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Effects of cisplatin administration during pregnancy

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Declaration

No part of this thesis has been submitted in Support of an application for any degree or qualification

of the University of Kent or any other University or institute of learning.

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Abstract

Cisplatin administration during pregnancy may pose risk to the child including congenital malformations and thus the foetus must be checked throughout chemotherapeutic administration. This systematic review was conducted using PubMed where clinical and pre-clinical articles were found. This study aims to understand the risks cisplatin poses to the mother and the unborn child. Many pregnant patients identified in this study were treated for gynecological malignancies (51, 76.1 % out of 67 patients) and were administered cisplatin-based therapy during the 2nd trimester (14 of 67 patients, 20.8 %). Unmodified treatments were administered in 57 (85.0 %) out of 67 patients. However, 10 (14.9 %) out of 67 patients received modified treatments as unmodified treatments was not a possible treatment option. Modifications to treatments may include reducing the interval between treatments to allow a longer period to recover from the cytotoxic effects of cisplatin. Of these 67 patients receiving cisplatin-based therapies administered in pregnancy 13 children reported complications as a neonate or during early childhood. Overall, the general health of the neonates was positive with majority reporting no abnormalities. However, a higher proportion of neonates (13 of 67, 19.4 %) displayed complications after intrauterine exposure to cisplatin-based therapies than in a control cohort, in which abnormalities were recorded in 4 % of newborns. Neonates of cisplatin-treated mothers presented with different complications, the most common of which was respiratory distress observed in 5 of 13 (38.4 %) neonates. Other complications were only recorded in one neonate and included bilateral hearing loss, growth restrictions, or death. It is still unknown whether these abnormalities are primarily caused by intrauterine cisplatin exposure, premature delivery, or a combination of both. Overall, our results support the European Society for Medical Oncology's guidelines for chemotherapy administration during pregnancy.

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Introduction

1.1 Cancer during pregnancy

Pregnancy-associated cancer diagnoses are increasing across the world (1). A rise in cases may be the consequence of an increase in maternal age resulting in a higher incidence of age-related malignancies including breast and cervical cancer may (2) (3). Available data suggest that pregnancy may not alter the mother's outcome when compared to non-pregnant women (4).

When cancer diagnosis is made during pregnancy, therapy decisions typically consider both the risks to the mother and the foetus. Normally, the health of the mother precedes that of the foetus. However, some mothers refuse all treatment during pregnancy to protect their children, which may have life-threatening for the mothers (2).

1.2 Stages of foetal development

All or none period:

This stage ranges from 8 to 14 days and finishes when clusters of mesenchymal cells form eventually giving rise to the vertebrae. If anticancer therapeutics were administered during this period, the implantation process may be disrupted potentially leading to miscarriage. If implantation is successful then the child usually survives. Administration of anticancer agents during this phase does not result in congenital malformations. However, the risk of malformations increases if administrations occur after this phase (2).

Organogenesis:

This stage ranges from 2 to 8 weeks after conception. During organogenesis, between the weeks 3 and 5, the foetus is particularly sensitive to anticancer agents, as the therapy can cause irreversible damage are dividing and differentiating cells. Different organ systems have different, not necessarily overlapping windows of susceptibility, which is why anticancer agents are contraindicated during this period (2).

Foetal phase:

This stage ranges from the end of the embryonic period (week 9) until birth in which the foetal organ systems start to become functional. Intrauterine exposure to anticancer agents increases the risk of congenital malformations such as growth restrictions and defects of several organ systems (2).

1.3 Diagnosis of tumours

Tumour diagnosis during pregnancy is often delayed as may symptoms are comparable to pregnancy. Symptoms may include anemia, vomiting, fatigue and nausea (1). Moreover, the expanding of the uterus and breast changes that occurs during pregnancy may mask the tumour during physical examinations. Hormone fluctuations observed with a tumour diagnosis may be overlooked as pregnancy influence similar hormone fluctuations similar (5). An example is the elevated oestrogen levels observed in breast cancer and is also expected during the 2nd and 3rd trimester potentially delaying the tumour diagnosis (6). Tumour markers used for cancer detection may change in sensitivity due to pregnancy.

Table 1 displays examples of cancer makers currently in use that is affected during pregnancy.

Table 1: A Table displaying examples of tumour markers that are affected during pregnancy (7)

Tumour marker	Affected during pregnancy
Alpha-fetoprotein	Marker for poor obstetric outcome
Beta-human chorionic gonadotropin (Beta-hCG)	Levels less than 1500 mIU/mL is a marker for a potential ectopic pregnancy
CA 125	Elevated during the 3rd trimester
CEA	Elevated during the 3rd trimester

CA 19-9	Elevated during the 3rd trimester
CA 27.29	Elevated during the 1st trimester
Calcitonin	Elevated during delivery
Cytokeratin fragment 21-1	Elevated in women with preeclampsia
Fibrin/fibrinogen	Slightly increased during pregnancy
Gastrin	Elevated in advanced pregnancy
HE4	Increases as the pregnancy progress
5-HIAA	Elevated with habitual abortion
Immunoglobulins	Increased at various points in pregnancy
Lactate dehydrogenase	Elevated in severe preeclampsia and chronic hypertension

Imaging to confirm the presence of a tumour during pregnancy is controversial due to the risk radiation poses to the developing foetus. Exposure to radiation above 100 mGγ may potentially result in congenital malformations (1)

1.4 Cisplatin

1.4.1 cisplatin mechanism of action

Cisplatin is a DNA damaging agent that (5) was first discovered in 1844, while its chemical structure was determined in 1893. Its cytotoxic properties were observed in 1960 as cisplatin's platinum compound inhibited the cell division of E. coli. Cisplatin is used as a frontline therapy (8) to treat many solid cancer types (9).

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It is a square planar platinum complex that contains 2 ligands of chloride in a cis configuration orientation (10). Cisplatin entry may depend on the cell type and can occur by passive diffusion, facilitated diffusion or active transport (8).

Outside of the cell there is an abundance of chloride ions stopping hydrolysis of cisplatin. However, inside the cell there is a lack of chloride ions allowing the hydrolysis and activation of cisplatin (8). With the platinum atom free it can bind to purine bases at the N7 position to form 1,2 or 1,3 intrastrand crosslinks altering the DNAs structure disrupting transcription and replicating resulting in apoptosis (8). Cisplatin interacts with the N7-sites of purine residues in DNA which leads to the formation of DNA-DNA interstrand and intrastrand crosslinks. It is believed that the ApG and GPG intrastrand interactions is the source of cisplatin's anti-cancer effects leading to a disruption of DNA replication and transcription (11)

Reactive oxygen species

Reactive oxygen species is produced from the mitochondria after cisplatin is administered as the cell is exposed to stress caused by cisplatin administration. This leads to the degradation of the membrane and potentially resulting in apoptosis (12)

Elevated levels of reactive oxygen species lead to the induction of cell cycle arrest and apoptosis. Stimulation of ferroptosis which, is apoptosis that is dependent on the ion levels occurs leading to the death of cancer cells. Cells can potentially display a higher sensitivity to cisplatin if KIF4 is overexpressed (13)

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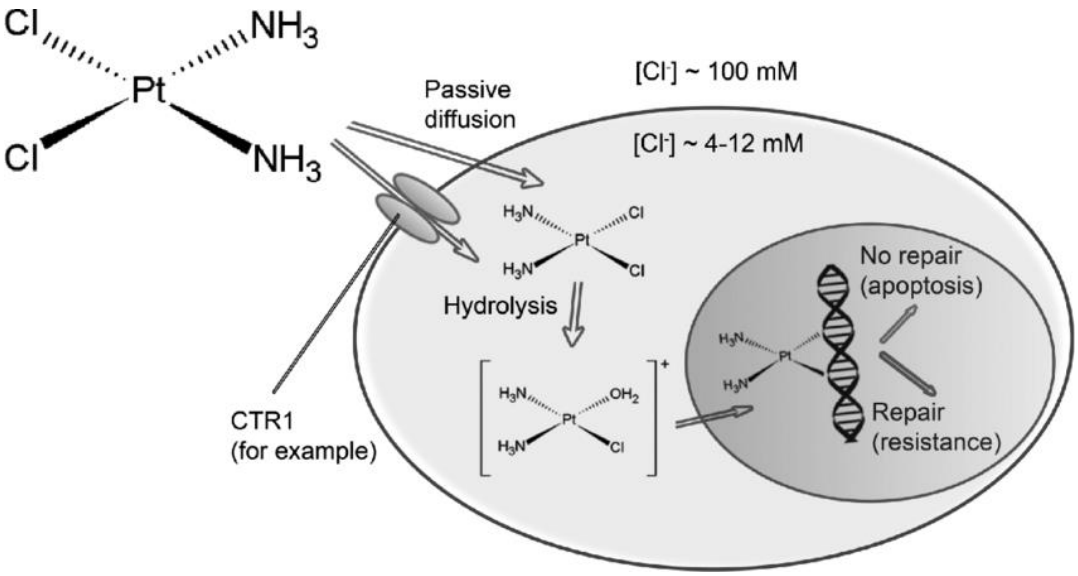

Figure 1: displays how cisplatin interacts with tumoral DNA. Once cisplatin enters the cell the chloride ions are substituted with guanine bases in the DNA as figure 1 displays. Cisplatin uses covalent bonds to achieve 1,2-intrastrand crosslinks that is most associated with cisplatin administration (14)

1.4.2 Unwanted side effects

Cisplatin is effective against many cancer types, but its use is also associated with severe side effects, which may include nausea, vomiting, nephrotoxicity, hepatotoxicity, and cardiotoxicity. Due to these side effects the patient must be monitored and treatment courses may be altered dependent in response to toxic effects (9)

Hepatotoxicity

Hepatotoxicity is induced via oxidative stress and is influenced by the reduction of antioxidants such as glutathione and elevation of hepatic malondialdehyde levels and can be detected by increased transaminase levels. Cisplatin-induced hepatotoxicity in the liver may result in liver cell necrosis and

reduced liver function. In cisplatin-treated patients, liver inflammation is observed around the portal area with enlarged capillaries obstructing outflow leading to tenderness of the abdomen (9)

Cardiotoxicity

Cisplatin-induced cellular damage can result in leakage of lactate dehydrogenase and creatine from cardiac myocytes because of peroxidation of membrane lipids. Cisplatin-induced necrosis of cardiac muscle cells can affect heart function (9)

Nephrotoxicity

Cisplatin concentrations in the kidneys, the main route of cisplatin excretion, have been found to be five times higher than in the serum. This accumulation of cisplatin in the kidneys can result in oxidative stress and impair the function of the proximal and distal tubes (9). Transporters such as copper transporters facilitate the transport of cisplatin into the kidneys (15).

Other side effects

Other cisplatin-induced toxicity can involve the peripheral nervous system potentially resulting in seizures and may be irreversible in a substantial fraction of cases. Cisplatin may also lead to hearing loss by damaging the outer hairs of the Corti (10).

1.4.3 Transplacental transport and effect to the foetus

The capacity of cisplatin seems to cross the blood-placenta barrier appears limited. About 13 % of cisplatin entered the placenta in an in vitro study using the perfused human placental lobule (16). Cisplatin detection in cord blood resulted in a concentration of 40µg/L 3 days after cisplatin administration and 0.82 µg/L two weeks after the final chemotherapy treatment cycle (16).

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1.4.4 DNA repair mechanisms

Cisplatin administration has been identified to cause the most drastic distortion in the DNA and can range from 45 to 79 degrees and can be repaired by nuclease excision repair (17). Nuclease excision repair is split into two pathways. Global genome repair and transcription coupled repair. This repair pathway is used to repair adducts and lesions in the DNA formed through cisplatin administration.

Global genome repair:

This pathway allows for the removal of adducts in the genome induced by cisplatin to be removed as well as conformational distortions (18) induced by cisplatin administration is recognized by XPC-hRAD23b-CENTRIN2 (19). Once cisplatin induced DNA damage is detected XPC will bind to the DNA and will recruit Factor II H, which forms a complex with XPB, XPD and XPA. This complex forms a bubble by opening the DNA strands around the cisplatin induced DNA damage. Once this is formed endonucleases such as ERCC1-XPF and XPG, which will cleave the lesion at the 5' and 3' ends of the DNA. Once cleaved the cisplatin induced DNA damage is released and the gap is filled through polymerases by using the undamaged strand as a template. DNA ligase I or IIIa is recruited to seal the complementary strand to the DNA backbone. This allows removal of cisplatin-induced damage to be removed. However, this will allow for the cancerous cell to continue replicating and is a mechanism of cisplatin resistance (20).

Transcriptional coupled repair:

Transcription coupled repair allows for the removal of intrastrand cross links found at genes that are being actively transcribed halting gene transcription by RNA polymerase II (18). RNA polymerase II stalling at cisplatin induced damage is a signal for the recruitment of CSB, CSA, XAB2, UVSSA and USP7. CSB once recruited will bind to RNA polymerase II leading to a conformation change via the DNA wrapping the DNA around CSB. This leads to a change in the interactions

between RNA polymerase II and the DNA. CSA recruits XAB2, HMGN1 and TFIIS to RNA polymerase II. Degradation of CSB via CSA allows for RNA synthesis to resume (21) as the transcription signal is restored (22). This is a potential mechanism of cisplatin resistance as tumour cells can overcome cisplatin induced damage. However, if this is unsuccessful then the cell will undergo apoptosis.

Studies involving testis cell lines identified that deficiency of above repair pathways heightens the sensitivity to cisplatin's cytotoxicity effects resulting in apoptosis. Testis cell lines have also shown to have a reduced capacity for repairing intrastrand cross links caused by cisplatin administration due to low levels of ERCCI-XPF complex inducing cell death (18).

1.4.5 apoptosis pathways

If the cell cannot repair cisplatin-induced damage then the cell will undergo apoptosis. Apoptosis results in both biochemical and morphological changes that includes: loss of cell-cell contact, chromatin condensation and changes on the cell surface (23). There are two pathways that the cell may undergo for apoptosis. The cell may undergo either intrinsic or extrinsic apoptosis dependent on the stimuli.

Many cancer cells are primed for apoptosis potentially due to environmental stressors that they are subjected to. Anticancer drugs such as cisplatin depends mostly on the intrinsic pathway.

Intrinsic pathway:

Cisplatin induced cellular stress such as reactive oxidative species inducing DNA damage or cell cycle arrest (13). Once apoptosis is triggered by cisplatin the BAK and BAX proteins bind together leading to the membrane to permeabilize at which point the cell has committed to apoptosis. Cytochrome C is released as well as apoptotic protease activity factor I. dATP and pro-caspase 9 forming the apoptosome. During this stage SMAC is released as well as MOMP which, will induce cell death if caspases are not activated. Once formed pro-caspase 9 is then converted into caspase 3 and 7.

Leading to the degradation of the cell membrane. Phagocytes engulf cells that display these change (23).

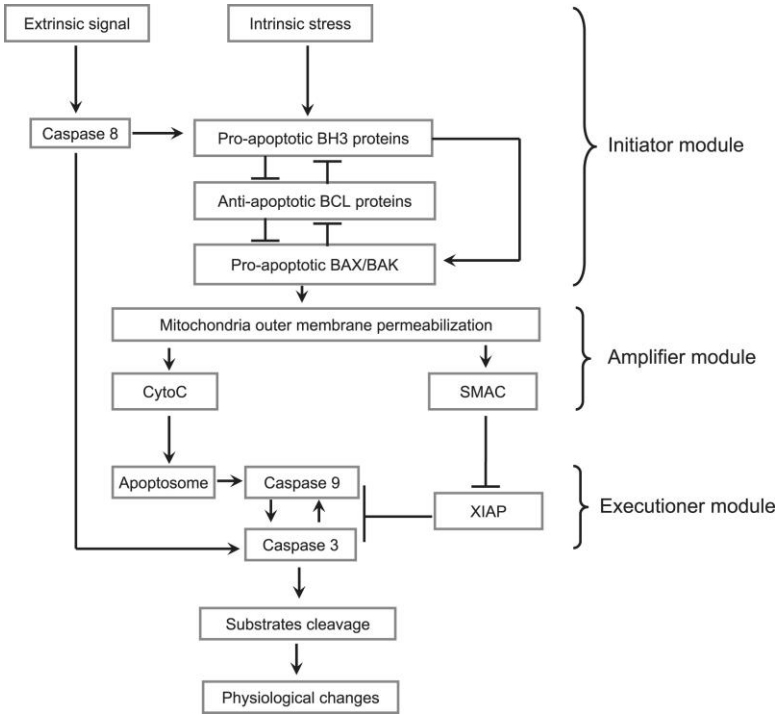

Figure 2: displays both the intrinsic and extrinsic pathway, how they are triggered and how the pathways converge leading to apoptosis of the cell (24). However, cisplatin depends mostly on the intrinsic apoptosis pathway.

1.4.6 Cisplatin in combination with other drugs

The use of combination therapy in patients can increase efficacy and reduce the risk of resistance formation, because of the combination of different mechanisms of action (25)

Advantages of combination therapy is additional anti-cancer agents to target further pathways when anti-cancer drugs are showing little affect to the tumour and can use previously ineffective drugs increasing the number of drugs that can be used in therapies (26). Using combination therapies however, may risk the drugs interacting resulting in unwanted side effects such as nausea, nephrotoxicity or cardiotoxicity.

