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Review

Placental pathology in cancer during pregnancy and after cancer treatment exposure

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ABSTRACT

Cancer during pregnancy has been associated with (pathologically) small for gestational age offspring, especially after exposure to chemotherapy in utero. These infants are most likely growth restricted, but sonographic results are often lacking. In view of the paucity of data on underlying pathophysiological mechanisms, the objective was to summarize all studies investigating placental pathology related to cancer(treatment). A systematic search in PubMed/Medline, Embase (OVID) and SCOPUS was conducted to retrieve all studies about placental pathology in cancer during pregnancy or after cancer treatment, published until August 2020. The literature search yielded 5784 unique publications, of which 111 were eligible for inclusion. Among them, three groups of placental pathology were distinguished. First, various histopathologic changes including maternal vascular malperfusion have been reported in pregnancies complicated by cancer and after cancer treatment exposure, which were not specific to type of cancer(treatment). Second, cancer(treatment) has been associated with placental cellular pathology including increased oxidative damage and apoptosis, impaired angiogenesis and genotoxicity. Finally, involvement of the placenta by cancer cells has been described, involving both the intervillous space and rarely villous invasion, with such fetuses are at risk of having metastases. In conclusion, growth restriction is often observed in pregnancies complicated by cancer and its cause can be multifactorial. Placental histopathologic changes, cellular pathology and genotoxicity caused by the cancer(treatment) may each play a role.

1. Introduction: cancer during pregnancy and placental involvement

Cancer is the second leading cause of death during the female reproductive years and is diagnosed in 1–2 per 1000 pregnant women [1]. Cancer incidence increases with age and as women in developed countries delay childbearing the incidence of cancer during pregnancy increases [2]. In addition, noninvasive prenatal testing with the ability to detect preclinical cancer is expected to further contribute to increasing incidences [3]. Results from large-scale studies show reassuring obstetric and short-term neonatal outcomes in offspring exposed to cancer treatment during pregnancy [4–6]. Knowledge about the occurrence of cancer during pregnancy and the possibility of treatment during pregnancy is increasing. Management strategies have changed accordingly: fewer pregnancies are terminated and fewer deliveries are prematurely induced to initiate maternal cancer treatment [4]. Consequently, more women are treated for cancer during pregnancy nowadays [4]. Timing of treatment, prematurity and fetal exposure require a balanced consideration. Offspring exposed to chemotherapy during pregnancy are born small for gestational age (SGA) more often (7%–28%) compared to unexposed controls (8.6%) [4,7–10], especially after exposure to platinum-based chemotherapy [4]. Which pathological

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processes underlie this growth restriction is unclear [11].

Although there is an important difference between SGA and fetal growth restriction (FGR), these terms are often used interchangeably. SGA is frequently used as proxy for FGR as it is known that the lower the size for gestational age (GA) the higher the chance of FGR [12]. However, as SGA is defined as an estimated fetal weight (EFW) or birthweight corrected for GA below the 10th percentile (<p10), it covers constitutionally small fetuses and growth restricted fetuses. In contrast to constitutionally small offspring, offspring with FGR has an increased risk of perinatal morbidity and mortality due to preterm birth, neonatal hypothermia or hypoglycemia [13]. They also have an increased risk of cardiovascular and metabolic diseases later in life [14]. It is likely that in pregnant women treated with chemotherapy, SGA fetuses are growth restricted and not constitutionally small. The definition of FGR is adjusted to a combination of low EFW or decline in growth percentile and abnormal Doppler result, allowing fetuses with seemingly normal size to be diagnosed with FGR, as their intrinsic growth percentile was higher [15]. Ultrasound results are often not reported in literature and therefore SGA is the only available definition to use as proxy for FGR in this review.

FGR is often related to placental dysfunction, with subsequent deficient placental nutrient and oxygen supply to the fetus [13,16,17]. Whether placental dysfunction after antenatal cancer treatment has similar features as in women without cancer remains unknown. This is difficult to study in pregnant women with cancer because of the rarity and heterogeneity of this population. Hence, literature about cancer treatment-related placental pathology is scarce. Due to the low incidence and use of multi-agent treatments, animal and in vitro studies have been performed to evaluate specific cancer treatment-related effects on the placenta [18–20].

Besides placental dysfunction, the placenta can be involved because of the presence of circulating tumor cells or metastases in the placenta. This placental involvement is rare, but is documented in the context of a broad variety of malignancies. Placental examination in pregnancies complicated by cancer is not always performed, but placental involvement can be the first sign of fetal metastasis with a very poor prognosis [21–23].

In this review, we provide an overview of published literature about placental pathology in pregnancies complicated by cancer and following cancer treatment. We categorize the studies evaluating placental histopathologic changes, placental cellular pathology and related intervention studies, placental genotoxicity and outcomes of pregnancies complicated by involvement of the placenta by maternal cancer.

2. Methods

2.1. Search strategy (see supplementary material)

2.1.1. Clinical definitions

To maintain consistency, the term SGA was used for all offspring born small for GA, independent of co-existent placental disease. Crude birthweight percentiles were calculated using reference curves for all birthweights mentioned in the summarized literature to obtain uniformity [24]. A birthweight < p10 was considered SGA, between p10-90 appropriate for GA (AGA), and >p90 large for GA (LGA).

2.1.2. Placental definitions

Placenta weights < p10 were defined as SGA, between p10-90 as AGA, and >p90 as LGA. Unless explicitly defined as SGA, AGA or LGA by the authors of the original paper, percentiles were calculated using reference curves [25] and classified accordingly.

To compare placental lesions between different studies, we used the criteria as published by Amsterdam Placental Workshop Group (i.e. maternal vascular malperfusion, fetal vascular malperfusion, acute inflammatory lesion, delayed villous maturation, villitis (of unknown etiology), and other lesions) to classify the described macro- and microscopic placental lesions [26].

Placental involvement by maternal cancer cells or metastases was defined as any macroscopic or microscopic evidence of maternal histologically proven cancer (excluding gestational trophoblastic disease) during that particular pregnancy, within any part of the placenta. Evidence of maternal cancer within the tissues of the offspring without evidence of a primary fetal cancer was considered a fetal metastasis.

2.1.3. Statistical analysis

The different types of placental involvement were presented using descriptive analyses of oncological, obstetric, and neonatal characteristics. Data are expressed as n (%) or mean ± standard deviation. Comparison of maternal survival between the different types of placental involvement was performed using the Kaplan Meier Method. A p-value <0.05 was considered statistically significant.

3. Results

The flowchart depicting the inclusion process is presented in [Fig. 1]. After duplicate removal, 5784 articles were screened on title and abstract. Full-text eligibility assessment of 205 articles resulted in 111 unique publications. These were subdivided in three groups of placental pathology: 1) studies reporting on histopathologic lesions, placental cellular pathology, and related intervention studies in pregnancies complicated by cancer or after cancer treatment exposure, 2) cancer treatment-induced genotoxicity, and 3) direct placental involvement of maternal cancer [Fig. 2].

Included clinical studies were limited in sample size (range 1–25) and concerned heterogeneous groups with regard to cancer and treatment type. In addition, nine animal and two in vitro studies were included in which cancer (treatment)-specific effects were addressed.

