

Clinicopathological features and maternal and foetal management of pregnancy-complicating Krukenberg tumours

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Received September 4, 2019; Accepted February 21, 2020

DOI: 10.3892/mco.2020.2025

Abstract. Krukenberg tumours are not uncommon, but pregnancy-complicating Krukenberg tumours are rare. To identify management strategies of pregnancies with Krukenberg tumours, the medical records of patients treated at Peking Union Medical College Hospital over the past 20 years were collected and analysed. Four patients were enrolled. The primary tumour sites were the stomach and colorectal region. Three patients presented with obvious and severe gastrointestinal symptoms at 11-18 weeks of gestation, and their symptoms gradually developed into physiological signs associated with malignancy. Three patients underwent termination of pregnancy via induced delivery and gestational hysterectomy. One patient underwent caesarean section at 31 weeks of gestation. Two patients underwent palliative surgery due to extensive lesions. The other two patients with metastatic lesions confined to the ovaries and liver, underwent satisfactory cytoreductive surgery and anti-tumour treatments postoperatively. Pregnant women who exhibit new gastrointestinal symptoms or aggravation of previous gastrointestinal symptoms after the end of the first trimester should be carefully examined for digestive system diseases. If ovarian metastasis is highly suspected, the pregnancy should be terminated as early as possible.

Introduction

Ovarian metastasis accounts for 15.7% of all ovarian malignancies (1). Ovarian metastases from gastrointestinal malignancies are commonly referred to as Krukenberg tumours (2,3). Krukenberg tumours are not rare and have a poor prognosis. However, pregnancy-complicating Krukenberg tumours are rare, and clinicians worldwide do not have much experience in their diagnosis and management.

Pregnancy is a physiological state that is unique to women. Symptoms caused by gastrointestinal cancer may be misdiagnosed as early pregnancy symptoms or be masked (4). In this context, conflicts regarding the well-being of the mother versus that of the foetus may exist and are a challenge for doctors. Owing to the rarity of this situation and limited information provided by a few published cases, a significant cognitive vacancy exists. Thus, there are currently no guidelines for the management of foetuses in pregnant women with complicating Krukenberg tumours for clinicians to refer to.

In the present study, we summarized the clinicopathological characteristics of pregnancy-complicating Krukenberg tumours diagnosed and treated in the Peking Union Medical College Hospital (PUMCH) from January 1999 to January 2019. Additionally, we analysed and discussed how to distinguish early pregnancy symptoms from gastrointestinal cancer symptoms and manage foetuses at different gestational weeks.

Materials and methods

From January 1, 1999 to January 1, 2019, four pregnant women of Chinese Han nationality with ovarian metastasis who were hospitalized and had complete clinical records at the Department of Obstetrics and Gynaecology, PUMCH, were enrolled into the present study. Data regarding the general condition, symptoms, preoperative examinations and diagnosis of each patient, as well as data regarding foetal treatment and outcome, surgery, postoperative pathology and prognosis were collected and analysed. SPSS Statistics (version 25.0) was used to calculate our descriptive statistics.

The median age of the four patients was 31.5 years. The median gestational age on admission was 21 weeks and 5 days (Table I). Two patients had no routine physical examination or obstetrical care; the other two patients were routinely examined

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Abbreviations: Alb, serum albumin; HGB, haemoglobin; CA125, carbohydrate antigen 125; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CA72-4, carbohydrate antigen 72-4; FDA, Food and Drug Administration

Key words: gastric cancer, colorectal cancer, ovarian metastasis, Krukenberg tumours, early pregnancy symptoms, preoperative diagnosis, termination of pregnancy, foetal management, exploratory laparotomy

at local hospitals. None of the four patients or their family members had any previous history of malignant tumours.