The combinations of drugs may vary on tumour requirements however, there are several types of chemotherapeutic agents that are used in combination with cisplatin.

Alkylating agents

These types of drugs act via three mechanisms: creating crosslinks in either one or both DNA strands preventing transcription from occurring. An example of alkylating agents is cyclophosphamide, which is administered in combination with cisplatin in case studies reported on in this study. Alkylating agents induce mutations in the DNA by mis-paring nucleotides causing induction of the intrinsic apoptosis pathway. Attaching alkyl groups onto DNA creating adducts within the genome leading to the termination of transcription and induction of apoptosis (27).

Antimetabolites

This group interferes with cell synthesis by incorporating itself into the DNA thus halting transcription. An example of an antimetabolite used in cisplatin-based combination therapies is 5-fluorouracil. Antimetabolites interrupt nucleic synthesis stopping DNA as nucleic bases cannot be added to the transcribed strand via RNA polymerase. Some agents inhibit protein synthesis potentially inhibiting cell proliferation resulting in cell death (28).

Antineoplastic antibiotics

Antineoplastic antibiotics such as bleomycin, which is administered in conjunction with cisplatin stops transcription by producing or inserting itself into the DNA. This induces breaks in the DNA preventing further cell division (29). This drug class can be ant-proliferative by inducing cell death in G0, pro-apoptic by targeting Bcl-2, caspases 3/8/9/ or by targeting p53 (30)

Cisplatin is usually administered with other drug classes to target various pathways of the tumour. However, when administered in combination therapies it is difficult to determine the molecular and cellular impact of each drug when administered in vivo. Studies would need to be conducted to understand the impact of each drug in vitro.

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1.5 Aim of the study

Pregnancy-associated cancers are estimated to affect approx. 1 in 1000 pregnancies (31). Cisplatin-based chemotherapies are used for a wide range of cancer types (9) and can be administered during gestation (32). Gynaecological, breast and melanoma cancers are the most diagnosed pregnancy-related tumours being observed in 70-80 % of cases (2). However, information on the impact of cisplatin on pregnancy outcomes and maternal survival is limited. To establish an overview of the available data on cisplatin administration during pregnancy, a systematic review of the scientific literature was performed in this study. These data were interpreted in the context of existing guidance.

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2. Methods

Relevant articles were identified by using the search term 'cisplatin pregnancy' in PubMed (https://pubmed.ncbi.nlm.nih.gov) on 1st April 2021. Articles in English were included in the analysis when they held original data on the treatment of pregnant cancer patients with a therapy regimen that included cisplatin or relevant original data from preclinical studies. The selection of articles was independently checked by a second scientist (Martin Michaelis).

3. Results

A literature search using the search term 'cisplatin pregnancy' resulted in 511 hits. 106 of these articles held original data on cisplatin treatment during pregnancy (Figure 3, Suppl. Table 1). 62 articles reported on the clinical treatment of pregnant cancer patients (Suppl. Table 1) and 23 articles on preclinical studies using experimental systems (Suppl. Table 2).

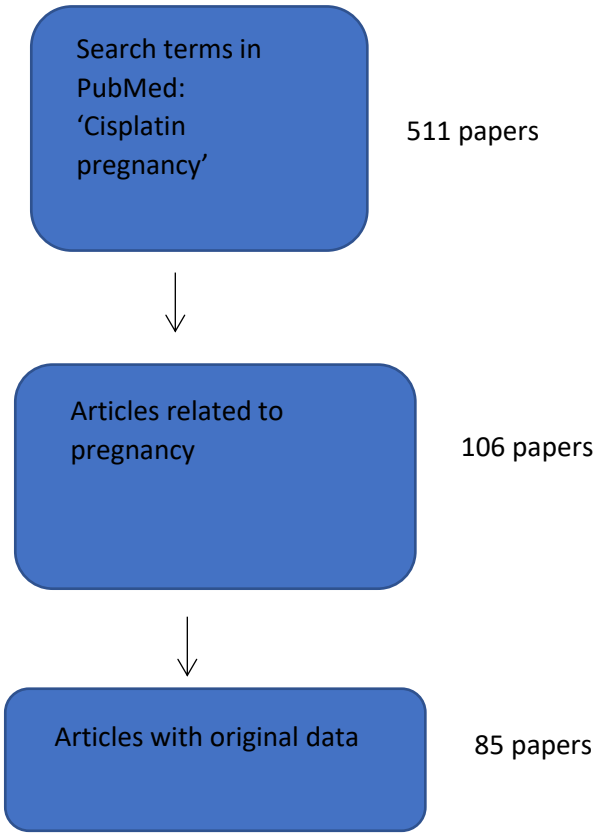

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Figure 3: Article decision chart used to Identify Appropriate Papers from the PubMed Database. Articles that did not investigate cisplatin administration during pregnancy was excluded from the study. Review papers were not included as they did not hold original pre-clinical or clinical data.

3.1 Maternal age at diagnosis

In total, we identified 62 case reports published between 1980 and 2020, which described 67 cases of pregnant cancer patients who were treated with cisplatin-based therapies (Suppl. Table 1). The age distribution of patients at the time of diagnosis is provided in Figure 4. Maternal age ranged from 19 to 41 years.

Fewer cases were detected in women under than in women over 30 years of age.

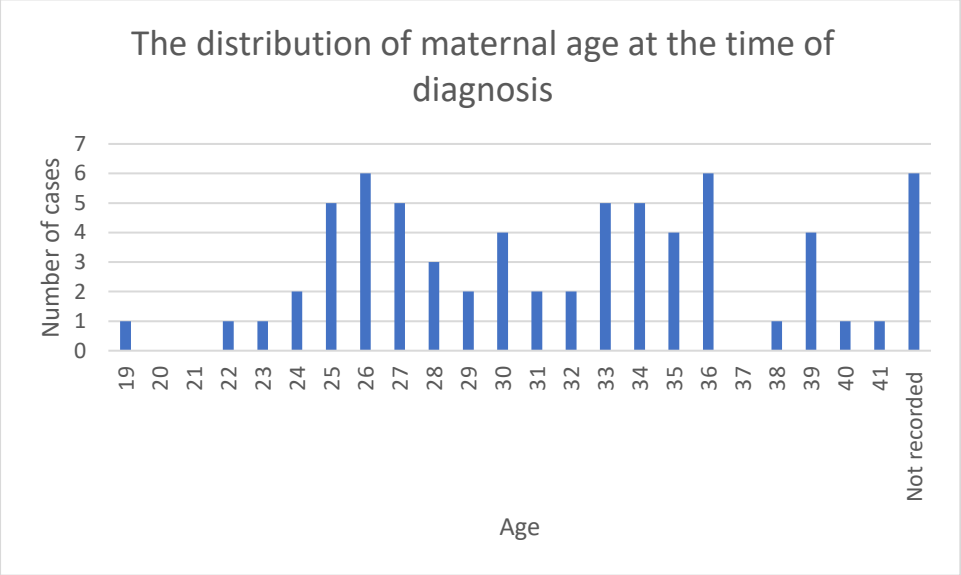

Figure 4: Maternal Age at the Time of Cancer Diagnosis During Pregnancy. The maternal age recorded in 61 papers was recorded. However, 6 papers did not have maternal age recorded. The graph shows women over 30 were more at risk of being diagnosed with malignancies during pregnancies.

The median gestational week at the time of diagnosis was 22.3, among the 26 cases for which gestational age was provided (Suppl. Table 3). Nineteen (73.0 %) of the 26 patients underwent

chemotherapy during the 2nd trimester (week 13-26) (Figure 5), while six (23.0 %) underwent chemotherapy during the 3rd trimester (week 27 onwards)

As expected, cisplatin therapy during the 1st trimester (week 1-12) was rare. If a cancer is detected in the 1st trimester of pregnancy, patients will typically be recommended to terminate the pregnancy (33). If pregnant women wish to continue the pregnancy, treatment will normally be postponed until the second trimester to reduce the risk of congenital malformations (34) and miscarriage (33).

In agreement, just 1 out of the 67 (1.5 %) pregnant patients were treated with cisplatin-based chemotherapy during the 1st trimester (35) (Figure 5), whose treatment was started before the pregnancy was recognised. This patient received treatment for stage IV non-small cell lung cancer and was administered a combination of docetaxel, gemcitabine, and cisplatin between weeks 9 and 16 (35)**.** When the pregnancy was detected during week 16, the treatment was stopped. The maternal outcome was not particularly unfavourable. The patient remained disease-free over a 6-month observational period, while the average disease-free period for stage IV non-small lung cell cancer is about 12.5 months (36). No developmental abnormalities were observed in the child during the first 2 years of life.

It is also not a surprise that more patients received cisplatin-based during the 2nd trimester than during the 3rd trimester, as a postponement of treatment until after birth becomes a more possible choice for treatment if the cancer is diagnosed in the latter half of the 3rd trimester (from week 25 onwards) (Figure 5) (33). Moreover, the ESMO guidelines recommend a three-week gap between the final dose of cisplatin-based therapy and delivery. This is to allow recovery of both the maternal and foetal bone marrow (33) and the replenishment of blood cells thus reducing the risk of infection (37).

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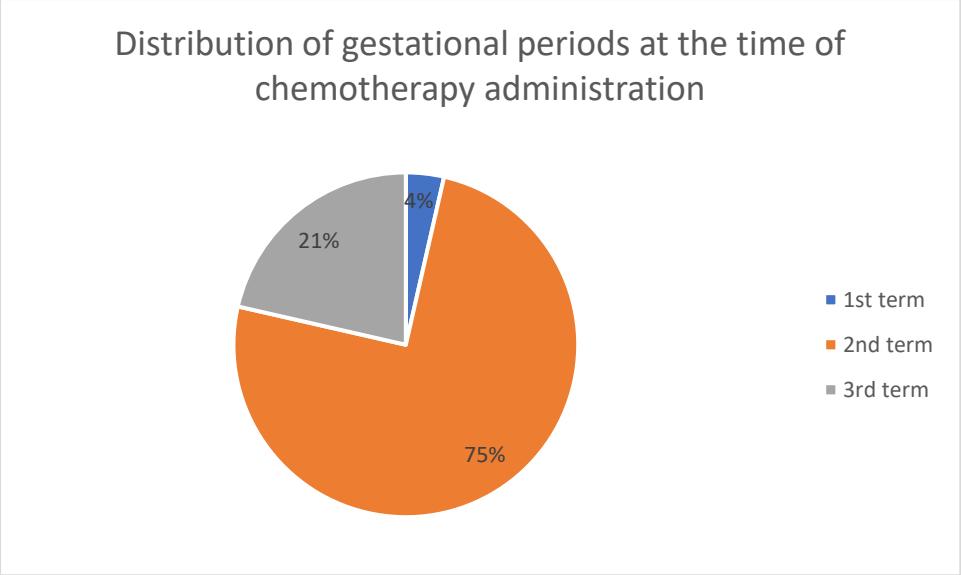

Figure 5: The Distribution of the Gestational Period Chemotherapy was Administered. Majority of cases were administered chemotherapy during the 2nd trimester. However, administration during the 3rd trimester occurred at a lower rate while administration during the 1st trimester was rare.

3.2 Geographical distribution and distribution of cancer types

Figure 6 shows that most cancer diagnosed during pregnancy were gynaecological malignancies. Cervical cancer was recorded in 27 (40.3 %) out of 67 patients, ovarian cancer in 22 patients (32.8 %) and lung cancer in 5 patients (7.5 %). This is in line with the published literature suggesting that gynaecological cancers play a dominant role in cancer diagnosed during gestation (38). The number of lung cancer in our cohort is higher than would be generally expected (39). However, it is believed that increased smoking among females during adolescence and young adulthood may increase the number of cancer cases diagnosed during pregnancy (40). Moreover, the numbers may not be representative, as cisplatin is not a standard treatment for all cancers in the same way as it is for lung cancer.

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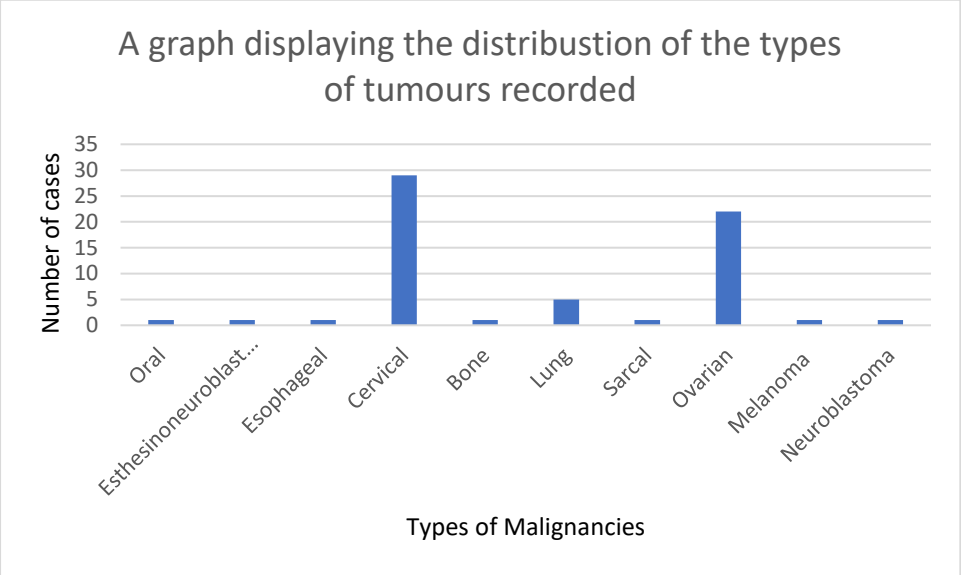

Figure 6: Distribution of cancer types among cisplatin-treated pregnant cancer patients. Cervical cancer was the most diagnosed malignancy during pregnancy followed by ovarian cancer.

Most case reports were from Europe (24, 35.8 % out of 67 patients), followed by Asia (19 of 67 cases, 28.3 %) (Figure 7). There is no data available that would allow a conclusion on whether these numbers reflect differences in cancer incidence during pregnancy or differences in reporting.

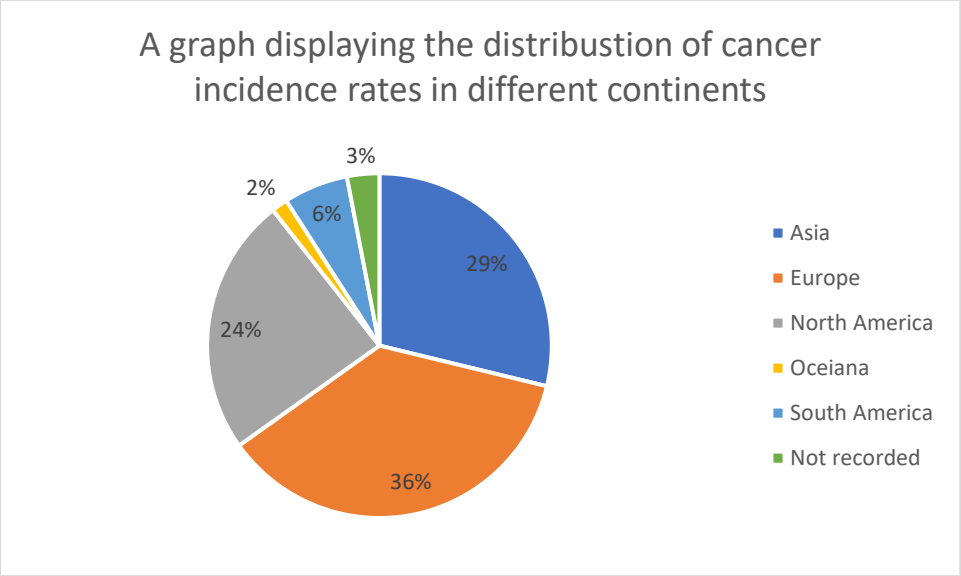

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Figure 7: Geographic distribution of cases of pregnant cancer patients treated with cisplatin-based therapy. Europe identified the highest volume of patients diagnosed with malignancies during pregnancy followed by Asia and North America.

The distribution of cancer types differed between the world regions (Figure 8 A to 8C) (Supp Table 4). Cervical cancer was the most prominent cisplatin-treated cancer among pregnant patients in Europe being diagnosed in 16 (66.6 %) out of 24 patients, followed by ovarian cancer (3 out of 24 patients, 12.5 %) (Figure 8A).

Ovarian cancer was the leading cancer entity in Asia being recorded in 8 (41. 1 %) out of 19 patients, followed by cervical cancer (7 out of 19 patients, 36.8 %).

Ovarian cancer was also the most common cancer in North America is recorded in 8 (50 %) out of 16 patients, followed by cervical cancer (4 out of 16 patients, 25 %) and lung cancer (2 out of 16 patients, 12.5 %) (Figure 8C).