3.1. Placental histopathologic changes other than metastatic disease

3.1.1. Histopathology in placentas from women with cancer during pregnancy

Eleven studies focused on the histopathology of placentas of women with cancer with and without the co-existing influence of cancer treatment exposure [Table 1]. Maternal vascular malperfusion leading to a disturbed utero-placental flow is most frequently observed in cancer (treatment)-exposed placentas leading to distal villous hypoplasia in more severe cases. Also fetal vascular malperfusion (e.g., umbilical or chorionic plate vessel thrombosis) and inflammatory lesions causing suboptimal exchange of nutrients, oxygen and waste products are reported.

3.1.2. Maternal primary non-hematological cancers

Three studies described the histopathology of placentas from women with non-hematological cancers (e.g. breast cancer, ovarian cancer, cervical cancer, and rhabdomyosarcoma), apart from placental involvement of maternal cancer [27–29]. Women were treated with chemotherapy and two received tamoxifen for a recurrence of cancer diagnosed before pregnancy [Table 1]. Although the number of patients per treatment type are low and placental weight was not always mentioned, SGA placentas occurred frequently. Described microscopic placental lesions were various and not specific to cancer(treatment) type (or dose), and included maternal and fetal vascular malperfusion, villitis (of unknown etiology), inflammatory responses and delayed villous maturation. The placenta from a woman with rhabdomyosarcoma who received oxaliplatin, vinoreline and irinotecan throughout pregnancy showed distinct hyperpolyploidization, characterised by cells with more than two sets of chromosomes, in the extravillous trophoblast [27]. The infant was born AGA, but with congenital anomalies including cleft palate, tracheoesophageal fistula, and esophageal atresia, whether this was a result of a preexistent chromosomal abnormality or related to chemotherapy exposure remains unknown [27]. With this case a

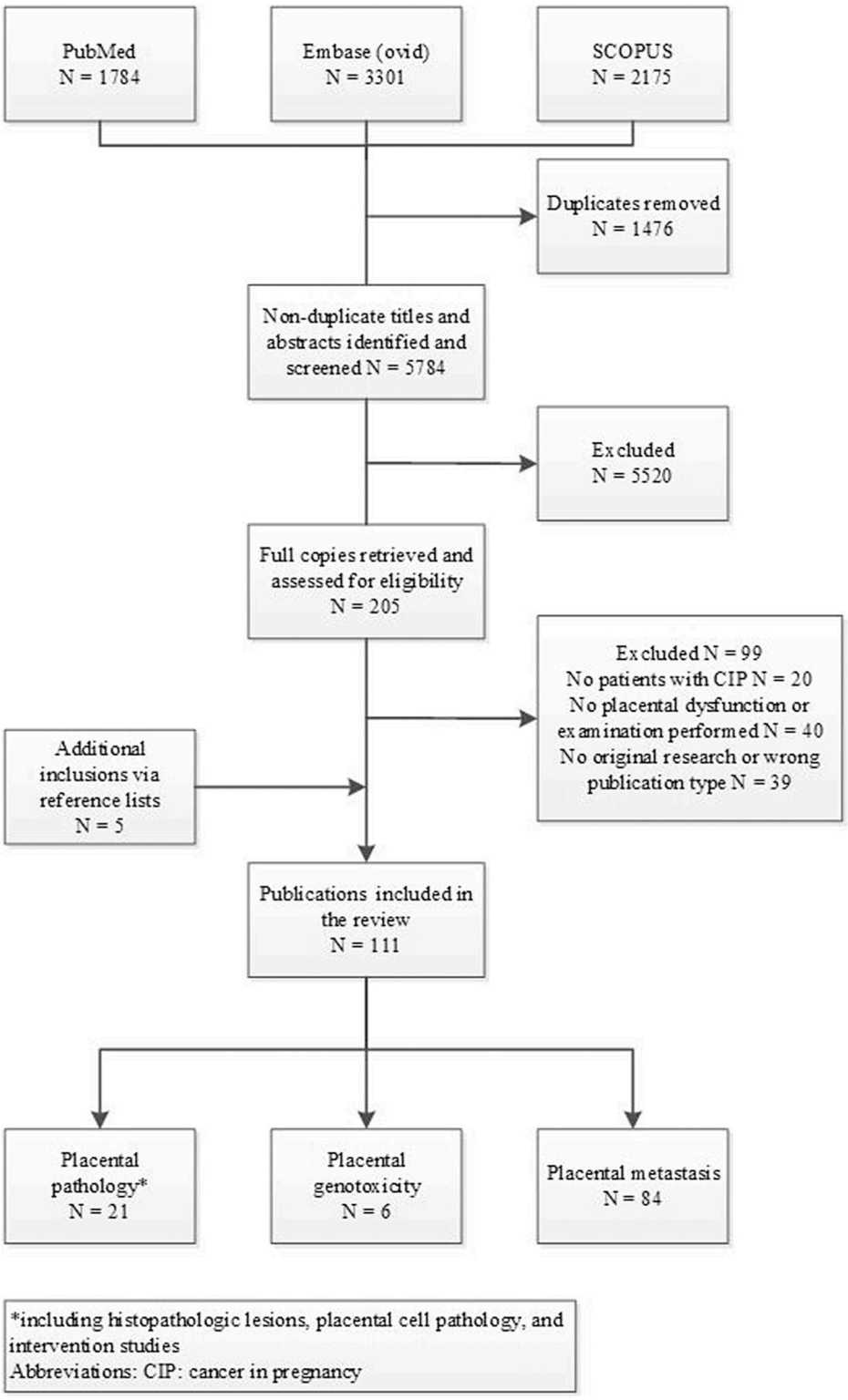

Fig. 1. Study selection process.

hypothetic association of early chemotherapy exposure (<2nd trimester) and placental pathology was formulated, but further studies are needed for confirmation. Polyploidization or genome multiplication is common to a lesser extent in highly differentiated tissues such as the placenta and believed to be part of the process of maintaining pregnancy. However, hyperpolyploidization might be a sign of adaptive response to treatment of which the underlying mechanism is still unclear. A greater degree of polyploidy was also seen in the placentas of women exposed to chemotherapy during the second and third trimester (18%) compared to controls (12%) [27]. SGA occurred in up to 60% of the offspring of women with non-hematological cancers, but no other (congenital) abnormalities were diagnosed [Table 1].