Results

Patient general condition, symptoms, and time of onset. Table I presents the symptoms and times of onset in these patients. One patient presented with intermittent upper abdominal dull pain prior and subsequent to eating one year before pregnancy. Two patients complained of an early pregnancy reaction with nausea and gastric distension, both of which appeared before 8 weeks of pregnancy. From the end of the first trimester to the beginning of the second trimester, three patients presented obvious and severe gastrointestinal symptoms, including haematochezia, anorexia, sudden weight loss, lower abdominal distending pain, and increased dull abdominal pain accompanied by nausea and vomiting. At 15-16 weeks of gestation, two patients developed pleural effusion causing chest tightness and shortness of breath.

Preoperative examinations and biopsies of patients. Table II presents the preoperative examinations and biopsies of the four patients who presented with hypoproteinaemia at admission, with a median serum albumin (Alb) of 25 g/l, three of whom presented with anaemia at admission, with a median haemoglobin (HGB) of 92 g/l. All four patients had elevated carbohydrate antigen 125 (CA125) prior to surgery, with a median level of 693.5 U/ml; two patients had elevated carcinoembryonic antigen (CEA), and one patient had elevated carbohydrate antigen 72-4 (CA72-4). No pelvic or abdominal masses were identified by ultrasound examination, after which the four patients were examined for ovarian enlargement or masses by ultrasound at intervals of 2-8 weeks. The last ultrasound prior to surgery showed that three patients had bilateral ovarian masses and that one patient had a left ovarian mass, with a median diameter of 10.6 cm (5.4-25.0 cm). The preoperative ultrasound of one patient also showed multiple intrahepatic lesions, and the largest lesion was 9.7x8.2 cm. One patient underwent gastroscopic biopsy during the first trimester, without positive findings. One patient underwent fine-needle aspiration and biopsy of the ovarian mass under ultrasound guidance at 22 weeks and 5 days, and gastroscopic biopsy at 24 weeks and 3 days. An ulcerative mass of approximately 3 cm was found in the small curvature of the stomach. Ovarian metastasis of signet-ring cell carcinoma of the stomach was confirmed by pathology of the biopsy specimen. Another patient underwent gastroscopic biopsy at 21 weeks and 6 days. Gastric body lesions were found to involve the cardia, and poorly differentiated gastric adenocarcinoma was confirmed by pathology of the biopsy specimen. Therefore, the two patients were preoperatively diagnosed with 'pregnancy-complicating gastric cancer with ovarian metastasis'. The other two patients were preoperatively diagnosed with 'pregnancy complicated by ovarian masses: Ovarian cancer cannot be excluded, and ovarian metastases cannot be excluded'.

Maternal and foetal management and outcomes of patients. The maternal and foetal management and outcomes of these patients are presented in Table III. Three patients had their pregnancies terminated in the second trimester,

and one patient had her pregnancy terminated in the third trimester. The termination procedures included one case of mid-term induction of labour, one case of caesarean section, and two cases of gestational hysterectomy. Laparotomy was performed concurrently with caesarean section or gestational hysterectomy.

All four patients underwent exploratory laparotomy, and the surgical indications were malignant masses, rapid growth of masses or ascites, and severe discomfort. Of the two patients diagnosed with gastric cancer preoperatively, one had gastric cancer involving the pancreas, bilateral ovaries, and the small intestine, which showed a cavity that was almost blocked. The surgeons performed palliative partial small-bowel resection plus anastomosis and bilateral salpingo-oophorectomy. The other patient was found to have gastric cancer involving only the bilateral ovaries, peritoneum and rectal fossa presenting as small miliary nodules. Gestational hysterectomy and bilateral salpingo-oophorectomy were performed. Postoperative pathology confirmed that the ovarian masses were ovarian metastases of gastric cancer (Table III).

