REVIEW ARTICLE

Carcinoma in Pregnancy: What is the Impact on Fetus?

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Received on: 25 March 2023; *Accepted on:* 20 April 2023; *Published on:* 30 June 2023

Abstract

Cancer association with pregnancy (CAP) is defined as cancer diagnosed from the 1st day of childbearing to 1 year postpartum. Malignant disease in pregnancy is rare, 1:1000 pregnancies, but it represents an important therapeutic and ethical problem for both, the patient and the physician. The most important goals in curing are—treating the patient with the optimal anticancer regimen as soon as possible in order to preserve the mother's health, without harming the developing fetus. Until recently, the pregnancy had to be either terminated or cancer treatment delayed until after the birth. Nowadays, state-of-art treatment should be provided for this vulnerable population to preserve maternal and fetal prognosis.

When suspicion of malignant disease in pregnancy is grounded, it is necessary to prove the same. It is recommended to apply standard methods, if possible. With some malignant tumors, some protocols for establishing diagnosis are changing sensitivity and specificity in pregnancy.

Ultrasound examination is a method of choice for the breast, abdomen, and pelvis. If necessary, chest X-ray and mammography can be done safely with abdominal shielding. Magnetic resonance imaging (MRI) may be conducted if there is any unclarity in the analysis or suspicion of brain or bone metastasis. The main challenge in managing cancer in pregnancy is treating the patient with an optimal anticancer regimen without harming the developing fetus.

Cancer during pregnancy is associated with a significantly increased risk of planned preterm birth, induction of labor, and a cesarean section. Women with CAP need psychological support during the pregnancy and after delivery.

Keywords: Pregnancy, Malignant disease, Treatment.

Donald School Journal of Ultrasound in Obstetrics and Gynecology (2023): 10.5005/jp-journals-10009-1972

Cancer association with pregnancy (CAP) is defined as cancer diagnosed from the 1st day of childbearing to 1-year postpartum.[1] Malignant disease in pregnancy is rare, 1:1000 pregnancies,[2–5] but it represents an important therapeutic and ethical problem for both, the patient and the physician. The most important goals in curing are—treating the patient with the optimal anticancer regimen as soon as possible in order to preserve the mother's health, without harming the developing fetus. Until recently, the pregnancy had to be either terminated or cancer treatment delayed until after the birth. Nowadays, state-of-art treatment should be provided for this vulnerable population to preserve maternal and fetal prognosis.

When selecting treatment, the desire of the patient, her attitude toward termination of pregnancy or damage of fetus, ethics, and possible religious stand, must be considered.[2] Apart from necessary medical treatment, there is also a need to render her psychological support, as the fear of disease and desire to overcome the same and to bear a healthy child are always strongly expressed.

Incidence

The incidence of malignant disease in pregnancy is about 0.1%. It corresponds to the incidence of nonpregnant women of the same age. It is estimated that about 3,500 new cases of cancer are diagnosed annually in pregnant women in the United States and 3,000–5,000 in Europe.[3–5] Postponing of pregnancy and labor for the end of the 3rd and 4th decade is the reason for the increase of CAP incidence in developed countries. Lee published that from 1994 to 2007, the crude incidence rate of pregnancy-associated cancer increased from 112.3 to 191.5/100,000 maternities ($p < 0.001$). During this period, maternal age also increased; the percentage of women aged 35 years and over increased from 13.2 to 23.6%.[6]

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How to cite this article: Crnogorac S, Vuksanovic Bozaric A. Carcinoma in Pregnancy: What is the Impact on Fetus? Donald School J Ultrasound Obstet Gynecol 2023;17(2):136–142.

Source of support: Nil

Conflict of interest: None

The most common malignant diseases that occur in pregnancy are the tumors whose incidence reaches its peak in the reproductive period—breast and cervical cancer followed by melanoma, leukemia, and lymphoma. They represent 85% of CAP.[3–5] In addition to the above, any other malignant disease, such as lung cancer or sarcomas, may also occur in pregnancy.