3.1.3. *Maternal primary hematological cancers*

Essential thrombocythemia (ET), a myeloproliferative neoplasm often considered malignant due to unrestrained cell proliferation, is

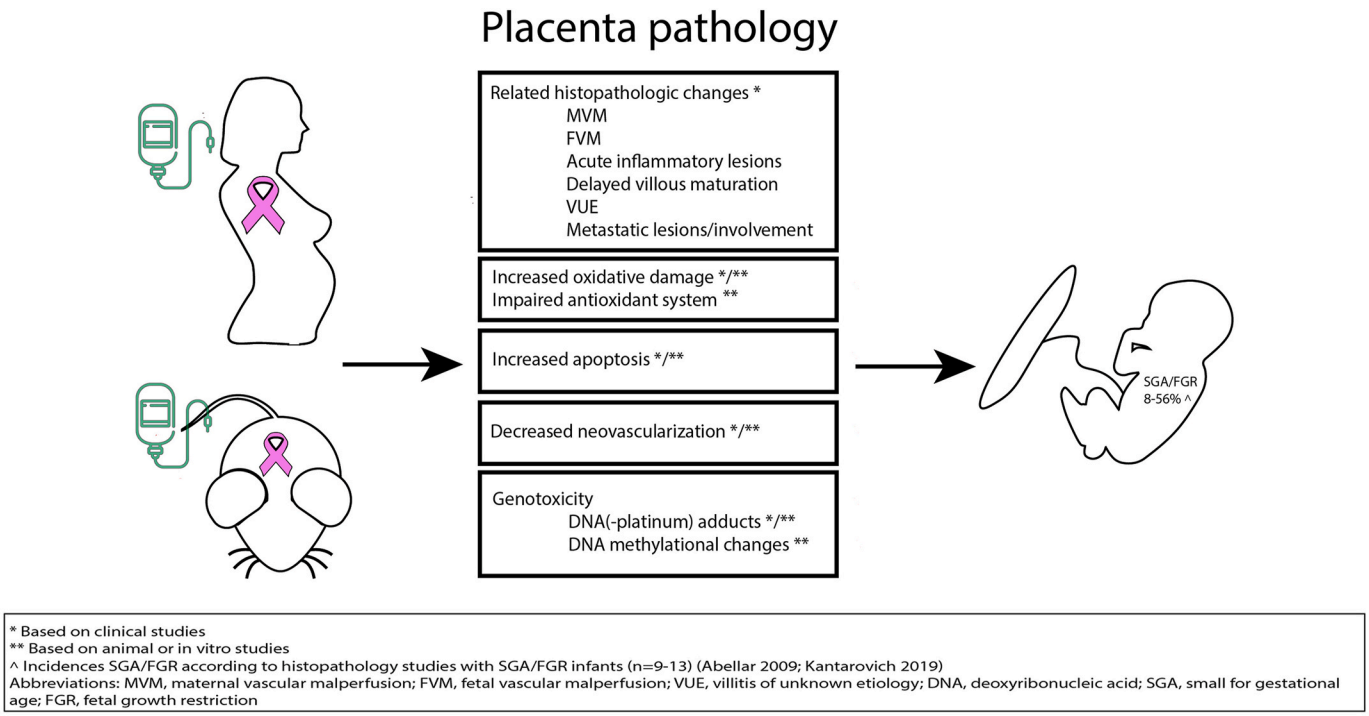

Fig. 2. A summary of placental pathologies observed in pregnancies complicated by cancer(treatment) potentially inducing SGA/FGR.

associated with recurrent miscarriages and SGA [30]. In these patients with high thrombogenic risk, placental pathophysiology shows maternal vascular malperfusion. In one case series of 40 pregnancies in 16 women with ET [31], 25 pregnancies ended in live birth (62%), and 24 infants were born AGA. Only two histology reports are available of these cases, describing placentas from pregnancies ending in intrauterine fetal death revealing multiple infarctions in one [Table 1].

Another article reports a case of a pregnant woman with untreated ET who developed preeclampsia and FGR at 34 weeks of gestation in which the placenta showed diffuse infarction (>15%) and increased syncytial knots, characteristic of maternal vascular malperfusion [32]. In a study of 14 women (27 pregnancies) with myeloproliferative neoplasms (9 ET, 5 polycythemia vera), most (93%) were treated during pregnancy with low-dose acetylsalicylic acid, low molecular weight heparin (LMWH) and/or interferon [33]. Only 8/27 (30%) had no obstetric complications. Seven pregnancies presented with SGA (15%) and/or abnormal uterine artery Dopplers (22%), indicating a potential utero-placental dysfunction. From only three pregnancies placental histology was described, revealing signs of maternal vascular malperfusion. These placentas were from two patients who also developed hypertensive disorders (preeclampsia, HELLP) and one also had FGR with abnormal Dopplers.

In three case reports, other hematological cancers (acute lymphatic leukemia (n = 2) and natural-killer-cell lymphoma (n = 1) without cancer treatment [34–36] were described [Table 1]. Only one of these placentas was SGA, but this pregnancy was also complicated by maternal HELLP syndrome and a SGA infant diagnosed with metastatic disease of the maternal lymphoma [34]. Two of the three placentas showed signs of maternal vascular malperfusion, without other microscopic lesions.

3.1.3.1. Cancer treatment-induced histopathologic placental changes. Cancer treatment-induced histopathologic placental changes in hematological cancers have been evaluated in four small clinical studies [27,29,37,38] [Table 1]. Inclusions ranged from 1 to 13 pregnancies without matched controls or information on dose-effects. The two relatively larger studies describe SGA placentas in 1/4 (after cyclophosphamide, vincristine, and doxorubicin exposure) and 2/4 (methotrexate exposure) of the women [27,29]. As vincristine acts through cell cycle arrest and methotrexate chelates folic acid, essential for cell division, this is not unexpected. Non-specific placental lesions, mostly maternal vascular malperfusion lesions, but also inflammatory lesions were seen.

Two other case reports of women with non-Hodgkin lymphoma treated with R–CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab) and chronic myeloid leukemia (CML) treated with interferon alpha [37,38] describe placental inflammatory lesions secondary to a suspected ascending uterine infection. An inadequate functioning immunological system due to the pregnancy, disease or treatment may have contributed to this inflammation [38]. However, further studies are needed to investigate cancer(treatment)-related impairment of the maternal immune system, potentially causing materno-fetal immunological disarray.

With the currently available literature, no definitive conclusions can be drawn with regard to specific treatment-related placental lesions. However, the lesions observed in the pregnant cancer population are also reported in association with SGA in the general population.

3.1.4. The effect of cancer(treatment) on placental histopathology in animal and in vitro studies

In clinical studies, it is often difficult to disentangle effects of cancer treatment from confounding factors such as the cancer itself, and the physical and nutritional status of the patient. Animal studies and in vitro experiments can be used to evaluate the solitary impact of a certain cancer(treatment). Four animal studies have been performed to evaluate cancer (n = 2) and (dose-independent) treatment effects (n = 2; imatinib and irradiation respectively) on placental histopathology [20,39–41]. To evaluate the independent effect of cancer, 'Walker 256 carcinosarcoma cells' were used in pregnant rats. A significant lower fetal and placental weight was observed in animals with cancer [20]. Placentas from rats with cancer showed hemorrhage in the labyrinth layer [20]. As the labyrinth is the main site of nutrient exchange, disturbances can underlie FGR; additional lesions suggestive of utero-placental or placenta-fetal flow disturbance were not reported. Another study reported a non-significant difference in placental weights between animals

Table 1
Placental histopathology results in clinical studies (n = 11).

