Review

Transplacental cancer transmission: a comprehensive review focusing on mechanisms, challenges, and maternal-fetal outcomes

Mishu Mangla[1], Seetu Palo[2], Naina Kumar[2]

[1]Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, Bibinagar, India
[2]Department of Pathology and Laboratory Medicine, All India Institute of Medical Sciences, Bibinagar, India

Abstract

The phenomenon of transplacental transmission of cancer, where cancer cells pass from a pregnant mother to her fetus is an extremely rare occurrence. This phenomenon has significant implications for maternal and fetal health, challenging our understanding of cancer biology and maternal-fetal interactions. The literature on transplacental cancer transmission is sparse, consisting mainly of case reports, small cohort studies, and reviews. Examples of cancers that have been transmitted in this way include melanoma, choriocarcinoma, leukaemia, and lymphoma. Understanding this phenomenon is important because it has direct clinical implications for managing pregnant women with cancer and the infant, raises questions about the placental barrier and immune interactions between mother and fetus, and offers insights that could influence cancer biology and treatment strategies. This review aims to evaluate existing data, identify and synthesize evidence on transplacental cancer transmission cases, evaluate cancer types involved, their transmission mechanisms, and clinical outcomes for both mothers and infants. A comprehensive electronic search of databases was conducted for relevant case reports and series, using specific keywords related to vertical and transplacental transmission of cancer. The review elucidates comprehensive information from the reports to understand how cancer transmission occurred and was confirmed as vertical transmission, aiming to enhance knowledge in this critical area of maternal-fetal medicine. [J Turk Ger Gynecol Assoc.]

Keywords: Cancer, choriocarcinoma, melanoma, transplacental transmission, vertical transmission

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Introduction

Transplacental transmission of cancer, also known as vertical transmission, is an exceedingly rare but intriguing phenomenon where cancer cells cross the placental barrier from a pregnant mother to her fetus. Although, about 1 in 1,000 live births involves a mother who has cancer, maternal transmission of cancer to offspring is exceedingly rare, estimated at approximately 1 in every 500,000 infants born to mothers with cancer (1,2). This mode of transmission has profound implications for both maternal and fetal health, challenging our understanding of cancer biology and maternal-fetal interactions. It presents a unique conundrum, combining elements of oncology, immunology, and obstetrics. Given the rarity and complexity of transplacental transmission of cancer, the existing literature is sparse and comprised of case reports, small cohort studies and reviews; types of cancer include melanoma, leukaemia, and lymphoma being transmitted from mother to fetus. Understanding the transplacental transmission of cancer is important for several reasons. Firstly, it has direct clinical implications for the management of pregnant women with cancer, influencing decisions regarding treatment and monitoring. Secondly, it raises fundamental questions about the nature of the placental barrier, the immune interactions

Address for Correspondence: *Seetu Palo*
e-mail: *seetu.pearl@gmail.com* ***ORCID:*** *orcid.org/0000-0001-9956-2246*

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between mother and fetus, and the unique environment that allows for transmitting malignant cells. Thirdly, insights gained from studying this rare event may have broader implications for cancer biology and treatment along with strategies to prevent metastasis and improve outcomes for patients with cancer. This review sought to critically analyze existing data, identify and consolidate evidence on transplacental cancer transmission, examine the types of cancers involved, their transmission mechanisms, and the clinical impact on both mothers and infants. By consolidating comprehensive data from these rare case scenarios, this review offers a novel perspective on previously overlooked patterns, proposing new insights into transplacental transmission pathways, maternal-fetal interactions, and potential diagnostic as well as therapeutic advances in this rare phenomenon.

Methodology

An electronic search of Scopus, PubMed, Embase and other databases was conducted for case reports and case series of suspected, probable and confirmed mother-to-child transmission or vertical transmission of cancer, published in English from inception until July 2024. The electronic search strategy used keywords such as “vertical transmission” and “transplacental transmission”, “mother to child transmission” and “cancer”, “carcinoma” and “transplacental transfer”, and “metastasis to the fetus” “mother to baby”; “mother and baby”. We analysed the titles and abstracts of all case reports identified by the initial search. The reference lists of relevant reports were also explored. Two reviewers double-checked the data to avoid duplication. Case reports with placental metastasis only, without metastasis to the fetus, were excluded. Review articles, original articles, clinical trials, conference abstracts, editorials, poorly described cases, and articles in language other than English language or commentary were also excluded. The article selection and screening process details are presented in the Preferred Reporting Items for Systematic Reviews and Meta-analysis flowchart (Figure 1). Of the eligible articles, information pertaining to author and year of publication, age