For two patients, whether the ovarian mass was primary or metastatic was unable to be determined before exploratory laparotomy. The intraoperative exploration in one patient revealed a transverse colon lesion that had almost blocked the intestinal cavity. In addition, the involved tissues and organs included the ileocaecal junction, sigmoid colon, bilateral ovaries, diaphragm, peritoneum, and omentum. The surgeons proposed that the colon cancer was at a late stage without the possibility of debulking surgery, and if the transverse colon lesion was not resected, then intestinal obstruction would appear in the immediate postoperative period. Palliative transverse colectomy plus anastomosis, gestational hysterectomy and bilateral salpingo-oophorectomy were performed. Intraoperative exploration in another patient revealed a lesion at the junction of the sigmoid colon and rectum, involving the left ovary and liver. The surgeons estimated that the primary lesion could be radically resected. Dixon surgery and left salpingo-oophorectomy were performed. Postoperative pathology confirmed ovarian metastases of moderately to poorly differentiated adenocarcinomas of the transverse colon and ovarian metastases of moderately differentiated adenocarcinoma of the rectum (Table III).

The two patients who underwent palliative enterotomy and anastomosis discontinued subsequent treatment after surgery because of advanced disease with poor prognosis and economic concerns. The other two patients, one with signet-ring cell carcinoma of the stomach and the second with moderately differentiated adenocarcinoma of the rectum, continued to receive standard anti-tumour therapies after surgery. Of the two patients, one survived for 43 months and died of septic shock after radiofrequency ablation of the liver lesions, and the other survived after surgery for 13 months. The premature infant delivered by caesarean section survived and is healthy (Table III).

Discussion

Although the preferred route of metastasis for Krukenberg tumours remains to be elucidated, there are three possibilities: The lymphatic, haematogenous and peritoneal routes of

metastasis (5). Some scholars believe that young women have a higher risk of developing Krukenberg tumours because of the higher ovarian blood flow in premenopausal women (6). Approximately 65% of Krukenberg tumours are found before the primary malignancies (5). Additionally, the lack of physical examinations or obstetric care for some women of childbearing age or who are pregnant may facilitate the development of pregnancy-complicating Krukenberg tumours.

It is difficult to distinguish the symptoms of early gastric colorectal cancer from those of early pregnancy because there is some overlap between them (4). The mean onset time of early pregnancy symptoms is 5-6 weeks of gestation; these symptoms usually peak at approximately 9 weeks of gestation and decrease by 16-20 weeks of gestation (7,8). Nausea with or without vomiting, which occurs in up to 70-80% of pregnancies, is the most common symptom of early pregnancy (9). However, the rate of severe vomiting, known as hyperemesis gravidarum, has been reported to vary from 0.3 to 3% of pregnancies (10,11). In addition, early pregnancy symptoms also include breast enlargement and pain, increased frequency of urination, fatigue, loss of appetite, and slight weight loss. Persistent epigastric pain and weight loss are the most common symptoms in early-stage gastric cancer; additionally, abdominal pain tends to be epigastric, vague and slight but becomes severe and fixed as the disease progresses (12). However, the majority of patients with early-stage colorectal cancer are asymptomatic, and the typical symptoms of colorectal cancer, including changes in bowel habits, haematochezia or melena, usually reflect advanced-stage disease (13). Haematochezia, which is not a specific symptom of colorectal cancer, can also be present in pregnant women with haemorrhoids and is usually accompanied by perianal itch during the third trimester and early postpartum period (14). In our study, early pregnancy symptoms appeared prior to 8 weeks of gestation, and then a set of gastrointestinal tract-related symptoms emerged at approximately 12 weeks of gestation. These symptoms worsened during the second trimester and gradually developed into more serious signs of illness. These signs were different from the symptoms of early pregnancy; the former were more severe than the latter and consisted of haematochezia or melena, a change in bowel habits, obvious weight loss, and severe abdominal pain, which should not be present in early pregnancy. Usually, these conditions do not appear in any part of pregnancy, but in our patients, they appeared during the second trimester. Although these conditions do not indicate specific diseases, they are strongly suggestive signs of malignancies.