Study	N	Cancer type(s)	Cancer treatment (s)	GA (wks)	Placenta weight	Maternal vascular malperfusion	Fetal vascular malperfusion	(acute) Inflammatory lesions	Delayed villous maturation	VUE	Other lesions	Fetal outcome
Abellar (‘09)	13	breast (3), ovary (2), cervix (2), salivary gland (1), rhabdomyosarcoma (1), lymphoma/ leukemia (4)	various	25–41	4/13 SGA	accelerated villous maturation (CIS+5FU, CIS + AC, oxaliplatin, vinoreline and irinotecan, AC + vincristine); accelerated villous maturation + distal villous hypoplasia (AC, plat, vinblastine, imatinib)	thrombus (unknown location) (plat, imatinib)	acute chorioamnionitis/ vasculitis(/funisitis) (CIS + AC, imatinib); subchorionitis (plat)	delayed villous maturation (AC)	n.r.	vacuolization and nuclear pleomorphism, extravillous trophoblast of chorion leave (oxaliplatin, vinoreline and irinotecan)	1/13 FGR (plat); oxaliplatin, vinoreline and irinotecan: cleft palate and TEF
Catlin (‘99)	1	natural-killer-cell lymphoma (1)	none	33	SGA	maternal vascular malperfusion (single infarction)	n.r.	n.r.	n.r.	n.r.	metastatic lesions within decidua and blood vessels of chorionic villi (in situ hybridization)	BW 1.6 kg (p3[a]). HELLP. Diagnosed with lymphoma at 1 month treated with interferon α. Died at 2 months due to side effects.
Chen (‘15)	1	Non-Hodgkin lymphoma	R–CHOP (1 day)	25	n.r.	maternal vascular malperfusion (infarction, unknown %)	n.r.	n.r.	n.r.	n.r.	extensive micro deposits of diffuse large B-cell lymphoma within the basal plate	Rupture of membranes+ IUFD 1 day after initiating R–CHOP
Del Gobbo (‘20)	23	breast (23)	EC or EPI	34–38	n.r.	20/23 accelerated villous maturation (n.s. compared to controls)	n.r.	n.r.	n.r.	n.r.	1/23 chorangioma	No FGR, no uneventful outcomes, perinatal mortality or malformations.
Falconer (‘87)	1	essential thrombocythemia	none	34	n.r.	accelerated villous maturation and >15% infarction	n.r.	n.r.	n.r.	n.r.	n.r.	FGR (<p3[a]) (PE)
Kantarovich (‘19)	9	cervical (3), breast (2), leukemia (3), Hodgkin lymphoma (1)	5FU, tamoxifen or MTX	31–38	5/9 SGA	no differences between SGA/AGA groups with regard to MVM	no differences between SGA/ AGA groups with regard to FVM	n.r.	n.r.	patchy high grade VUE (5-FU); diffuse high grade VUE (MTX) Negative viral/ bacterial cultures	massive intervillositis (>50%) (tamoxifen)	5/9 FGR, no increased incidence of infections compared to unexposed children, no abnormal growth curves and/or neurocognitive disorders.
Lapoirie (‘18)	3	essential thrombocythemia (2), polycythemia vera (1)	none (or IFN α)	1/3 stillbirth; 2/3 premature birth	n.r.	3/3 multiple infarctions incl 1/3 preterm (=MVM); 1/3 retroplacental hematoma	n.r.	n.r.	n.r.	n.r.	n.r.	1/3 abruptio placentae and stillbirth; 1/3 premature birth (HELLP); 1/3 FGR (PE + HELLP)
Niittyvuopio (‘04)	2	essential thrombocythemia (2)	none	22–28	n.r.	multiple infarctions (caused by maternal disease?) (28w IUFD)	n.r.	n.r.	n.r.	n.r.	n.r.	2 IUFDs at respectively 22 and 28w

(*continued on next page*)

Table 1 (*continued*)

Study	N	Cancer type(s)	Cancer treatment (s)	GA (wks)	Placenta weight	Maternal vascular malperfusion	Fetal vascular malperfusion	(acute) Inflammatory lesions	Delayed villous maturation	VUE	Other lesions	Fetal outcome
Nummi ('73)	1	acute lymphatic leukemia (1)	none	30	AGA	n.r.	n.r.	n.r.	n.r.	n.r.	Intervillous metastatic lesions (aggregates of immature lymphocytes)	BW 1,3 kg (p11[a]). No evidence of disease at 3 years of age.
Staley ('18)	1	chronic myeloid leukemia (1)	(IFN α)	37,6	n.r.	not observed	n.r.	acute subchorionitis and chorionic vasculitis	n.r.	n.r.	n.r.	BW 3,0 kg (p37[a]). No congenital anomalies.
Wang ('83)	1	acute lymphatic leukemia (1)	none	35	AGA	accelerated villous maturation	n.r.	n.r.	n.r.	n.r.	n.r.	BW 2,5 kg (p56[a]). No evidence of hematological disease.

Abbreviations: AC: adriamycine-cyclophosphamide; AGA: appropriate for gestational age; BW: birthweight; CIS: cisplatin; EC: epirubicin-cyclophosphamide; EPI: epirubicin; FGR: fetal growth restriction; FVM: fetal vascular malperfusion; HELLP: hemolysis elevated liver enzymes low platelets syndrome; IFN: interferon; IUFD: intrauterine fetal demise; LMWH: low molecular weight heparin; MTX: (deoxycoformycin) methotrexate; MVM: maternal vascular malperfusion; PE: preeclampsia; Plat: platinum agents; pts: patients; R–CHOP: doxorubicine, cyclophosphamide, vincristine and rituximab; SGA: small for gestational age; TEF: tracheoesophageal fistula; trim: trimester; VUE: villitis of unknown etiology; 5FU: 5-fluoro-uracil; n.s.: not significant; n.r.: not reported.

[a] Birth weight percentile according to Hoftiezer [24].

with cancer and controls [39].

The effect of imatinib, a tyrosine kinase inhibitor (TKI) mainly used to treat CML, was evaluated in murine placentas [41]. Mice treated with imatinib before conception or during pregnancy showed a significant decreased surface of the placental implantation side compared to untreated controls. This effect was particularly evident in the labyrinth layer [41].

Irradiation is known to cause vascular damage and thus during pregnancy would also be expected to lead to maternal vascular malperfusion. Only one study has evaluated the impact of irradiation on placental histology in mice [40]. A single dose of irradiation (4 Gy; dose rate of 70 cGy/min) on gestational day (GD) 13.5 resulted in a mean placental weight reduction of 9%. No placental pathological lesions were observed in the irradiated group.

3.2. Placental cellular pathology after cancer(treatment) exposure

3.2.1. Placental oxidative damage

Cancer(treatment) may cause hypoxia-reoxygenation injury, or oxidative damage, which may affect parenchymal and circulatory function [42]. In a series of 25 women with cancer treated with chemotherapy, there was a significantly increased expression of 8-hydroxy-2' –deoxyguanosine (8OHdG), a biomarker for oxidative stress, in the syncytiotrophoblast compared to healthy controls [43].

To disentangle the potential effect of cancer treatment from the cancer itself, untreated animals with cancer were used to investigate the oxidative damage and antioxidant activity. In animals with cancer, the antioxidant enzyme system failed to eliminate free radicals in placental tissue despite unaffected (glutathione-S-transferase) and even increased (catalase) antioxidant activity levels, resulting in oxidative stress [19]. This may explain why increased placental oxidative damage is accompanied by significantly reduced placental weights in pregnancies complicated by cancer [43].

