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STOMACH CANCER AND PREGNANCY

Stomach cancer during pregnancy is extremely rare and accounts for 0.025-0.1% of all pregnancies, while most cases of stomach cancer associated with pregnancy are diagnosed by specialists at a late stage, since its main symptoms (vomiting, nausea, loss of appetite, increased abdominal size) are mistaken for early toxicosis during pregnancy and the likelihood of the development of malignant neoplasms is underestimated. Survival rates for stomach cancer are directly related to its early diagnosis, in such a situation, doctors face two problems: the need to treat stomach cancer in the mother and prolonging pregnancy. Optimal management of this category of patients requires a multidisciplinary approach (including oncologist, obstetrician, surgeon, anesthesiologist, gastroenterologist, radiologist and neonatologist), which establishes the sequence of therapy. Psychological supportive therapy should not be neglected, since the patient's decision is crucial, while the woman's decision is very much connected with the survival of the fetus, sometimes with her victim. In the article, we presented our own experience of treating and monitoring this category of patients in the form of two clinical cases that clearly demonstrate an extremely unfavorable prognosis for a combination of stomach cancer and pregnancy. According to the literature, the five-year survival rate in this category of patients is zero, while in most cases the patient's death occurs within six months after surgery.

Keywords: cancer, stomach, pregnancy, treatment, prognosis

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Stomach cancer (SC) is one of the most common types of cancer with very specific ethnic and socio-economic features in the incidence. According to GLOBACAN, in 2021, about 1 million new cases of stomach cancer were reported worldwide, and almost 70% of them occur in developing countries, most of which are located in East Asia. Known risk factors for stomach cancer include: old age, smoking, ethnicity and geography, a history of gastric ulcers and Helicobacter pylori, immunosuppressive disease, gastroesophageal reflux disease, and obesity. This pathology is more common in men and is diagnosed on average at the age of 70, but in 1% of cases it is registered in people younger than 34 years [1, 2]. Stomach cancer is diagnosed according to the TNM classification system of the American Joint Committee on Cancer / Union of the International Fight against Cancer, depending on the size of the tumor (T), invasion of lymph nodes (N) and metastatic lesion (M). Early SC (at stage I) is limited to the mucous membrane or submucosa (T1), while the tumor is considered clinically localized after invasion of the muscular layer (T2). In stage II, the lymph nodes are affected and (or) the tumor spreads to the subserous or serous membrane. At stage III, the tumor grows into both the (sub)serous membrane and the lymph nodes; at stage IV, it spreads to neighboring organs with damage to the lymph nodes of other areas or distant metastasis occurs. The distribution by stage in the general population of patients with stomach cancer is as follows: 21.6% – stage I, 22.3% – stage II, 44.0% – stage III and 12.1% – stage IV [3]. Stomach cancer during pregnancy is extremely rare and, according to various authors, accounts for 0.025–0.1% of cases. The main inducing factors are: Helicobacter pylori infection, specific susceptibility due to genetic changes in inflammatory mediators to Helicobacter pylori. Most cases of pregnancy-related stomach cancer are diagnosed in the late stages, as its main symptoms (nausea, vomiting, loss of appetite) are mistaken for early toxicosis, and the likelihood of developing SC is underestimated. There are contraindications to instrumental examinations during pregnancy, which can complicate its course, therefore, in most cases, diagnosis and treatment are carried out at a later date. Survival rates in