Imaging examinations are also helpful in diagnosing tumours. Ultrasound is a simple, quick, safe, and non-radiative method. During the first trimester, physiological luteal enlargement or luteoma of pregnancy can be mistaken for a non-physiological ovarian mass under ultrasound, but ovarian physiological changes are usually smaller in diameter and disappear after the establishment of placental function (15). Computerized tomography and magnetic resonance imaging can be useful adjuncts when ultrasound imaging is inconclusive. There is very little risk associated with their use after the first trimester, and these modalities are considered to be among the safest imaging-based diagnostic procedures. However, no associated risks of congenital malformations or

Table I. The patients' general condition, symptoms and their times of onset.

Patients	Age (years)	Gestational age on admission	Symptoms before pregnancy	Symptoms at the first trimester			Symptoms at the second trimester
				Early pregnancy symptoms	Other symptoms		
Case 1	30	15 w ^{+2 d}	No	No	At 11-12 weeks of gestation, anorexia, sudden weight loss, lower abdominal distending pain occurred	At 14 weeks of gestation, abdominal pain suddenly increased	
Case 2	32	29 w ^{+6 d}	No	At 6-7 weeks of gestation, mild gastric distension occurred	At 12 weeks of gestation, haematochezia, lower abdominal pain occurred	At 13 weeks of gestation, abdominal pain and distension gradually increased; at 16 weeks of gestation, pleural effusion found	
Case 3	25	21 w ^{+5 d}	Intermittent upper abdominal dull pain before and after eating for one year	No	At 12 weeks of gestation, increased abdominal dull pain accompanied by nausea and vomiting occurred	At 18 weeks of gestation, persistent dull pain in the left lower abdomen appeared with paroxysmal aggravation	
Case 4	32	21 w ^{+5 d}	No	From 8 to 18 weeks of gestation, mild nausea	No	At 15-16 weeks of gestation, pleural effusion found	

Table II. Preoperative examinations and biopsies of patients.

Patients	Preoperative laboratory examinations			Interval between no abnormal findings and the initial discovery of ovarian masses by ultrasound	Biopsies
	Alb (g/l)	HGB (g/l)	CA125 (U/ml)	Other tumour markers	
Case 1	19	91	602.4	No	No
Case 2	31	81	816.4	CA19-9 (-) CEA 87.7 ng/ml	At 5 weeks of gestation, gastroscopic biopsy was negative
Case 3	32	111	102.1	CA19-9 (-) CEA 10.9 ng/ml	At 21 weeks and 6 days of gestation, gastroscopic biopsy revealed low differentiation of adenocarcinoma of the stomach
Case 4	17	92	784.6	CA72-4>600 U/ml	At 22 weeks and 5 days of gestation, fine-needle aspiration of ovarian mass revealed metastatic signet ring cell carcinoma of the ovary At 24 weeks and 3 days of gestation, gastroscopic biopsy revealed signet ring cell carcinoma of the stomach

Alb: Serum albumin; HGB: Haemoglobin; CA125: Carbohydrate antigen 125; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; CA72-4: Carbohydrate antigen 72-4.

mental delay in the foetus have been reported in the literature (16). Among our patients, the interval between no abnormal findings and the initial discovery of ovarian masses by ultrasound was 2-8 weeks. Then, two patients developed a sudden increase in abdominal pain, which was considered to be related to torsion or intra-tumoural haemorrhage and the necrosis of ovarian masses. This finding suggests that Krukenberg tumours can appear in the short term and rapidly increase in size, even causing acute abdominal pain.

Serum CEA, CA125, CA19-9 and CA72-4 may be elevated in patients with gastric cancer, but their sensitivity and specificity are low (17) as tumour markers for colorectal cancer, serum CA19-9 and CEA have similar problems (18). Currently, serum CA125 is the most commonly used serum marker for screening ovarian cancer, but its levels can also increase in metastatic ovarian tumours and the first trimester of pregnancy (19). Specifically, CA125 levels are low in maternal serum but high in amniotic fluid in the second and third trimesters (20). Therefore, limited by their low sensitivity and specificity and by the pregnancy itself, serum tumour markers could not be used in an effort to establish the diagnosis of primary malignancies.