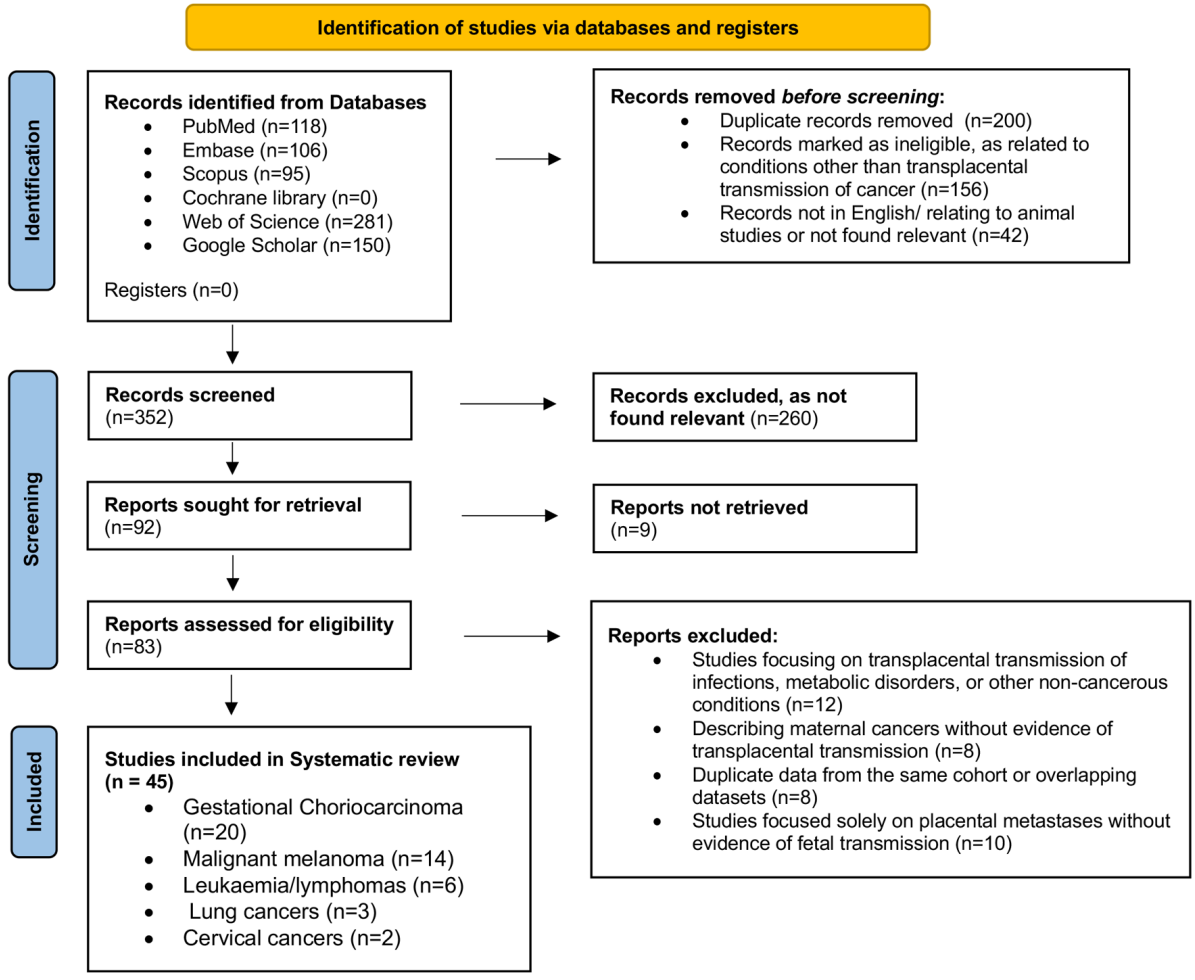

Figure 1. PRISMA flow-chart of study selection

of the patient at the time of presentation, the type of primary cancer in the mother and its stage if available, primary site in the mother, gestational age at the time of delivery, age at diagnosis, presenting clinical features, and sites of metastasis for the baby, and the outcome of the case in the form maternal and fetal/neonatal/infant outcome was extracted. An attempt was made to extract all the possible information mentioned in the report regarding how the cancer transmission occurred and how it was confirmed to be "vertical transmission". By systematically reviewing the literature, we hope to enhance the understanding of transplacental cancer transmission and provide a foundation for informed clinical practice and future research directions in this important area of maternal-fetal medicine.

Overview of published cases of transplacental cancer transmission

A summary of all probable and confirmed cases of transplacental cancer transmission reported in the literature to date are summarised in Table 1: all cases of choriocarcinoma (3-23), Table 2: all cases of malignant melanoma (24-40) and Table 3: other cancers, including leukaemia, lymphomas, lung cancers and cervical cancers (41-51). Choriocarcinoma is the most common tumor showing mother-to-child transmission. In a previous systematic review, conducted by one of the authors of this article, the 12-month overall survival rate for mothers was 71.8%±10.7%, while for infants, it was 22.2%±9.8% (52). The median time to diagnose gestational trophoblastic neoplasia in mothers was six weeks post-partum. For infants, the median age at presentation was 1.75 weeks [interquartile range (IQR): 0.1 to 6.75 weeks], and the median age at diagnosis was 5.00 weeks (IQR: 3.55 to 8 weeks). However, the diagnosis of vertical transmission was not confirmed in most cases (16/20). It was not clear whether the infant's tumor was primary or secondary to maternal choriocarcinoma. Another diagnostic dilemma with choriocarcinoma is whether it has arisen from the present pregnancy or hydatiform mole in a previous pregnancy or from previous abortions where histopathology was not done, as they could have been molar pregnancy of choriocarcinoma, and this is usually not clear (52).

Malignant melanoma was found to be the second most common tumor, showing transplacental transmission after gestational choriocarcinoma. After analyzing the existing literature, we found that the tumor might have a higher incidence in male fetuses, with a male-to-female ratio of 2:1. However, in two cases where the tumor metastasis led to intrauterine fetal demise, the sex was not mentioned. All infants presented during infancy with cutaneous metastasis. The mastoid cavity and external auditory meatus were other favoured sites, followed by brain, lung, liver, testicles and adrenal glands. Interestingly, in two cases, auto-regression of the tumour was noted (28,32). In 4/14 cases, vertical transmission was confirmed because the placenta was grossly and microscopically involved. In 5/14 cases, karyotypically female cells in a male baby were presumed to be of maternal origin, or genetically identical mutations in both tumours were confirmatory. The prognosis was very poor, both for the mother and the baby. Most (9/14, 64.3%) of the babies died, while in one case, the details were not available. For mothers, if vertical transmission had occurred, the result was invariably fatal when outcome was reported; 13/14 mothers died, while in one patient, the details were not available.

There are three cases of cervical cancer reported to be transmitted vertically (47,48). In all three cases, the authors stressed mother-to-infant vaginal transmission through aspiration of tumour-contaminated vaginal fluids during birth. In the case described by Herskovic et al. (47), the authors acknowledged that the spread could have been hematogenous transplacental or through direct inoculation or transbronchial spread. In the cases reported by Arakawa et al. (48), the transmission was evidenced by the fact that the tumors in both male children lacked the Y chromosome and shared multiple somatic mutations, an human papilloma virus genome, and single nuclear polymorphic (SNP) alleles with their mothers' tumors. In addition, the peri-bronchial growth pattern of the tumors in both children suggested that they originated from mother-to-infant transmission via aspiration of tumor-contaminated vaginal fluids during birth. Maternal tumor cells were likely present in the amniotic fluid, cervical secretions, or blood and were aspirated by the infants during vaginal delivery.

We found six reported cases of haemato-lymphoid malignancies that have been reported to be transmitted from mother to child trans-placentally (41-46). Transplacental transmission of cancer appears to have a predisposition for male fetuses. In cases of leukaemia and lymphoma, 5 out of 6 reported instances involved male fetuses, with the remaining one case involving a female fetus (46). Similarly, in lung cancer, 2 out of 3 cases involved male fetuses (with the sex of the baby in the third case not reported). For cervical cancer also, 2 out of 3 cases, involved male fetuses (with the sex of the baby in the third case not reported). The confirmation in these cases (where done) is either by gross/microscopic involvement of the placenta, of the finding of XX genotype in cancer cells of the male fetus, which is presumed to be of maternal origin or by identical mutations found in maternal and fetal tumors.

Table 1. A summary of all cases of gestational choriocarcinoma, reported in literature with suspected or confirmed, vertical transmission