The procedures carried out during establishing of diagnosis and staging, ionizing radiation treatment, chemotherapy, and surgical treatment undertaken sometimes may have adverse effects on fetus development. Special attention should be drawn to possible metastasis occurring in the placenta and fetus. The ethical approach and specificity of malignant disease in pregnancy are a particular burden for both the mother and the physician. Gynecological malignancies especially affect fetuses and curing.

Diagnosis and Staging

When suspicion of malignant disease in pregnancy is grounded, it is necessary to prove the same. It is recommended to apply standard methods, which would also be used in nonpregnant women. The pathological examination requires standard analysis, including immunohistochemical or molecular analysis as well. With some malignant tumors, some protocols for establishing diagnosis are changing sensitivity and specificity in pregnancy. Some procedures may damage the fetus or result in termination of pregnancy; thus, they are not recommendable if there is another way a diagnosis can be established. Serum tumor markers in pregnancy, especially CA-125 and CA-15.3, are very important, and therefore, their application is inadequate and not recommendable.[7] In suspicion of cervical cancer in pregnancy, colposcopy and biopsy are common procedures allowed. The risk of hemorrhage from colposcopically directed biopsies is extremely low. Endocervical curettage in pregnancy is not allowed.

Indications for conization and loop excision are decreasing as pregnancy progresses due to possible risks of abortion, preterm labor, or preterm rupture of the membrane. In case there is a suspected microinvasive or invasive form of cervical cancer, conization or comprehensive loop excision can be done in early pregnancy.[9,10]

In suspicion of breast cancer, besides ultrasound also, mammography and MRI can be performed. Definitive diagnosis is achieved by tissue biopsy and should be performed for any clinically suspicious lump.

Esophagogastroscopy, bronchoscopy, lumbar puncture, and bone marrow aspiration/biopsy are quite safe and should be done in pregnancy when clinically indicated.[4]

Once the diagnosis of cancer during pregnancy is confirmed, it is necessary to determine the clinical stage in order to conduct appropriate treatment. The following imaging procedures are in use today—X-ray, ultrasonography (US machine), computed tomography (CT) scan, nuclear medicine, MRI, and positron emission tomography (PET).

In pregnancy, it is necessary to select the methods which will give satisfactory clinical answers without harming the fetus. If possible, ionizing radiation should be either avoided or, at least, doses should be limited within recommended scale.

Ultrasonography (US Machine)

Ultrasonography (US machine) and MRI procedure are methods of choice for pregnant women when their use is expected to answer relevant clinical questions. There have been no reports of documented adverse fetal effects for diagnostic US machine procedures, including Doppler imaging. With the proper application of appropriate US machines, US machine does not pose a risk to the fetus.

Magnetic Resonance Imaging (MRI) Procedure

Magnetic resonance imaging (MRI) has priority to image deep soft tissue structures without using ionizing X-rays. There are no contraindications or special precautions in pregnancy for MRI. Animal studies have not shown any teratogenic risk. The pregnant patients are recommended to be imaged at field strengths of no >3T to keep the specific absorption rate low.[11]

Ray et al., in a population-based cohort study involving >1.4 million pregnancies, show that MRI in the first trimester is not associated with a higher risk of stillbirth or neonatal death, congenital anomalies, neoplasm, or hearing loss. The slightly higher risk of vision loss was only seen in a subgroup analysis of MRI exposure at 5–10 weeks gestation.[12]

Magnetic resonance imaging (MRI) is commonly followed by the usage of contrast agents, gadolinium-based contrast agents (GBCAs). It is a water solution that passes the placenta, enters the blood vessels of the fetus, and is eliminated through the kidneys and urine. GBCAs may accumulate in amniotic fluid, with the possibility of dissociation and release of the toxic free gadolinium ion, conferring a potential risk for the development of nephrogenic systemic fibrosis in the child or mother.[13–15]