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SC are directly related to its early diagnosis. In such a situation, doctors face a dilemma: the need to treat SC in a pregnant woman and prolong pregnancy. The most common symptoms of stomach cancer, with the exception of weight loss and melena, are common during pregnancy and do not attract the attention of doctors and patients themselves [4, 5]. Nausea and vomiting often begin a few weeks after the start of the first trimester, then peak simultaneously with the peak of HCG production between the 10th and 16th weeks of pregnancy and subside by the 20th week. However, up to 10% of pregnant women may not have symptoms until the 22nd week. Another hormone associated with this clinical picture is PGE2, which affects the smooth muscles of the stomach. The highest level of PGE2 during pregnancy is observed between the 9th and 12th weeks [2, 6]. Hyperemesis is a severe form of nausea and vomiting associated with the loss of more than 5% of body weight before pregnancy, dehydration and electrolyte imbalance. It begins before the 22nd week of pregnancy, affects 0.3–2.0% of pregnant women and in some cases requires hospitalization [2, 7]. In a Canadian population-based cohort study conducted by D.B. Fell et al. (2006), an increased risk of pregnancy hyperemesis associated with hyperthyroidism, mental illness, previous molar pregnancy, diabetes mellitus, and a history of asthma was identified [3]. Timely diagnosis of SC is often difficult, as up to 80% of patients have an asymptomatic course in the early stages. If nausea and vomiting continue until the 20th week of pregnancy, then doctors should pay special attention to this. Currently, three main causes of vomiting are described in the literature. Firstly, high levels of hCG can have a stimulating effect on the secretory process in the upper gastrointestinal tract. In addition, estrogen stimulation increases the production of thyroid-binding globulin, which leads to a decrease in the level of free thyroxine (T4). A transient decrease in free T4 levels causes thyroid stimulation, and the patient may develop transient gestational thyrotoxicosis, which leads to vomiting. Secondly, HCG is similar in its action to thyroid-stimulating hormone (TSH) and may cause hyperemesis by stimulating the TSH receptor [8, 9]. Thirdly, there is a negative relationship between prolactin levels and nausea/vomiting, while estrogens show a positive relationship. Consequently, higher estrogen levels during pregnancy may increase the risk of hyperemesis [10, 11, 12]. The condition is usually accompanied by hyponatremia, hypokalemia, low serum urea, elevated hematocrit, metabolic hypochloremia, alkalosis, and ketonuria. The level of liver enzymes can be increased by almost 2 times. Such patients are usually diagnosed with exicosis, they suffer from food intolerance and weight loss due to prolonged vomiting [6, 13]. In the study by M.J. Song et al. (2016) revealed that 25% of patients had abdominal pain, 20% had nausea and vomiting, and the rest had bleeding and symptoms of metastasis [7]. T. Cift et al. (2011) recommend an X-ray examination of the stomach of pregnant women complaining of epigastric pain, refractory nausea and vomiting that occur during pregnancy of more than 16 weeks [8]. Bleeding from the upper digestive tract (described in 20% of cases of stomach cancer) may be associated with Mallory–Weiss syndrome, the most common cause of vomiting blood during pregnancy [9, 14]. However, there are no protocols in the literature for optimal endoscopy in pregnant women with nausea and vomiting in the first trimester, when HCG and PGE2 levels reach their maximum values.

In the case of an acute complication of SC (perforation or bleeding), specific clinical signs appear with severe consequences for both the pregnant woman and the fetus. In such situations (vomiting with blood, melena), urgent surgical treatment is required.

Thus, the clinical component of the diagnosis of prostate cancer is quite complex: the initial symptoms are nonspecific, they can develop over a long period of time, and they are often mistakenly attributed to other pathologies. In most patients, the initial forms of prostate cancer are either asymptomatic or have non-specific symptoms of stomach diseases (non-ulcerative dyspepsia, peptic ulcer). The diagnosis of advanced stages of prostate cancer becomes obvious due to complications of the disease [5, 15].

If stomach cancer is suspected in pregnant women, fibroesophagogastroduodenoscopy with biopsy is recommended. CT scans of the abdominal organs in the first trimester are undesirable due to exposure to ionizing radiation. Magnetic resonance imaging is considered a relatively safe method of investigation because it avoids exposure to ionizing radiation on the patient and fetus and often does not require intravenous administration of a contrast agent. Treatment depends on the duration of pregnancy and the stage of stomach cancer. In addition, when choosing a treatment method, the choice of a woman to have a child is an important factor. Surgical intervention during pregnancy should not be postponed if the woman's health and the outcome of the disease depend on it. [10, 12, 13, 16].