Author and year of publication	Age/type of cancer/primary site	Mode of delivery/ GA at birth	Child's Sex/age at diagnosis	Presenting features for the baby	Site of metastasis in the baby	Route of transmission	How was vertical transmission confirmed?	Placental histopathology, if available. (Villous invasion, if present)	Outcome in the baby	Outcome in the mother	Remarks
Mercer et al. (3)	NM/ Choriocarcinoma/ Uterus (a blackish-red nodule 1.5 X 1.5 cm, located in the fundus)	VD/Full-term	NM/3 months	Small red nodule in the upper anterior alveolar ridge	Upper maxilla, nasal fossa and later head and neck	Transplacental ?	Not confirmed	Not done	Died at 6 months of age d/t extensive invasion of the tumor about the head and face.	Death at 8 months pp due to widely metastatic disease.	Whether the tumor of the alveolar ridge of the infant represented a primary or a secondary metastasis is unknown.
Brooks and Nolting (4)	NM/ Choriocarcinoma/ Diagnosed with metastatic disease after child's confirmation.	VD/35 weeks	Female/11 days	Right-sided facial mass, Recurrence of facial mass after resection	lung	Transplacental ?	Not confirmed	Not done	Survived	Alive and Healthy	Not clear whether the infant's tumor was primary, or secondary to maternal CC
Hanson et al. (5)	NM/ Choriocarcinoma/ Diagnosed with metastatic disease after child's confirmation.	NM	Male/6 weeks	Fever, pallor, and fatigue, Recurrent severe anaemia, hepatomegaly	Liver	Transplacental ?	Not confirmed	Not done	Survived	Survived	Not clear whether the infant's tumor was primary, or secondary to maternal CC
Sashi et al. (6)	NM/ Choriocarcinoma/ Diagnosed with metastatic disease after child's confirmation.	NM/full term	Female/At birth	Anaemia, abdominal distension, Tachycardia, cyanosis, liver tumours	Liver, lung, brain	Transplacental ?	Not confirmed	Not done	Died at 38 days d/t metastatic disease.	Survived till 14 months from diagnosis and later	In this case there were two possible primary sites: the placenta of this pregnancy and the hydatidiform mole occurring 2 years before.
Andreitchouk et al. (7)	36/ Choriocarcinoma WHO score 13/ Uterus with widespread metastasis diagnosed after confirmation in child	CS (CPD)/ full-term	Female/At birth	Severe anaemia Hepatomegaly	Liver, lung, brain.	Transplacental ?	Not confirmed	Placenta grossly normal. HPE not done	Died at 38 days of life d/t metastatic disease.	Remission	Origin could have been from hydatiform mole 2 years before this pregnancy. Feto-maternal haemorrhage was noted.

Table 1. Continued

Author and year of publication	Age/type of cancer/primary site	Mode of delivery/ GA at birth	Child's Sex/age at diagnosis	Presenting features for the baby	Site of metastasis in the baby	Route of transmission	How was vertical transmission confirmed?	Placental histopathology, if available. (Villous invasion, if present)	Outcome in the baby	Outcome in the mother	Remarks
Avril et al. (8)	21/ choriocarcinoma/ placenta with lung metastasis	VD/ full-term	Female/At birth	Cutaneous lesions Disseminated cutaneous tumours, hepatomegaly, lung rales	Skin, lung, bone, pelvis	Transplacental	Confirmed because placenta was involved pathologically	An abnormal 5 cm wide white growth on the uterine surface, pathologically confirmed as choriocarcinoma	Died at day 24 of life d/t lung haemorrhage	Alive at 14 months No further details available	None
Bolze et al. (9)	35/ Choriocarcinoma FIGO Stage 4 Score 14/ Uterus	NM/NM	Male/ 5 month	Dyspnea and anaemia, Liver mass, mediastinal lymphadenopathy.	Liver, lung, mediastinal lymph nodes	Transplacental confirmed	Genotyping	Placenta grossly normal. HPE not done	Died at 11 months of age	Normal at 3 years f/u.	None.
Flam et al. (10)	30/ choriocarcinoma/ uterus	VD/ full-term	Female/ 24 hours of life	Anaemia Liver tumour	Liver	Transplacental?	Not confirmed	Placenta grossly normal. HPE not done	Died at 20 days of life (sudden death at home)	Alive at 7 years	Not clear whether the infant's tumor was primary, or secondary to maternal CC
Rzanny-Owczarzak et al. (11)	NM/ choriocarcinoma/ uterus	CS (NPOL)/ full-term	Male/ 1 month	Hematemesis Liver tumour	Lung, liver, intestine, lymph nodes	Transplacental?	Not confirmed	Not mentioned	Died at 1.5 months d/t MODS	Alive and pregnant at 1 year	Not clear whether the infant's tumor was primary, or secondary to maternal CC
Liu and Guo (12)	35/ Choriocarcinoma stage IIIa (FIGO score 4) / Uterus, metastatic to lungs.	VD/ full-term	Male/ Day 13 of life	Unexplained melena, Jejunal mass	lung, jejunum,	Transplacental?	Not confirmed	Not mentioned	Survived	Normal at 1 year f/u	Not clear whether the infant's tumor was primary, or secondary to maternal CC
Tsukamoto et al. (13)	24/ choriocarcinoma/ uterus	VD of dead baby/ full-term	Male/ Intrauterine fetal demise	Unexplained intrauterine fetal death Metastatic liver disease	Liver, lungs, hilar lymph nodes, diaphragm, and subcutaneous tissue of the head.	Transplacental?	Not confirmed	Placenta was enlarged but grossly normal, sent for HPE but found normal	Intrauterine fetal death	Asymptomatic at 9 months f/u	Not clear whether the infant's tumor was primary, or secondary to maternal CC

Table 1. Continued

Author and year of publication	Age/type of cancer/primary site	Mode of delivery/ GA at birth	Child's Sex/age at diagnosis	Presenting features for the baby	Site of metastasis in the baby	Route of transmission	How was vertical transmission confirmed?	Placental histopathology, if available. (Villous invasion, if present)	Outcome in the baby	Outcome in the mother	Remarks
Buckell and Owen (14)	25/ choriocarcinoma/ uterus	NM/ full-term	Male/ 7 weeks	Vomiting, abdominal distension, Anaemia, epigastric mass	Liver, ribs and nodes	Transplacental?	Not confirmed	Not mentioned	Died at 52 days of life	Alive at 13 months pp	Not clear whether the infant's tumor was primary, or secondary to maternal CC
Kruseman et al. (15)	20/ choriocarcinoma/ uterus and vagina	VD of dead baby/ full-term	Female/ Intrauterine fetal death	Still birth, polyhydramnios, Tumour in left kidney 1.2x1.8 cm	Kidney	Transplacental ?	Both tumours were similar on Immuno-histochemistry.	Not mentioned	Intrauterine fetal death	Alive at 6 months	Massive Feto-maternal haemorrhage. Not clear whether the infant's tumor was primary, or secondary to maternal CC
Mosayebiet al. (16)	22/ choriocarcinoma	CS (morbid maternal condition)/ 31 weeks	Female/ 6 weeks	Recurrent vomiting and poor feeding, Sick child, decreased neonatal reflexes, systolic murmur, bilateral megalo-cornea and leukocoria	Brain, lung, liver and eye	Transplacental?	Not confirmed	Not done	Died	Died at 30 days pp	Not clear whether the infant's tumor was primary, or secondary to maternal CC
Mcnally et al (17); Heath and Tiedemann (18)	35/ choriocarcinoma/ Uterus and placenta	VD/ full term	Male/ 3 months	Solitary liver nodule	Liver	Transplacental	Confirmed by HPE of placenta	Placenta involved grossly and microscopically (Villous invasion present)	Alive and Healthy at 3 years	Alive and healthy at 36 months, following multiple courses of chemotherapy and related complications	h/o hydatiform mole, before this pregnancy, which went on to develop CC
Aozasa et al. (19)	NM/ choriocarcinoma not confirmed on HPE/ Uterus	VD/ full-term	Female/ 2 months	Weakness of feeding and oedema in the right inguinal and labial region, Hepatomegaly, abdominal distension, thrombocytopenia,	Liver, lung	Transplacental?	Not confirmed	No comment on placental examination	Died	Died at 5 months pp	Not clear whether the infant's tumor was primary, or secondary to maternal CC