Exposure to gadolinium-enhanced MRI at any gestation was not associated with a greater risk of congenital anomalies. According to the last recommendation of the American College of Gynecologists and Obstetricians (ACOG) given in 2017, gadolinium use should be limited to situations in which the benefits clearly outweigh the possible risks.[15]

European Society for Medical Oncology, in the guideline, has given the following recommendations—ultrasound examination is a method of choice for breast, abdomen, and pelvis. If necessary, chest X-ray and mammography can be done safely with abdominal shielding. MRI may be conducted if there is any unclarity in the analysis or suspicion of brain or bone metastasis.[7]

Ionizing Radiation

Due to the possible damaging effect of X-rays on the fetus, it is necessary to know the evidence and to follow the latest recommendations, so as not to scale down adequate treatment of pregnant patients.

Developing conceptus (embryo and fetus) is very sensitive to ionizing radiation. Three following processes are significant in fetus development—cell proliferation, cell differentiation, and cell migration. Proliferating cells are the most sensitive to radiation effects.

It is necessary to have knowledge of measurement units for ionizing radiation and also radiation doses for adults and fetuses. Currently, system of units (SI) measure units are valid, while conventional units are in use in older literature. The SI unit for exposition (amount of ion pairs created in the air by X-ray or γ radiation) is Coulomb/kg (C/kg); the conventional unit is Roentgen (R). 1 R = 2.58 × 10 − 4 C/kg. The unit for absorbed doses (energy absorbed from ionizing radiation per unit mass) in SI is gray (Gy) and the conventional unit is radiation absorbed dose (rad) 1 Gy = 100 rad. The term equivalent dose has been introduced as the absorbed dose in various conditions does not present damaging effects precisely (converts absorbed dose in equivalent tissue damage for different types of radiation). This refers only to external radiation. The unit for the equivalent dose is Sievert (Sv) and the conventional unit is rem, 1 SI is equal to 100 rems.

The risk to the fetus of ionizing radiation in pregnant women depends on gestational age at the time of exposure and dose.

This risk can be considered in terms of the deterministic and stochastic effects of radiation.

Deterministic effects of radiation result from damage to a number of cells, with a dose threshold before damage occurs. Such effects of ionizing radiation may cause the death of the embryo and fetus, intrauterine growth retardation (IUGR), microcephalia, significant mental retardation, decreased intelligence coefficient, and organ malformations. Stochastic effects of ionizing radiation that originate from damage to a single cell do not result in a loss of tissue function. It results in DNA mutations and can lead to carcinogenesis and the occurrence of malignant disease in childhood. There is no absolute threshold dose, but the risk of damage increases with the increase in radiation dose.[16]

The prenatal period is divided into three phases—the preimplantation phase (up to 2 weeks after conception), the organs formation-organogenesis phase (from the 1st to the 8th week after conception), and the fetal phase (from the 8th to the 38th week after conception), with special importance of early fetal period up to the 15th week for the possibility of teratogenesis.

In the preimplantation period, exposure to radiation over 50–100 mGy has an "all or nothing effect" on the embryo, causing its death, spontaneous pregnancy loss, or orderly continuation of fetal structure development.[8,11] The risk of provoking pregnancy loss with doses below 50 mGy is very low.[17] Fetus is the most sensitive to teratogenic radiation effect in the early fetal period up to the 15th week of gestation. Radiation exposure during the organ formation phase can trigger functional disorders, growth inhibition, or organ malformations. The risk to the central nervous system (CNS) is the greatest in the period from the 8th to 15th week of gestation when rapid neuronal development and migration take place. The risk to CNS after exposure to radiation before the 8th and after the 25th week has not been proved.[11,17] The brain is the most sensitive organ and radiation exposure above 100 mGy during that time may lead to mental retardation and microcephaly.[11,14] The risk is negligible below 50 mGy, and not any individual standard diagnostic procedure reaches that limit.