Tumour biopsy is one diagnostic option. In our study, gastroscopic biopsy and ovarian mass biopsy led to diagnoses of gastric cancer in two patients prior to exploratory laparotomy. One should note that common gastroscopy may cause obvious discomfort and then induce uterine contractions or other obstetric complications; thus, painless gastroscopy is preferred. Painless gastroscopy requires the intravenous administration of short-acting anaesthetic drugs to quickly sedate patients and help them sleep. Anaesthetic drugs may have the potential risk of adverse effects on the foetal brain. The Food and Drug Administration (FDA) recently released a drug safety communication warning that the use of general anaesthetic or sedation drugs during surgeries or procedures in pregnant women during the third trimester may affect brain development in children (21). However, considering the severity of the disease, the short duration of anaesthesia and the small dosages of the drugs, the patients can usually undergo the examination. If the ovarian mass is close to the abdominal wall, then ultrasound-guided puncture biopsy can also be considered. As the rectum and uterus are adjacent to one another, colonoscopy should not be considered. We suggest that gastroscopy biopsy and ovarian mass biopsy be performed as early as possible for pregnant patients with suspicious ovarian malignant tumours to determine whether the primary tumour is gastric cancer.

At present, the treatment protocol is mainly decided based on clinician experience. With treatment advancements for premature infants, the current gestational age of viability has decreased to 23-24 weeks (22), but traditionally, caesarean section would ideally be performed at 32-34 weeks (23). The management experience in treating our four patients with different gestation is summarized below. For patients at more than 24 weeks of gestation (or who have reached the gestational age of viability), the foetus is typically transferred to the paediatric clinic immediately after caesarean section, and the mother undergoes surgery and other anti-tumour treatments as soon as possible. For patients at less than 20 weeks of gestation (or whose gestational age is significantly lower than

Table III. Maternal and foetal management and outcomes of patients.

Patients	Gestational age at termination	Foetal management outcomes	Surgery and histopathology				Postoperative survival time (months)
			Extent of surgery	Residual tumour	Histopathology of primary cancer	Postoperative treatment	
Case 1	16 w ^{+1 d}	Gestational hysterectomy	Palliative transverse colectomy plus anastomosis, gestational hysterectomy and bilateral salpingo-oophorectomy	A mass in ileocaecal junction, approximately 5 cm in diameter A mass in sigmoid colon, approximately 5 cm in diameter Peritoneum, and small intestine surface scattered in miliary nodules	Moderately-poorly differentiated adenocarcinoma of transverse colon	No	Not available
Case 2	31 w ^{+0 d}	Caesarean section, the premature infant is healthy	Dixon surgery and left salpingo-oophorectomy	Multiple liver metastases, ranging in diameter from 1 to 8 cm	Moderately differentiated adenocarcinoma	Chemotherapy and radiofrequency ablation of liver of rectum	43
Case 3	22 w ^{+3 d}	Mid-term induction of labour	Palliative small intestine partial resection plus anastomosis and bilateral salpingo-oophorectomy	A large ulcerative lesion at the fundus of stomach involving the pancreas Strip-like metastatic nodules at rectal anterior wall	Poorly differentiated adenocarcinoma of fundus of stomach	No	Not available
Case 4	24 w ^{+5 d}	Gestational hysterectomy	Gestational hysterectomy and bilateral salpingo-oophorectomy	Primary lesion of the lesser curvature of the stomach, approximately 3 cm in diameter Peritoneum and rectal fossa scattered in miliary nodules	Signet ring cell carcinoma of lesser curvature of stomach	Chemotherapy	13 ^a

^aThe patient in Case 4 is still alive and in follow-up.

the age of viability), typically, the pregnancy is terminated by induced abortion or induced labour, immediately followed by anti-tumour treatments. However, for patients at 21-22 weeks of gestation (or who are near the gestational age of viability) and their families who are extremely eager to have children, postponing the termination of pregnancy and prolonging gestation for a short time is a risky and controversial attempt, and there are no relevant reports in the literature.

