnosis. Antenatal chemotherapy can be considered to reach fetal maturity, taking possible complications such as growth restriction, preterm delivery, and hematopoietic suppression at birth into account.

KEYWORDS

chemotherapy, gastric cancer, maternal outcome, obstetric outcome, pregnancy

1 | INTRODUCTION

Gastric cancer is one of the most common cancers, with very specific geographical, ethnic and socioeconomic differences in incidence. GLOBACAN (Global cancer observatory, WHO) data estimated about 1 million new patients in 2018.[1] More than 70% of gastric cancer cases occur in developing countries and most patients come from Eastern Asia. Known risk factors for gastric cancer include age, smoking, ethnicity and geography, history of gastric ulcer, and immunosuppressive disease. Exposure to *Helicobacter pylori* plays a role in the development of non-cardiac cancer, whereas gastroesophageal reflux disease and obesity are risk factors especially for cardiac cancer. Typically gastric cancer has a male predominance and is diagnosed at a median age of 70 years, whereas only 1% of patients are <34 years at diagnosis.[2] Pregnancy-associated gastric cancer, defined as a diagnosis of gastric cancer during pregnancy or up to 1 year after delivery, is estimated to complicate 0.026%-0.1% of all pregnancies.[3]

Gastric cancer is staged according to the American Joint Committee on Cancer/Union for International Cancer Control TNM staging system, based upon tumor size (T), lymph node invasion (N), and metastatic disease (M). Early gastric cancer is limited to the mucosa or submucosa (T1), whereas the tumor is assumed to be clinically localized once the muscular layer (T2) is invaded. Stage I gastric cancer is limited to the stomach, whereas in stage II lymph nodes are affected or the tumor spreads to the subserosa or serosa (T3-4aN0). In stage III the tumor invades both (sub)serosa and lymph nodes, in stage IV the tumor has spread to the adjacent organs with lymph nodes affected or distant organs. The stage distribution in the general population is 21.6% for stage I, 22.3% for stage II, 44.0% for stage III, and 12.1% for stage IV.[4] Pregnant women are at risk for delayed diagnosis of gastric cancer because symptoms may be regarded as gestational features and because of the reluctance to perform invasive diagnostic procedures such as gastroscopy.[5] As a result, gastric cancer is often diagnosed in more advanced cancer stages. Gastric cancer that invades through the submucosa stage II or higher with no evidence of distant metastases, or locally advanced inoperable disease can be treated with curative intent by surgical resection and perioperative chemotherapy.[6] In locally advanced unresectable or metastatic gastric cancer, surgery is not a feasible option and palliative chemotherapy can be considered. Standard cytotoxic treatment for primary gastric cancer consists of a platinum-fluoropyrimidine-based regimen, such as FOLFOX (5-fluorouracil [5-FU], leucovorin and oxaliplatin), CAPOX (capecitabine, oxaliplatin), ECF/ECC (epirubicin, cisplatin, 5-FU/capecitabine) or EOX (epirubicin, oxaliplatin, capecitabin). Trastuzumab combinations may be administered in case of HER2-overexpressing gastric cancers. Alternatively, taxane-based schedules may be applied, such as FLOT (5-FU, leucovorin, oxaliplatin, docetaxel).

Key message

Early recognition of symptoms of gastric cancer in pregnant women allows curative treatment but is hampered by low incidence of complaints in early cancer and the overlapping symptoms with pregnancy. Chemotherapy during pregnancy might be considered if parents are counseled for neonatal risks.

Various chemotherapy regimens are feasible during pregnancy without an increased risk of congenital malformations if administered after the first trimester.[7] More pregnant women with cancer are now treated with chemotherapy so as to not delay treatment

while avoiding preterm birth or pregnancy termination as much as possible.[7] To date, the relative safety of antenatal chemotherapy is mainly demonstrated for treatments used in breast and cervical cancer, and lymphomas, but experience with gastric cancer is limited.[7] Most large case series on gastric cancer during pregnancy do not report on the use and consequences of cytotoxic treatment and include only Asian patients.[3,8,9] However, biological behavior and response to treatment may show geographic differences.[10] Therefore, we selected all women with a diagnosis and/or treatment of gastric cancer during pregnancy from the international "cancer in pregnancy" International Network on Cancer, Infertility and Pregnancy (INCIP) registry (www.cancerinpregnancy.org). We conducted a review of cases where chemotherapy was initiated during pregnancy and assessed neonatal outcome in this population.