Absolute risk to the fetus, also including carcinoma in childhood, is low for doses of 100 mGy and minor for doses lower than 50 mGy.[17] ACOG gives recommendations that women who were exposed to diagnostic procedures in pregnancy should be advised that exposure to X-ray on one diagnostic procedure does not lead to damaging effects on the fetus, especially a dose lower than 50 mGy (5 rad) and it is not associated with fetal anomalies or pregnancy loss either.[15]

Fetal exposure varies with gestational age, maternal body habitus and exact acquisition parameters. Fetal radiation doses can be classified into three groups[16]:

- Very low-dose examinations <0.1 mGy.
  Chest radiography (two views), mammography (two views), and radiography of any extremity.
- Low- to moderate-dose examinations 0.1–10 mGy.
  Intravenous pyelography, lumbar spine radiography, abdominal radiography, head or neck CT, chest CT, or CT pulmonary angiography.
- Higher-dose examinations 10–50 mGy.

Abdominal CT, Pelvic CT, and PET/CT

Increased risk of cancerogenesis after high exposure to ionizing radiation has been proved with atomic bomb survivor population.

Carcinogenesis is a stochastic effect of radiation. The risk of carcinogenesis depends on the trimester in which the fetus is exposed to ionizing radiation. It is assumed that the risk is the highest in the first trimester.[11,14]

The risk of carcinogenesis as a result of *in utero* exposure to ionizing radiation is unclear but is probably very small. It is estimated that a 10–20 mGy fetal exposure may increase the risk of leukemia by a factor of 1.5–2.0 over a background rate of approximately 1 in 3,000.[15]

Computed Tomography (CT)

In CT, the conceptus dose (except abdomen and pelvis) is lower than 10 mGy. If the uterus is outside the field of view, the conceptus is exposed to scattered radiation only and the conceptus dose is minimal.[16] With typical use, the radiation exposure to the fetus from spiral CT is comparable with conventional CT.[15]

Diagnostic iodinated contrast media used for CT examination have been shown to cross the placenta and enter the fetus when given in usual clinical doses. There is no evidence of either mutagenic or teratogenic effects on the fetus. Intravenous administered contrast does not lead to a change in the neonatology level of thyroid stimulating

hormone (TSH) and neonatal hypothyroidism has not been described either.[18] Intravenous administration of iodinated contrast media does not affect short-term neonatal TSH.

Whenever possible, radiation should be avoided and modalities that use nonionizing techniques like US and MRI should be considered and offered to the patient first. Ideally, every radiology center should have its own data on fetal radiation exposure produced with its own equipment to determine the risks.[14]

Cancer Therapy during Pregnancy

After confirming the diagnosis of malignant disease in pregnancy and determining the stage it is necessary to decide on further treatment. The proper management of this clinical situation is crucial. There are two important questions—for which option to decide and when to start it. The treatment can be selected based on the following circumstances—intention to maintain the pregnancy, gestational age, and cancer type and stage. Treatment decisions must take into account the welfare of the patient and the fetus.

The gold standard of treatment in pregnancy should—(1) try to benefit the mother's life; (2) try to treat curable malignant diseases of pregnant women; (3) try to protect the fetus and newborn from harmful effects of cancer treatment; (4) try to preserve fertility for future gestations.[19]

In essence, the treatment of malignant disease in pregnancy should not be significantly different from the treatment regimens in nonpregnant women—surgery, chemotherapy, and immunotherapy. In pregnancy, radiotherapy should be avoided and postponed after delivery if the maternal condition allows it.