3.2.2. Placental apoptosis

Apoptosis is an important process in the normal development of the placenta throughout pregnancy [44]. However, excessive or accelerated apoptosis can result in disturbed placental development and low birthweight. Placental tissue of rats injected subcutaneously with Walker 256 carcinosarcoma cells showed enhanced expression of apoptotic signals such as cleaved PARP, caspase 3 and cytochrome-c [18]. Accordingly, placental apoptopic damage, defined as reduced placental total protein content, was more evident in the group with cancer. After exposure to doxorubicin both increased apoptosis and increased (secondary) proliferation was seen in placental tissue suggesting a compensatory mechanism to reach normal placental weight at term [45].

3.2.3. Placental angiogenesis and vascularization

In an attempt to explain the association between cancer treatment exposure and SGA, the effect of different treatments on placental angiogenesis and vascular damage has been studied. Exposure of term cytotrophoblast explants to epirubicin or vinblastine resulted in decreased Placental Growth factor (PlGF) mRNA expression and protein secretion, whereas docetaxel showed no effect on PlGF expression compared to untreated cells [46]. In mice, use of imatinib was associated with reduced angiogenesis [41]. Placental vascular toxicity of anthracyclines has been demonstrated in mice treated with doxorubicin [45]. Although protein concentrations (in homogenized placental tissue) involved in platelet adhesion after vascular damage, regulation of damage-induced angiogenesis and neovascularization differed, immunohistochemical analysis (CD34) could not confirm a significant difference in neovascularization between cases and controls. In contrast, epirubicin-exposed human placentas ($n = 7$) showed decreased neovascularization compared to chemotherapy-naïve controls ($n = 10$) ($p < 0.05$). With these results, it becomes plausible that anthracyclines induce vascular toxicity initiating a cascade that ultimately results in

SGA [45].

3.3. Intervention studies to reduce cancer-induced placental damage

The effect of diet to prevent cancer-induced placental damage has been investigated in animals [47,48]. Leucine is an amino acid known to enhance protein synthesis. A leucine-rich diet improved protein synthesis-degradation balance and increased placental cell number in rats [47] and in mice with cancer [48]. The mTOR (mammalian target of rapamycin) signaling pathway regulates cellular protein synthesis, is often deregulated in cancer and known for its association with SGA when activity is decreased [49]. In mice with cancer, leucine did not influence placental protein expression involved in the mTOR pathway [48]. Fetal weight increased significantly in mice receiving leucine [48] but not in rats [47], while placental weight and protein content did not improve in either mice or rats.

3.4. Placental genotoxicity after cancer treatment exposure

3.4.1. Placental platinum-DNA adducts

Cytotoxic effects of chemotherapy leading to DNA damage and genomic instability in somatic cells have been well established [50]. Intended (tumor-related) and unintended (healthy cell-related) DNA damage caused by chemotherapy include DNA breaks, cross-linking of platinum derivatives to DNA, DNA methylation, and abnormal DNA rearrangements. Although chemotherapy-related genetic damages are mostly resolved with DNA repair mechanisms, they may occasionally lead to long-lasting gross chromosomal abnormalities, numerical chromosome changes and genomic instability. This can lead to long-term effects such as miscarriage, developmental defects, infertility and (secondary) cancer in both mother and offspring. Evaluation of fetal DNA damage after chemotherapy exposure often starts with placental studies as the placenta serves as an important (partial) barrier. Chemotherapy-induced placental genetic changes such as DNA cross-linking and methylation have been studied in animals. As platinum derivatives are known to pass the placental barrier relatively easily and cause DNA damage, these are commonly studied.

Platinum derivatives are alkylating agents, used in for example the treatment of gynecological cancers [51]. Concerns about the oncogenic potency of these drugs, especially in offspring, have led to studies evaluating its genotoxic effects on maternal and fetal tissues in pregnant animals [52,53]. Platinum derivatives bind covalently to (tumor and healthy) DNA forming DNA crosslinks or adducts, inhibiting DNA synthesis and function, ultimately leading to cell apoptosis. Apart from the oncolytic effect, the concentration of DNA-adducts reflects the fraction of the dose that has reached the target tissue. The establishment of DNA-adducts in fetal tissues was a proof of transplacental passage and potential fetal DNA damage in pregnant woman treated during pregnancy. The occurrence of placental DNA adducts and maternal concentration fraction were determined in two studies. In rats, a 2–10 fold higher level of cisplatin-DNA adducts in maternal tissues compared to fetal tissues (kidney, liver, and lung) was found [52]. Cisplatin-DNA adduct levels in maternal liver tissue of Patas monkeys were shown to be higher than in placental tissue, certainly after exposure later in pregnancy [53]. Although transplacental passage of cisplatin is leading to substantial DNA adducts, gross abnormalities in offspring were not seen.

3.4.2. Placental epigenetic changes after chemotherapy exposure

Chemotherapy-induced epigenetic changes may affect gene activity and expression and are associated with fetal growth impairment and long-term morbidity [54]. DNA methylation, an example of a mechanism that causes epigenetic alterations, has been observed after exposure to several chemotherapeutics in pregnancy in maternal and fetal tissues. Whether this affects placental function and short- and long-term health of offspring is currently investigated. Procarbazine, used in hematological cancers and high-grade glioma, has been shown to cause DNA methylation in placental and fetal rat tissue [55]. A single dosage of procarbazine shortly before sacrification caused methylation in both maternal and fetal tissues especially in the maternal liver, but also detectable in placental and other fetal tissues. Whether this has long-term clinical consequences is unknown. Furthermore, significant hypomethylation of genes, important in placental function, was noted in murine placental tissue preconceptionally exposed to imatinib [41]. Hypomethylation was not present in mice exposed to imatinib before conception and continued during pregnancy. The authors hypothesize that the effect of imatinib is underestimated in the last group because of an early loss of embryos with extensive methylational changes [41].

3.4.3. Irradiation-induced placental genotoxicity

Pelvic irradiation is not compatible with preserving pregnancy, and is therefore not started in patients who wish to preserve pregnancy and only initiated when the consequence of fetal demise is accepted for oncological reasons. However, radiation is used for treatment of cancer in organs distant from the uterus and to some extent 'scatter radiation' may reach the placenta and fetus. In vitro studies and animal studies are the only option to study direct irradiation effects on the placenta. Primary (term) human trophoblast cells were exposed to a single dose of 10 Gy radiation [40]. Cyclin-dependent kinase inhibitor 1A (CDKN1A), a gene known to be involved in the p53-dependent cell cycle arrest, was highly upregulated compared to the control group. However, in pregnant mice exposed to irradiation at GD 13.5, fetal and placenta weight were significantly lower compared to unexposed controls, but no gene expression alterations were found. The authors suggest that altered placental gene expression does not fully explain the impact of irradiation on fetal growth. However, as the placenta barely grows after GD 13.5 but fetal growth should still accelerate requiring a sufficient increase in placental function, the lower fetal weight may indicate a lack of this increase. An irradiation effect on the fetal neurons, soft tissue and epithelial tissue could also explain a lower fetal weight [40].