2 | MATERIAL AND METHODS

All women diagnosed with primary or recurrent gastric cancer during pregnancy were selected from the database of the International Cancer in Pregnancy registration study (Clinicaltrials.gov, number NTC00330447). The registry contains retrospectively, and since 2005 prospectively, collected oncological and obstetrical data of women diagnosed with any pregnancy-associated malignancy. The registered cases are reported by physicians, INCIP members, with a special interest in cancer in young women. Currently the registry contains 2059 women with a cancer diagnosis during pregnancy, registered by European (Belgium 25%, the Netherlands 21%, Italy 13%, Czech Republic 6%) and non-European (Philadelphia, USA 13%, Russia 8%, Mexico 6%) centers. For the present study, patient data on treatment and obstetrical outcomes were collected. Referring physicians were contacted to complete missing data. Small-for-gestational-age (SGA) was defined as a birthweight below the 10th centile, and centiles were corrected for gestational age, sex, maternal height, maternal weight, ethnicity, and parity according to the calculator from the Gestation Network (www.gestation.net; v8.0.2, 2018) Preterm delivery was defined as birth before 37 weeks of gestation.

In addition, we performed a narrative review and searched for case reports and case series, as well as articles on treatment options for gastric cancer during pregnancy, published in the English literature. Articles were identified by a PUBMED search with the following MESH terms: "pregnancy", "gastric cancer", and "chemotherapy" and variations thereof. For statistics, we used descriptive analysis. Comparative analysis was not performed because of the small number of patients.

2.1 | Ethics approval

The international registration study "Cancer in Pregnancy" was approved by the Ethics Committee of University Hospitals of Leuven (B322201421061) 23 May 2014 and participating centers according to local policies.

3 | RESULTS

3.1 | Patient and tumor characteristics

In total, 13 women diagnosed with primary or recurrent gastric cancer during pregnancy were retrieved from the registry (see Supplementary material, Table S1). They were diagnosed between March 2002 and November 2017 in 6 countries (The Netherlands, n = 5; USA, n = 3; Belgium, n = 2; Czech Republic, n = 1; Italy, n = 1; and France, n = 1). One woman with a diagnosis of gastric carcinoma in situ treated with surgery and in remission for 1 year before pregnancy was excluded.

All women, except one, were diagnosed with advanced or metastatic disease (12/13, 92.3%). Patient demographics are described in Table 1. Median maternal age at diagnosis was 32 years (range 26-39 years), median gestational age at diagnosis was 21 weeks (range 6-30 weeks). Most patients were diagnosed with a diffuse type (signet ring cell carcinoma) of gastric cancer. One woman was found to be pregnant on the computed tomography scan that was performed during trastuzumab maintenance therapy. This case highlights the importance of pregnancy testing because young women can still be fertile despite amenorrhea secondary to cancer treatment. Most women (9/13, 69%) presented with gastrointestinal symptoms (nausea and vomiting [5/13, 39%], diarrhea [1/13, 8%], distended abdomen [3/13, 23%]). One woman presented with a palpable cervical adenopathy. Because the origin of the primary tumor was initially uncertain, she was initiated with carboplatin and paclitaxel during pregnancy and switched postpartum to cisplatin, doxorubicin and trastuzumab when a computed tomography scan revealed a gastric tumor. Another woman presented with vertebral pain caused by bone metastasis. Two had ascites, in combination with liver metastasis or peritoneal metastasis. Five women were diagnosed with ovarian Krukenberg tumors.

3.2 | Surgical and chemotherapeutic management during pregnancy

One woman with stage II cancer started with chemotherapy at 23 weeks of gestation followed by curative gastrectomy after delivery. In total, 10 women had ongoing pregnancies with inoperable gastric cancer and in 5 women chemotherapy was initiated in the second trimester of pregnancy. The chemotherapeutic regimens used during pregnancy were: 5-FU, FOLFOX and carboplatin/paclitaxel. One woman underwent surgery with a curative intent but was diagnosed with intestinal metastasis perioperatively and initiated palliative chemotherapy after elective cesarean section at 32 weeks. Four patients received no definitive surgical or cytotoxic treatment during pregnancy aside from adnexectomies.