Despite its rarity, stomach cancer diagnosed during pregnancy can pose a fatal clinical situation for the pregnant woman and the fetus: patients with stomach cancer diagnosed during pregnancy have an unfavorable prognosis. This may partly be due to the fact that most cases of stomach cancer associated with pregnancy are diagnosed in the late stages, and only 45-56% of patients undergo surgery.

Optimal management of this category of patients requires the work of a multidisciplinary team (including an oncologist, an obstetrician-gynecologist, a surgeon, an anesthesiologist, a gastroenterologist, a radiologist and a neonatologist) who will establish the sequence of therapy. Psychological supportive therapy should not be neglected, since the patient's decision to maintain pregnancy is crucial [17].

One of the largest studies on this problem was published in May 2023 [13]. This review is based on an analysis of the results of relevant studies and articles published over 23 years (from 2000 to 2022), hosted by Embase, PubMed Central, Cochrane Library and MEDLINE Complete. Analyzing the data from this study, we can formulate the main recommendations for the management of this category of patients.

The following tactics of managing patients with stomach cancer during pregnancy have been determined: in the first trimester, with an operable tumor, termination of pregnancy followed by surgical treatment of stomach cancer is indicated. If the patient is in the second trimester of pregnancy, it is recommended to perform a simultaneous gastric resection and a small caesarean section. In the third trimester, if the fetus is viable, a simultaneous gastric resection with cesarean section is performed. If an inoperable tumor is diagnosed, only palliative treatment is possible [18, 19]. The presence of metastases in the ovaries is not a contraindication for gastric surgery. A wait-and-see approach is strongly discouraged in case of operable prostate cancer, as it is difficult to predict the rate of tumor growth and spread. With advanced SC, when the prognosis for a pregnant woman is unfavorable, the life of the unborn child becomes a priority choice. Two studies have found that pregnancy is a "psychological obstacle to the correct diagnosis of stomach cancer." Women suffering from gastric ulcer are recommended to undergo medical or surgical treatment

before conception, otherwise constant endoscopic monitoring with targeted biopsy is necessary throughout pregnancy [20, 21].

As for cytotoxic agent therapy, there is a problem of its effectiveness associated with physiological changes in a woman's body during pregnancy (redistribution of circulating blood volume, changes in hepatic clearance, increased renal elimination due to a decrease in binding protein levels, a decrease in albumin). However, there are currently no dosage recommendations other than those for non-pregnant women. The doses of chemotherapy drugs should be recalculated as body weight and gestation period increase [22, 23]. Teratogenic and mutagenic effects are among the most feared long–term complications. The risk of carcinogenesis over time appears to be critical. The toxic effect on the fetus may result from the penetration of cytostatics through the maternal-fetal barrier. The fetal liver will be metabolized, and the kidneys will remove toxins into the amniotic fluid, from where they can be swallowed by the fetus and reabsorbed into the gastrointestinal tract. The most studied teratogens are anthracyclines found in the placenta, umbilical cord, and fetal tissues [91].

The risk of using cytostatics during pregnancy is classified by the FDA into two categories: C and D [15, 17, 14, 24].

The standard cytostatic treatment for primary prostate cancer consists of a combination of platinum and fluoropyrimidine, such regimens as FOLFOX (folinic acid (FOL), 5-fluorouracil (F) and oxaliplatin (OX)), CAPOX (capecitabine, oxaliplatin), ECF/ECC (epirubicin, cisplatin, 5-fluorouracil/capecitabine) or EOX (epirubicin, oxaliplatin, capecitabine). Trastuzumab combinations can be prescribed for gastric cancer with overexpression of the HER2 gene. Alternatively, it is possible to use taxane-based schemes, for example, FLOT (docetaxel, leucovorin, oxaliplatin, 5-fluorouracil) [16, 17]. The progress of neoplasia is probably enhanced by hyperestrogenism. Estrogen receptors (ER) are detected in 22% of tumor cells, especially in the low-grade type. Estrogen receptors in gastric cancer, unlike in other target organs, such as the breast, seem to be a sign of the tumor's adaptation to treatment.