Table 1. Continued

Author and year of publication	Age/type of cancer/primary site	Mode of delivery/ GA at birth	Child's Sex/age at diagnosis	Presenting features for the baby	Site of metastasis in the baby	Route of transmission	How was vertical transmission confirmed?	Placental histopathology, if available. (Villous invasion, if present)	Outcome in the baby	Outcome in the mother	Remarks
Getrajdman et al. (20)	33/ choriocarcinoma	VD/ 37 weeks	Male/At birth	Pallor Hepatomegaly and anaemia	Liver, lung, eyes	Transplacental?	Not confirmed.	No comment on placental examination	Survived and disease free at 2 years	Alive and Healthy at 2 years	Not clear whether the infant's tumor was primary, or secondary to maternal CC
Kishkurno et al. (21)	36/ choriocarcinoma	CS (CPD)/ full-term	Female/	Anaemia, hepatomegaly	Liver, brain, lungs	Transplacental?	Not confirmed	Placenta grossly normal. HPE not done	Died at 38 days of life d/t widespread metastasis	Alive and healthy	Origin could have been from hydatiform mole 2 years before this pregnancy. Feto-maternal haemorrhage was noted
Picton et al. (22)	24/ choriocarcinoma high risk with prognostic score 17/ Diagnosed with metastatic disease after child's confirmation	CS (fetal distress)/40 weeks	Male/Day 22 of life	Feeding difficulty, poor weight gain, anaemia, vomiting Failure to thrive, hepatosplenomegaly	Brain, liver, lung	Transplacental??	Not confirmed.	On gross examination, membranes appeared ragged, but HPE not done.	Died at 1 month d/t widespread metastasis.	Alive and healthy at 11 months	Feto-maternal haemorrhage was noted
Monclair et al. (23)	32/PSTT high risk WHO prognostic score 9	NM/ 37 weeks	Male/4 months	General malaise, common cold Hepatomegaly, dyspnoea, tachycardia, pneumothorax,	Liver, lung, mesentery	Transplacental??	Not confirmed. Both tumours were similar on Histology and Immunohistochemistry	Placenta was grossly normal, but histopathology was not done	Died at 5 months d/t MODS	Alive and Healthy at 26 months	Not clear whether the infant's tumor was primary, or secondary to maternal PSTT

CC: Choriocarcinoma, CPD: Cephalo-pelvic disproportion, CS: Caesarean section, CT: Computer tomography, d/t: Due to, f/b: Followed by, f/u: Follow-up, HPE: Histopathological examination, IUFD: Intra-uterine fetal death, LSCS: Lower segment caesarean section, NAD: No abnormality detected, NM: Not mentioned, NPOL: Non-progress of labour, MODS: Multi-organ dysfunction syndrome, pp: Post-partum, PSTT: Placental site trophoblastic tumor, VD: Vaginal delivery, WHO: World Health Organization

Table 2. A summary of all cases of Malignant Melanoma, reported in literature with suspected or confirmed, vertical transmission

Author and Year of publication	Age/type of cancer/ primary site	Mode of delivery/ GA at birth	Child's Sex/age at diagnosis	Presenting features for the baby	Site of metastasis in the baby	Route of transmission	How was vertical transmission confirmed?	Placental histopathology, if available. (villous invasion, if present)	Outcome in the baby	Outcome in the mother	Remarks
Weber et al. (24), Holland (25)	27/melanoma/ skin (left thigh)	CS (morbid maternal condition)/38 weeks	Male/8 months	Abdominal distension, cachexia, hepato-splenomegaly,	Subcutaneous nodules	Trans-placental	Histopathology of placenta.	Placenta involved, Gross and Microscopic (villous invasion present)	Death at 10 months of age	Died at 3 months	None
Gottron and Gertler (26)	25/melanoma/ skin (back)	NM/Term	Male/5 months	NM	NM	Trans-placental	Not confirmed	Microscopic examination not done (not known)	Death at 14 days of life	Died at 2 months	None
Aronsson (27); Cavell (28)	NM/melanoma/ not known	VD/ 32 weeks	Female/2.5 months	Tumor-like masses in her right thigh and right lower leg	Skin	Trans-placental likely.	Melanin + ve pigments in the tumor of the infant and the presence of metastasizing malignant melanoma in the mother	Placental microscopic examination was not done (not known)	Alive and Healthy at 2 years	4 days, death due to sepsis	Spontaneous regression occurred
Trumble et al. (29)	NM/melanoma/ skin	NM/ term	Male/7 months	2-week h/o bulging fontanel, diminished oral intake, and lethargy	posterior fossa	Trans-placental	Sex Chromosome FISH	NM	Died of recurrence at 18 months	Died, but duration not mentioned	Karyotype analysis was done to confirm maternal origin of cancer
Brodsky et al. (30)	28/melanoma/ skin (mid-interscapular region)	CS (failed induction)/37 weeks	Male/day 11 of life	pin point brown lesion on anterior chest wall, that progressed rapidly to involve skin of the left shoulder and posterior chest wall	Skin	Trans-placental	HPE of placenta	Malignant cells found in the cord blood. (villous invasion present).	Died at 48 days of age, MODS	Sudden death at 17 days post-partum	None
Raso et al. (31)	NR/melanoma/ not reported	NM/NM	Male/6 months	Tumor Swelling in temporal region	Middle ear, temporal bone	Trans-placental	Quantitative PCR	NAD	Alive and Healthy at 12 years	Died few weeks after delivery	None
Valenzano Menada et al. (32)	28/melanoma/ skin (right gluteus), f/b multiple bilateral breast masses and a growing right inguinal lymph node	CS (morbid maternal condition)/ 31 weeks	Male/3 months	Restlessness and peripheral defect of the left facial nerve	left mastoid	Trans-placental	Sex Chromosome FISH	Placenta normal grossly and microscopically (absent)	Alive and healthy at 2 years	Died at 2 weeks post-partum d/t liver failure.	Spontaneous regression
Pourtsidis et al. (33); Chrysouli et al. (34)	31/melanoma/ not mentioned	CS/33 weeks	Female/8 months	Swelling and erythema of the left cheek and the mastoid region, f/b a 4-day otorrhea and fever	mastoid cavity	Transplacental	Real Time PCR and High resolution melt analysis	Placental microscopic examination was not done	Alive and healthy at 16 months	Died at 3 months post-partum.	None