3.3 | Obstetrical outcome

As described in Table 1, there was 1 termination of pregnancy, 2 pregnancy losses and 10 live births. One woman pregnant with

TABLE 1 Patient characteristics

	Present cases, n (%)
Total number of cases	13
Age (years), median (range)	31.7 (26.9-39.9)
Gestational age at diagnosis (wk),[a] median (range)	22 (6-30)
Gestational age at delivery (wk), median (range)	32(19-39)
History of smoking	4 (31%)
Histopathology	
Diffuse type	12 (100%)
Signet ring cell	8 (67%)
Intestinal type	0
Unknown	1
Disease stage at diagnosis	
Stage II	1 (8%)
Stage IV	12 (92%)
Treatment during pregnancy	
Chemotherapy	6 (46%)
Surgery with curative intent	1 (8%)
Exploratory surgery (palliative)	3 (23%)
Deferral of treatment until after delivery	3 (23%)
Obstetrical outcome	
Termination of pregnancy	1 (8%)
Late miscarriage/IUD	2 (15%)
Live birth	10 (77%)
<28 wk	1
<34 wk	5
<37 wk	2
Term	2
Complications	
Preeclampsia	3 (23%)
Spontaneous preterm delivery	1 (8%)
Low birthweight (<P10)[a]	4 (44%)
Mode of delivery	
Vaginal delivery	2 (20%)
Cesarean section	8 (80%)
Placental metastasis	0
Maternal outcome	
Deceased during pregnancy	1 (8%)
Alive in 3 mo	9 (69%)
Alive in 6 mo	7 (54%)
Alive in 12 mo or more	4 (31%)

Abbreviation: IUD, intrauterine death (deceased with mother).
Excluded 1 patient with recurrent gastric cancer during pregnancy.
[a]1 case birthweight unknown.

twins opted for a termination of pregnancy at 23 weeks of gestation because of metastatic disease. One woman died from the disease 2 weeks after diagnosis at 22 weeks of gestation. One woman miscarried at 19 weeks of gestation following an exploratory laparotomy and adnexectomy. Three women underwent an emergency cesarean section for preeclampsia between 27 and 33 weeks of gestation, and another was delivered at 29 weeks of gestation by cesarean section because of clinical maternal deterioration. Four women had an iatrogenic preterm delivery for therapy planning. Only 2 women delivered at term, both received chemotherapy during pregnancy and had an elective cesarean section for maternal reasons.

3.4 | Maternal outcome

All mothers with stage IV gastric cancer were deceased within 24 months after pregnancy, the majority within 6 months. Overall 1-year survival was 31%. The only woman in remission 12 months after diagnosis had stage II gastric cancer and was treated with chemotherapy during pregnancy followed by gastrectomy.

3.5 | Outcome of the children

In total 10 pregnancies ended in a live birth. All six neonates prenatally exposed to chemotherapy were born without congenital malformations and all, except one with a birthweight of 2950 g and term delivery, were admitted to the neonatal intensive care unit, mostly for prematurity (4/5 or 80%). One infant born at term was admitted for neonatal abstinence syndrome due to maternal use of methadone. Two neonates prenatally exposed to chemotherapy, to 6 cycles FOLFOX and 3 cycles carboplatin/paclitaxel, respectively, (2/6 or 33%) were SGA at birth. The four non-exposed neonates were admitted to the neonatal intensive care unit for prematurity and two of them where SGA (2/4 or 50%). The neonatal period of one child born at 32 weeks of gestation, 2 weeks after the last administration of carboplatin, was complicated by a *Bacillus cereus* infection with a cerebral abscess. This was treated with antibiotics, but the neonate had residual cerebral palsy, epilepsy and hemianopia. Despite these symptoms requiring intensive physiotherapy, the child was doing well in cognitive development at 15 months, 3 years and 6 years of follow up according to standardized and clinical measures of neurocognitive functions. One child born at 34 weeks of gestation was cognitively assessed at 18 months of age and had appropriate cognitive development when corrected for his prematurity at birth. Available middle- to long-term follow up of four children that are included in the INCIP study is shown in Table 2.