Surgery

Surgical procedures are very important in the treatment of solid tumors and can be performed in pregnancy. In the first trimester, surgery does not increase the risk of fetal anomalies, but the risk of miscarriage is slightly higher. The safety of anesthesia in pregnancy is of great importance. It is considered that 1.5–2% of pregnant women undergo general anesthesia for obstetric or nonobstetric reasons. The teratogenicity of a drug is determined by the dose administered, the route of administration, and the timing of exposure, which seems to be of crucial importance. During the first 2 weeks of gestation, an all-or-nothing phenomenon occurs. Structural abnormalities can be expected in the period of organogenesis (2–8 weeks of gestation) and functional changes afterward. Local anesthetics, volatile anesthetics, induction agents, muscle relaxants, and opioids are not teratogenic when used in clinical concentrations and when normal maternal physiology is maintained. The most challenging goal of the anesthetist is to avoid fetal hypoxia and asphyxia during anesthesia.[20] Surgery, if possible, should be postponed for the second trimester, as the risks to the fetus are lower after the 14th week of gestation.[21]

In 2017 Balinskaite et al. published a large retrospective study that included about 6.5 million pregnant women. They found that the risk associated with nonobstetric surgery was relatively low, confirming that surgical procedures during pregnancy are generally safe.[22]

Independently of the gestational age, the surgery should never be postponed if deemed to be crucial in the management plan.[23] Large operative procedures in the abdomen and pelvis can be associated with increased morbidity and complications in all periods of pregnancy.[7]

Special recommendations refer to gynecological malignancies in pregnancy—cervical and less commonly ovarian cancer. In those cases, the focus is on the conflict between the treatment of malignancy—maternal benefits and continuation of pregnancy.[24,25]

Chemotherapy

The main challenge in managing cancer in pregnancy is treating the patient with an optimal anticancer regimen without harming the developing fetus. A few decades ago a woman with a diagnosis of malignancy in pregnancy had two options—pregnancy termination or postponing treatment after delivery. Evidence-based medicine did not have data about the harmful effects of chemotherapy on the fetus, the consequences for the mother and fetus if the medical treatment is postponed as well as effects of malignant disease on pregnancy.

Poor evidence regarding the fetal safety of maternal chemotherapy was limited to small retrospective studies or case reports. In the last few decades, evidence is growing and we have encouraging results from either prospective multicenter studies with large numbers of patients and follow-up children over a long period of time. Leading oncological associations have published encouraging recommendations for the diagnosis and treatment of malignant disease in pregnancy.[5–7,11,15,19]

The decision to start systemic therapy in pregnancy is influenced by disease stage, gestational age, type of cancer, the expected benefit and risks of therapy, and patient preference. All this requires the development of tailored strategies for these patients. Management should be undertaken by a dedicated multidisciplinary team consisting of a surgeon, a clinical oncologist, a specialist in radiation therapy, an obstetrician, a neonatologist, and a psychologist.

Animal studies show high rates of teratogenicity for most cancer chemotherapeutics. The United States Food and Drug Administration has defined and classified medications into risk categories. Antineoplastic drugs are listed as category C and D because of a lack of human evidence, potential, or known harm. Most chemotherapeutic drugs have a molecular weight of <600 Da and can cross the placenta in varying amounts, appearing in fetal circulation. Fetal exposure to drugs depends on maternal pharmacokinetics including the volume of distribution, the rate of metabolism and excretion by the placenta, and the pH difference between maternal and fetal fluids. The effect of physiologic changes in pregnancy also has to be taken into account. Maternal blood volume increases in pregnancy. An increase

in plasma volume and dilution of maternal blood leads to a decrease in hematocrit and decreased concentration of plasma proteins. Other hemodynamic changes include increases in cardiac output, systemic blood pressure, pulmonary vascular resistance, heart rate, and blood flow distribution.[26] Drug concentration may be affected by increased renal clearance and faster hepatic metabolism. Consequently, chemotherapy concentration may be reduced.[27] All the drugs used to treat cancer reach the fetus in a relatively low concentration.