Table 2. Continued

Author and Year of publication	Age/type of cancer/ primary site	Mode of delivery/ GA at birth	Child's Sex/age at diagnosis	Presenting features for the baby	Site of metastasis in the baby	Route of transmission	How was vertical transmission confirmed?	Placental histopathology, if available. (villous invasion, if present)	Outcome in the baby	Outcome in the mother	Remarks
De Carolis et al. (35)	31/melanoma/ left ovary with positive peritoneal fluid cytology associated with bilateral breast masses.	CS/27 weeks	Male/4 months	Epileptic seizure. A brain CT scan documented the presence of metastatic lesions	Brain	transplacental ?	Placenta was involved pathologically	Placenta involved, Gross and Microscopic (Villous invasion present)	Died at 5 months due to metastasis to brain	Died at 12 weeks post-partum	Autopsy of baby not performed. HPE of baby's tumors not done. Baby has brain tumors, but not known, what they were ??
Canu and Dutriaux (36)	39/melanoma/ skin (left arm)	CS/IUFD	NR/ intrauterine fetal death	Ultrasound at 32 weeks, suggested IUFD of one twin	Skin (about 20 subcutaneous nodules, six of which were pigmented)	Trans-placental	Not confirmed	Not known	Intrauterine fetal death	Not mentioned	IUFD d/t feto-maternal haemorrhage, most likely secondary to a breach caused by a placental metastasis
Naidu et al. (37)	NR/melanom/ skin (face)	CS (prev. LSCS)/ full term	Female/3 months	6-week h/o multiple bluish-black cutaneous lesions on scalp and buttocks	skin, brain (multiple), lung and liver	Trans-placental	Both the mother and the infant's melanoma tested positive for the B-Raf proto-oncogene (BRAF) mutation.	Placenta involved, Gross and Microscopic (villous invasion not mentioned)	Died at 2 years of age	Died at 8 months d/t widespread metastasis.	None
Dargeon et al. (38)	28/melanoma/ skin (right leg)	CS/8 months	Male/9 months	Left facial palsy	Left EAC, mastoid, left preauricular lymph node, liver, subpleural, right adrenal, left testicle	transplacental ?	Not confirmed	Microscopic examination not done (not known)	Died at 10.5 months.	Died at 4 days post-partum	Post-mortem brain examination not performed
Sekulic et al. (39)	33/melanoma/ not reported	NM/NM	Female/5 months	Skin lesion on forehead	Skin	transplacental ?	Not confirmed	NM	Died of disease at 28 months	Died 10 months after delivery	None
Ferreira et al. (40)	33/melanoma breslow 10.7 mm/left shoulder	CS/full-term	NM/ IUFD	Multiple skin lesions	Skin	Transplacental	Placenta was involved pathologically	Placenta involved, Gross and Microscopic (villous invasion present)	NM	Died after 2 days of delivery	None

CS: Caesarean section, CT: Computer tomography, d/t: Due to, EAC: External auditory canal, FISH: Fluorescent *in-situ* hybridisation, f/b: Followed by, h/o: History of, HPE: Histopathological examination, IUFD: Intra-uterine fetal death, LSCS: Lower segment caesarean section, NAD: No abnormality detected, NM: Not mentioned, PCR: Polymerase chain reaction, VD: Vaginal delivery

Table 3. A summary of all cases of other cancers (leukaemia, lymphoma, lung cancer and cervical cancer), reported in literature with suspected or confirmed, vertical transmission

Author and year of publication	Age/type of cancer/primary site	Mode of delivery/GA at birth	Child's sex/age at diagnosis	Presenting features for the baby	Site of metastasis in the baby	Route of transmission	How was vertical transmission confirmed?	Placental histopathology, if available. (villous invasion, if present)	Outcome in the baby	Outcome in the mother	Remarks
Cramblett et al. (41)	32/ALL	VD/full term	Male/9 months	Irritable, anorexic for a few days, easy bruisability, bleeding gums, petechiae, ecchymosis and hepato-splenomegaly	Widespread	Transplacental ?	Not confirmed	Not done, because not suspected (not known)	Details not available, At last follow up, mentioned to be in partial remission	Died of disease	Transplacental transmission not confirmed
Osada et al. (42)	32/AML M5a/ presented with continuous vaginal bleeding after delivery	VD/full term	Male/20 months	1 week h/o un-explained fever, exophthalmos, gingival swelling, and pronounced hepatosplenomegaly.	NM	Transplacental transmission probable	Karyotype and Immunohistochemistry Immune adherence assay (no serological reaction between infant serum and maternal & self-leukemic cells)	Not done, because not suspected (not known)	Alive and in remission at 2 years	Alive and in remission at 3.5 years after chemotherapy and bone marrow transplantation.	karyotype of the mother's marrow cells at diagnosis was 47,XX,+8 in 55%, 47,XX,+8,t(11;12)(q23;q22) in 30%,and 46,XX in 15%.
Catlin et al. (43)	15/NK cell lymphoma/ bilateral nodular masses in the mesosalpinx	CS (fetal distress)/33 weeks	Male/4 weeks	pyrexia of unknown origin, and hepato-splenomegaly.	NM	Transplacental	Karyotype and immuno-histochemistry	Placenta involved microscopically (villous invasion present)	Died of disease at day 59 of life	Died at 20 days after delivery	The karyotype of this boy's lymphoma was female and carried the same translocation as his mother's tumor cells.
Maruko et al. (44)	29/NHL	CS (fetal distress)/ 29 weeks	Male/8 months	Till 8 months asymptomatic, developed high fever	NM	Trans-placental	FISH and Immuno-histochemistry	Placenta involved, Gross and Microscopic (villous invasion present)	Died at 9 months.	Died at 5 months post-partum	None
Yagasaki et al. (45)	32/EBV-related NK/T-cell leukaemia,	CS (fetal distress)/ 30 weeks	Male/8 months	Enlarged Scrotum, d/t a testicular tumor	NM	Transplacental ?	FISH and microsatellite analysis	Not mentioned, (not known)	Not clearly mentioned. Received Multiagent chemotherapy and cord blood transplantation	Died at 25 days post-partum d/t of hepatic failure and DIC	None
Isoda et al. (46)	28/B-cell precursor Ph + ALL	VD/40 weeks	Female/11 months	Right cheek swelling	NM	Transplacental	Loss of heterozygosity analysis, STR microsatellite analysis of the DNA	NM	NM	NM	None