3.6 | Results of narrative literature review

The largest review to date of 137 Japanese women with pregnancy-associated gastric cancer was published in 2009; one-third of the women with reported timing of delivery were diagnosed with gastric cancer postnatally.[3] The authors identified that 92.5% of the patients had advanced stage gastric cancer and the diffuse type was the most common histological diagnosis. Maternal outcome was poor with 1- and 2-year survival rate of 18.3% and 15.1%. A review

TABLE 2 Pediatric outcome of 4 children prenatally exposed to chemotherapy for gastric cancer, included in the INCIP follow-up study

Case	Gestational age at diagnosis (wk)	Gestational age at delivery (wk)	Age at follow up	Chemotherapy during pregnancy	General outcome	Cardiac outcome	Neurological outcome	Cognitive outcome	Supportive care
8	22	39	4 mo	FOLFOX 6 cycles	Normal growth	No details	No details	No details	No supportive care
9	15	34	18 mo	FOLFOX 7 cycles Radiation exposure: 12 mGy[a] Trastuzumab exposure during first trimester	Normal growth and development	No details	No neurological abnormalities	18 mo: normal cognitive development for his premature age	No supportive care
11	6 (first trimester)	32	15 mo 3 years 6 years	Carboplatin and paclitaxel 3 cycles	Normal growth and development	No abnormalities	Cerebral palsy left, epilepsy and hemianopia left side	15 mo: normal cognitive development for his premature age 3 years: normal cognitive development 6 years: normal cognitive development	0-12 mo physiotherapy once a week
13	30	38	6 mo	FOLFOX 4 cycles	Normal growth and development	No abnormalities	No neurological abnormalities	No details	No supportive care

Note: OVERVIEW of examinations in INCIP follow-up study.

Pediatric consultation: A general physical examination and neurological assessment performed by a pediatrician.

Cardiac assessment: 12-lead electrocardiograph (ECG) and a full ECG assessment for structural and functional characteristics was collected by a cardiologist/experienced sonographer.

Cognitive assessment: an age-adapted test battery for the assessment of intelligence, verbal and non-verbal memory, attention, working memory and executive functions by an experienced psychologist (Bayley Scales of Infant and Toddler Development, third edition, Child Behavior Checklist, Behavior Rating Inventory of Executive Function—Preschool Version, Wechsler Preschool and Primary Scale of Intelligence, third edition, Subtask of Children's Memory Scale, Subtasks of Amsterdam Neuropsychological Tasks, Behavior Rating Inventory of Executive Function).

[a]Below recommended fetal radiation exposure of 50 mGy.

of 31 cases (42% postpartum diagnosis) from western academic journals between 1969 and 1999 and a case series of 65 Asian women (35% postpartum diagnosis) published in 2014 had similar findings.[8,9]

In the literature we identified five women receiving a 5-FU-based regimen for advanced gastric cancer during pregnancy, with re-assuring fetal outcomes.[11-13] Details are summarized in Table 3. One woman received paclitaxel and S1 (tegafur [=prodrug of active substance 5-FU], gimeracil, oteracil) and delivered a growth restricted baby at 34 weeks of gestation.[14] Nishie et al summarized three additional Japanese cases with re-assuring neonatal outcome after prenatal exposure to S1 and taxanes (cases not included as reported in Japanese language).[14]

4 | DISCUSSION

In this case series the obstetrical and maternal outcomes of 13 women with a diagnosis of primary or recurrent gastric cancer during pregnancy are reported. Most women were diagnosed at an advanced stage with a diffuse type adenocarcinoma, including 8 women with signet ring cell carcinoma. Larger case series had similar findings, but none of these studies reported on the use of chemotherapy during pregnancy or neonatal outcome in detail and most included a large percentage of women diagnosed postnatally.[3,8,9]