Thus, women with pregnancy-complicating Krukenberg tumours may extend their pregnancies under the following conditions: i) The patient and her family strongly hope to continue the pregnancy and understand the potential risks, including disease progression, poor prognosis, various complications of premature birth, or premature death, after being fully informed; ii) the patient is generally in good condition and has no obvious adverse signs, such as hypoproteinaemia or anaemia; iii) the metastatic lesions are confined to the ovaries; iv) the disease does not show significant progression on close monitoring; v) the foetus is in good intrauterine condition and is developing normally; and vi) the local department of paediatrics is well equipped to treat premature infants. Otherwise, the pregnancy should be terminated immediately.

The appearance of Krukenberg tumours suggests that the disease is advanced. Specifically, poorly differentiated gastric cancer or signet-ring gastric cancer, are known rare gastric cancers with very poor prognosis and unpredicted natural history. Thus, it is not surprising to observe the rare and unpredicted clinical presentation of these cases series described in the present study. The prognoses of Krukenberg tumours with different primary sites are significantly different. Wu *et al* (24) found that the median overall survival times of colorectal cancer and gastric cancer patients with ovarian metastasis were 11 and 21.5 months, respectively. A larger survival gap between the two groups was shown by Ayhan *et al* (25), wherein the median overall survival times were 48 and 18 months, respectively. Furthermore, the prognosis was improved when the metastatic lesions were confined to the ovaries, satisfactory cytoreductive surgery was performed (largest residual tumour diameter <2 cm) and the patient received postoperative adjuvant chemotherapy (6,25). To the best of our knowledge, the effects of pregnancy on the prognosis of patients with Krukenberg tumours have not been reported. A retrospective study analysed the treatment and prognosis of 41 pregnant patients with primary ovarian malignancies or ovarian metastatic tumours and showed that surgery was considered to be the main treatment method, and postponement of cytoreductive surgery was not recommended for patients with highly suspicious ovarian malignancy (26). To the best of our knowledge, there are currently only a few single-case reports of pregnancies complicated by ovarian metastases since 1950s. Findings of those studies show that prognosis seems to be mainly related to the primary site and the resectability of the primary and metastatic lesions (27,28). Of the four patients included herein, two with limited lesion involvement underwent satisfactory cytoreductive surgeries and assisted standard anti-tumour therapies with survival of 43 and 13 months respectively. Although the number of studies addressing pregnancy-complicating Krukenberg tumours is small, our finding is consistent with those of earlier case reports. However, additional related studies are still required.

This was a retrospective study with a small sample size. It was difficult to find four pregnant patients with complicating Krukenberg tumours due to the rarity of this disease, and thus, a prospective study of the disease is not possible and may be unethical. According to several published case reports and our study, the conclusion can be summarized as follows. First, we recommend that women of childbearing age increase their awareness regarding their personal health and receive routine physical examinations and obstetric care. Special attention should be paid to patients with new gastrointestinal symptoms or aggravations of the original gastrointestinal symptoms at the end of the first trimester or the beginning of the second trimester. The possibility of pregnancy-complicating Krukenberg tumours should be considered, especially when ovarian masses are found and are gradually enlarged. Biopsy by painless gastroscopy or fine-needle aspiration of the ovarian mass are methods to establish a definitive diagnosis. Furthermore, once a Krukenberg tumour is highly suspected or diagnosed, an appropriate method for termination of pregnancy based on gestational age should be selected, and the termination of pregnancy should be completed as soon as possible. Exploratory laparotomy can be performed concurrently with gestational hysterectomy or caesarean section. If the extent of lesion involvement is limited, the primary and metastatic lesions should be removed as much as possible via multidisciplinary collaborations. If the lesions are widely spread, palliative surgery may be considered to relieve patient discomfort. Regular anti-tumour therapies, the most common of which is intravenous chemotherapy, should be performed after surgery. Notably, an uneventful treated case of a pregnancy-complicating Krukenberg tumour that was managed with intraperitoneal chemotherapy after caesarean section has been reported (29). For patients whose gestational times are close to the gestational age at which a viable preterm infant can be delivered and who strongly wish to continue their pregnancies, doctors may provide personalized treatment after a comprehensive assessment of the disease status, the patient's general condition, her willingness to continue the pregnancy, and the level of paediatric medical support. However, this is not a routine treatment protocol; thus, full informed consent is essential.