Table 3. Continued

Author and year of publication	Age/type of cancer/primary site	Mode of delivery/GA at birth	Child's sex/age at diagnosis	Presenting features for the baby	Site of metastasis in the baby	Route of transmission	How was vertical transmission confirmed?	Placental histopathology, if available. (villous invasion, if present)	Outcome in the baby	Outcome in the mother	Remarks
Herskovic et al. (47)	NM/ neuroendocrine cervical cancer	Induced VD/27 weeks	NR/8 months	3 month history of persistent and occasionally bloody bilateral otorrhea	lobulated, enhancing, solid lesions of the b/l petro-mastoid temporal bones	Transplacental ??; Could be by direct inoculation/ transbronchial ??	Not confirmed	Not done. (not known)	Died at 3 years and 4 months age	Died 3 days after delivery due to metastatic disease	Could have been two separate tumours with similar histopathology
Arakawa et al. (48)	35/poorly differentiated SCC of cervix with focal neuroendocrine differentiation admixed with a minor component of adenocarcinoma	VD/39 weeks	Male/23 months	2-week history of a productive cough. Lung biopsy revealed neuroendocrine carcinoma with focal glandular differentiation	Lung f/b multiple	Aspiration of tumour cells into the lung	NGS - Both tumors had the same pathogenic mutations FISH - Tumor in the boy lacked Y chromosome. Both tumors – HPV-18 +	Not done. (not known)	Child survived	Died at 3.5 years d/t disease progression	Some tumor nodules showed Spontaneous Regression.
Arakawa et al. (48)	NM/ adenocarcinoma cervix	VD/38 weeks	Male/6 years	Chest pain on the left side. CT revealed a mass at hilar region of the left lung; On HPE- mucinous adenocarcinoma	Lung f/b multiple	Mother-to-infant vaginal transmission through aspiration of tumor-contaminated vaginal fluids during birth.	NGS and FISH WES - Additional 14 somatic mutations that were present in tumors from both the mother and the child. Both tumors – HPV-16 +	Not done. (not known)	Child survived	Died after 2 years of Radical hysterectomy	NGS- Both tumors had the same KRAS (c.G35A:p. G12D) and STK11 (c.464+1G→A) mutations.
Tolar et al. (49)	37/small-cell carcinoma of the lung	CS/33 weeks	Male/5 months	Detected on imaging	Liver and right lung	Transplacental	Placenta infiltrated with small-cell carcinoma Karyotype and FISH	Placenta involved microscopically (villous invasion not mentioned)	Child survived	Died at 5 months d/t metastatic disease.	None
Walker et al. (50)	45/poorly differentiated carcinoma of Lung Stage 4	CS (morbid maternal condition)/32 weeks	Male/2 weeks	Four rapidly growing scalp nodules	Scalp	Transplacental ?; direct implantation ?	Not confirmed	Not done. (not known)	Child survived	Died.	None
Teksam et al. (51)	37/small-cell carcinoma of the lung	CS (fetal distress)/ 33 weeks	NM/5 months	lung nodules on imaging, hypermetabolic on PET scan	lung, liver, brain	Transplacental	Not confirmed, assumed because placenta was involved	Placenta involved microscopically (villous invasion not mentioned)	Died at 23 months	Died at 5 months d/t metastatic disease.	None

AML: Acute myelogenous leukemia, b/l: Bilateral, CS: Caesarean section, CT: Computer tomography, DIC: Disseminated intravascular coagulation, d/t: Due to, EBV: Epstein barr virus, FISH: Fluorescent *in-situ* hybridisation; f/b: Followed by, HPE: Histopathological examination, HPV: Human papilloma virus, NGS: Next generation sequencing, NHL: Non-hodgkin lymphoma, NK: Natural killer, NM: Not mentioned, SCC: Squamous cell carcinoma, STR: Short tandem repeat, VD: Vaginal delivery, WES: Whole exome sequencing

Mechanisms of transplacental cancer transmission, engraftment and survival

Unlike vertical transmission of infectious agents, cancer cells typically cannot cross the placental barrier due to robust immune surveillance and the placental membrane's selective permeability (Figure 2). However, certain conditions can allow this rare transmission, leading to significant clinical and research implications. Several hypotheses explain how cancer cells might breach the placental barrier and establish themselves in the fetus (Figure 3) including the following.

Immune tolerance

In pregnancy, immune tolerance, the immune system's ability to recognize and not attack the own body's cells, is critical (53). The mother's immune system must tolerate the fetus, which expresses maternal and paternal antigens, to avoid attacking it as foreign tissue. This tolerance is mediated by

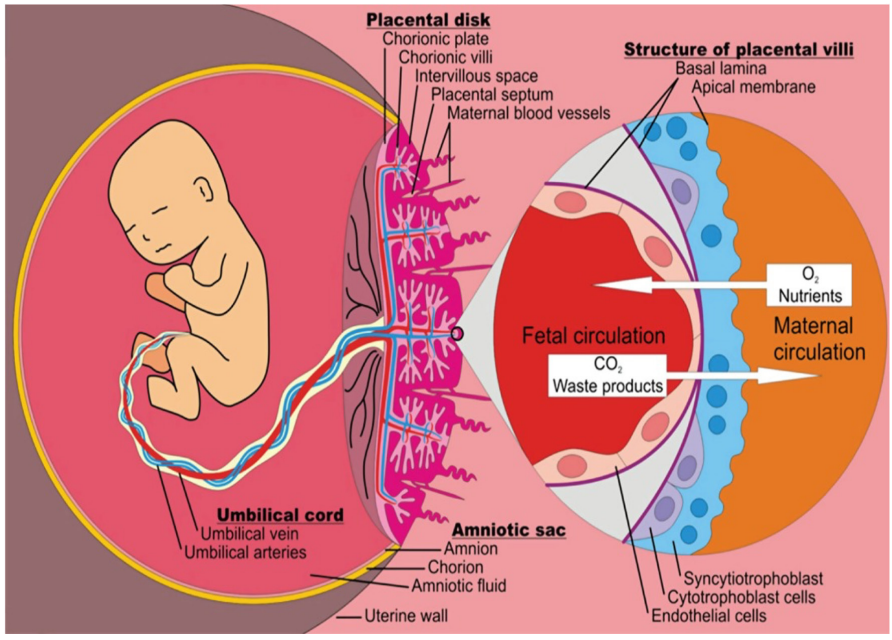

Figure 2. Diagrammatic illustration of the placental membrane that separates fetal and maternal circulations in the human placenta. (Image courtesy of Prof. Christiane Albrecht, University of Bern. All rights and permissions to use this figure are owned by her. Reproduced with permission)