Five-year survival in young (≤40 years) patients is 47.6% in general, but is highly dependent on tumor stage (range 83.3% for stage I and 0% for stages III and IV).[15] Young patients are reported to have lower overall survival compared with patients >40 years of age if curative resection is not achieved.[15] Furthermore, in a retrospective analysis of clinical-pathological features and outcome of 4722 non-pregnant patients, female sex was significantly associated with a younger age at diagnosis, poorly differentiated adenocarcinoma and signet ring cell carcinoma.[16] Due to these features, overall survival was poorer for female than for male patients, especially among patients younger than 45 years of age with advanced disease. The histological features of the gastric cancer in pregnant patients are similar to those reported in non-pregnant female patients. Nevertheless, gastric cancer during pregnancy has a poor prognosis with reported median overall survival of 7 months and 3-year overall survival of 23.3%. One-year overall survival in this series was 31% (4/13 alive 12 months after diagnosis).To evaluate the effect of pregnancy on gastric cancer, Lee et al compared 15 pregnant patients with 53 age-matched non-pregnant patients.[5] During gestation, 93% of patients were diagnosed with advanced stage gastric cancer, 60% of tumors were unresectable and 3-year survival rate was 23.3%. Significant differences between both groups were found regarding the tumor stage, but in multivariate analysis, pregnancy was not found to be an independent risk factor. It is unknown if a delay in diagnosis due to pregnancy explained this difference in tumor stage. A more recent study that compared overall survival of 20 patients with pregnancy-associated gastric cancer with 39 age- and stage-matched non-pregnant females concluded that advanced stage and tumor location but not pregnancy status are poor prognostic factors.[17]

Estrogen receptors (ER) are found in about 20%-30% of human gastric cancers, mainly in the poorly differentiated type.[8] A recent meta-analysis suggested that the tumoral expression of ERα might indicate poor survival and the absence of ERβ is associated with lymph node metastasis.[18] However, the clinical significance of ER and (if there is) estrogen-dependent tumor growth in gastric cancer is still unclear.

There is no evidence of severe adverse neonatal outcome or increased risk of congenital malformations if regimens are administered after fetal organogenesis (occurring 2-8 weeks after conception) while avoiding preterm delivery.[7,19] The degree of placental transfer of drugs depends on molecular weight, lipophilicity, ionization at physiological pH and plasma protein binding, besides drug dose and gestational age at exposure. Also, interaction with active drug transporters, like p-glycoprotein and BCRP (Breast Cancer Resistance Protein) might affect the transfer rate. Preclinical data and the limited clinical data of individual drugs used in the treatment of gastric cancer during pregnancy are summarized in Table 4.[19-29] Albeit, in clinical practice, most chemotherapeutic agents are given in combination regimens with co-medication, which might also influence the placental transfer through drug interactions.

Most pregnant patients presented with extensive intra-abdominal disease that theoretically might provoke spontaneous preterm contractions. Interestingly all preterm deliveries, except 1, were iatrogenic for oncological or obstetrical reasons. Four out of 10 infants were SGA and this is of special interest because perinatal morbidity and mortality, and cardiovascular and metabolic diseases, are more frequently seen in SGA children than in children of average weight (according to gestational age) at birth.[30] SGA in this population might be explained by the poor maternal general and nutritional status inherent to gastric cancer. In addition, 2 of these children were prenatally exposed to chemotherapy, which is also reported to be associated with SGA.[7] In this series 3 women developed preeclampsia, possibly explained by the relatively high maternal age (diagnoses at the age of 27, 37 and 39 for the 3 cases, respectively).

Current recommendations for the management of pregnant women with a diagnosis of gastric cancer is based on available case series.[3,5,8] Treatment options depend on gestational age and cancer stage. If possible, the best oncologic management for the mother should be aimed for. An individualized management plan is required, always taking patient's perspective into account. In case of primary resectable disease, curative treatment should be aimed for with or without perioperative chemotherapy, depending on stage. Depending on the surgeon's expertise and the gestational age, a laparoscopic approach is feasible. In late pregnancy, preterm delivery can be considered as the gravid uterus and maternal general condition can complicate surgery; however, for optimal fetal outcome, term delivery should always be aimed for if possible. When perioperative chemotherapy is indicated, cytotoxic agents

TABLE 3 Literature review: Case reports on chemotherapy for gastric cancer during pregnancy