Acknowledgements

Not applicable.

Funding

This study was funded by the CAMS Innovation Fund for Medical Sciences (CIFMS) [CAMS-2018-I2M-1-002].

Availability of data and materials

The datasets used and analysed during the present study are available from the two co-corresponding authors on reasonable request.

Authors' contributions

DC, JY and KS were involved in the diagnosis, treatment and follow-up of the patients. DC and JZ proposed the research

idea. JZ and PP collected and analysed the data and were involved in drafting the manuscript. All authors read and gave their final approval of the version to be published.

Ethics approval and consent to participate

Ethics approval has been granted by the Institutional Review Board (IRB) of Peking Union Medical College Hospital (PUMCH). The reference number is S-K817. Written informed consent was obtained from the patients or their relatives.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

- Alvarado-Cabrero I, Rodriguez-Gómez A, Castelan-Pedraza J and Valencia-Cedillo R: Metastatic ovarian tumors: A clinicopathologic study of 150 cases. *Anal Quant Cytopathol Histopathol* 35: 241-248, 2013.
- Young RH: From Krukenberg to today: The ever present problems posed by metastatic tumors in the ovary: Part I. Historical perspective, general principles, mucinous tumors including the Krukenberg tumor. *Adv Anat Pathol* 13: 205-227, 2006.
- Young RH: From Krukenberg to today: The ever present problems posed by metastatic tumors in the ovary. Part II. *Adv Anat Pathol* 14: 149-177, 2007.
- Papantoniou N, Belitsos P, Hatzipapas I, Rodolakis A, Papaspyrou I and Antsaklis A: Excessive hirsutism in pregnancy because of Krukenberg tumor. *J Matern Fetal Neonatal Med* 25: 869-871, 2012.
- Agnes A, Biondi A, Ricci R, Gallotta V, D'Ugo D and Persiani R: Krukenberg tumors: Seed, route and soil. *Surg Oncol* 26: 438-445, 2017.
- Kim WY, Kim TJ, Kim SE, Lee JW, Lee JH, Kim BG and Bae DS: The role of cytoreductive surgery for non-genital tract metastatic tumors to the ovaries. *Eur J Obstet Gynecol Reprod Biol* 149: 97-101, 2010.
- Goodwin TM: Hyperemesis gravidarum. *Obstet Gynecol Clin North Am* 35: 401-417, viii, 2008.
- Fell DB, Dodds L, Joseph KS, Allen VM and Butler B: Risk factors for hyperemesis gravidarum requiring hospital admission during pregnancy. *Obstet Gynecol* 107: 277-284, 2006.
- Lee NM and Saha S: Nausea and vomiting of pregnancy. *Gastroenterol Clin North Am* 40: 309-334, vii, 2011.
- Matthews A, Haas DM, O'Mathuna DP, Dowswell T and Doyle M: Interventions for nausea and vomiting in early pregnancy. *Cochrane Database Syst Rev*: CD007575, 2014.
- Bailit JL: Hyperemesis gravidarum: Epidemiologic findings from a large cohort. *Am J Obstet Gynecol* 193: 811-814, 2005.
- Wanebo HJ, Kennedy BJ, Chmiel J, Steele G Jr, Winchester D and Osteen R: Cancer of the stomach. A patient care study by the American college of surgeons. *Ann Surg* 218: 583-592, 1993.