Neoadjuvant chemotherapy is recommended during pregnancy at 10 to 28 weeks of age for stage II and III tumors. In addition to surgery, adjuvant therapy is recommended, usually after childbirth [17, 25].

As for radiation therapy, this option is not recommended for the treatment of patients with SC associated with pregnancy.

Over time, new descriptions of the combination of stomach cancer and pregnancy have appeared in the literature. In 1962 Molinie summarized 33 observations, in 1974 Verhagen provided 84 descriptions, and in 1978 Querleu reported 127 such cases [14]. The clinical picture most often shows a lack of appetite, nausea, vomiting, a feeling of heaviness and pain in the epigastrium. The pain is similar to that of peptic ulcer. At the same time, almost all the symptoms are unstable, the clinic is lubricated by anemia. The diagnosis is based on fibrogastroscopy with targeted biopsy. In almost 90% of cases, the diagnosis of stomach cancer is established in the second and third trimesters of pregnancy. Late diagnosis, disease progression, and a high risk of termination of pregnancy worsen the prognosis for mother and fetus [23]. In pregnancy-associated SC, only 38% of babies are born alive. In some cases, metastatic lesions were observed in the placenta and in the newborn. The prognosis for the mother remains extremely unfavorable: the five-year survival rate for combined SC and pregnancy is only 2.9% [17].

S. Maggen et al. (2020) conducted an analysis of patients with SC in combination with pregnancy for the period from 2002 to 2018. A total of 13 women were registered. The minimum gestation period of the patients at the time of diagnosis was 6 weeks, the maximum was 30 weeks. 12 out of 13 women were diagnosed with II–

Stage IV of the disease. In total, eight out of 10 live births ended in premature birth due to preeclampsia and deterioration of the mother's condition. Two out of six women who started chemotherapy during pregnancy gave birth on time.

Two newborns who underwent chemotherapy prenatally had growth retardation, and one of them developed a systemic infection with a brain abscess after preterm birth due to preeclampsia 2 weeks after chemotherapy [17]. According to the results of the study, it was also confirmed that the prognosis of the course of prostate cancer during pregnancy is poor, mainly due to the late stage of the disease at the time of diagnosis. Taking into account possible complications such as growth retardation, premature birth and suppression of hematopoiesis at birth, it is advisable to prescribe chemotherapy after delivery.

Thus, stomach cancer during pregnancy is a rare diagnosis. Women usually go to the doctor in the late stages of the disease and have a poor prognosis. Pregnant women with persistent gastrointestinal symptoms that cannot be explained solely by pregnancy should have a low threshold for further diagnostic procedures. When balancing the risks to the patient and the fetus, the possibility of starting chemotherapy may be considered. An interdisciplinary approach is needed to make adequate decisions in this difficult and rare situation.

We present clinical cases of observation and treatment of patients who were conducted on the basis of the Tomsk regional oncological dispensary.

Clinical observation 1

Patient K., 28 years old, turned to an oncologist at the direction of an obstetrician-gynecologist at the Tomsk Regional Perinatal Center . The patient complained of periodic nagging pains in the lower abdomen, periodic nausea and vomiting. At the time of treatment, the woman was found to be 16-17 weeks pregnant. According to ultrasound and MRI of the pelvic organs, bulky ovarian formations of a solid nature were detected, up to 14 cm in size on the right, up to 16 cm on the left, with limited mobility. Tumor markers CA-125 = 35.82 IU, HE-4 = 41.44 pmol/L. Upon further examination according to fibrogastroduodenoscopy: at the level of the border of the upper and middle third of the stomach body, a tumor formation in the form of a flat ulcerative defect with a convergence of folds up to 1.5 cm in diameter and an infiltration zone along the perimeter is determined by a large curvature. A biopsy of 4 fragments was performed: the tissue is dense, the gastric lumen is moderately stenosed at this level. The epithelium of the subcardia and the fundus of the stomach corresponds to the fundus type of structure. The gatekeeper does not close, the lumen of the gatekeeper channel is not changed, oval in shape, freely passable for the device. The bulb of the duodenum (duodenum) is capacious, slimy, and finely fibrous. The post-bulbar section has a smooth angle. The large duodenal papilla is located behind the guard hood of the duodenal mucosa, bile is supplied in portions. Conclusion: Insufficiency of the lower esophageal sphincter. Epithelial formation of the O-Is esophageal transition zone. A tumor of the middle third of the stomach body. Moderate tumor stenosis of the stomach. Chronic duodenogastric reflux.