The distribution of cancer types appears to reflect cancers that are typically treated by cisplatin and not necessarily the general distribution of cancer types during pregnancy. The Danish registry recorded high incidences of melanoma, cervical, and breast cancer during gestation. An Italian study recorded elevated levels of breast cancer during gestation, while an Australian study also recorded elevated levels of breast cancer as well as thyroid cancer during gestation (31). Melanoma and thyroid cancers are not normally treated with cisplatin, and only certain types of breast cancer are treated with cisplatin-containing therapies (27,28)

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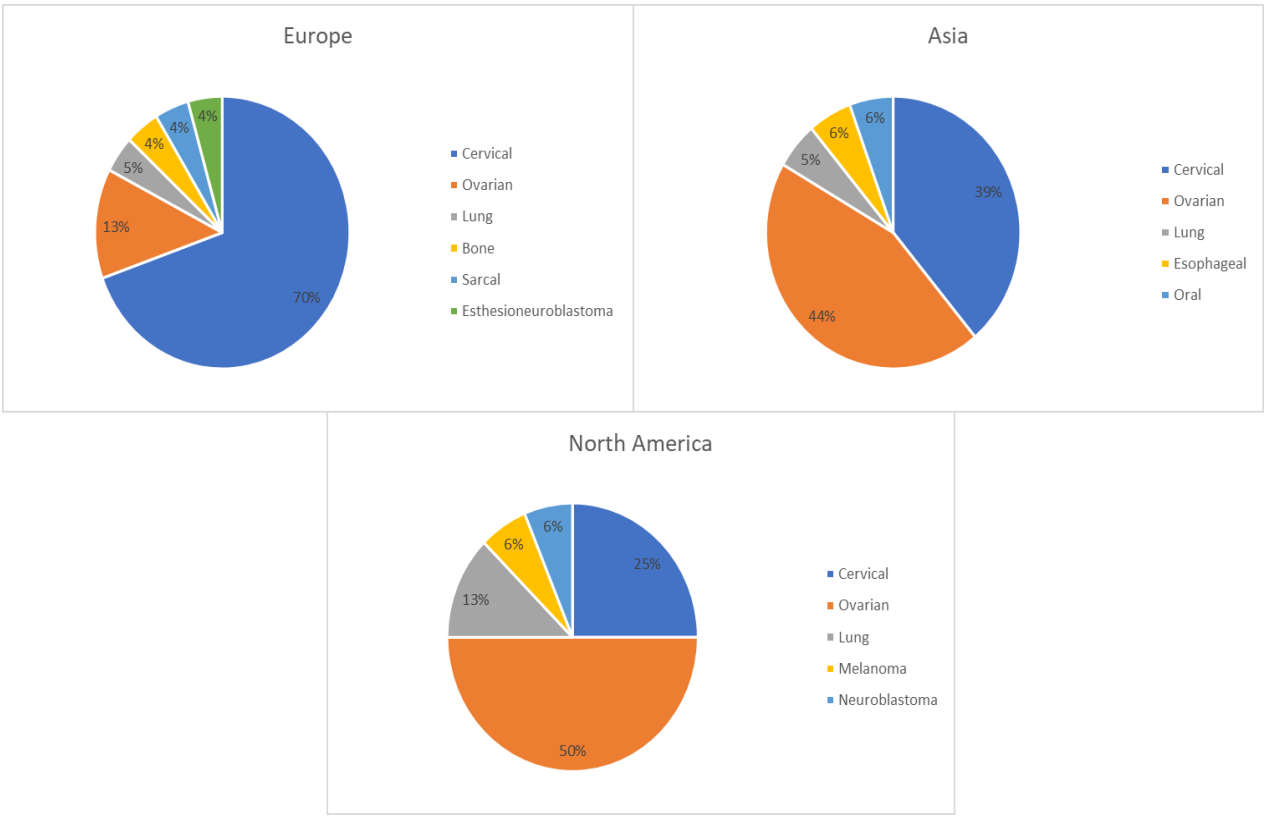

Figure 8A: The Distribution of Tumours Recorded in Europe. 8B: The Distribution of Tumours Recorded in Asia. 8C: The Distribution of Tumours Recorded in North America. Gynaecological cancers were the most prominent malignancy diagnosed during pregnancy.

3.3 Treatment regimens

There were considerable differences between the drug combinations used for the treatment of cervical cancer, ovarian cancer, and lung cancer (figure 9), which reflected different and treatment protocols (33) (41). More detail on the exact nature of the diagnosis, patient characteristics, and treatment alterations are provided in chapter 3.5).

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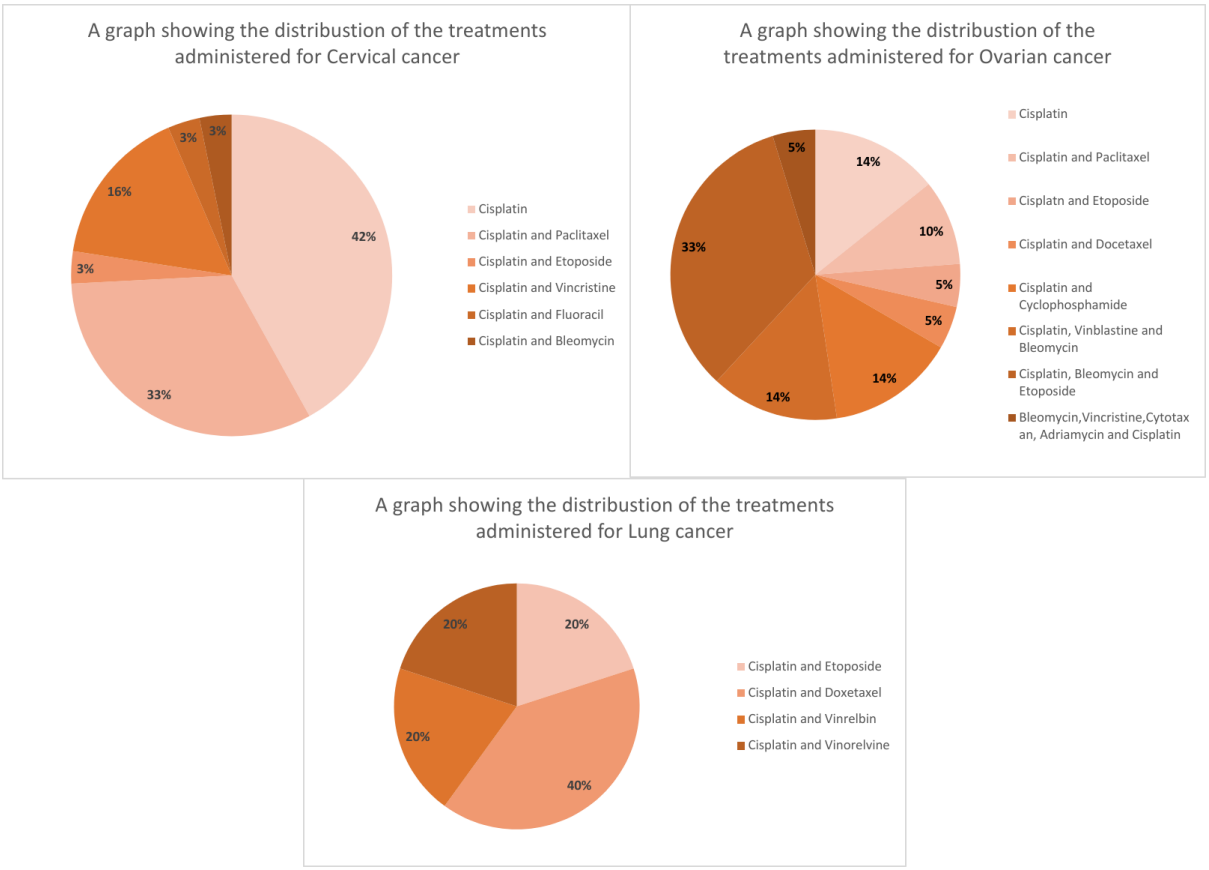

Figure 9A: Distribution of Treatments Used for Cervical Cancer. Figure 9B: Ovarian cancer patients. Figure 9C: Lung Cancer patients. Cisplatin monotherapies were administered in majority of cases for cervical cancers. Whereas cisplatin monotherapy was administered in 14 % of cases for ovarian cancers and was not administered in lung cancer patients. Instead, cisplatin combination therapy was used in all cases.

3.4 Pregnancy-related changes to therapy

Cancer treatment may be modified in pregnant cancer patients to mitigate harm to the unborn child (33). However, 57 (85.0 %) out of 67 patients received the unmodified standard therapy (Figure 10). In only 10 cases (15 %), treatment was modified (Figure 10, Table 1).

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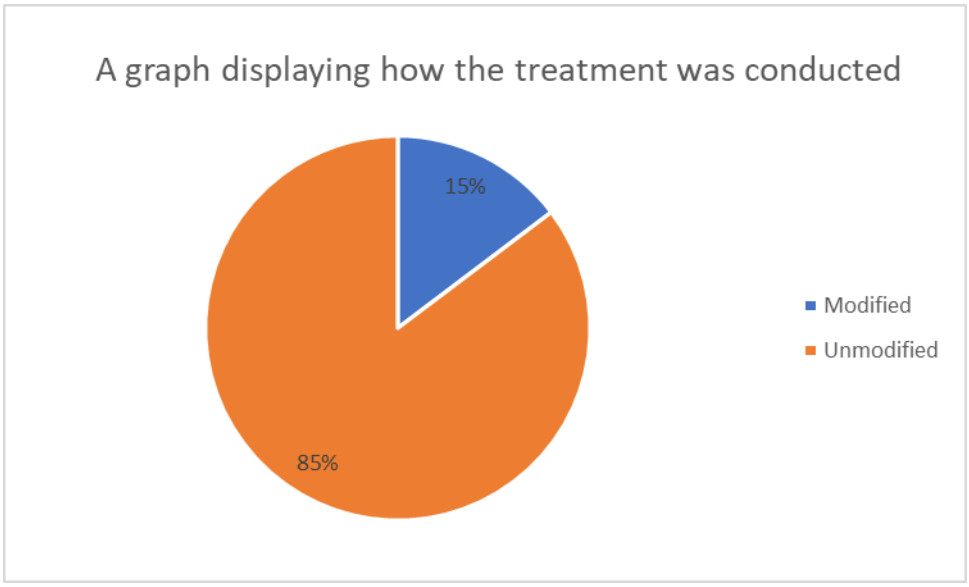

Figure 10: Proportion of cisplatin-treated pregnant cancer patients in whom the therapy protocol was modified compared to the standard treatment. 85 % of patients received unmodified cisplatin therapies. Whereas 15 % received modified chemotherapy.

In one case, 5 doses of 20 mg/m^2 cisplatin were administered over 5 consecutive days instead of one dose of 100 mg/m^2, to reduce the potential impact of exceedingly high cisplatin concentrations on the foetus (Case 6, Table 2) (42). The child was delivered during the 32nd week of gestation displayed normal development during the first 2 years of life.

In another study, two pregnant patients received 75 mg/m^2 paclitaxel and 50 mg/m^2 cisplatin every two weeks. This was a reduction of paclitaxel, of which 135 mg/m^2 would have been used in non-pregnant patients to shorten the recovery time before delivery (43). In Case 1, the mother was disease-free during the 21-month observational period, while the child was showing normal development. In Case 2, the mother was disease-free during the 13-month observational period and the child was recorded to have normal development (Case 19 in Table 2) (44).

Overall treatment modifications did not influence either foetal outcome compared to standard treatments. Low rates of foetal complications were observed when modifications were administered.

In Case 56 (Table 2) (45) dose-intensive cisplatin therapy was administered during gestation however, the amount administered was unknown. From the information, this would be higher compared to the 50mg/m^2 administered in other pregnancy-associated cancer cases. This dose-intensive therapy increases the recovery time before delivery. No adverse foetal effects were recorded. Dose intensity is defined as the drug dose delivered per time unit which is expressed as mg/m^2 per week (46).

Cases 1 and 3 received reduced doses of radiotherapy, because the radiation may reduce the mental ability of the child if undertaken between 8 to 25 (5) (47). In Case 1 (Table 2) (48) radio chemotherapy was decided. Eighty mg/m^2 tri-weekly cisplatin was administered, which is higher than the 50 mg/m^2 administered in unmodified cases. Sixty Gy was prescribed to the involved nodes over 33 fractions. The standard dose varies on the case due to being tailored to the patient in both pregnant and non-pregnant women. The mother died 6 months after birth, while the child was delivered without complications. Due to access restrictions, the developmental progress of the child is unknown.

In Case 3 (Table 2) (49) radio chemotherapy was decided. The treatment regimen involved 750 mg/m^2 5-fluorouracil and 60 mg/m^2 cisplatin compared to the 50 mg/m^2 administered in standard cases. The mother was prescribed 50.4 Gy over 28 fractions. The standard dose varies on the case due to being tailored to the patient in both pregnant and non-pregnant women. The mother was disease-free over the 12-month observational period while the child recorded normal development.

Table 2. Therapy Modifications in Pregnant Cancer Patients Receiving Cisplatin-Based Therapies. Modifications made occurred in the form of reduction of dose, scheduling of when doses are administered and changing the components involved in treatment.

Case report	Modification

1 Takahashi W et al. (48)	Administered tri-weekly cisplatin chemotherapy at 80 mg/m^2 with radiotherapy. To determine an optimal modality for foetal dose reduction during radiotherapy a comparison was performed using helical tomotherapy, single-arc volumetric arc therapy and flattening filter-free - volumetric modulated arc treatment
2 Guerreiro IM at al (50)	No modifications
3 Yamada K et al. (49)	Cisplatin and 5-fluorouracil were administered in conjunction with radiotherapy. An irradiation plan was created and identified the foetal dose was between 1.56 to 5.28 mGy
4 Gil-Ibañez B et al. (51)	No modifications
5 Oliveira AF et al. (52)	No modifications
6 Weidema M et al. (42)	100 mg/m^2 of cisplatin was split into 5 doses of 20 mg/m^2 to be administered over 5 consecutive days
7 De Vincenzo R et al. (53)	No modifications
8 Kayahashi K et al. (54)	No modifications
9 Surbone A (55)	No modifications
10 Yates R et al. (56)	No modifications

11 Iliaz S et al. (57)	No modifications
12 Kong TW et al. (58)	No modifications
13 Wiesweg M et al. (42)	No modifications
14 Geijteman ECT et al. (59)	No modifications
15 Dawood R et al. (60)	No modifications
16 Zagouri F et al. (61)	No modifications
17 Guo Q et al. (62)	No modifications
18 Manikandan K et al. (63)	No modifications
19 Li J et al. (44)	Potencies of cisplatin and paclitaxel were increased in 2 cases
20 da Fonseca AJ et al. (64)	No modifications
21 Lanowska M et al. (32)	No modifications
22 Serkies K (65)	No modifications
23 Chvatal R et al. (66)	No modifications
24 Marnitz S et al. (67)	No modifications
25 Benjapibal M et al. (68)	No modifications
26 Rabaiotti E et al. (69)	No modifications
27 Favero G et al. (70)	No modifications
28 Ghaemmaghami F et al. (71)	No modifications
29 Marnitz S et al. (67)	No modifications

30 Seamon LG et al. (72)	No modifications
31 Boyd A et al. (73)	No modifications
32 Rouzi AA et al. (74)	No modifications
33 Poujade O et al. (75)	No modifications
34 García-González J et al. (76)	No modifications
35 Kluetz PG et al. (77)	No modifications
36 Garrido M et al. (78)	No modifications
37 Palaia I et al. (79)	Paclitaxel was removed from the treatment regimen due to an allergic reaction and cisplatin was administered as a monotherapy
38 Kim JH et al. (35)	No modifications
39 Karimi Zarchi M et al. (80)	No modifications
40 Robova H et al. (81)	No modifications
41 Karam A et al. (82)	Cisplatin was administered weekly
42 Bader AA et al. (83)	No modifications
43 Motegi M et al. (84)	No modifications
44 Caluwaerts S et al. (85)	No modifications
45 Huang H et al. (86)	No modifications
46 Han JY et al. (87)	No modifications
47 Otton G et al. (88)	No modifications
48 A K Sood et al. (89)	No modifications

49 Marana HR et al. (90)	No modifications
50 Elit L et al. (91)	No modifications
51 Tewari K et al. (92)	Bleomycin was removed from the treatment regimen due to pulmonary complications. Second case had no modifications
52 Dipaola RS et al. (93)	No modifications
53 Arango HA et al. (94)	No modifications
54 Zemlickis D et al. (95)	No modifications
55 Henderson CE et al. (96)	No modifications
56 King LA et al. (45)	Dose intensive cisplatin therapy was administered
57 Christman JE et al. (97)	No modifications
58 Malfetano JH et al. (98)	No modifications
59 Kim DS et al. (99)	No modifications
60 Malone JM et al. (100)	No modifications
61 Pride GL et al. (101)	No modifications
62 Jacobs AJ et al. (102)	No modifications

3.5 Maternal outcome

Maternal outcomes were recorded in 47 out of 67 cases (Table 3, Suppl. Table 6). During the observational period, 37 patients were recorded to be disease-free. However, in 8 (11.9 %) out of 67 cases maternal death was recorded from recurrence and/or metastasis during this

observational period. However, the observational period was not long enough to draw overall conclusions on the maternal outcome.

Cases 18 and 51 were undergoing further treatment for deteriorating disease at the time of reporting (63)(79). Case 18 (63) (Suppl. Table 7) recorded weekly treatment involving cisplatin, bleomycin, and etoposide for mediastinal dysgerminoma. The mother received post-natal external beam radiotherapy. Despite receiving post-natal treatment, the disease progressed two weeks after completing radiotherapy.