3.5. Direct placental involvement by maternal cancer

The frequency of direct placental involvement by maternal cancer is difficult to determine since placental examination is not routinely performed in women with cancer, and changes may be focal.

In the only animal study evaluating placental involvement, 1 of the 20 pregnant mice inoculated with $6.5*10^6$ cancer cells showed widespread maternal metastasis and placental involvement in the labyrinth near the chorion without a clear demarcation from the villi and the fetal vessels [56].

All full-text available individual cases and the one case series [57] relating to placental involvement in human pregnancy published since 1866 are listed in [Table 2] (n = 87 cases; n = 82 publications). Placental lesions are frequently identified by macroscopic examination, but additional microscopic inspection is required in many cases to identify placental involvement [58,59]. Placental involvement may include maternal intervillous space, villi, umbilical cord or fetal vessels. Intervillous involvement is most common, due to 1) the hematogenous dissemination of most cancers, 2) the suggested existence of a (partial) barrier between the maternal and fetal interface and 3) the protective role of the fetal immune system [21,60,61].

Although many cancers can show placental involvement, melanoma (30%), lung cancer (12%) and breast cancer (12%) are most commonly reported [Table 3]. Cancer in women with placental involvement is diagnosed at a mean age of 29.8 years and a mean GA of 27 weeks, if diagnosed during pregnancy (n = 69) [Table 3]. The outcome of women with placental involvement is poor with a mortality of 81.0%, mainly due to presence of other distant metastases (96.2%). The median survival of women with intravillous and without intravillous (intervillous, umbilical cord or fetal vessels) involvement is 28.0 (95% CI 19.2 to 36.8) and 57.0 (95% CI 11.3 to 102.7) days postpartum respectively (p =

Table 2
Published cases with placental involvement by maternal cancer.

Author	Year	Maternal disease	Metastatic disease (other than placenta)	Placental metastasis			Fetal/ infant metas-tasis	Infant outcome
				Inter-villous involve-ment	Villous involve-ment	Other placental involve-ment		
Al-Adnani, M [71].	2007	Pancreatic cancer	+	+	–	–	–	WED, age 12 months.
Alexander, A [72].	2004	Malignant melanoma (vulva)	+	+	–	–	–	WED, age 10 months.
Almanza-Marquez, R [73].	2002	Unknown primary	N/A	+	–	–	–	WED (unknown follow up)
Altman, J. F [74].	2003	Malignant melanoma (arm)	+	+	–	–	–	WED, age 19 months.
Anderson, J. F [75].	1989	Malignant melanoma	+	+	+	–	–	WED, age 12 months.
Baergen, R. N [76].	1997	Malignant melanoma (shoulder)	+	+	+	–	–	WED, age 7 months.
Baker, A. M [77].	2010	Gastric cancer	+	+	–	–	–	WED, age 18 months.
Barr, J. S [78].	1953	Bronchial cancer	+	+	–	–	–	WED, age 36 months.
Bender, S [79].	1950	Ethmoid cancer	+	+	–	–	–	WED, age 6 months.
Bender, S [79].	1950	Gastric cancer	+	+	–	–	–	Died, 36h after birth due to bilateral lung atelectasis (no cancer).
Bovio, I. M [80].	2011	Renal cell cancer	+	+	–	–	N/A	N/A
Brodsky, I [64].	1965	Malignant melanoma (back)	+	+	+	–	+	Died, age 48 days due to widespread malignant melanoma.
Brossard, J [81].	1994	Medulloblastoma	+	+	–	–	–	WED, age 6 months due to RDS.
Brossard, J [81].	1994	Malignant melanoma (gluteus)	+	+	–	–	–	WED, age 12 months.
Can, N. T [82].	2013	Cervical cancer	+	+	–	–	–	WED at birth, lost to follow up.
Catlin, E. A [34].	1999	Natural-killer-cell lymphoma (mesosalpinx)	N/A	–	+	yes, decidual and chorionic blood vessel invasion	+	Died, age 59 days. Lymphoma, died due to adrenal insufficiency after treatment with interferon alfa.
Chen, G [37].	2015	Non-Hodgkin lymphoma	N/A	–	–	+	N/A	IUFD at 25 weeks gestation.
Chen, Y [83].	2014	Gastric cancer	+	+	+	–	–	WED, age 6 months.
De Carolis, S [65].	2015	Malignant melanoma (back)	+	N/A	N/A	N/A	+	Died, age 4.5 months. Metastatic lesion brain.
Delerive, C [84].	1989	Bronchial cancer	+	+	–	–	–	WED, age 18 months.
Dillman, R. O [85].	1996	Malignant melanoma	+	N/A	N/A	N/A	–	N/A
Dipaola, R. S [86].	1997	Malignant melanoma (shoulder)	+	+	+	–	–	WED, age 17 months.
Eltorky, M [87].	1995	Breast cancer	+	+	–	–	–	WED (unknown follow up). NEC, discharged alive.
Eltorky, M [87].	1995	Pancreatic cancer	+	+	–	–	–	WED, age 24 months.
Fei, F [88].	2019	Acute myeloid leukemia	N/A	+	–	–	N/A	IUFD at 26 weeks gestation due to placental abruption.
Fei, F [88].	2019	Acute myeloid leukemia	N/A	+	–	–	–	WED (unknown follow up)
Folk, J. J [89].	2004	Lung cancer	+	+	–	–	–	WED, age 6 months.
Freedman, W. L [90].	1960	Malignant melanoma (jaw)	+	+	–	–	–	WED, age 14 months.
Frick, R [91].	1977	Angioblastic vaginal sarcoma	+	+	+	–	–	WED, age 3 months.
Froehlich, K [92].	2018	Breast cancer	+	+	–	–	–	WED (unknown follow up)
Gilles, H. 2nd [93]	1976	Malignant melanoma (arm)	+	+	–	–	–	WED, age 24 months.
Gnecco, C [94].	2018	Burkitt's lymphoma (B cell lymphoma)	+	+	–	–	–	WED, age 5 months.
Gourley, C [95].	2002	Unknown primary	+	+	–	–	–	IUFD at 23 weeks gestation.
Hanaoka, M [96].	2007	B-cell lymphoma	–	+	–	–	N/A	WED, age 12 months. RDS.
Holcomb, B. W [97].	1975	Malignant melanoma	+	+	+	–	–	WED, age 3 months.
Honore, L. H [98].	1990	Acute myeloid leukemia	N/A	+	–	yes, decidual invasion	N/A	Missed abortion (partial hydatidiform mole)
Hormann, G [69].	1965	Breast cancer	N/A	+	+	yes, fetal vessel invasion	N/A	N/A
Horner, E. N. [99]; Hormann, G [69].	1960/ 1965	Ovarian cancer	+	+	–	–	–	WED, age 24 months.
Jackisch, C [100].	2003	Lung cancer	+	+	+	–	–	WED, age 15 months.
Jeong, B [101].	2014	Gastric cancer	+	–	–	yes, invasion of vessels basal plate	N/A	Termination of pregnancy.
Johnston, S. R [102].	1998	Malignant melanoma (back)	+	+	+	–	–	WED, age 12 months.
Jones, E. M [103].	1969	Bronchial cancer	+	+	–	–	–	WED, age 6 months.
Kochman, A. T [104].	2001	Bronchial cancer	+	+	–	–	–	WED, age 12 months.