Cancer drugs are designed to kill dividing cells rapidly. During the preembryonic stage rapid cell division occurs. Damage to the majority of the cells of the conceptus is likely to result in miscarriage. Organogenesis and the early fetal period until the 11th week may result in structural anomalies, depending on the critical period of development of each organ. The risk of congenital malformation in that period is very high, 10–20%.[27] Chemotherapy is contraindicated in the first trimester of gestation.[1,27]

Pregnancy termination should be considered in pregnant patients with cancer who need chemotherapy administration in the first trimester. After the first trimester cell death will mainly result in functional damage. Available clinical data suggest that fetuses exposed to chemotherapy in the second trimester do not experience significant long-term complications.[1]

Chemotherapy can inhibit trophoblast migration and proliferation, which may contribute to neonatal low birth weight, but these data are limited.[29]

In the second and third trimesters, organogenesis is complete except for CNS and gonads. In this period exposure to chemotherapy may lead to an increased incidence of IUGR, preterm delivery, and fetal death, as well as may be the cause of sterility and diminished intelligence quotient in later life.[4,26] Recent studies have concluded that prenatal exposure to maternal cancer with or without treatment does not impair the cognitive development of children. Cardonick et al. and Amant et al. did not find a significant difference in cognitive ability, school performance, or behavioral competence for children exposed to chemotherapy *in utero* compared with nonexposed controls.[30,31]

Exposure to chemotherapy can lead to temporary myelosuppression of the mother and fetus. Fetal transient myelosuppression is maximally evident in the first days of life and is resolved within 2–10 weeks. The delay of delivery for 3 weeks after chemotherapy is recommended.[32] That's why chemotherapy should not be administered after the 35th week of gestation in order to allow the fetus to eliminate the cytotoxic drugs.[26]

Some kinds of chemotherapy, especially anthracyclines may have cardiac toxic effects and can be associated with fetal cardiac toxicity including reversible arrhythmias. Recent studies show that global heart function between chemotherapy-exposed children and nonexposed controls is comparable.[27,31] Biphosphonates cross the placenta and they have been incriminated for bone developmental abnormalities.

Immunotherapy for breast cancer has become commonplace in the past decades. Targeted agents have different structures, metabolism, and pharmacokinetics compared to chemotherapy. Monoclonal antibodies are mostly of the immunoglobulin G (IgG) 1 subclass and they require active transport across the placental barriers *via* a specific receptor-mediated mechanism. It has been stated that such transport systems only appear after 14 weeks of gestational age. Transplacental studies suggest very low IgG fetal concentration during the first trimester.[33] Immunotherapy has several representatives as they are:

Trastuzumab–Herceptin—is a monoclonal antibody (mAb) to the human epidermal growth factor receptor type 2 (HER2), which is found in about a third of invasive breast cancers[34] HER2 expression is high in embryonic tissues. Trastuzumab is contraindicated, as it has been associated with severe oligohydramnios in the second or third trimester, which was encountered in >50% of cases exposed to trastuzumab during pregnancy.[33] Oligohydramnios seems specific to trastuzumab because of blockage of the epidermal growth factor receptor-2 (EGFR-2) expressed in the fetal kidney.[27]

Rituximab is a chimeric IgG1k anticluster of differentiation 20 mAb that is used to treat B-cell indolent and aggressive nonHodgkin's lymphoma as well as in the management of some autoimmune diseases.[33] Rituximab seems to be safer than trastuzumab in pregnancy.[35] Both of them could be considered in pregnancy but only in particular situations.[33]

Bevacizumab, mAb against vascular endothelial growth factor (VEGF) acts as a key regulator of angiogenesis, both physiological and pathological. Angiogenesis is crucial for the normal development of the placenta and fetus. Preclinical models using bevacizumab, thalidomide, and other VEGF tyrosine kinase inhibitors were associated with serious pregnancy complications. Thus, these medications should not be considered in treating patients in pregnancy.

It is still a matter of debate whether *in utero* exposure to anthracyclines is cardiotoxic to the fetus in general. However, serial prenatal sonographic assessment of fetal cardiac function might have a role in monitoring anthracycline cardiotoxicity or cardiac failure. Transient neonatal cardiomyopathy has been reported.