Histological conclusion based on the results of biopsy of the gastric mucosa: the preparations contain fragments of the gastric mucosa with the presence of a large number of discrete tumor cells and small tubule-like structures, cells with

pronounced polymorphism, and atypical mitoses. The stroma is pronounced, represented by fibrous-muscular layers. An IHC study was conducted using the Leica Bond Max immunostainer (USA) (in sections from the paraffin block: the bright expression of Cytokeratin 7 (clone OV-TL, Dako, Germany) is detected in tumor cells. There is no expression of c-erB-2 (Her2/neu) in tumor cells (Polyclonal Rabbit, Dako, Germany).

Conclusion: Gastric adenocarcinoma, High Grade (ICD-O code 8140/3). c-erB-2 (Her2/neu) tumor status is negative (0).

A consultation was held on the basis of the Tomsk OPC with the participation of oncogynecologists from the Research Institute of Oncology of the Tomsk NIMC and the Tomsk OOD. According to the results of the consultation, the patient was given explanations on the clinical picture, the features of the course, the prognosis and possible treatment methods. The woman agreed with the proposal about the need for surgical treatment with simultaneous termination of pregnancy.

The patient underwent surgical intervention in the following areas: adhesiolysis, extirpation of the uterus with appendages, extirpation of the large omentum, peritoneal biopsy, drainage of the abdominal cavity.

In the postoperative period, on the 8th day, complications arose in the form of small intestinal obstruction, in connection with which a relaparotomy, dissection of adhesions, and drainage were performed.

Histological conclusion based on postoperative material: fragments of the uterine wall with immature placenta structures. The placenta is mostly represented by longitudinal and transverse sections of intermediate mature villi with the presence of vessels. Cell-free fibrinoid deposits are detected in the interstitial space. The basal plate is represented by a layer of Rohr with cytotrophoblast fields, cytotrophoblast cells with their obstruction are detected in the lumen of spiral arteries and veins. Areas of necrosis with focal leukocyte infiltration are noted in a number of visual fields. Fragments of a large omentum with uneven blood filling of blood vessels, small diapedous hemorrhages, focal lymph and leukostasis. There are foci of inflammatory infiltration, represented by lymphocytes and a few segmented leukocytes. No tumor cells were found.

The preparations labeled as "fragments of the peritoneum" revealed signs of subacute inflammation, represented by dilated vessels with erythrostases, diapedous hemorrhages. Fibrin filaments are detected on the surface of the peritoneum. There is diffuse moderate infiltration in the thickness, represented by macrophages, fibroblasts, lymphocytes and single neutrophilic leukocytes. Fragments of the fallopian tube with uneven blood vessels. In the formations of the right and left ovaries Krukenberg's metastases have been identified. The histological pattern in both ovaries is identical. In the stroma of numerous cystic cavities, areas of an invasive tumor are identified, represented by tubular structures of various shapes and sizes lined with multi-row epithelium. Atypical cells are moderately polymorphic with normochromic rounded nuclei and moderate eosinophilic cytoplasm. Between the glandular structures, in the desmoplasmic stroma, small tumor clusters and individual discretely located tumor cells are detected.