In Case 51 (92) (Suppl. Table 7), a partial tumour reduction was recorded after receiving cisplatin and vincristine, which was followed by cisplatin monotherapy. During an elective Caesarean section, a radical hysterectomy was performed with pelvic lymphadenectomy and lateral ovarian transposition. The mother received postnatal external beam radiation therapy. However, 5 months after the surgery, disease recurrence was observed. It was recorded that the tumour had metastases to the external oblique muscles of the abdominal wall as well as in the rectosigmoid solon, anterior mesentery of the sigmoid colon and pelvic sidewalls and the patient was receiving salvage chemotherapy.

Modifications that were recorded in 10 patients (Table 2) did not appear to affect the maternal outcome negatively. This suggests that modifications to treatment regimens as described in Table 2 proved effective as inducing tumour regression.

Table 3: Displays the Maternal Outcome Recorded During the Observational Period. The period in which the mother was observed varies on the study. However, 13.4 % of mothers succumbed to the disease.

Case	Maternal outcome
1 Takahashi W et al. (48)	The mother died 6 months after the radiotherapy from lung metastases

2 Guerreiro IM et al (50)	The mother is clinically well but is undergoing treatment for a grade 1 diminution of visual acuity in the right eye, xerostomia grade 1, and cervical fibrosis grade 1
3 Yamada K et al. (49)	The mother is disease-free 12 months after the caesarean section
4 Gil-Ibañez B et al. (51)	The mother is disease-free 38 months postoperatively
5 Oliveira AF et al. (52)	The mother is disease-free after 2 years
6 Weidema M et al. (42)	The mother is disease-free after 2 years
7 De Vincenzo R et al. (53)	Not recorded
8 Kayahashi K et al. (54)	The mother is disease-free 34 months post operatively
9 Surbone A (55)	The mother is disease-free after 6 years
10 Yates R et al. (56)	The mother is disease-free after 16 months
11 Iliaz S et al. (57)	The mother died after 10 months due to metastasis
12 Kong TW et al. (58)	The patient is disease-free after 4 years

	The mother is disease-free after 3 years
	The mother is disease-free after 3 years
13 Wiesweg M et al. (42)	The mother died after 14 months
14 Geijteman ECT et al. (59)	Not recorded
15 Dawood R et al. (60)	Cisplatin allowed a good outcome for most patients
16 Zagouri F et al. (61)	The median progression-free survival was 48.5 months
17 Guo Q et al. (62)	Not recorded
18 Manikandan K et al. (63)	The disease worsened two weeks after radiotherapy
19 Li J et al. (44)	The mother is disease-free after 21 months
	The mother is disease-free after 13 months
20 da Fonseca AJ et al. (64)	The mother is disease-free after 12 months
21 Lanowska M et al. (32)	Not recorded
22 Serkies K (65)	The mother dies 35 after cancer diagnosis
23 Chvatal R et al. (66)	The mother is disease-free after 16 months
24 Marnitz S et al. (67)	Not recorded

25 Benjapibal M et al. (68)	The mother is disease-free after 23 months
26 Rabaiotti E et al. (69)	The mother died after 2 years
27 Favero G et al. (70)	No complications in the mother were observed
28 Ghaemmaghami F et al. (71)	The mother is disease-free after 8 months
29 Marnitz S et al. (67)	Not recorded
30 Seamon LG et al. (72)	The mother is disease-free after 4.1 years
31 Boyd A et al. (73)	The mother is disease-free after 15 months
32 Rouzi AA et al. (74)	The mother is disease-free after 6 months
33 Poujade O et al. (75)	The mother is disease-free after 6 months
34 García-González J et al. (76)	The mother died 10 mothers after diagnosis
35 Kluetz PG et al. (77)	Not recorded
36 Garrido M et al. (78)	The mother is disease-free after 11 months
37 Palaia I et al. (79)	The mother is disease-free after 10 months
38 Kim JH et al. (35)	Not recorded

39 Karimi Zarchi M et al. (80)	The mother is disease-free for 1.5 years
40 Robova H et al. (81)	Not recorded
41 Karam A et al. (82)	The mother is disease-free after 14 months
42 Bader AA et al. (83)	The mother is disease-free after 80 months
43 Motegi M et al. (84)	The mother is disease-free after 65 months
44 Caluwaerts S et al. (85)	Not recorded
45 Huang H et al. (86)	Not recorded
46 Han JY et al. (87)	The mother is disease-free after 6 years
	The mother is disease-free after 2 years
47 Otton G et al. (88)	Not recorded
48 A K Sood et al. (89)	The mother died 29 months after diagnosis
49 Marana HR et al. (90)	The mother died almost 1 month after birth
50 Elit L et al. (91)	The mother is disease-free after 16 months
51 Tewari K et al. (92)	The mother is receiving salvage chemotherapy

	The mother is disease-free after two years
52 Dipaola RS et al. (93)	Not recorded
53 Arango HA et al. (94)	Not recorded
54 Zemlickis D et al. (95)	Not recorded
55 Henderson CE et al. (96)	Not recorded
56 King LA et al. (45)	Not recorded
57 Christman JE et al. (97)	Not recorded
58 Malfetano JH et al. (98)	Not recorded
59 Kim DS et al. (99)	The mother is disease-free after 2 years
60 Malone JM et al. (100)	Not recorded
61 Pride GL et al. (101)	Not recorded
62 Jacobs AJ et al. (102)	Not recorded

3.6 Foetal outcomes

Figure 11 displays the average birth weight in Europe, North America, Asia, and South America in children of cisplatin-treated mothers as derived from the investigates studies. For regions for which we could data acquire data from control cohorts, the birth weights appear to be lower than in the general population. For example, the average birth weight in England and Wales is recorded as 3316 g (103), while the average birth weight of children born to mothers receiving cisplatin-based therapies in Europe was recorded to be 2082g (figure 11).

Moreover, the control cohorts average birth weight in the United States of America was recorded to be 3446g, (104) while, the average new-born weight recorded after intrauterine exposure to cisplatin-based therapies in North America was 2279g. Similarly, in Asia, the control

cohorts average birth weight was recorded to be 3196g (105) and the average birth weight after intrauterine exposure to cisplatin-based therapies was 2058g.

Generally, low birthweight is defined as a new-born weighing 2500g or under (106). Hence, children born to mothers treated with cisplatin-based therapies are typically characterised by low birth weights.

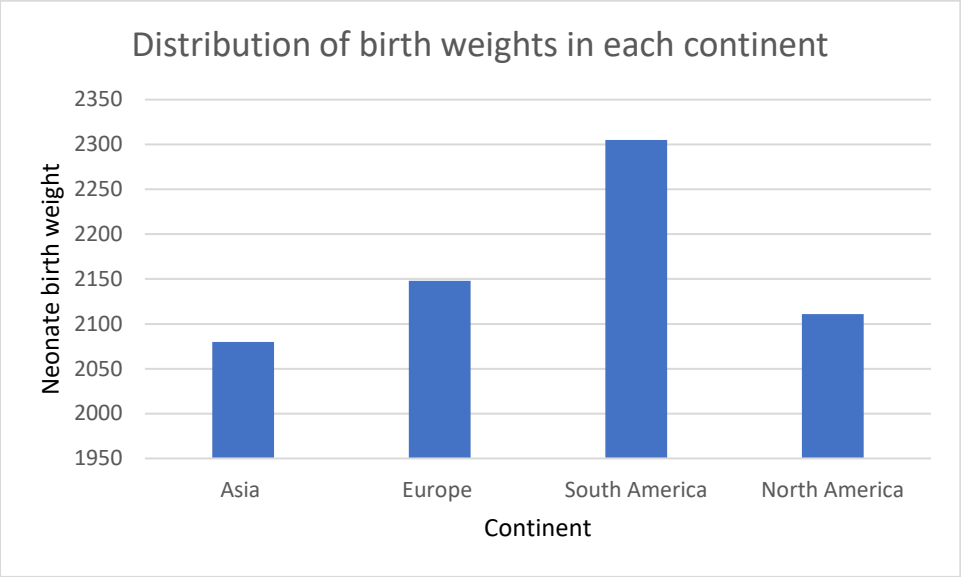

Figure 11: A Graph Displaying the Foetal Weights Across the Continents. The graph shows the average foetal weight recorded in South America is 2471g compared to Europe's average birth weight in 2082g, North America 2279g and Asia 2058g. (Supp Table 5).

The birth weight of new-borns born to mothers receiving cisplatin-based therapies was recorded (blue) and the foetal weights in the control cohort (orange) were recorded at each gestational period delivery occurred. Figure 12 shows critical differences in foetal weight between the control cohorts' weight and the children born to mothers receiving cisplatin-based therapy during gestation.

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Both in children of cisplatin-treated mothers and control cohorts, birth weights increased with the gestational week of delivery (Figure 12). Highly similar values suggest that cisplatin did not reduce the birth weights in children of mothers treated with cisplatin-containing therapies during pregnancies when they were delivered at the same time.

Figure 12 displays the birth weight at each gestational period (blue) compared to a control cohort (orange). Children of cancer patients have similar weights compared to the control cohort. However, week 35 identified a difference of 478g less compared to the control sample, however, the reason for this change is unknown. Gestational week 30 recorded a difference of 166g suggesting that despite intrauterine exposure to cisplatin it had negligible impact on foetal weight. Generally, birth weights seem to reflect the gestational age at birth. Cisplatin-based therapies do not seem to have a substantial impact on the weight of children at birth.

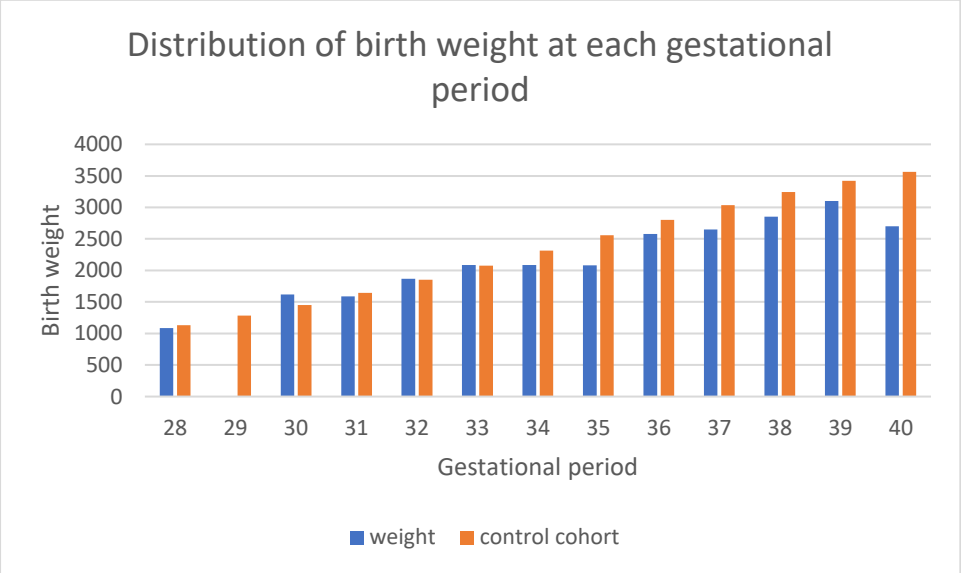

Figure 12: new-born weight at different gestational stages after intrauterine exposure to cisplatin. Average birth weights of control cohorts (107) are provided in orange. While average birth weights of children of mothers, who received cisplatin-based therapies during pregnancy are supplied in (blue).

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3.7 Health status of new-borns

APGAR scores are a worldwide scale and are used to evaluate the health status of new-borns immediately after birth (108). APGAR scores are determined by five factors that have a value between 0 and 2. These factors are heart rate, respiratory effort, muscle tone, reflex irritability and colour (109). Normal APGAR scores in new-borns in the general population are expected to be between 7 and 10. Lower APGAR scores are a marker for short- or long-term complications that require further intervention (109). Figure 13 A and 13B shows that most new-borns exposed to intrauterine cisplatin-based therapies received a score between 7 and 10. Notably, this included some new-borns suffering from respiratory distress syndrome that did not require further interventions as described in Table 4.

Low APGAR scores were only detected in 3 (4.4 %) out of 67 children born to mothers administered cisplatin-based therapies during gestation. In untreated cohorts born between 28 and full-term low APGAR scores were observed in 0.76 % of 1028705 new-borns (110).

Low APGAR scores were recorded in Case 8 (54), Case 34 (76), and Case 53 (94).These cases experienced premature birth between 30 and 35 weeks implying that premature birth influenced a reduction in APGAR scores. Here, a conclusion is needed on whether these lower APGAR scores may be caused by the early birth week or not.

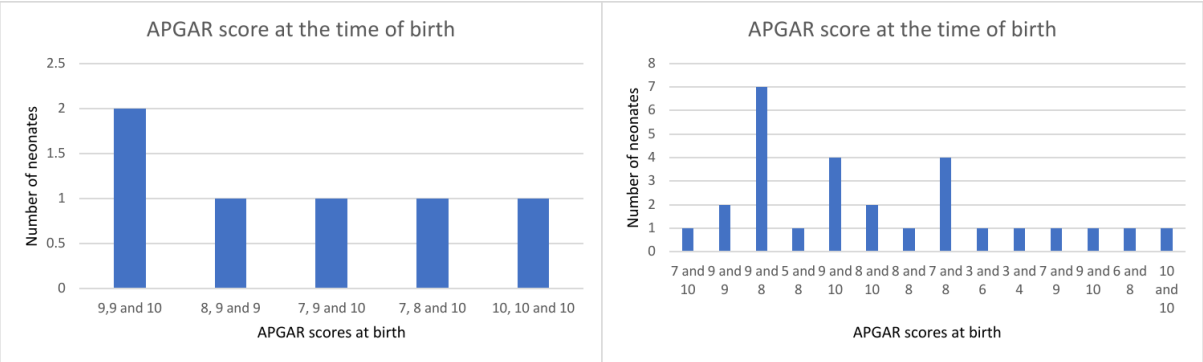

Figure 13A: A graph displaying the APGAR scores at 1 and 5 and minutes after birth. Overall, APGAR scores in children exposed to cisplatin therapy during utero is between 7 and 10. Figure 12B: A graph

displaying the APGAR scores at 1, 5 and 10 minutes after birth. Overall, scores in children exposed to cisplatin-based therapies in utero are between 7 and 10. These scores align with the general population; however, 2 children were given low scores.

3.8 Neonatal complications

Thirteen (19.4 %) out of 67, children born to mothers treated with cisplatin-based therapies displayed abnormalities either at birth or during neonatal development (Table 4). This agrees with earlier findings suggesting that chemotherapy during pregnancy results in complications of 8-25% of children, compared to only 4 % of children in the general population (111).

The most observed complication in neonates is respiratory distress being observed in 4 out of the 13 (30 %) children recorded with malformations. Respiratory distress in the general population is observed in 7 % of cases. However, prematurity likely influenced this increase in cases.

The child in Case 8 (Table 4) (54) was diagnosed with respiratory distress at birth which persisted for several days. Palms and soles were recorded to be encased in a cellophane-like membrane and showed skin slip depilation. The child developed generalised erythroderma, hyperkeratosis of the epidermis, hyper granulosis, and keratohyaline granules. These symptoms are compatible with ichthyosiform erythroderma. After genetic testing, the child was diagnosed with congenital ichthyosiform erythroderma and Keratitis-ichthyosis-deafness syndrome. Her skin improved over 65 days and had gradual regression of the erythema. This is one of the few cases that was confirmed to be caused by intrauterine exposure to cisplatin.

Premature delivery has possibly influenced the complications displayed in Table 4 as complications were not observed in children born full-term. However, cisplatin may have the ability to influence growth restrictions via its transplacental ability although the impact is minimal.

Long term effects of intrauterine exposure to chemotherapeutic agents are limited as many studies do not follow the maturation of the child and instead focuses on the clinical outcome of the mother. Due to this limited information abnormalities such as transplacental carcinogenesis, infertility,

developmental and neurological development reduces cannot be linked to chemotherapeutic exposure. However, a review from the national medical center in Mexico was carried out and showed 89 women were treated for cancer during pregnancy. Unfortunately, 5 mothers succumbed to the disease before treatment. The 84 children that were delivered revealed no cytological abnormalities, no cardiac cytotoxicity was present. The study also revealed educational performance was not inhibited in these children (112)

Table 4: A Table describing foetal complications recorded after birth or during the neonate's development. A high percentage 19.4 % of neonates presented with complications. Respiratory distress was the most common complication that was observed at birth.