Fractionation of the dose on weekly bases allows easy pregnancy monitoring and easy interruption of chemotherapy if needed.

Tamoxifen as a representative of hormone therapy is contraindicated in pregnancy. It is associated with a considerable risk of fetal congenital anomalies.[27]

Almost all drugs can be excreted into breast milk, which may potentially lead to exposure of the neonate to chemotherapy. Breastfeeding is not recommended during and until at least 2–4 weeks after the completion of chemotherapy. Cases of infant neutropenia were reported in a baby breasted by a mother while she was on treatment with cyclophosphamide.[4,29]

Ionizing Radiation for Therapeutic Purpose

It is recommended that ionizing radiation for therapeutic purposes is delayed for the period after labor regardless of the treated site. An exception is an urgent clinical necessity for the mother (when fetal well-being should be preserved) radiation site is to be located sufficiently far from the uterus.[8]

Obstetric Care and Fetal Follow-up

Pregnancy in women with cancer should be considered as a high-risk situation especially when chemotherapy is initiated. Those pregnancies could be associated with increased risks of rare but fatal outcomes, including stillbirth and neonatal mortality. The positive association with preterm birth was due to iatrogenic instead of spontaneous preterm birth. Preterm birth explained 89% of the association of maternal cancer during pregnancy with neonatal mortality.[36] Prevention of iatrogenic prematurity should be a very important issue in the near future.

Rates of small gestational age (SGA) infants are increased after prenatal exposure to chemotherapy.[6,27] There are numerous causes for SGA, such as the compromised placental supply of nutrients and oxygen to the fetus, reduced uteroplacental blood flow, nausea, and reduced food intake as well as direct placental and fetal cell damage. Regular fetal monitoring is highly recommended as well as continued follow-up of newborns until puberty. Cancer during pregnancy is associated with a significantly increased risk of planned preterm birth, induction of labor, and a cesarean section.[6] In general, a normal vaginal delivery in the absence of maternal or neonatal complications is recommended although the mode of delivery is determined by the obstetricians.

The risks of thromboembolic events, sepsis, and severe morbidity, which are recognized cancer complications, were higher among women with CAP.[6]

Increased knowledge in this field can reduce inadequate management of CAP including delayed treatment, unnecessary termination of pregnancy as well as consequences of iatrogenic preterm birth.

Metastasis of Maternal Tumors to Placenta and Fetus

As cell transfer is possible between mother and fetus, it is highly conceivable that the mother's cancer cells could pass through the placenta to reach the fetus as well. But maternal malignancy metastatic to the fetus is a rare event, with most neoplasms being either melanocytic or hematopoietic in origin.[37] Malignant melanoma, lung cancer, leukemia, and lymphoma have the potential to metastasize to the placenta. They have high percentages of placental metastasis and low percentages of fetal metastasis, fortunately. Metastatic transmission to the placenta or fetus mostly occurs through the hematogenous route.

The risk of metastasis to the placenta and fetus is low and occurs in patients with widely metastatic melanoma.[38] Even in pregnant women with maternal metastasis originating from the trophoblast in the placenta fetal metastasis are rare. There must be a defense mechanism blocking the metastasis of cancer cells to the fetus. We still do not know what is in the matter. Some reports indicated that probably the trophoblast plays the role of a physical barrier. Yang and Chao published the hypothesis that Wharton's Jelly (WJC) in the umbilical cord also plays a role in the fetal defense against the invasion of maternal or placental cancer cells. In the event of cancer cell occurrence in the placenta, WJCs may induce apoptosis of the cancer cells.[39]

The placentas and umbilical cords of women with known or suspected metastatic melanoma should be carefully examined histologically. With placental involvement, the fetal risk of melanoma metastasis is approximately 22%. Neonates delivered with concomitant placental involvement should be considered a high-risk population.[40] Some authors recommend follow-up every 6 months for at least 2 years, with a focus on the primary malignancy.

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