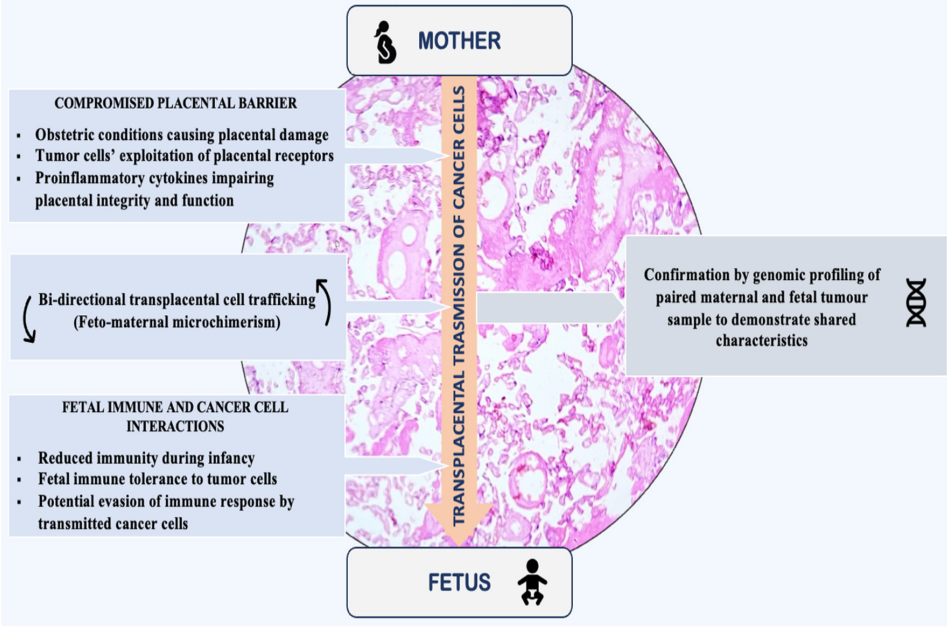

Figure 3. Various mechanisms of vertical transmission of cancer

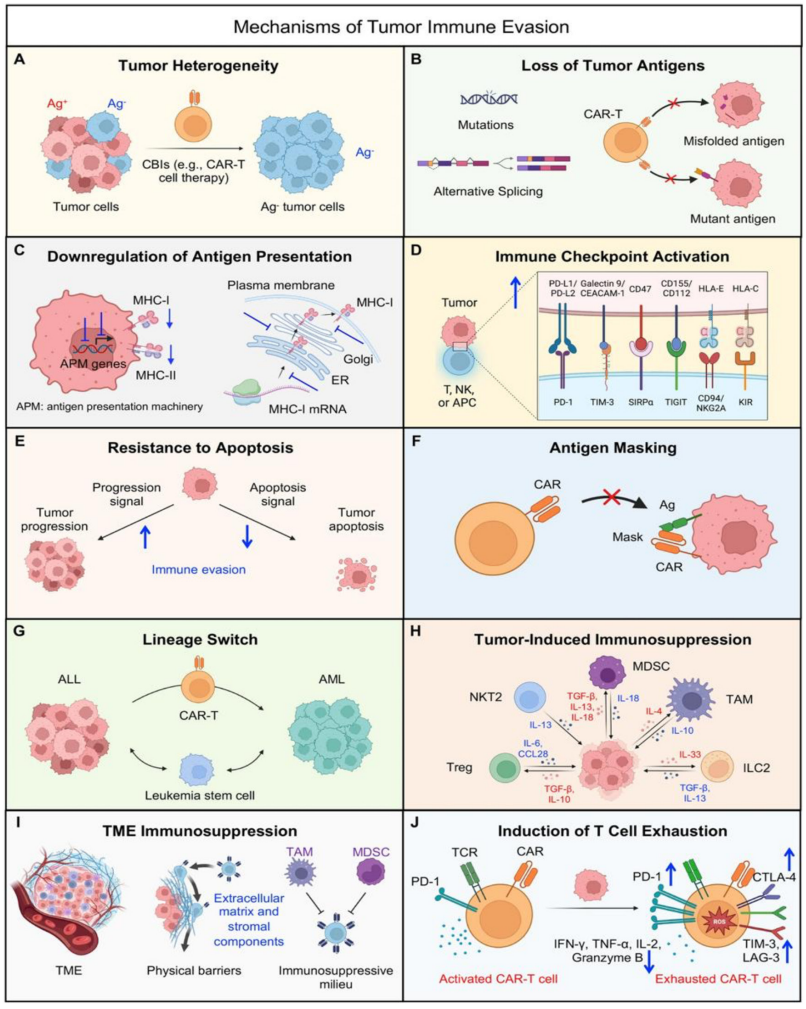

Figure 4. Mechanisms of tumor immune evasion. Tumor cells employ a diverse array of immune evasion mechanisms that curtail the effectiveness of cell-based immunotherapies, such as CAR-T cell therapies. These multifaceted strategies encompass tumor heterogeneity (A), tumor antigen loss (B), antigen presentation downregulation (C), immune checkpoint activation (D), apoptosis resistance (E), antigen masking (F), tumor lineage switch (G), tumor-induced immunosuppression (H), tumor microenvironment (TME) immunosuppression (I), and induction of T cell exhaustion (J) [Reproduced from Li YR, Halladay T, Yang L. Immune evasion in cell-based immunotherapy: unraveling challenges and novel strategies. J Biomed Sci. 2024;31(1):5. doi: 10.1186/s12929-024-00998-8]

various mechanisms, including the action of regulatory T cells, placental hormones, and other immunomodulatory factors that help maintain a healthy pregnancy (54).

Vertical cancer cell transmission occurs during the perinatal period, a time when the fetus is still developing immunity. Thymic development begins around week 8 of human gestation, and initial fetal T cells populate the periphery by weeks 12-14 of gestation (55). If cancer cells are transmitted before this period, they may not be recognized as foreign antigens, potentially evading an immune response, resulting in their engraftment or growth. Moreover, maintaining pregnancy requires tolerance to self-in and non-inherited maternal antigens, primarily regulated by regulatory T cells. Intrauterine hypoxia or placental hormones may influence maternal tolerance by modulating T-cell function. Taken together, fetal immune immaturity/tolerance could play a role in facilitating the engraftment and survival of maternal-derived cancer cells within the body. However, the specific mechanistic evidence for fetal cancer immune tolerance remains to be demonstrated conclusively (56-60).

Bi-directional transplacental cell trafficking (feto-maternal micro-chimerism)

It is well-documented that normal blood cells migrate between mother and fetus and *vice versa*, leading to micro chimerism. Micro-chimerism refers to a small population of cells originating

from another individual, making them genetically distinct from the host individual's cells (61,62). During pregnancy, there are two types of feto-maternal micro-chimerism: fetal micro-chimerism (FMc) and maternal micro-chimerism (MMc). FMc occurs when fetal cells persist in maternal tissues, while MMc involves the presence and maintenance of maternal cells in fetal tissues (63-65). It is, therefore, quite plausible that maternal cancer cells can sometimes take advantage of this mechanism of micro chimerism, leading to carcinogenesis in the infant (1).

Immune evasion: How cancer cells escape immunity

Cancer cells can escape the immune system through various mechanisms, enabling them to survive, proliferate, and spread within the body (Figure 4) (66). Tumour cells gradually develop mechanisms to evade immune surveillance, a process known as "cancer immunoediting," to avoid elimination by immune cells with antitumor properties. Cancer cells can exploit immune checkpoints, regulatory pathways in the immune system that prevent excessive immune responses. For instance, they may overexpress proteins like PD-L1 (Programmed Death-Ligand 1), which binds to PD-1 receptors on T cells, leading to T cell inactivation and immune evasion (67,68). Tumor microenvironment might further dampen the immune response by recruitment of regulatory T cells (Tregs) and myeloid-derived suppressor cells that inhibit other immune cells and elaboration of immunosuppressive cytokines like transforming growth factor-beta and interleukin 10 (IL-10).

Tumor cells can downregulate the expression of major histocompatibility complex molecules on their surface, essential for presenting tumor antigens to T cells (69). This prevents the immune system from recognizing and attacking the cancer cells. Immune evasion through the loss of heterozygosity of *HLA* genes has also been proposed (70). Loss or mutation of molecules involved in the antigen-processing machinery can also impair antigen presentation. Cancer cells can develop resistance to apoptosis, which allows them to survive despite immune attacks (71). Cancer cells can secrete various substances that inhibit immune cell function, such as indoleamine 2,3-dioxygenase, which depletes tryptophan and suppresses T-cell activity.