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Table 2 (*continued*)

Author	Year	Maternal disease	Metastatic disease (other than placenta)	Placental metastasis			Fetal/ infant metas-tasis	Infant outcome
				Inter-villous involve-ment	Villous involve-ment	Other placental involve-ment		
Kurtin, P. J [105].	1992	Peripheral T-cell lymphoma	+	+	–	–	–	WED, age 24 months.
Lakshminarayana, P [106].	2007	Malignant melanoma (right thigh)	+	–	+	–	–	WED, age 10 months.
Looi, L. M [107].	1979	Malignant melanoma (shoulder)	+	–	+	–	–	WED, age 1 month.
Marsh, R. D [108].	1996	Ocular malignant melanoma	+	+	–	–	–	WED (unknown follow up)
Matsika, A [109].	2015	Colorectal cancer	+	+	–	–	–	Both WED, age 24 months.
Meguerian-Bedoyan, Z [110].	1997	Anaplastic large cell lymphoma	+	+	–	–	–	WED, age 10 years.
Miller, K [111].	2012	Gastric cancer	+	+	–	–	–	WED, age 12 months. RDS.
Møller, D [112].	1986	Malignant melanoma (leg)	+	+	+	+	–	WED, age 6 months.
Nishi, Y [113].	2000	B-cell-type mediastinal malignant lymphoma	+	–	+	–	–	WED, age 24 months.
O'day, M. P [114].	1994	Orbital rhabdomyosarcoma	+	+	–	–	–	WED (unknown follow up)
Orr, J.W. Jr [115]	1982	Neck cancer (squamous cell cancer)	+	+	–	–	–	WED, age 4 months.
Pages, C [116].	2009	Malignant melanoma (leg)	+	N/A	N/A	N/A	–	WED, age 60 months. RDS.
Patan, S [117].	2019	Gastric cancer	+	+	–	–	–	WED, age 9 months.
Patsner, B [118].	1989	Ovarian cancer	+	N/A	N/A	N/A	–	Termination because of presumed chorioamnionitis
Pfuhl, J. P [119].	1991	Breast cancer	+	+	+	–	–	WED, age 17 months.
Pollack, R. N [120].	1993	Non-Hodgkin lymphoma	N/A	+	–	–	–	WED, age 9 months. HIV positive.
Pollack, R. N [121].	1993	Medulloblastoma	+	+	–	–	–	WED (unknown follow up)
Popnikolov, N [122].	2020	Breast cancer	+	–	–	+	–	WED (unknown follow up)
Read Jr, E. J [123].	1981	Lung cancer	+	+	–	–	–	WED, age 16 months.
Reintgen, D [124].	1995	Malignant melanoma	+	+	–	–	–	WED, age 24 months.
Rewell, R. E [125].	1966	Breast cancer	+	+	–	–	–	WED (unknown follow up)
Reynolds, A. G [126].	1955	Malignant melanoma (foot)	+	N/A	N/A	N/A	–	WED, age 10 months.
Rothman, L. A [59].	1973	Rectal cancer	+	+	–	–	–	WED, age 8 months.
Sahin Aker, S [127].	2016	Pancreatic cancer	+	–	+	–	N/A	Died, age 1 month. Sepsis.
Salamon, M. A [128].	1994	Breast cancer	+	+	–	–	–	WED (unknown follow up)
Sedgely, M. G [129].	1985	Breast cancer	+	+	+	–	–	WED, age 12 months.
Sheikh, S. S [130].	1996	Acute monocytic leukemia	–	–	–	yes, basal plate invasion	–	WED, age 18 months.
Shuhaila, A [131].	2008	Malignant melanoma (gluteus)	+	–	+	–	–	WED, age 18 months. SGA.
Silva, L. B [132].	2006	Cervical cancer	+	–	–	yes, vessel invasion placental bed	N/A	Abortion at 14 weeks gestation (no external malformations)
Sokol, R. J [133].	1976	Amelanotic melanoma (back)	+	–	+	–	–	Died, age 2 days. RDS (no cancer)
Steffensen, T. S [134].	2008	Epitheloid sarcoma (knee)	+	+	–	–	–	WED, age 17 days. RDS.
Stephenson Jr, H. E [135].	1971	Malignant melanoma (back)	+	+	+	–	–	WED, age 24 months.
Suda, R [136].	1986	Lung cancer	+	N/A	N/A	N/A	–	WED, age 22 days.
Tan, K [137].	2010	Breast cancer	+	+	–	–	–	WED (unknown follow up)
Teksam, M [68].	2004	Lung cancer	+	N/A	N/A	N/A	+	Died, age 23 months. Multiple cancer lesions right lung, liver and cerebellum.
Thelmo, M. C [138].	2010	Lung cancer	+	+	–	–	–	WED, age 3 months.
Valenzano Menada, M [66].	2010	Malignant melanoma (gluteus)	+	N/A	N/A	N/A	+	WED, age 24 months. At age 3 months metastases mastoid and lungs (resistant to ifosfamide and adriamycin), disease regressed spontaneously.
Varveris, H [139].	2002	Peripheral primitive neuroextodermal tumor (pPNET)	+	+	–	–	–	Died, age 1 months. Cardiopulmonary insufficiency (no cancer)
Vetter, G [140].	2014	Breast cancer	+	+	–	–	–	WED, age 54 days. RDS.
Weber F.P. [67]; Holland, E. [70]; Hormann, G [69].	1930/ 1949/ 1965	Malignant melanoma (thigh)	+	+	+	yes, chorionic and umbilical cord invasion	+	Died, age 9.5 months. Liver metastasis.
Wei P [141].	2017	Gastric cancer	+	+	–	–	–	WED, age 20 months.

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Table 2 (*continued*)

Author	Year	Maternal disease	Metastatic disease (other than placenta)	Placental metastasis			Fetal/ infant metas-tasis	Infant outcome
				Inter-villous involve-ment	Villous involve-ment	Other placental involve-ment		
Wei P [141].	2017	Gastric cancer	+	+	–	–	–	WED, age 19 monhts.
Yeung, P. Jr [142].	2008	Malignant melanoma (arm)	+	N/A	N/A	N/A	N/A	Lost to follow up
Zhang, L [143].	2019	Acute promyelocytic leukemia	N/A	+	–	–	–	Died shortly after birth (reason unknown). Caesarean section because of fetal distress.

Abbreviations: N/A: not available; WED: without evidence of disease; IUFD: intrauterine fetal death; RDS: Respiratory distress syndrome; SGA: small for gestational age.

Table 3
Placental metastasis review case reports: Patient characteristics and outcome.