- Hamilton W, Round A, Sharp D and Peters TJ: Clinical features of colorectal cancer before diagnosis: A population-based case-control study. *Br J Cancer* 93: 399-405, 2005.
- Saleeby RG Jr, Rosen L, Stasik JJ, Riether RD, Sheets J and Khubchandani IT: Hemorrhoidectomy during pregnancy: Risk or relief? *Dis Colon Rectum* 34: 260-261, 1991.
- Clement PB: Tumor-like lesions of the ovary associated with pregnancy. *Int J Gynecol Pathol* 12: 108-115, 1993.
- Boussios S, Han SN, Fruscio R, Halaska MJ, Ottevanger PB, Peccatori FA, Koubková L, Pavlidis N and Amant F: Lung cancer in pregnancy: Report of nine cases from an international collaborative study. *Lung Cancer* 82: 499-505, 2013.
- Carpelan-Holmström M, Louhimo J, Stenman UH, Alfthan H and Haglund C: CEA, CA 19-9 and CA 72-4 improve the diagnostic accuracy in gastrointestinal cancers. *Anticancer Res* 22: 2311-2316, 2002.
- van der Schouw YT, Verbeek AL, Wobbes T, Segers MF and Thomas CM: Comparison of four serum tumour markers in the diagnosis of colorectal carcinoma. *Br J Cancer* 66: 148-154, 1992.
- Lowry KP and Lee SI: Imaging and screening of ovarian cancer. *Radiol Clin North Am* 55: 1251-1259, 2017.
- Boussios S, Moschetta M, Tatsi K, Tsiouris AK and Pavlidis N: A review on pregnancy complicated by ovarian epithelial and non-epithelial malignant tumors: Diagnostic and therapeutic perspectives. *J Adv Res* 12: 1-9, 2018.
- Houck CS and Vinson AE: Anaesthetic considerations for surgery in newborns. *Arch Dis Child Fetal Neonatal Ed* 102: F359-F363, 2017.
- Glass HC, Costantino AT, Stayer SA, Brett CM, Cladis F and Davis PJ: Outcomes for extremely premature infants. *Anesth Analg* 120: 1337-1351, 2015.
- Boussios S and Pavlidis N: Renal cell carcinoma in pregnancy: A rare coexistence. *Clin Transl Oncol* 16: 122-127, 2014.
- Wu F, Zhao X, Mi B, Feng LU, Yuan NA, Lei F, Li M and Zhao X: Clinical characteristics and prognostic analysis of Krukenberg tumor. *Mol Clin Oncol* 3: 1323-1328, 2015.
- Ayhan A, Guvenal T, Salman MC, Ozyuncu O, Sakinci M and Basaran M: The role of cytoreductive surgery in nongenital cancers metastatic to the ovaries. *Gynecol Oncol* 98: 235-241, 2005.
- Gui T, Cao D, Shen K, Yang J, Fu C, Lang J and Liu X: Management and outcome of ovarian malignancy complicating pregnancy: An analysis of 41 cases and review of the literature. *Clin Transl Oncol* 15: 548-554, 2013.
- Mackey JR, Hugh J and Smylie M: Krukenberg tumor complicated by pregnancy. *Gynecol Oncol* 61: 153-155, 1996.
- Glisić A and Atanacković J: Krukenberg tumor in pregnancy. The lethal outcome. *Pathol Oncol Res* 12: 108-110, 2006.
- Burgazli KM, Mericliiler M, Kavukcu E, Erdogan A and Ertan AK: Discovery of asymptomatic Krukenberg tumors diagnosed during caesarean section: Therapy with hyperthermic intraperitoneal chemotherapy. *Postgrad Med* 125: 87-90, 2013.