Case	Foetal complication
7 De Vincenzo R et al. (53)	At 22 months the child experienced acute myeloid leukaemia
8 Kayahashi K et al. (54)	The child suffered from respiratory distress syndrome for several days. Palms and soles were encased in a cellophane-like membrane, and skin slip depilation. Developed generalised erythroderma. Hyperkeratosis of the epidermis, hyper granulosis and keratohyaline granules are compatible with ichthyosiform erythroderma.
9 Surbone A (55)	The daughter was diagnosed with retroperitoneal embryonal rhabdomyosarcoma

14 Geijteman ECT et al. (59)	The child was diagnosed with severe bilateral perceptive hearing loss
17 Guo Q et al. (62)	One patient that experienced cisplatin and fluorouracil the child died as a neonate
18 Manikandan K et al. (63)	Foetal growth restriction required a premature delivery. The child died 24 hours after delivery caused by prematurity
26 Rabaiotti E et al. (69)	The child developed respiratory distress syndrome requiring intubation.
29 Marnitz S et al. (100)	One child required respiratory support.
34 García-González J et al. (76)	The child developed acute respiratory distress syndrome
43 Motegi M et al. (84)	The child suffered from intrauterine growth restriction.
46 Han JY et al. (87)	The child suffered from intussusception at 7.5 months of age but at 26 months the infant was developing normally
49 Marana HR et al. (90)	The child has developed ventriculomegaly with cerebral atrophy
56 King LA (45)	The child developed tachypnoea and respiratory distress syndrome requiring intubation

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3.9 Preclinical studies using experimental model systems and pharmacokinetic studies.

The findings of experimental studies on the impact of cisplatin during pregnancy are summarised in Suppl. Table 2 and Suppl. Table 9.

Experimental and pharmacokinetic investigated the impact that cisplatin may have on the placenta (Table 6). Cisplatin treatment of placental villous tissues reduced cell viability by 17 to 21 %. However, it is unclear whether the concentrations used are administered in clinical studies (113). However, only 0.52% of a cisplatin bolus was detected in the foetal vein 5 minutes after administration (113). This was interpreted as a minimal cisplatin transport across the placenta, posing minimal risk to the neonate.

Table 5: The Effects of Cisplatin Against Placental Tissue. Cisplatin was administered to placental tissue to understand cisplatin-induced toxicity and how this could potentially affect nutrient transference.

Paper	Chemotherapeutic agent	Dose of chemotherapeutic agent	Outcome
Eliesen GAM et al. (113)	Cisplatin	1 mM	Reduced tissue viability to 17 – 21 %.
Al-Saleh E et al. (114)	Cisplatin	100 µL	Cisplatin transport rates averaged 0.97, 0.97, 0.96, 0.97 and 0.99 times the antipyrine reference value.

Table 6 displays the impact of cisplatin administration in 18 animal models. Rats were most used as animal models, in 8 (44.4 %) out of 18 studies. Other species used were guinea pigs, mice, monkeys and chick embryos. Seventeen (94.4 %) out of 18 studies reported various forms of

damage to the foetus. There were no obvious differences between the investigated species. These findings contrast with the clinical observations in the case reports analysed here. The reasons for these discrepancies are not clear. Notably, the pharmacokinetics may differ between humans and the species used as model organisms. Hence, future animal studies should be informed by clinical drug concentrations in humans and model the impact of the appropriate concentrations.

Table 6: The Effects of Cisplatin in Animal Models. Preclinical models were induced with tumours and subjected to cisplatin chemotherapy to understand the toxic effects cisplatin may pose to developing offspring.

Paper	Species	Chemotherapeutic agent	Dose of chemotherapeutic agent	Outcome
Hassan MS et al. (115)	Rats	Cisplatin	Intraperitoneally 5 mg/kg.b.wt	Foetal weights were reduced. Increased chances of Foetal dwarfs which, may show s/c haemorrhages, skeletal abnormalities, or foetal death.
Hassan MS et al. (116)	Rats	Cisplatin	0.5 mg/kgb wt	Visceral abnormalities, skeletal abnormalities. Severe

				pathological alterations.
Podratz JL et al. (117)	Mice	Cisplatin	1, 5, 10, and 50 µg/ml cisplatin	Mice were sensitive to cisplatin. Shorter neurites were observed.
Furukawa S et al. (118)	Rats	Cisplatin	2 mg/kg/day during gestational days 11-12	Foetal mortality rates were increased to 65 %. Foetal weights were decreased. Placental weights were decreased. Increases in apoptosis were discovered.
Hao S et al. (119)	Guinea pigs	Cisplatin	1.5 mg/kg bw	Induced hearing loss. This occurred by the activation of caspase- 3.
Ognio E et al. (120)	Mice	Cisplatin	8 or 12 mg/kg	Higher volumes caused foetal death. Caused

				growth restriction. Dose-dependency caused varying foetal survival. Skeletal anomalies were observed.
Náprstková I et al. (121)	Chick embryos	Cisplatin	0.03 and 0.3 µg	A dose-dependent increase in renal malformations. Impairment to the vascular network.
Gerschenson M et al. (122)	Rats	Cisplatin	15 mg/kg bw	Severe toxicity was observed within the kidneys. Activities of OXPHOS complexed II and IV were decreased. Damage to the mitochondria was mild.
Jirsová K et al. (123)	Rats	Cisplatin	10 µg	The lowest concentration cause neurite

				outgrowth alteration at 10 microM. Cisplatin was discovered after 72 hours.
Giurgiovich AJ et al. (124)	Patas monkeys	Cisplatin	5.3 mg/m^2	DNA adducts were observed in the foetal adrenal, brain, heart, kidney, liver, skin, spleen and thymus. Mitochondrial DNA adducts were high in the foetal liver, brain and kidney.
Giurgiovich AJ et al. (125)	Rats	Cisplatin	5 or 15 mg/kg bw	Extensive DNA adducts formed in the brain and liver mitochondria in foetal rats.
Giurgiovich AJ et al. (126)	Rats	Cisplatin	5, 10 or 15 mg/kg bw	DNA damage in foetal rat tissues such as the

				kidney, lung and the brain
Diwan BA et al. (127)	Rats	Cisplatin	5 mg/kg bw	Renal cell adenomas were identified. Kidney tumours were more common. Frank cell carcinomas were identified. Tumours of the central nervous and peripheral nervous systems were recorded.
Shamkhani H et al. (128)	Patas Monkeys	Cisplatin	200 mg/m^2	Elevated levels in the placenta and high adduct levels in the brains of the foetus that survived the treatment.
Diwan BA et al. (129)	Mice	Cisplatin	7.5 mg/kg bw	High incidences of papilloma were observed in

				offspring. Development in thymic lymphomas, lung tumours and kidney lesions in offspring.
Köpf-Maier P et al. (130)	Mice	Cisplatin	2.5, 5, 10 or 20 mg	Dose reduction of the number of foetuses in the litter, a decrease in foetal weight and skeletal malformations. Most foetal internal organs were without anomalies.
Köpf-Maier P et al. (131)	Mice	Cisplatin	20 mg/kg	An elevated level of necrosis began with chromatin condensation and fragmentation of the cytoplasm.

Keller KA et al. (132)	Mice	Cisplatin	0.3, 1.0, 2.5 or 3.0 mg/kg	No increase in embryo lethality. An increase in growth reduction but no malformations were observed.

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4. Discussion

The findings of this systematic review indicate that cisplatin-based therapies can be administered during the 2nd and 3rd term of pregnancy with an acceptable risk for the unborn child. These findings support the appropriateness of the ESMO guidelines on chemotherapy during pregnancy stating that it can be administered after the 1st trimester (33). ESMO is a medical oncology organisation that strives to improve prevention, diagnosis, treatment, supportive and palliative care of patients with cancer (133). This organisation supplies guidelines for the treatment of cancers during pregnancy. These guidelines are used to supply effective treatment regimens whilst minimising risk to the foetus.

Overall, new-borns of mothers, whose mothers had received cisplatin-based therapies during pregnancy displayed an enhanced level of complications. In total, 13 (19.4 %) out of 67 neonates showed some complications. This is higher than the 4 % observed in normal control cohorts (111). However, many issues seem to be rather associated with a premature delivery than with the direct impact of cisplatin-based therapies.

In only two cases (89) (90) there is evidence of a potential direct impact of cisplatin-based therapies on child health.

Another child was diagnosed with severe hearing loss (89). This may be associated with cisplatin-based therapies, as they are known to affect hearing by inducing apoptosis in cochlea hairs. (119) (134)

Intrauterine exposure to chemotherapy may reduce foetal weight by interfering with cell division. The extent to which this may occur varies on the treatment regimen and may range from 7 to 17 % (113). However, our findings did not indicate differences in weight between babies born to mothers treated with cisplatin-based therapies and control cohorts, when we compared birth

weights in the same delivery weeks (Figure 12). This may suggest that other drugs than cisplatin are more likely to be responsible for such effects.

Similar findings were made concerning APGAR scores. APGAR scores are used to determine the new-borns' health and if further intervention is needed (96). Low APGAR scores were recorded in three children that were delivered early between 30 and 35. Hence, these APGAR scores appear to reflect rather the time of delivery than the direct impact of cisplatin-based therapies (135).

Recommendations on how to treat pregnant cancer patients have been set out by the ESMO (33). The ESMO guidelines recommend 3 weeks between the last dose of cisplatin-based therapies and delivery (33). Only a few cases did not adhere to this recommendation and examples of this are Case 11 (57) administered cisplatin during the 31st week of gestation and undergoing an elective caesarean section during the 32nd week of gestation. The child was developing normally over the 10-month observational period. Case 26 (68) administered its final cycle at week 30 with delivery occurring at week 32. The child was developing normally over the 2-year observational period. Case 42 (83) administered treatment 6 days before an elective caesarean section. The child is developing normally over the 80-month observational period. Case 46 (87) spontaneously delivered the child at week 40 two weeks after the last course. The child developed normally over 6 years. Case 48 (65) delivered the child a week after the last course. The child developed normally over the 30-month observational period. Case 62 (102) performed a caesarean section two weeks after final chemotherapy administration. There is no further information on the child's development. Overall, not adhering to this guideline did not affect foetal health at birth.

Overall, this study supports the ESMO guidelines on cancer therapy during pregnancy (33).

Pre-clinical studies using placental villous tissues and animal models to investigate the impact of cisplatin-based therapies during pregnancies do not seem to be indicative of clinical outcomes. Animal models suggested that foetal mortality increased by 65 %, which was not witnessed in the clinical case reports that we identified and analysed. Other malformations such as adenomas and skeletal malformations were also not observed in clinical studies. This suggests that improved animal models need to be developed and that this should begin with the identification of species that resemble the human situation as much as possible. Moreover, pharmacokinetics that reflects the human situation is needed to examine the impact of cisplatin-based therapies on unborn offspring in animal models.

5. Future directions

“Chemotherapy during pregnancy is ethically challenging due to the risks posed to both the mother and the child. Due to these ethical issues, controlled clinical trials are not possible. Hence every effort should be made to collect as much data on treatment outcomes as possible. However, the current study was limited by the small number of documented cancer cases during pregnancy. Ideally, a depository would be established where all data on the treatment of pregnant cancer patients are collected. Moreover, longer observation periods are needed that monitor the long-term effects and outcomes of cisplatin-based therapies during pregnancy both in the mothers and their children.

Moreover, the available data from animal experiments did not reflect the clinical situation. Therefore, animal models are needed that better reflect the clinical situation of drug therapy in pregnant human cancer patients.”.

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7. Conclusions

In conclusion from the data gathered in this study, a low rate of New-born complications was recorded after intrauterine exposure to cisplatin. From the complications recorded from these studies, the majority could not be linked to cisplatin exposure causing uncertainty to the aftereffects of cisplatin after intrauterine cisplatin exposure. The data appears to favour administration in the 2nd and 3rd trimesters as recommended by the ESMO guidelines. Our data do not suggest that cisplatin-based therapies administered in the 2nd and 3rd trimesters have a major impact on child health. Overall, this paper supports the current ESMO guidelines as these recommendations protect both foetal and maternal wellbeing.

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Supplementary Tables

Clinical studies

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31709307 Acceptable fetal dose using flattening filter-free volumetric arc therapy (FFF VMAT) in postoperative chemoradiotherapy of tongue cancer during pregnancy Takahashi W, Nawa K, Haga A, Yamashita H, Imae T, Ogita M, Okuma K, Abe O, Nakagawa K. Clin Transl Radiat Oncol. 2019 Oct 14;20:9-12. doi: 10.1016/j.ctro.2019.10.002. eCollection 2020 Jan. Takahashi W Clin Transl Radiat Oncol 2019 12/11/2019 PMC6833340 10.1016/j.ctro.2019.10.002 Primary Included as the paper investigates treatment in pregnancy identifying the treatment determined was tri-weekly cisplatin, IMRT or FFF-VMAT depending on a lower fetal dose delivered

31531255 Management of Locally Advanced Esthesioneuroblastoma in a Pregnant Woman Guerreiro IM, Vieira C, Soares A, Braga A, Jácome M, Dinis J. Case Rep Oncol Med. 2019 Aug 19;2019:3789317. doi: 10.1155/2019/3789317. eCollection 2019. Guerreiro IM Case Rep Oncol Med 2019 19/09/2019 PMC6721265 10.1155/2019/3789317 Primary Included as the paper investigates treatment during pregancy which was cisplatin and hydrocortisone, metoclopramide and ondansetron was also administered as well as daily folic acid, iron, iodine and prophylatic enoxaparin to preserve the pregnancy

30627462 A Case of Recurrent Esophageal Cancer Treated with Concurrent Chemoradiation Therapy in Pregnancy Yamada K, Chigusa Y, Nomura M, Sakanaka K, Nakamura M, Yano S, Tsunoda S, Kondoh E, Mandai M. Case Rep Obstet Gynecol. 2018 Dec 3;2018:1280582. doi: 10.1155/2018/1280582. eCollection 2018. Yamada K Case Rep Obstet Gynecol 2018 11/01/2019 PMC6304601 10.1155/2018/1280582 Primary Included as the paper investigates chemotherapy in pregnancy the treatment plan was cisplatin and 5-fluorouracil along with radiotherapy as well as supportive therapy

30402233 Challenges in the management of neuroendocrine cervical cancer during pregnancy: A case report Gil-Ibañez B, Regueiro P, Llurba E, Fariñas-Madrid L, Garcia A, Diaz-Feijoo B. Mol Clin Oncol. 2018 Nov;9(5):519-522. doi: 10.3892/mco.2018.1717. Epub 2018 Sep 13. Gil-Ibañez B Mol Clin Oncol 2018 08/11/2018 PMC6200965 10.3892/mco.2018.1717 Primary Included as the paper investigates treatment within pregnancy which included cisplatin treatment causing the tumour to which caused the tumour to remain stable and the child was delivered via caserian along with a radical hysterectomy

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30264644 Bone sarcoma during pregnancy: an example of personalized multidisciplinary care Weidema M, Kaal S, de Jong L, van Erp N, Jansen R, Schreuder B, Heidema W, van der Graaf W, Desar I. Acta Oncol. 2019 Jan;58(1):128-131. doi: 10.1080/0284186X.2018.1512754. Epub 2018 Sep 28. Weidema M Acta Oncol 2019 29/09/2018

10.1080/0284186X.2018.1512754 Primary Included as the paper investigates treatment of bone sarcoma in pregnancy, the patient was administered cisplatin, doxorubicin and methotrexate

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30043438 A successful case of neoadjuvant chemotherapy and radical hysterectomy during pregnancy for advanced uterine cervical cancer accompanied by neonatal erythroderma Kayahashi K, Mizumoto Y, Myojo S, Mitani Y, Tajima A, Fujiwara H. J Obstet Gynaecol Res. 2018 Oct;44(10):2003-2007. doi: 10.1111/jog.13746. Epub 2018 Jul 25. Kayahashi K J Obstet Gynaecol Res 2018 26/07/2018 10.1111/jog.13746 Primary Included as the paper investigates treatment of cervical cancers in pregnancy, the treatment administered was paclitaxel and cisplatin

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26858921 Lung Cancer in Pregnancy: An Unusual Case of Complete Response to Chemotherapy Yates R, Zhang J. Cureus. 2015 Dec 29;7(12):e440. doi: 10.7759/cureus.440. Yates R Cureus 2015 10/02/2016 PMC4739751 10.7759/cureus.440 Primary Included as th paper investigates the treatment of squamous cell carcinoma of the lung during pregnancy

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25004323 A child with severe hearing loss associated with maternal cisplatin treatment during pregnancy Geijteman ECT, Wensveen CWM, Duvekot JJ, van Zuylen L. Obstet Gynecol. 2014 Aug;124(2 Pt 2 Suppl 1):454-456. doi: 10.1097/AOG.0000000000000389. Geijteman ECT Obstet Gynecol 2014 09/07/2014 10.1097/AOG.0000000000000389 Primary Included as the paper investigates the treatment of cervical cancer during pregnancy

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21625793 [Neoadjuvant chemotherapy followed by radical surgery in pregnant patient with invasive cervical cancer: case report and literature review] da Fonseca AJ, Dalla-Benetta AC, Ferreira LP, Martins CR, Lins CD. Rev Bras Ginecol Obstet. 2011 Jan;33(1):43-8. doi: 10.1590/s0100-72032011000100007. da Fonseca AJ Rev Bras Ginecol Obstet 2011 01/06/2011 10.1590/s0100-72032011000100007 Primary Included as the paper investigates squamous cell carcinoma during pregnancy

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Chvatal R, Oppelt P, Koehler C, Habelsberger A, Yaman C. J Turk Ger Gynecol Assoc. 2011 Jun 1;12(2):121-3. doi: 10.5152/jtgga.2011.27. eCollection 2011. Chvatal R J Turk Ger Gynecol Assoc 2011 05/03/2014 PMC3939103 10.5152/jtgga.2011.27
Primary Included as the paper investigates the treatment of squamous cell carcinoma of the cervix during pregnancy