Placental microscopic trauma

Trophoblasts, chorionic villi, and capillary endothelium separate the fetal and maternal circulations (Figure 2). Along with the fetal immune system, the placental barrier prevents the spread and allografting of maternal tumors into the fetus. Despite this protection, the transmission of neoplastic and non-neoplastic maternal cells to the fetus does occur during pregnancy. Suppose the separation between the fetal and maternal blood systems is breached, maternal intravascular tumour cells can cross the placenta and reach the fetal liver through the umbilical vein or the fetal lungs via the ductus venosus (49).

Several obstetric conditions can cause microscopic damage to the placenta, affecting its structure and function. Preeclampsia and placental fetal growth restriction can lead to placental infarcts, intervillous fibrin deposition, and increased syncytial knots, resulting in reduced placental perfusion and placental insufficiency. Gestational diabetes leads to villous immaturity, and villous hyperplasia. There can also be increased deposition of glycogen in the placental tissue. Placental abruption can cause haemorrhage into the placental tissue, leading to infarcts, necrosis, and fibrin deposition. Maternal infections, such as chorioamnionitis, may cause inflammatory changes in the placenta, including villitis and funisitis, leading to damage and sometimes necrosis of the placental tissue. Each of these conditions may compromise placental ability to effectively control cell and nutrient traffic across the placental membrane, potentially leading to adverse pregnancy outcomes (49,50).

Placental receptor similarity and reduced placental function

Tumor cells may exploit receptors on placental cells to gain entry into fetal circulation, mimicking the way nutrients and other substances pass through. Also, given the similarities between tumor cells and trophoblastic cells in biological processes, there is substantial evidence that maternal tumour-induced effects could impact placental function (72). Studies have indicated that the presence of maternal cancer or certain tumor factors, such as proinflammatory cytokines IL-6, interferon-gamma (IFN-γ), and tumour necrosis factor, can impair the placental integrity and function (73,74). These factors may play a role in the vertical transfer of cancer clones. However, more research is needed on how the damage caused by cancer cells in the placenta facilitates transplacental cancer spread.

Diagnostic confirmation of vertical transmission

Modern genetic tools, such as DNA sequencing and genomic profiling, can compare the genetic material of maternal and fetal tumors, providing concrete evidence of the origin of the cancer. Next-generation sequencing (NGS) can be used to look for mutations in the tumor that are present in the maternal DNA but absent in the patient's germline DNA, which can help determine if the cancer was inherited from the mother. Since mitochondrial DNA (mtDNA) is inherited maternally, analyzing mtDNA from the tumor and comparing it to the maternal mtDNA can provide additional clues. SNP arrays can be used to compare genetic variations between the tumor, patient's germline or maternal DNA, which can further help identify the source of the cancer (75-77).

Most of the studies have used karyotyping or fluorescent *in situ* hybridisation (FISH) techniques, as the absence of Y

chromosome in the cancer tissue, in a male fetus, provides indirect evidence that the tumor originated from the mother. Involvement of placenta by the tumor, on gross and microscopic examination, particularly the presence of villous invasion, also implies that the transmission occurred through the placenta. Arakawa et al. (48) recently reported two intriguing cases of perinatal transmission of maternal cervical cancer to the infant, subsequently developing into lung cancer. FISH analysis revealed the absence of the Y chromosome in tumor in the male babies and upon sequencing, both the tumors in the mothers and babies showed shared genomic tumor characteristics, which substantiates mother-to-infant vaginal transmission through aspiration of tumor cell-contaminated vaginal fluids during birth.

Treatment considerations: Why is an understanding of transplacental cancer transmission essential?

Clinicians must distinguish whether the tumor in the newborn is a primary disease or a metastasis from the mother as treatment protocols differ drastically between congenital cancers and those acquired through transmission. Vertical transmission of metastases could be viewed as a "haploidentical transplant" (78). In this scenario, the newborn's already functional immune system might reject non-inherited maternal antigens. Consequently, administering modified or reduced therapeutic regimens could be justified, allowing the newborn's immune system time to develop effective responses. The possibility of transplacental cancer transmission also brings forth ethical dilemmas. Decisions regarding the continuation of pregnancy, the timing of delivery, and the treatment options for both mother and child are complex and emotionally charged. Counselling and psychological support for affected families are critical components of care.

Due to the rarity of infant melanoma, infants and children have not been included in the majority of clinical trials for treatment, resulting in a lack of specialized treatment standards for this population. Consequently, current treatment strategies for melanoma in this age group are derived from adult treatment protocols. Surgery remains the primary treatment for melanoma in both children and adults. For pediatric patients with more advanced disease, biologic therapies are more commonly used than chemotherapy or radiation therapy (79). Since *BRAF* mutations are present in approximately 50% of melanoma patients, BRAF inhibitors like Vemurafenib and Dabrafenib, and other specific inhibitors like Trametinib, which targets other components of the MAPK signal transduction pathway, such as MEK1 and MEK2, provide an effective therapeutic option for patients with this mutation. Another treatment approach involves modulating the host's immune system to target melanoma. Immunotherapy drugs, such as Ipilimumab, use monoclonal antibodies to suppress CTLA-4, enhancing the immune system's response to tumor cells. Agents like IL-2 activate the immune system to attack malignant cells. High-dose interferon alfa-2b has shown promising results in children with melanoma with an acceptable risk-benefit profile. In addition, anti-PD1 antibodies, such as Pembrolizumab and Nivolumab, have the potential to improve prognosis with long-lasting effects (80,81). One such case with successful treatment with nivolumab therapy has been reported by Arakawa et al (48).

As with other germ cell tumors, the management of choriocarcinoma in infants and children involves a comprehensive approach with multi-agent neoadjuvant chemotherapy, reassessment after 2-4 cycles, surgical removal of persistent disease, and adjuvant chemotherapy. This complex therapy aims to control the metastatic nature of the disease and prevent relapse. Upfront chemotherapy is particularly crucial for children with multi-systemic involvement who are not candidates for immediate surgery. The excellent survival rates observed in this review reinforce the effectiveness of these treatment principles, which are well-established and readily available (82,83). In most current protocols, treatment is stratified based on an initial risk assessment that includes age, site, histology, stage, completeness of resection, and tumor markers alpha1-fetoprotein and human chorionic gonadotropin (β-HCG). Using these modern protocols, overall cure rates exceed 80%. Moreover, previously high-risk groups can now expect a favourable prognosis with risk-adapted treatment, while an increasing number of low-risk patients are managed expectantly or with significantly reduced chemotherapy (82).

Conclusion

Transplacental transmission of cancer, while rare, poses significant medical and ethical challenges. It underscores the complexity of the placental barrier and the interactions between maternal and fetal health. Advances in genetic diagnostics and a deeper understanding of immune mechanisms hold promise for better management and outcomes for both mothers and their children. NGS of paired tumors (both mother and baby) and normal tissue samples might be a valuable method for diagnosing cancer transmitted from mothers to infants and for understanding how common this transmission is. Furthermore, analysing the HLA haplotype of cancer cells and peripheral normal lymphocytes may offer insights into the risk of maternal-to-fetus transmission. Continued research and interdisciplinary collaboration are essential in unravelling the mysteries of this unique cancer transmission pathway.

Footnotes

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