An IHC study was performed using a Leica Bond Max immunostainer on sections from paraffin blocks. The tumor cells show diffuse bright expression of Cytokeratin 7 (clone OV-TL, Dako, Germany), CDX2 (clone DAK-CDX2, Dako, Germany), moderate cytoplasmic expression of PAX8 (Poly-clonal, Cell Marque, USA). There is no expression of CA125 (clone Ov185:1, Leica, Germany), Wilms'TUMOR (clone 6F-H2, Dako, Germany), Calretinin (clone CAL6, Leica), Inhibin (clone R1, Dako), CD 56 (clone 123C3, Dako), Progesterone receptor (clone PgR636, Dako), Napsin A (clone of IP64, Leica).

Conclusion: Gastric adenocarcinoma, High Grade (ICD-O code 8140/3). c-erB-2 (Her2/neu) tumor status is negative (0). Krukenberg metastases in both ovaries. No tumor cells were found in the peritoneum and omentum.

After receiving the histological findings, a consultation with a chemotherapist was conducted. It is recommended to carry out polychemotherapy according to the scheme: paclitaxel + carboplatin. The patient underwent three courses of polychemotherapy.

4 months after the surgery, the woman died.

The second clinical case is almost identical to the first, but the tumor process was verified at a later stage of pregnancy.

Clinical observation 2

Patient Yu., 32 years old, turned to an oncologist at the Tomsk OOD in the direction of an obstetrician-gynecologist.

From the medical history: the patient had no previous gynecological diseases, this is the first pregnancy. The family history is burdened by his father's side – stomach cancer. The patient complained of aching, pulling pains in the lower abdomen, which were practically not relieved by antispasmodics and tocolytics. During pregnancy, the woman suffered from frequent nausea and vomiting, but considered it a normal discomfort associated with pregnancy. The patient was under the supervision of a doctor at a women's clinic, and previous examinations did not reveal any pathological abnormalities.

Pain in the lower abdomen, corresponding to premature contractions of the uterus, began at the 29th week of pregnancy, the intensity of pain increased over the last 2 weeks, at the time of treatment, the pain was almost constant, mostly of moderate intensity.

In terms of follow-up, ultrasound and MRI of the pelvic and abdominal organs were performed: moderate ascites and a single homogeneous formation in the left ovary with suspected torsion were detected. Upon additional examination, fibrogastroduodenoscopy revealed a stomach tumor with extensive local spread. Histological conclusion: gastric adenocarcinoma of low degree of differentiation, c-erB-2 (Her2/neu) tumor status is positive.

A consultation was held on the basis of the Tomsk OPC with the participation of oncologists from the Tomsk OOD, as a result of which a decision was made to conduct surgical treatment.

At the 33rd week of pregnancy, surgical treatment was performed in the following volume: cesarean section, adnexectomy on the left (during the revision, a leg twist was revealed), a biopsy of the contralateral ovary, and a biopsy of the peritoneum. A live girl was born, her birth weight was 1620 g, and the Apgar score was 7 and 9 points on the 1st and 5th minutes after birth.

Intraoperatively, the following features were identified: moderate ascites, multiple metastatic formations of various diameters on the large omentum, multiple metastases on the surface of the liver and the peritoneal peritoneum. The left ovary was tightly attached to the uterine wall and fixed to the peritoneum. Histological conclusion: data for Krukenberg's tumor, diffuse infiltration of poorly adhering cells with abundant intracytoplasmic mucin and eccentric nuclei was detected in the tumor of the left ovary.

The course of the postoperative period was smooth, without any special features. Histological conclusion based on the results of biopsy of the peritoneum and large omentum: the presence of multiple metastatic lesions.

The patient was finally diagnosed with stage IV gastric adenocarcinoma.

Due to the inoperable process, a chemotherapist was consulted, and palliative chemotherapy courses were prescribed according to the scheme: oxaliplatin + 5-fluoro-uracil.

The patient died 2 months after giving birth. The child is alive, currently growing and developing according to age.

Thus, both presented cases clearly demonstrate an extremely unfavorable prognosis with a combination of stomach cancer and pregnancy. According to the literature, the five-year survival rate in this category of patients is zero, while in most cases the patient's death occurs within six months after surgery.

The authors declare no conflict of interest in the submitted article.

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