21071993 Cisplatin application in pregnancy: first in vivo analysis of 7 patients Marnitz S, Köhler C, Oppelt P, Schmittel A, Favero G, Hasenbein K, Schneider A, Markman M. Oncology. 2010;79(1-2):72-7. doi: 10.1159/000320156. Epub 2010 Nov 12. Marnitz S Oncology
2010 13/11/2010 10.1159/000320156 Primary
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21058449 Ruptured ovarian endodermal sinus tumor diagnosed during pregnancy: case report and review of the literature Benjapibal M, Chaopotong P, Leelaphatanadit C, Jaishuen A. J Obstet Gynaecol Res. 2010 Oct;36(5):1137-41. doi: 10.1111/j.1447-0756.2010.01254.x. Benjapibal M J Obstet Gynaecol Res 2010 09/11/2010 10.1111/j.1447-0756.2010.01254.x Primary Included as the paper investigates the treatment of ovarian cancer during pregnancy

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Rabaiotti E, Sigismondi C, Montoli S, Mangili G, Candiani M, Viganò R. Tumori. 2010 Jul-Aug;96(4):623-6. Rabaiotti E Tumori 2010 26/10/2010
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Favero G J Minim Invasive Gynecol 2010 05/02/2010
10.1016/j.jmig.2009.10.005 Primary Included as the paper investigates the treatment of cervical cancer during a twin pregnancy

20041106 A favorable maternal and neonatal outcome following chemotherapy with etoposide, bleomycin, and cisplatin for management of grade 3 immature teratoma of the ovary
Ghaemmaghami F, Abbasi F, Abadi AG. J Gynecol Oncol. 2009 Dec;20(4):257-9. doi: 10.3802/jgo.2009.20.4.257. Epub 2009 Dec 28. Ghaemmaghami F J Gynecol Oncol 2009
31/12/2009 PMC2799028 10.3802/jgo.2009.20.4.257
Primary Included as the paper investigates the treatment of a immature teratoma during pregnancy

19765705 The therapeutic management of a twin pregnancy complicated by the presence of cervical cancer, following laparoscopic staging and chemotherapy, with an emphasis on cisplatin concentrations in the fetomaternal compartments amnion fluid, umbilical cord, and maternal serum Marnitz S, Schmittel A, Bolbrinker J, Schmidt FP, Fons G, Kalache K, Schneider A, Köhler C. Fertil Steril. 2009 Nov;92(5):1748.e1-4. doi: 10.1016/j.fertnstert.2009.07.1000. Epub 2009 Sep 18. Marnitz S Fertil Steril 2009 22/09/2009 10.1016/j.fertnstert.2009.07.1000 Primary Included as the paper investigates the treatment of cervix uteri during pregnancy

19523669 Neoadjuvant chemotherapy followed by post-partum chemoradiotherapy and chemoconsolidation for stage IIIB glassy cell cervical carcinoma during pregnancy Seamon LG, Downey GO, Harrison CR, Doss B, Carlson JW. Gynecol Oncol. 2009 Sep;114(3):540-1. doi: 10.1016/j.ygyno.2009.05.025. Epub 2009 Jun 11. Seamon LG Gynecol Oncol 2009 16/06/2009 10.1016/j.ygyno.2009.05.025 Primary Included as the paper investigates the treatment of cervical cancer during pregnancy

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19242705 Cisplatinum and docetaxel for ovarian cancer in pregnancy Rouzi AA, Sahly NN, Sahly NF, Alahwal MS. Arch Gynecol Obstet. 2009 Nov;280(5):823-5. doi: 10.1007/s00404-009-0992-5. Epub 2009 Feb 26. Rouzi AA Arch Gynecol Obstet 2009 27/02/2009 10.1007/s00404-009-0992-5 Primary Included as the paper investigates ovarian cancer during pregnancy

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18558586 Paclitaxel and cisplatin in the treatment of metastatic non-small-cell lung cancer during pregnancy García-González J, Cueva J, Lamas MJ, Curiel T, Graña B, López-López R. Clin Transl Oncol. 2008 Jun;10(6):375-6. doi: 10.1007/s12094-008-0215-8. García-González J Clin Transl Oncol 2008 19/06/2008 10.1007/s12094-008-0215-8 Primary Included as the paper investigates the treatment of lung cancer during pregnancy

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17996977 Prolonged survival of a woman with lung cancer diagnosed and treated with chemotherapy during pregnancy. Review of cases reported Garrido M, Clavero J, Huete A, Sánchez C, Solar A, Alvarez M, Orellana E. Lung Cancer. 2008 May;60(2):285-90. doi: 10.1016/j.lungcan.2007.09.019. Epub 2007 Nov 9. Garrido M Lung Cancer 2008

13/11/2007 10.1016/j.lungcan.2007.09.019 Primary Included as the paper investigates the treatment of lung cancer during pregnancy

17904952 Neoadjuvant chemotherapy plus radical surgery in locally advanced cervical cancer during pregnancy: a case report Palaia I, Pernice M, Graziano M, Bellati F, Panici PB. Am J Obstet Gynecol. 2007 Oct;197(4):e5-6. doi: 10.1016/j.ajog.2007.07.034.Palaia I Am J Obstet Gynecol 2007 02/10/2007 10.1016/j.ajog.2007.07.034 Primary Included as the paper investigates the treatment of poorly differentiated squamous cell carcinoma during pregnancy

17688967 Docetaxel, gemcitabine, and cisplatin administered for non-small cell lung cancer during the first and second trimester of an unrecognized pregnancy Kim JH, Kim HS, Sung CW, Kim KJ, Kim CH, Lee KY. Lung Cancer. 2008 Feb;59(2):270-3. doi: 10.1016/j.lungcan.2007.06.017. Epub 2007 Aug 3. Kim JH Lung Cancer 2008 11/08/2007 10.1016/j.lungcan.2007.06.017 Primary Included as the mother was treated with chemotherapy without knowledge of a pregnancy

17653741 Good pregnancy outcome after prenatal exposure to bleomycin, etoposide and cisplatin for ovarian immature teratoma: a case report and literature review Karimi Zarchi M, Behtash N, Modares Gilani M. Arch Gynecol Obstet. 2008 Jan;277(1):75-8. doi: 10.1007/s00404-007-0416-3. Epub 2007 Jul 25. Karimi Zarchi M Arch Gynecol Obstet 2008 27/07/2007 10.1007/s00404-007-0416-3 Primary Included as the paper investigates the treatment of immature teratoma during pregnancy

17635618 Endodermal sinus tumor diagnosed in pregnancy: a case report Robova H, Rob L, Hrehorcak M, Zoban P, Prusa R. Int J Gynecol Cancer. 2007 Jul-Aug;17(4):914-6. doi: 10.1111/j.1525-1438.2007.00850.x. Robova H Int J Gynecol Cancer 2007 20/07/2007 10.1111/j.1525-1438.2007.00850.x Primary Included as the paper investigates treatment of endodermal sinus tumour during pregnancy

17534393 Neoadjuvant cisplatin and radical cesarean hysterectomy for cervical cancer in pregnancy Karam A, Feldman N, Holschneider CH. Nat Clin Pract Oncol. 2007 Jun;4(6):375-80. doi: 10.1038/ncponc0821. Karam A Nat Clin Pract Oncol 2007 31/05/2007 10.1038/ncponc0821 Primary Included as the paper investigates the treatment of cervical cancer during pregnancy

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16681782 Neoadjuvant chemotherapy followed by radical hysterectomy for invasive cervical cancer diagnosed during pregnancy: report of a case and review of the literature Caluwaerts S, VAN

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Calsteren K, Mertens L, Lagae L, Moerman P, Hanssens M, Wuyts K, Vergote I, Amant F. Int J Gynecol Cancer. 2006 Mar-Apr;16(2):905-8. doi: 10.1111/j.1525-1438.2006.00223.x. Caluwaerts S Int J Gynecol Cancer 2006 10/05/2006 10.1111/j.1525-1438.2006.00223.x Primary Included as the paper investigates the treatment of squamous cell carcinoma of the cervix during pregnancy

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9554531 Neoadjuvant chemotherapy in the treatment of locally advanced cervical carcinoma in pregnancy: a report of two cases and review of issues specific to the management of cervical carcinoma in pregnancy including planned delay of therapy Tewari K, Cappuccini F, Gambino A, Kohler MF, Pecorelli S, DiSaia PJ. Cancer. 1998 Apr 15;82(8):1529-34. doi: 10.1002/(sici)1097-0142(19980415)82:8<1529::aid-cncr15>3.0.co;2-6. Tewari K Cancer 1998 29/04/1998 10.1002/(sici)1097-0142(19980415)82:8<1529::aid-cncr15>3.0.co;2-6 Primary Included as there are two cases treating squamous cell carcinoma of the cervix during pregnancy

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2304734 Cis-platinum combination chemotherapy during pregnancy for advanced epithelial ovarian carcinoma Malfetano JH, Goldkrand JW. Obstet Gynecol. 1990 Mar;75(3 Pt 2):545-7. Malfetano JH Obstet Gynecol 1990 01/03/1990 Primary Included as the paper investigates the treatment of ovarian cancer during pregnancy

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Primary Included as the paper investgiates the treatment of sertoli leydig cell tumour during pregnancy

6247253 Oat cell carcinoma of the uterine cervix in a pregnant woman treated with cis-diamminedichloroplatinum Jacobs AJ, Marchevsky A, Gordon RE, Deppe G, Cohen CJ. Gynecol Oncol. 1980 Jun;9(3):405-10. doi: 10.1016/0090-8258(80)90052-9. Jacobs AJ Gynecol Oncol 1980 01/06/1980 10.1016/0090-8258(80)90052-9
Primary Included as the paper investigates the treatment of oat cell carcinoma of the cervix during pregnancy

Preclinical studies

PMID Title Authors Citation First Author Journal/Book Publication Year Create Date PMCID NIHMS ID DOI Type of paper Description

33083868 Toxicity of anticancer drugs in human placental tissue explants and trophoblast cell lines Eliesen GAM, van Hove H, Meijer MH, van den Broek PHH, Pertijs J, Roeleveld N, van Drongelen J, Russel FGM, Greupink R. Arch Toxicol. 2020 Oct 20. doi: 10.1007/s00204-020-02925-w. Online ahead of print. Eliesen GAM Arch Toxicol 2020 21/10/2020 10.1007/s00204-020-02925-w Primary Included as the paper investigates how various drugs affects the placenta during pregnancy cell culture

31401317 Molecular mechanisms of Cisplatin- induced placental toxicity and teratogenicity in rats and the ameliorating role of N-acetyl-cysteine Hassan MS, Morgan AM, Mekawy MM, Zeineb MA. Int J Biochem Cell Biol. 2019 Oct;115:105579. doi: 10.1016/j.biocel.2019.105579. Epub 2019 Aug 8. Hassan MS Int J Biochem Cell Biol 2019 12/08/2019 10.1016/j.biocel.2019.105579 Primary Included as the paper investigates the effects on cisplatin in pregnant rats, during the 12th day of gestation cisplatin was administed

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Primary Included as the paper investigates the effects of cisplatin on foetus when administered during pregnancy

26944133 Neurotoxicity to DRG neurons varies between rodent strains treated with cisplatin and bortezomib Podratz JL, Kulkarni A, Pleticha J, Kanwar R, Beutler AS, Staff NP, Windebank AJ. J Neurol Sci. 2016 Mar 15;362:131-5. doi: 10.1016/j.jns.2015.12.038. Epub 2015 Dec 28. Podratz JL J Neurol Sci 2016 06/03/2016 PMC4779499 NIHMS754847

10.1016/j.jns.2015.12.038 Primary Included as the paper uses pregnant rats and mice and removes the foetus during the embryognic phase

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12779017 Assessment of nephrotoxicity in the chick embryo: effects of cisplatin and 1,2-dibromoethane Náprstková I, Dusek Z, Zemanová Z, Novotná B. Folia Biol (Praha). 2003;49(2):78-86. Náprstková I Folia Biol (Praha) 2003 05/06/2003 Primary Included as the paper investigates the effects of CDDP or DBE on embryos

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9619421 Differences in the inhibition of neuritic outgrowth in organotypic cultures of rat foetal dorsal root ganglia treated with cisplatin and carboplatin: a comparative study Jirsová K, Mandys V. Folia Histochem Cytobiol. 1997;35(4):215-9. Jirsová K Folia Histochem Cytobiol 1997 01/01/1997 Primary Included as the paper investigates the effects of cisplatin and carboplatin on foetal dorsal root ganglia

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9054594 Elevated mitochondrial cisplatin-DNA adduct levels in rat tissues after transplacental cisplatin exposure Giurgiovich AJ, Diwan BA, Olivero OA, Anderson LM, Rice JM, Poirier MC. Carcinogenesis. 1997 Jan;18(1):93-6. doi: 10.1093/carcin/18.1.93. Giurgiovich AJ Carcinogenesis 1997 01/01/1997 10.1093/carcin/18.1.93 Primary Included as the paper investigates the effects of cisplatin on foetus when administered during pregnancy

8761423 Cisplatin-DNA adduct formation in maternal and fetal rat tissues after transplacental cisplatin exposure Giurgiovich AJ, Diwan BA, Lee KB, Anderson LM, Rice JM, Poirier MC. Carcinogenesis. 1996 Aug;17(8):1665-9. doi: 10.1093/carcin/17.8.1665. Giurgiovich AJ Carcinogenesis 1996 01/08/1996 10.1093/carcin/17.8.1665 Primary Included as the paper investigates the effects of cisplatin to the foetus

7747274 Transplacental carcinogenesis by cisplatin in F344/NCr rats: promotion of kidney tumors by postnatal administration of sodium barbital Diwan BA, Anderson LM, Ward JM, Henneman JR, Rice JM. Toxicol Appl Pharmacol. 1995 May;132(1):115-21. doi: 10.1006/taap.1995.1092. Diwan BA Toxicol Appl Pharmacol 1995 01/05/1995 10.1006/taap.1995.1092 Primary Included as the paper investgiates the effects of cis-DDP on the foetus

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8358711 Transplacental carcinogenicity of cisplatin: initiation of skin tumors and induction of other preneoplastic and neoplastic lesions in SENCAR mice Diwan BA, Anderson LM, Rehm S, Rice JM. Cancer Res. 1993 Sep 1;53(17):3874-6. Diwan BA Cancer Res 1993 01/09/1993 Primary Included as the paper investigates the effects of cis-DDP on the foetus

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6685925 Effects of the cytostatic drug cis-platinum on the developing neocortex of the mouse Köpf-Maier P, Merker HJ. Teratology. 1983 Oct;28(2):189-99. doi: 10.1002/tera.1420280207. Köpf-Maier P Teratology 1983 01/10/1983 10.1002/tera.1420280207 Primary Included as the paper investigates the effects of cisplatinum on the foetus

6683433 Embryotoxicity of cisplatin in rats and mice Keller KA, Aggarwal SK. Toxicol Appl Pharmacol. 1983 Jun 30;69(2):245-56. doi: 10.1016/0041-008x(83)90305-8. Keller KA Toxicol Appl Pharmacol 1983 30/06/1983 10.1016/0041-008x(83)90305-8 Primary Included as the paper investigates the effects of cisplatin on foetus

6683188 Stage of pregnancy-dependent transplacental passage of 195mPt after cis-platinum treatment Köpf-Maier P. Eur J Cancer Clin Oncol. 1983 Apr;19(4):533-6. doi: 10.1016/0277-5379(83)90118-9. Köpf-Maier P Eur J Cancer Clin Oncol 1983 01/04/1983 10.1016/0277-5379(83)90118-9 Primary Included as the paper investigates if cisplatinum can pass the placental barrier

Gestational period when chemotherapy was administered

Case	Gestational period chemotherapy was administered
3 (A Case of Recurrent Esophageal Cancer Treated with Concurrent Chemoradiation Therapy in Pregnancy)	19 weeks
5 (Chemotherapy for cervical cancer in pregnancy)	24 weeks
8 (A successful case of neoadjuvant chemotherapy and radical hysterectomy during pregnancy for advanced uterine cervical cancer accompanied by neonatal erythroderma)	17 weeks
9 (Embryonal rhabdomyosarcoma in a child exposed to chemotherapy in utero: a mere coincidence?)	28 weeks
10 (Lung Cancer in Pregnancy: An Unusual Case of Complete Response to Chemotherapy)	23 weeks
11 (Lung cancer presenting with choroidal metastasis in a pregnant woman)	31 weeks
12 (Neoadjuvant and postoperative chemotherapy with paclitaxel plus cisplatin for the treatment of FIGO stage IB cervical cancer in pregnancy)	22 weeks