Ref.	Number of cases	Patient age (years), AGP, gestational age at diagnosis (wk)	Histology	Stage at diagnosis	Symptoms at diagnosis	Treatment	Period of treatment (gestational weeks)	Complications during pregnancy, Obstetrical outcome, Gestational age at delivery (wk)	Weight at birth (g), neonatal outcome	Maternal outcome (months after delivery)
Cift et al, 2011[11]	Case 1	26, A0G2P1, 24	Poorly differentiated adenocarcinoma with signet ring cell morphology	Stage IV (bilateral adnexal masses)	Abdominal pain, nausea and vomiting	4 days of 5-FU (425 mg/m^2 and 10 mg/m^2 calcium folinate)	29-29$^{4/7}$	Preterm contractions, spontaneous vaginal delivery, 29$^{4/7}$ wk	930 g, healthy	DOD (2 days)
Pacheco et al 2016[12]	Case 1	27, A0G3P2 12	Poorly differentiated adenocarcinoma with signet ring cell	cT3N3M1 (stage IV) (peritoneal metastasis)	Epigastric pain, weight loss	Palliative chemotherapy (5-FU [1000/m^2] and cisplatin [75 mg/m^2] day 1,2,3,4 every 28 d, 4 cycles during pregnancy)	12-24	Preterm contractions, spontaneous vaginal delivery, 26 wk	850 g, Deceased (0.5 mo) due to respiratory failure	DOD (7 mo)
	Case 2	33, A0G2P1 15	Poorly differentiated adenocarcinoma with signet ring cell morphology	cT3N0M0 (stage IIA) pT4aN3M0 (stage pIIIC)	Epigastric pain, weight loss	FOLFOX (oxaliplatin 85 mg/m^2, leucovor 200 mg/m^2, 5-FU (400 mg/m^2 day 1, 600 mg/m^2 day 1 and 2) every 14 days), 4 cycles during pregnancy, total radical gastrectomy after delivery, adjuvant chemoradiation	18-26	Preterm contractions, spontaneous vaginal delivery, 36 wk	3150 g, healthy	Deceased (41 mo)
Kim et al 2016[13]	Case 1	36, AxGxPx, 18	unknown	Locally advanced stage	unknown	Totally laparoscopic distal gastrectomy followed by FOLFOX, 4 cycles during pregnancy	28-33	No complications, elective delivery 36 wk	healthy	NED (12 mo)
Nishie et al 2015[14]	Case 1	>30y, AxGxPx, 23	Poorly differentiated adenocarcinoma, no HER2 overexpression	Stage IV (bilateral adnexal masses, cervical lymph node	Epigastralgi, left cervical lymph node swelling	2 cycles of Paclitaxel (50 mg/m^2) on days 1 and 8 and S1* daily (100 mg/body), Continued Cisplatin and S1 after pregnancy	24-33$^{4/7}$	IUGR and peripheral neuropathy, elective cesarean section, 34 wk	1442 g, healthy	Progressive disease with meningitis carcinomatosis, DOD (6.3 mo)

Note: S1*: tegafur (=prodrug of active substance 5-FU), gimeracil, oteracil.

Abbreviations: APG, Abortion(miscarriage)/Gravidity/Parity; DOD, Dead of disease; IUGR, intrauterine growth restriction; NED, no evidence of disease.

TABLE 4 Preclinical and clinical data on placental transfer for most common cytotoxic drugs used for gastric cancer