Oncological characteristics (n = 87)	
Malignancy type	
Melanoma	26 (29,9)
Lung cancer	10 (11,5)
Breast cancer	10 (11,5)
Gastric cancer	8 (9,2)
Non-Hodgkin lymphoma	8 (9,2)
Acute myeloid leukemia	5 (5,7)
Other[a]	20 (23,0)
Maternal age at diagnosis (years) (n = 83)	29,8 ± 6,5
Gestational age at diagnosis (weeks)[b] (n = 69)	27,2 ± 8,4
Diagnosis during pregnancy	
Primary	65 (74,7)
Recurrence	22 (25,3)
Treatment during pregnancy (n = 76)	
None	53 (69,7)
Surgery	9 (11,8)
Chemotherapy	8 (10,5)
Radiotherapy	2 (2,6)
Surgery and chemotherapy	1 (1,3)
Chemoradiotherapy	1 (1,3)
Surgery, chemo- and radiotherapy	1 (1,3)
Immunotherapy	1 (1,3)
Obstetric characteristics (n = 87)	
Gestational age at delivery (weeks) (n = 68)	32,3 ± 4,1
Birth weight (gram) (n = 60)	1913 ± 788
Birth weight percentile[c] (n = 48)	
<p3	5 (10,4)
<p10	15 (31,3)
Metastatic disease (n = 79)	76 (96,2)
Placental metastases (n = 78)	
Intervillous	66 (85,7)
Intravillous	22 (28,2)
Other	10 (12,8)
Maternal outcome (n = 84)	
Died	68 (81,0)
Median survival (days) [median (95%CI)]	
Villous involvement (n = 20)	28,0 (19,2–36,8)
No villous involvement (n = 46)	57,0 (11,3–102,7)
Fetal/infant outcome	
Metastatic disease (n = 77)	6 (7,8)
Within villous involvement (n = 20)	3 (15,0)
Miscarriage/stillbirth/termination (n = 83)	7 (8,4)
Without evidence of disease (n = 83)	66 (79,5)
Died (n = 83)	10 (12,0)
Due to metastatic disease	5 (50,0)

Data given as n (%) or mean ± standard deviation.

[a] Includes vaginal cancer, cervical cancer, colorectal cancer, epitheloid cancer, ethmoid cancer, medulloblastoma, ovarian cancer, pancreatic cancer, primary neuroectodermal tumor, renal cancer, neck cancer, rhabdomyosarcoma and unknown primary.

[b] When diagnosed during pregnancy.

[c] According to Hoftiezer [24].

0.050) [Table 3]. Only 10.2% (n = 9) of the patients achieved complete remission at the end of follow-up (mean 197 days) (not shown).

Intravillous involvement is rare due to the maternofetal barrier, but should be regarded as a sign of invasion into the fetal compartment of the placenta and, when present, fetal metastases are nearly always reported with co-existence of intravillous involvement. Reported frequencies of fetal metastasis in pregnancies with placental involvement range between 22 and 50% [22,23,62,63]. Fetal metastasis (7.8%, n = 6) are most commonly reported in women with melanoma (n = 4), but have been reported with lung cancer and non-Hodgkin lymphoma [34, 64–68]. Among the cases with placental involvement and known infant outcome (n = 83), the majority of the liveborn offspring had no evidence of disease at birth or during follow up (79.5%). 12% (n = 10) of the offspring died, of whom 50% were due to metastatic disease [Table 3]. Three infants (5.4%) in the group without intravillous metastases (n = 56) died for neonatal reasons unrelated to infant metastasis. In contrast, in offspring with intravillous metastases (n = 22) five infants (22.7%) died before the end of follow up. Among them, three had metastatic disease (60%) [34,64,67,69,70] [Table 2].

To our knowledge, only one case series has been published with regard to cancer of unknown primary (n = 18) of whom four (23%) had placental involvement [57]. 67% of these women had metastatic disease (other than placental involvement). Details about the type of placental involvement are lacking, but no fetal metastasis were reported.

3.6. New cases (preliminary data)

Since the establishment in 2005, the International Network on Cancer, Infertility and Pregnancy (INCIP) has registered over 3000 women with a cancer diagnosis or oncological treatment during pregnancy (www.cancerinpregnancy.org). Currently, three women have been registered with placental involvement (breast, ovarian and gastric cancer) [Table 4]. Two had only intervillous space involvement and the third did not report any specification of site, but without involvement of the chorionic plate. All infants were AGA and had no evidence of metastatic disease.

Placental involvement from a maternal origin is rare, but women with melanoma or metastasized disease of any kind seem to be more vulnerable. Especially when villous tissue is invaded by cancer cells, fetuses are at risk to develop metastases (14%). When fetal metastases are present, infant mortality is high (83%).

4. Conclusion

From this review, we can conclude that placental pathology in women with cancer during pregnancy is insufficiently investigated and only studies with small sample sizes and significant heterogeneity are available. This hinders definite conclusions about the effect of cancer (treatment) on the placenta. Because of increasing numbers of continued pregnancies after cancer diagnosis, fetal growth restriction will occur more frequently and further research into underlying mechanisms is

Table 4
Placental involvement INCIP: Patient characteristics and outcome.

Patient no	Tumor type	Metastatic disease	Oncological treatment during pregnancy	Neonatal outcome	Maternal outcome	Placental histopathology	Placental metastasis
1	Breast (recurrence)	No	None	Induction (deterioration mother), live birth at 37 + 5, BW p85[a], WED	Persistent disease 5yrs pp (last FU 2018)	466 g (p8[b]), macro: na, micro: na	Intervillous lesions throughout entire parenchyma, ER/PR pos.
2	Ovarian	Yes	None	Elective CS (treatment planning), live birth at 30 + 5, BW p33[a], WED	Died 3mo pp	335 g (p23[b]), macro: na, micro: delayed villous maturation	Sparse lesions in intervillous spaces, no involvement of villi or fetal vessels.
3	Gastric	Yes	None	Emergency CS (eclampsia), live birth at 27 + 3, BW p33[a], WED	Died 3mo pp	210 g (p10[b]), macro: na, micro: accelerated villous maturation. Membranes and cord: na.	Multiple lesions with similar immunohistochemical profile as tumor biopsy. Chorionic plate: na.

Abbreviations: BW: birthweight; WED: without evidence of disease; pp: postpartum; FU: follow-up; na: no abnormalities; ER/PR: estrogen/progesterone receptor; CS: caesarean section.
[a] Birthweight percentile according to Hoftiezer [24].
[b] Placenta weight percentile according to Thompson [25].

indispensable. Routine placental examination and a core outcome set for placental histology are essential to overcome this. To avoid underestimation of the problem, evaluation of fetal growth impairment (and underlying causes) according to the latest definitions, also requires serial ultrasound morphometric and Doppler results rather than birthweight only.

Placental histologic lesions that have been described are similar to those found in women with SGA. The majority of lesions belong to the category of maternal vascular malperfusion, ultimately leading to fetal growth impairment, but there is limited additional evidence of underlying causes of treatment-related placental damage such as angiogenic impairment, oxidative stress and genotoxicity.

Although the incidence of direct placental involvement is low, it can be a sign of fetal metastasis. With the current available data, distant metastases, other than in the placenta, at the time of delivery seem to be an important indicator for women with cancer most vulnerable to placental involvement.

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Declaration of competing interest

All authors declared that they have nothing to disclose. For each author we have a disclosure statement (ICMJE Form) available upon request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.placenta.2021.06.003.

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