14 (A child with severe hearing loss associated with maternal cisplatin treatment during pregnancy)	26 weeks
15 (Neo-adjuvant chemotherapy for cervical cancer in pregnancy: a case report and literature review)	27 weeks
19 (Neo-adjuvant chemotherapy for cervical cancer in pregnancy: a case report and literature review)	29 weeks
21 (A case of early-stage epithelial ovarian cancer in pregnancy)	16 weeks
20 (A case of early-stage epithelial ovarian cancer in pregnancy)	25 weeks
21 (Addressing concerns about cisplatin application during pregnancy)	21 weeks
25 (Ruptured ovarian endodermal sinus tumor diagnosed during pregnancy: case report and review of the literature)	15 weeks
26 (Management of locally advanced cervical cancer in pregnancy: a case report)	18 weeks
30 (Neoadjuvant chemotherapy followed by post-partum chemoradiotherapy and chemoconsolidation for stage IIIB glassy cell cervical carcinoma during pregnancy)	28 weeks
31 (The use of cisplatin to treat advanced-stage cervical cancer during pregnancy allows fetal development and prevents cancer progression: report of a case and review of the literature)	21 weeks
33 (Ovarian malignant immature teratoma associated with pregnancy--a case report)	23 weeks
38 (Docetaxel, gemcitabine, and cisplatin administered for non-small cell lung cancer during the first and second trimester of an unrecognized pregnancy)	9 weeks
39 (Good pregnancy outcome after prenatal exposure to bleomycin, etope2wwwoside and cisplatin for ovarian immature teratoma: a case report and literature review)	29 weeks

41 (Neoadjuvant cisplatin and radical cesarean hysterectomy for cervical cancer in pregnancy)	24 weeks
42 (Long-term follow-up after neoadjuvant chemotherapy for high-risk cervical cancer during pregnancy)	23 weeks
44 (Neoadjuvant chemotherapy for advanced stage cervical cancer in a pregnant patient: report of one case with rapid tumor progression)	24 weeks
46 (Pregnancy outcome after prenatal exposure to bleomycin, etoposide and cisplatin for malignant ovarian germ cell tumors: report of 2 cases)	22 weeks
51 (Neoadjuvant chemotherapy followed by radical hysterectomy for invasive cervical cancer diagnosed during pregnancy: report of a case and review of the literature)	17 weeks
57 (Neoadjuvant cisplatin and radical cesarean hysterectomy for cervical cancer in pregnancy)	19 weeks
59 (Maternal and fetal survival following surgery and chemotherapy of endodermal sinus tumor of the ovary during pregnancy: a case report)	16 weeks

Type of malignancies diagnosed during gestation and the treatment administered

Case	Type of cancer	Type of treatment
1 (AccepTable fetal dose using flattening filter-free volumetric arc therapy (FFF VMAT) in postoperative chemoradiotherapy of tongue cancer during pregnancy)	Oral cancer	Tri-weekly cisplatin at 80 mg/m^2 FFF-VMAT therapy used to deliver 66 Gy to the involved nodes, 60 Gy to the tumor bed and ipsilateral neck, and 54 Gy to the contralateral neck over 33 fractions.
2 (Management of Locally Advanced Esthesioneuroblastoma in a Pregnant Woman)	Right esthesioneuroblastoma	75 $mg/^2$ on day 1 and etoposide 75 mg/m^2 on days 1 to 3 and occurred every 28 days

3 (A Case of Recurrent Esophageal Cancer Treated with Concurrent Chemoradiation Therapy in Pregnancy)	Oesophageal cancer	Cisplatin 60 mg/m^2 and 5-fluorouracil 750 mg/m^2 on days 1 to 4 60 Gy in 30 fractions
4 (Challenges in the management of neuroendocrine cervical cancer during pregnancy: A Case report)	Cervical cancer	Cisplatin 50 mg/m^2 and etoposide 100 mg/m^2 every 3 weeks
5 (Chemotherapy for cervical cancer in pregnancy)	Cervical cancer	50 mg/m^2 cisplatin and 1 mg/m^2 vincristine every 21 days
6 (Bone sarcoma during pregnancy: an example of personalized multidisciplinary care)	Bone cancer	100 mg/m^2 cisplatin was split into 5 doses of 20 mg/m^2 to be administered over 5 days
7 (Locally advanced cervical cancer complicating pregnancy: A Case of competing risks from the Catholic University of the Sacred Heart in Rome)	Cervical cancer	Cisplatin 75 mg/m^2 and paclitaxel 135 mg/m^2
8 (A successful Case of neoadjuvant chemotherapy and radical hysterectomy during pregnancy for advanced uterine cervical cancer accompanied by neonatal erythroderma)	Cervical cancer	Paclitaxel 135 mg/m^2 and cisplatin 50 mg/m^2
9 (Embryonal rhabdomyosarcoma in a child exposed to chemotherapy in utero: a mere coincidence?)	Cervical cancer	Cisplatin 75 mg/m^2 and paclitaxel 175 mg/m^2
10 (Lung Cancer in Pregnancy: An Unusual Case of Complete Response to Chemotherapy)	Lung cancer	Cisplatin 75 mg/m^2 and docetaxel 75 mg/m^2
11 (Lung cancer presenting with choroidal metastasis in a pregnant woman)	Lung cancer	Cisplatin and Vinorelbin
12 (Neoadjuvant and postoperative chemotherapy with paclitaxel plus cisplatin for the treatment of FIGO stage IB cervical cancer in pregnancy)	Cervical Cancer	Paclitaxel 135 mg/m^2 and cisplatin 60 mg/m^2 Paclitaxel 135 mg/m^2 and cisplatin 60 mg/m^2 Paclitaxel 135 mg/m^2 and cisplatin 60 mg/m^2
13 (Administration of Gemcitabine for Metastatic Adenocarcinoma during	Sarcal tumour	Cisplatin 50 mg/m^2 and gemcitabine 1,000 mg/m^2

Pregnancy: A Case Report and Review of the Literature)		
14 (A child with severe hearing loss associated with maternal cisplatin treatment during pregnancy)	Cervical Cancer	Weekly cisplatin and paclitaxel
15 (Neoadjuvant chemotherapy for cervical cancer in pregnancy: a Case report and literature review)	Cervical Cancer	Cisplatin 50 mg/m^2
16 (Platinum derivatives during pregnancy in cervical cancer: a systematic review and meta-analysis)	Cervical cancer	Cisplatin monotherapy or combination
17 ([Management of invasive cervical cancer in pregnancy: clinical analysis of 13 Cases])	Cervical cancer	Cisplatin with fluorouracil or cisplatin monotherapy
18 (Mediastinal dysgerminoma complicating pregnancy)	Ovarian cancer	Bleomycin, cisplatin and etoposide
19 (Neoadjuvant chemotherapy with paclitaxel plus platinum for invasive cervical cancer in pregnancy: two Case report and literature review)	Cervical cancer	Paclitaxel 75 mg/m^2 and cisplatin 50 mg/m^2
20 (Neoadjuvant chemotherapy followed by radical surgery in pregnant patient with invasive cervical cancer: Case report and literature review)	Cervical cancer	Cisplatin 75 mg/m^2 and vincristine 1 mg/m^2
21 (Addressing concerns about cisplatin application during pregnancy)	Cervical cancer	Cisplatin monotherapy
22 (Paclitaxel and cisplatin chemotherapy for ovarian cancer during pregnancy: Case report and review of the literature)	Ovarian cancer	Paclitaxel 175 mg/m^2 and cisplatin 75 mg/m^2
23 (Simple trachelectomy of early invasive cervix carcinoma in the second trimester)	Cervical cancer	Cisplatin monotherapy
24 (Cisplatin application in pregnancy: first in vivo analysis of 7 patients)	Cervical cancer	Cisplatin monotherapy
25 (Ruptured ovarian endodermal sinus tumor diagnosed during pregnancy: Case report and review of the literature)	Ovarian cancer	Bleomycin 20 mg/m^2 on days 1 and 5, etoposide 100 mg/m^2 1 to 5 and cisplatin 20 mg/m^2 on days 1 to 5

26 (Management of locally advanced cervical cancer in pregnancy: a Case report)	Cervical cancer	Cisplatin monotherapy
27 (Laparoscopic pelvic lymphadenectomy in a patient with cervical cancer stage Ib1 complicated by a twin pregnancy)	Cervical cancer	Cisplatin monotherapy
28 (A favorable maternal and neonatal outcome following chemotherapy with etoposide, bleomycin, and cisplatin for management of grade 3 immature teratoma of the ovary)	Ovarian cancer	Bleomycin 20 mg/m^2, etoposide 100 mg/m^2, cisplatin 20 mg/m^2
29 (The therapeutic management of a twin pregnancy complicated by the presence of cervical cancer, following laparoscopic staging and chemotherapy, with an emphasis on cisplatin concentrations in the fetomaternal compartments amnion fluid, umbilical cord, and maternal serum)	Cervical cancer	Cisplatin monotherapy
30 (Neoadjuvant chemotherapy followed by post-partum chemoradiotherapy and chemoconsolidation for stage IIIB glassy cell cervical carcinoma during pregnancy	Cervical cancer	Cisplatin and vincristine
31 (The use of cisplatin to treat advanced-stage cervical cancer during pregnancy allows fetal development and prevents cancer progression: report of a Case and review of the literature)	Cervical cancer	Cisplatin monotherapy 100 mg/m^2
32 (Cisplatinum and docetaxel for ovarian cancer in pregnancy)	Ovarian cancer	Cisplatin 75 mg/m^2 and docetaxel 75 mg/m^2
33 (Ovarian malignant immature teratoma associated with pregnancy--a Case report)	Ovarian cancer	Etoposide and cisplatin
34 (Paclitaxel and cisplatin in the treatment of metastatic non-small-cell lung cancer during pregnancy)	Lung cancer	Cisplatin 75 mg/m^2 and paclitaxel 175 mg/m^2
35 (Successful treatment of small cell lung cancer during pregnancy)	Lung cancer	Cisplatin 80 mg/m^2 day 1 and etoposide 100 mg/m^2 on days 1 to 3

36 (Prolonged survival of a woman with lung cancer diagnosed and treated with chemotherapy during pregnancy. Review of Cases reported)	Lung cancer	Cisplatin 75 mg/m^2 and vinorelvine 30 mg/m^2
37 (Neoadjuvant chemotherapy plus radical surgery in locally advanced cervical cancer during pregnancy: a Case report)	Cervical cancer	Cisplatin 75 mg/m^2 and paclitaxel 175 mg/m^2
38 (Docetaxel, gemcitabine, and cisplatin administered for non-small cell lung cancer during the first and second trimester of an unrecognized pregnancy)	Lung cancer with brain metastasis	Whole brain irradiation 30 Gy/10 fraction. Docetaxel 40 mg/m^2 and cisplatin 35 mg/$m^{2.}$ Geftinib was also administered as a third line treatment
39 (Good pregnancy outcome after prenatal exposure to bleomycin, etoposide and cisplatin for ovarian immature teratoma: a Case report and literature review)	Ovarian cancer	Bleomycin 15 mg, etoposide 100 mg/m^2 and cisplatin 20 mg/m^2
40 (Endodermal sinus tumor diagnosed in pregnancy: a Case report)	Ovarian cancer	Cisplatin monotherapy followed by cisplatin, bleomycin and etoposide combination therapy
41 (Neoadjuvant cisplatin and radical cesarean hysterectomy for cervical cancer in pregnancy)	Cervical cancer	Cisplatin monotherapy
42 (Long-term follow-up after neoadjuvant chemotherapy for high-risk cervical cancer during pregnancy)	Cervical cancer	Cisplatin 50 mg/m^2 and vincristine 1 mg/m^2
43(Adjuvant chemotherapy in a pregnant woman with endodermal sinus tumor of the ovary)	Ovarian tumour	Cisplatin, vinblastine, and bleomycin
44 (Neoadjuvant chemotherapy followed by radical hysterectomy for invasive cervical cancer diagnosed during pregnancy: report of a Case and review of the literature)	Cervical cancer	Cisplatin 75 mg/m^2
45 (Chemotherapy for ovarian mucinous cystadenocarcinoma during pregnancy: a Case report)	Ovarian cancer	Cyclophosphamide 500 mg/m^2 and cisplatin 50 mg/m^2

46 (Pregnancy outcome after prenatal exposure to bleomycin, etoposide and cisplatin for malignant ovarian germ cell tumors: report of 2 Cases)	Ovarian cancer	Bleomycin 15 mg weekly, 100 mg/m^2 of etoposide and cisplatin 70 mg/m^2
47 (A Case of early-stage epithelial ovarian cancer in pregnancy)	Ovarian cancer	Cisplatin monotherapy
48 (Paclitaxel and platinum chemotherapy for ovarian carcinoma during pregnancy)	Ovarian cancer	Paclitaxel 135 mg/m^2 and cisplatin 75 mg/m^2
49 (Chemotherapy in the treatment of locally advanced cervical cancer and pregnancy)	Cervical cancer	30 mg bleomycin and 50 mg/m^2 cisplatin
50 (An endodermal sinus tumor diagnosed in pregnancy: Case report and review of the literature)	Ovarian cancer	Bleomycin, cisplatin, and etoposide
51 (Neoadjuvant chemotherapy in the treatment of locally advanced cervical carcinoma in pregnancy: a report of two Cases and review of issues specific to the management of cervical carcinoma in pregnancy including planned delay of therapy)	Cervical cancer	Vincristine 1 mg/m^2 and cisplatin 50 mg/m^2 (followed by cisplatin monotherapy 50 mg/m^2 only in Case 1)
52 (Chemotherapy for metastatic melanoma during pregnancy)	Melanoma	Tamoxifen 80 mg/m^2 and cisplatin 25 mg/m-2-
53 (Management of chemotherapy in a pregnancy complicated by a large neuroblastoma)	Neuroblastoma	Cisplatin and etoposide
54 (Cisplatin protein binding in pregnancy and the neonatal period)	Ovarian cancer	Cisplatin
55 (Platinum chemotherapy during pregnancy for serous cystadenocarcinoma of the ovary)	Ovarian cancer	Cisplatin 100 mg/m^2 and cyclophosphamide 60 mg/m^2
56 (Treatment of advanced epithelial ovarian carcinoma in pregnancy with cisplatin-based chemotherapy)	Ovarian cancer	Cisplatin and cyclophosphamide
57 (Delivery of a normal infant following cisplatin, vinblastine, and bleomycin (PVB) chemotherapy for malignant teratoma of the ovary during pregnancy)	Ovarian cancer	Cisplatin, vinblastine and bleomycin

58 (Cis-platinum combination chemotherapy during pregnancy for advanced epithelial ovarian carcinoma)	Ovarian cancer	Cisplatin combination therapy
59 (Maternal and fetal survival following surgery and chemotherapy of endodermal sinus tumor of the ovary during pregnancy: a Case report)	Ovarian cancer	Cisplatin combination chemotherapy
60 (Endodermal sinus tumor of the ovary associated with pregnancy)	Ovarian cancer	Vinblastine, bleomycin and cisplatin
61 (Metastatic Sertoli-Leydig cell tumor of the ovary during pregnancy treated by BV-CAP chemotherapy)	Ovarian cancer	Bleomycin, vincristine, Cytoxan, Adriamycin and cisplatin
62 (Oat cell carcinoma of the uterine cervix in a pregnant woman treated with cis-diamminedichloroplatinum)	Cervical cancer	Cisplatin monotherapy

Table containing neonate weight, APGAR scores, gestational period at the time the pregnancy was terminated and the continent where the case was recorded

Case	Birth weight (g)	Gestational period at the time of delivery	Region	APGAR scores
1 (Acceptable fetal dose using flattening filter-free volumetric arc therapy (FFF VMAT) in postoperative chemoradiotherapy of tongue cancer during pregnancy)	Not recorded	37	Asia	Not recorded
2 (Management of Locally Advanced Esthesioneuroblastoma in a Pregnant Woman)	Not recorded	31	Europe	Not recorded
3 (A Case of Recurrent Esophageal Cancer Treated with Concurrent Chemoradiation Therapy in Pregnancy)	2,480	38	Asia	7 and 10 at 1 and 5 minutes
4 (Challenges in the management of neuroendocrine cervical	Not recorded	31	Europe	Not recorded

cancer during pregnancy: A case report)				
5 (Chemotherapy for cervical cancer in pregnancy)	2160	35	South America	9 and 9
6 (Bone sarcoma during pregnancy: an example of personalized multidisciplinary care)	1870	32	Europe	9 and 8 at 1 and 5 minutes
7 (Locally advanced cervical cancer complicating pregnancy: A case of competing risks from the Catholic University of the Sacred Heart in Rome)	2450	Not recorded	Europe	8 and 9
8 (A successful case of neoadjuvant chemotherapy and radical hysterectomy during pregnancy for advanced uterine cervical cancer accompanied by neonatal erythroderma)	1446	31	Asia	5 and 8 at 1 and 5 mins
9 (Embryonal rhabdomyosarcoma in a child exposed to chemotherapy in utero: a mere coincidence?)	2040	34	Europe	9, 9 and 10
10 (Lung Cancer in Pregnancy: An Unusual Case of Complete Response to Chemotherapy)	2166	35	North America	8 and 9 at 1 and 5 minutes
11 (Lung cancer presenting with choroidal metastasis in a pregnant woman)	Not recorded	32	Europe	Not recorded
12 (Neoadjuvant and postoperative chemotherapy with paclitaxel plus cisplatin for the treatment of FIGO stage IB cervical cancer in pregnancy)	Not recorded	34	Asia	Not recorded
	Not recorded	35		Not recorded
	Not recorded	35		Not recorded