Drug	Drug characteristics[a]	Pre-clinical data (placental transfer)	Reference	Clinical data	Reference
5-FU (Fluorouracil)	MW[b]: 130 g/mol Negligible PB (8%-12%)	28% (rat model)	Boike et al[20]	Large case series on use of anthracycline-based chemotherapy (including FEC and FAC) during pregnancy in breast cancer patients; use during second and third trimester of pregnancy seems relatively safe.	Amant et al[19] Cardonick et al[25]
Capecitabine (prodrug of 5-FU)	MW[b]: 359 g/mol Limited PB (<60%)	No data		One case report, colorectal cancer, treated in first trimester; no congenital malformations	Cardonick et al[25]
Platinum-derivates Oxaliplatin Cisplatin Carboplatin	MW[b]: 397 g/mol High PB (>90%) MW[b]: 298 g/mol, High PB (>90%) MW[b]: 371 g/mol Limited PB (25%-40%)	No data 2%-24% (ex vivo placental perfusion model) up to 57% (baboon model)	Al-Saleh et al[21] Van Calsteren et al[22]	Few case reports on oxaliplatin (one case of neonatal hypothyroidism in 8 patients treated with FOLFOX for colorectal cancer) Reports of hearing loss when cisplatin used during pregnancy. Carboplatin appears to be a safer alternative.	Pellino et al[26] Amant et al[19]
Epirubicin	MW[b]: 543 g/mol Moderate PB (~77%)	Less than 10% (baboon model)	Van Calsteren et al[23]	Large case series on use of anthracycline-based chemotherapy during pregnancy in breast cancer patients; use during second and third trimester of pregnancy seems relatively safe.	Amant et al[19] Cardonick et al[25]
Taxanes Paclitaxel Docetaxel	MW[b]: 854 g/mol High PB (89%-98%) MW[b]: 808 g/mol High PB (94%-97%) Drug efflux by placental p-glycoprotein transporter	Low (<2%, paclitaxel) or undetectable (docetaxel) in fetal plasma, but accumulation in fetal tissue (metabolization of taxanes still immature) (baboon model) Paclitaxel modulates expression of placental drug transporters of anticancer agents (ex vivo placental perfusion model)	Van Calsteren et al[22] Berveiller et al[24]	Favorable toxicity profile in small case series when administered during second or third trimester of pregnancy (12-25 patients)	Cardonick et al[27]
Trastuzumab	IgG monoclonal antibody MW[b]: 14 5531 g/mol	Placental transfer by specific receptor-mediated active transport (not active in early pregnancy), up to 85% (baboon model)	Van Calsteren et al[22]	Risk of oligohydramnios, hypoplastic lungs and fetal death by its ligation to HER2-receptors that are present in the renal epithelium of the fetus Exclusive exposure during first trimester of pregnancy appears not to be associated with abnormalities (HERA trial)	Azim et al[28]

Abbreviations: FAC, 5-FU, adriamycin (doxorubicin), cyclophosphamide; FEC, 5-FU, epirubicin, cyclophosphamide; 5-FU, 5-fluorouracil; FOLFOX, 5-FU and oxaliplatin; HER2, human epidermal growth factor receptor 2; HERA, Herceptin Adjuvant Trial; MW, molecular weight; PB, protein binding.

[a]Reference for drug characteristics: Drugbank 5.0.[29]

[b]Agents with low molecular weight (<500 g/mol) and low protein binding will easily cross the placenta.

may be administered during pregnancy (from the second trimester onwards) so as to not delay treatment and to enhance fetal maturity. In patients diagnosed with advanced stages of disease, where no cure is possible, immediate onset of systemic (palliative) treatment might be indicated to treat symptoms and to enhance fetal maturity if there is a wish to continue pregnancy. In early pregnancy, and especially in advanced cases, termination of pregnancy can also be considered. Available case reports on chemotherapy during pregnancy for gastric and colorectal cancer suggest that 5-FU-based regimens (i.e. FOLFOX) are feasible.[11-14,26] In general, the use of cytotoxic drugs can only be justified if the risks of both mother and child are balanced and the benefits for maternal outcome outweigh the possible adverse effects on the child. Studies on the short-term neurocognitive development of children reveal that preterm delivery rather than prenatal exposure to cancer treatment is responsible for impaired cognitive outcome.[19] However, long-term outcome of children prenatally exposed to chemotherapy remains under investigation and further follow up of these children is indispensable.

Although this series on western patients is small, we report on the use of chemotherapy for gastric cancer during pregnancy and the neonatal outcome in detail including follow up. Continuous prospective registration of cases will facilitate future patient counseling. International collaboration is welcomed in order to collect data in larger numbers to improve treatment approach during pregnancy.

5 | CONCLUSION

In summary, gastric cancer during pregnancy is a rare diagnosis. Women present usually in advanced stage and have a poor prognosis. Early recognition of symptoms is indispensable for diagnosis at a curative stage. In pregnant women with persistent gastrointestinal symptoms that cannot be explained by pregnancy alone there should be a low threshold for further diagnostic procedures. While balancing maternal and fetal risks, the initiation of chemotherapy during pregnancy may be considered in order to reach fetal maturity.

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CONFLICT OF INTERESTS

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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