13 (Administration of Gemcitabine for Metastatic Adenocarcinoma during Pregnancy: A Case Report and Review of the Literature)	1840	35	Europe	9, 10 and 10
14 (A child with severe hearing loss associated with maternal cisplatin treatment during pregnancy)	2085	34	Europe	8 and 9
15 (Neo-adjuvant chemotherapy for cervical cancer in pregnancy: a case report and literature review)	Not recorded	Not recorded	Europe	Not recorded
16 (Platinum derivatives during pregnancy in cervical cancer: a systematic review and meta-analysis)	2213	Not recorded	Europe	Not recorded
17 ([Management of invasive cervical cancer in pregnancy: clinical analysis of 13 cases])	Not recorded	Not recorded	Asia	Not recorded
18 (Mediastinal dysgerminoma complicating pregnancy)	1400	31	Not recorded	Not recorded
19 (Neoadjuvant chemotherapy with paclitaxel plus platinum for invasive cervical cancer in pregnancy: two case report and literature review)	2200	33	Asia	9 and 10 at 1 and 5 minutes
	2200	33	Asia	8 and 10 at 1 and 5 minutes
20 ([Neoadjuvant chemotherapy followed by radical surgery in pregnant patient with invasive cervical cancer: case report and literature review])	2450	37	South America	8 and 9

21 (Addressing concerns about cisplatin application during pregnancy)	2070	31	Europe	Not recorded
22 (Paclitaxel and cisplatin chemotherapy for ovarian cancer during pregnancy: case report and review of the literature)	1900	34	Europe	8 at 5 minutes
23 (Simple trachelectomy of early invasive cervix carcinoma in the second trimester)	Not recorded	Not recorded	Europe	8, 9 and 9
24 (Cisplatin application in pregnancy: first in vivo analysis of 7 patients)	Not recorded	32	Europe	Not recorded
25 (Ruptured ovarian endodermal sinus tumor diagnosed during pregnancy: case report and review of the literature)	1560	36	Asia	9 and 10 at 1 and 5 minutes after birth
26 (Management of locally advanced cervical cancer in pregnancy: a case report)	1920	32	Europe	8 and 8
27 (Laparoscopic pelvic lymphadenectomy in a patient with cervical cancer stage Ib1 complicated by a twin pregnancy)	Not recorded	32	Europe	Not recorded
28 (A favorable maternal and neonatal outcome following chemotherapy with etoposide, bleomycin, and cisplatin for management of grade 3 immature teratoma of the ovary)	2000	Not recorded	Asia	9 and 10
29 (The therapeutic management of a twin pregnancy complicated by the presence of cervical cancer, following laparoscopic staging and chemotherapy, with an	1790 2020	32	Europe	9 and 10

emphasis on cisplatin concentrations in the fetomaternal compartments amnion fluid, umbilical cord, and maternal serum)				
30 (Neoadjuvant chemotherapy followed by post-partum chemoradiotherapy and chemoconsolidation for stage IIIB glassy cell cervical carcinoma during pregnancy)	1660	31	North America	7 and 8
31 (The use of cisplatin to treat advanced-stage cervical cancer during pregnancy allows fetal development and prevents cancer progression: report of a case and review of the literature)	2380	35	Europe	7, 9 and 10
32 (Cisplatinum and docetaxel for ovarian cancer in pregnancy)	2245	34	Asia	3 and 6 at 1 and 10 minutes
33 (Ovarian malignant immature teratoma associated with pregnancy--a case report)	2700	40	Europe	7 and 8
34 (Paclitaxel and cisplatin in the treatment of metastatic non-small-cell lung cancer during pregnancy)	1720	30	Europe	3 and 4 at 1 and 5 minutes
35 (Successful treatment of small cell lung cancer during pregnancy)	Not recorded	Not recorded	North America	Not recorded
36 (Prolonged survival of a woman with lung cancer diagnosed and treated with chemotherapy during pregnancy. Review of cases reported)	Not recorded	39	South America	Not recorded

37 (Neoadjuvant chemotherapy plus radical surgery in locally advanced cervical cancer during pregnancy: a case report)	2400	35	Europe	7 and 9 at 1 and 5 minutes
38 (Docetaxel, gemcitabine, and cisplatin administered for non-small cell lung cancer during the first and second trimester of an unrecognized pregnancy)	1490	33	Asia	Not recorded
39 (Good pregnancy outcome after prenatal exposure to bleomycin, etoposide and cisplatin for ovarian immature teratoma: a case report and literature review)	3100	39	Asia	9 and 10 at 1 and 5 minutes
40 (Endodermal sinus tumor diagnosed in pregnancy: a case report)	1980	35	Europe	7, 8 and 10
41 (Neoadjuvant cisplatin and radical cesarean hysterectomy for cervical cancer in pregnancy)	2450	33	North America	Not recorded
42 (Long-term follow-up after neoadjuvant chemotherapy for high-risk cervical cancer during pregnancy)	1920	32	Europe	10, 10 and 10 at 1, 5 and 10 minutes
43 (Adjuvant chemotherapy in a pregnant woman with endodermal sinus tumor of the ovary)	1070	31	Asia	Not recorded
44 (Neoadjuvant chemotherapy followed by radical hysterectomy for invasive cervical cancer diagnosed during pregnancy: report of a case and review of the literature)	Not recorded	32	Europe	Not recorded

45 (Chemotherapy for ovarian mucinous cystadenocarcinoma during pregnancy: a case report)	Not recorded	30	Asia	Not recorded
46 (Pregnancy outcome after prenatal exposure to bleomycin, etoposide and cisplatin for malignant ovarian germ cell tumors: report of 2 cases)	Not recorded	Not recorded	Asia	Not recorded
	Not recorded	Not recorded		Not recorded
47 (A case of early-stage epithelial ovarian cancer in pregnancy)	Not recorded	32	Oceania	Not recorded
48 (Paclitaxel and platinum chemotherapy for ovarian carcinoma during pregnancy)	Not recorded	37	North America	Not recorded
49 (Chemotherapy in the treatment of locally advanced cervical cancer and pregnancy)	2805	38	South America	8 and 10
50 (An endodermal sinus tumor diagnosed in pregnancy: case report and review of the literature)	1085	28	North America	7 and 8
51 (Neoadjuvant chemotherapy in the treatment of locally advanced cervical carcinoma in pregnancy: a report of two cases and review of issues specific to the management of cervical carcinoma in pregnancy including planned delay of therapy)	2160	34	North America	Not recorded
	1700	32		Not recorded
52 (Chemotherapy for metastatic melanoma during pregnancy)	1520	30	North America	Not recorded
53 (Management of chemotherapy in a	1825	35	North America	6 and 8

pregnancy complicated by a large neuroblastoma)				
54 (Cisplatin protein binding in pregnancy and the neonatal period)	Not recorded	Not recorded	North America	Not recorded
55 (Platinum chemotherapy during pregnancy for serous cystadenocarcinoma of the ovary)	3600	36	North America	9 and 9
56 (Treatment of advanced epithelial ovarian carcinoma in pregnancy with cisplatin-based chemotherapy)	3060	Not recorded	North America	7 and 8
57 (Delivery of a normal infant following cisplatin, vinblastine, and bleomycin (PVB) chemotherapy for malignant teratoma of the ovary during pregnancy)	3232	Not recorded	North America	8 and 9
58 (Cis-platinum combination chemotherapy during pregnancy for advanced epithelial ovarian carcinoma)	3275	37-38	North America	10 and 10
59 (Maternal and fetal survival following surgery and chemotherapy of endodermal sinus tumor of the ovary during pregnancy: a case report)	2850	37	Asia	Not recorded
60 (Endodermal sinus tumor of the ovary associated with pregnancy)	1900	31	Not recorded	8 and 9
61 (Metastatic Sertoli-Leydig cell tumor of the ovary during pregnancy treated by BV-CAP chemotherapy)	Not recorded	Not recorded	North America	Not recorded

62 (Oat cell carcinoma of the uterine cervix in a pregnant woman treated with cis-diamminedichloroplatinum)	Not recorded	Not recorded	North America	Not recorded

Cases where the clinical case report could not be accessed

Case showing abstract only
17 ([Management of invasive cervical cancer in pregnancy: clinical analysis of 13 cases])
27 (Laparoscopic pelvic lymphadenectomy in a patient with cervical cancer stage Ib1 complicated by a twin pregnancy)
44 (Neoadjuvant chemotherapy followed by radical hysterectomy for invasive cervical cancer diagnosed during pregnancy: report of a case and review of the literature)
45 (Chemotherapy for ovarian mucinous cystadenocarcinoma during pregnancy: a case report)
47 (A case of early-stage epithelial ovarian cancer in pregnancy)

Maternal age and clinical outcome

Case	Age	Maternal outcome
1 (Acceptable fetal dose using flattening filter-free volumetric arc therapy (FFF VMAT) in postoperative chemoradiotherapy of tongue cancer during pregnancy)	36	The mother died 6 months after the radiotherapy from lung metastases
2 (Management of Locally Advanced Esthesioneuroblastoma in a Pregnant Woman)	27	The mother is clinically well but is undergoing treatment for a grade 1 diminution of visual acuity in the right eye, xerostomia grade 1, and cervical fibrosis grade 1
3 (A Case of Recurrent Esophageal Cancer Treated with Concurrent Chemoradiation Therapy in Pregnancy)	41	The mother is disease free 12 months after the caesarean section

4 (Challenges in the management of neuroendocrine cervical cancer during pregnancy: A case report)	34	The mother is disease free 38 months postoperatively
5 (Chemotherapy for cervical cancer in pregnancy)	32	The mother is disease free after 2 years
6 (Bone sarcoma during pregnancy: an example of personalized multidisciplinary care)	31	The mother is disease free after 2 years
7 (Locally advanced cervical cancer complicating pregnancy: A case of competing risks from the Catholic University of the Sacred Heart in Rome)	35	Not recorded
8 (A successful case of neoadjuvant chemotherapy and radical hysterectomy during pregnancy for advanced uterine cervical cancer accompanied by neonatal erythroderma)	33	The mother is disease free 34 months post operatively
9 (Embryonal rhabdomyosarcoma in a child exposed to chemotherapy in utero: a mere coincidence?)	33	The mother is disease free after 6 years
10 (Lung Cancer in Pregnancy: An Unusual Case of Complete Response to Chemotherapy)	26	The mother is disease free after 16 months
11 (Lung cancer presenting with choroidal metastasis in a pregnant woman)	28	The mother died after 10 months due to metastasis
12 (Neoadjuvant and postoperative chemotherapy with paclitaxel plus cisplatin for the treatment of FIGO stage IB cervical cancer in pregnancy)	31	The patient is disease free after 4 years
		The mother is disease free after 3 years
13 (Administration of Gemcitabine for Metastatic Adenocarcinoma during Pregnancy: A Case Report and Review of the Literature)	38	The mother died after 14 months
14 (A child with severe hearing loss associated with maternal	34	Not recorded

cisplatin treatment during pregnancy)		
15 (Neo-adjuvant chemotherapy for cervical cancer in pregnancy: a case report and literature review)	Not recorded	Cisplatin permitted a good outcome for most patients
16 (Platinum derivatives during pregnancy in cervical cancer: a systematic review and meta-analysis)	Not recorded	The median progression free survival was 48.5 months
17 ([Management of invasive cervical cancer in pregnancy: clinical analysis of 13 cases])	Not recorded	Not recorded
18 (Mediastinal dysgerminoma complicating pregnancy)	26	The disease worsened two weeks after radiotherapy
19 (Neoadjuvant chemotherapy with paclitaxel plus platinum for invasive cervical cancer in pregnancy: two case report and literature review)	36	The mother is disease free after 21 months
	39	The mother is disease free after 13 months
20 ([Neoadjuvant chemotherapy followed by radical surgery in pregnant patient with invasive cervical cancer: case report and literature review])	30	The mother is disease free after 12 months
21 (Addressing concerns about cisplatin application during pregnancy)	Not recorded	Not recorded
22 (Paclitaxel and cisplatin chemotherapy for ovarian cancer during pregnancy: case report and review of the literature)	24	The mother is died 35 after cancer diagnosis
23 (Simple trachelectomy of early invasive cervix carcinoma in the second trimester)	Not recorded	The mother is disease free after 16 months
24 (Cisplatin application in pregnancy: first in vivo analysis of 7 patients)	33.8	All women were disease free
25 (Ruptured ovarian endodermal sinus tumor diagnosed during pregnancy: case report and review of the literature)	23	The mother is disease free after 23 months

26 (Management of locally advanced cervical cancer in pregnancy: a case report)	27	The mother died after 1 year
27 (Laparoscopic pelvic lymphadenectomy in a patient with cervical cancer stage Ib1 complicated by a twin pregnancy)	35	No complications in the mother were observed
28 (A favorable maternal and neonatal outcome following chemotherapy with etoposide, bleomycin, and cisplatin for management of grade 3 immature teratoma of the ovary)	25	The mother is disease free after 8 months
29 (The therapeutic management of a twin pregnancy complicated by the presence of cervical cancer, following laparoscopic staging and chemotherapy, with an emphasis on cisplatin concentrations in the fetomaternal compartments amnion fluid, umbilical cord, and maternal serum)	35	Not recorded
30 (Neoadjuvant chemotherapy followed by post-partum chemoradiotherapy and chemoconsolidation for stage IIIB glassy cell cervical carcinoma during pregnancy)	30	The mother is disease free after 4.1 years
31 (The use of cisplatin to treat advanced-stage cervical cancer during pregnancy allows fetal development and prevents cancer progression: report of a case and review of the literature)	26	The mother is disease free after 15 months
32 (Cisplatinum and docetaxel for ovarian cancer in pregnancy)	32	The mother is disease free after 6 months
33 (Ovarian malignant immature teratoma associated with pregnancy--a case report)	36	The mother is disease free after 6 months
34 (Paclitaxel and cisplatin in the treatment of metastatic non-	39	The mother died 10 mothers after diagnosis

small-cell lung cancer during pregnancy)		
35 (Successful treatment of small cell lung cancer during pregnancy)	39	Not recorded
36 (Prolonged survival of a woman with lung cancer diagnosed and treated with chemotherapy during pregnancy. Review of cases reported)	34	The mother is disease free after 11 months
37 (Neoadjuvant chemotherapy plus radical surgery in locally advanced cervical cancer during pregnancy: a case report)	30	The mother is disease free after 10 months
38 (Docetaxel, gemcitabine, and cisplatin administered for non-small cell lung cancer during the first and second trimester of an unrecognized pregnancy)	35	Not recorded
39 (Good pregnancy outcome after prenatal exposure to bleomycin, etoposide and cisplatin for ovarian immature teratoma: a case report and literature review)	26	The mother is disease free for 1.5 years
40 (Endodermal sinus tumor diagnosed in pregnancy: a case report)	34	The mother is disease free for 28 months
41 (Neoadjuvant cisplatin and radical cesarean hysterectomy for cervical cancer in pregnancy)	28	The mother is disease free after 14 months
42 (Long-term follow-up after neoadjuvant chemotherapy for high-risk cervical cancer during pregnancy)	39	The mother is disease free after 80 months
43 (Adjuvant chemotherapy in a pregnant woman with endodermal sinus tumor of the ovary)	33	The mother is disease free after 65 months
44 (Neoadjuvant chemotherapy followed by radical hysterectomy for invasive cervical cancer	28	Not recorded

diagnosed during pregnancy: report of a case and review of the literature)		
45 (Chemotherapy for ovarian mucinous cystadenocarcinoma during pregnancy: a case report)	36	Not recorded
46 (Pregnancy outcome after prenatal exposure to bleomycin, etoposide and cisplatin for malignant ovarian germ cell tumors: report of 2 cases)	25	The mother is disease free after 6 years
	27	The mother is disease free after 2 years
47 (A case of early-stage epithelial ovarian cancer in pregnancy)	Not recorded	Not recorded
48 (Paclitaxel and platinum chemotherapy for ovarian carcinoma during pregnancy)	33	The mother died 29 months after diagnosis
49 (Chemotherapy in the treatment of locally advanced cervical cancer and pregnancy)	26	The mother died almost 1 month after birth
50 (An endodermal sinus tumor diagnosed in pregnancy: case report and review of the literature)	26	The mother is disease free after 16 months
51 (Neoadjuvant chemotherapy in the treatment of locally advanced cervical carcinoma in pregnancy: a report of two cases and review of issues specific to the management of cervical carcinoma in pregnancy including planned delay of therapy)	34	The mother is receiving salvage chemotherapy
	36	The mother is disease free after two years
52 (Chemotherapy for metastatic melanoma during pregnancy)	27	Not recorded
53 (Management of chemotherapy in a pregnancy complicated by a large neuroblastoma)	22	Not recorded
54 (Cisplatin protein binding in pregnancy and the neonatal period)	29.3	Not recorded

55 (Platinum chemotherapy during pregnancy for serous cystadenocarcinoma of the ovary)	40	Not recorded
56 (Treatment of advanced epithelial ovarian carcinoma in pregnancy with cisplatin-based chemotherapy)	24	The mother was disease free for 28 months
57 (Delivery of a normal infant following cisplatin, vinblastine, and bleomycin (PVB) chemotherapy for malignant teratoma of the ovary during pregnancy)	29	The mother is disease free for 61 months
58 (Cis-platinum combination chemotherapy during pregnancy for advanced epithelial ovarian carcinoma)	28	The mother is disease free for 19 months
59 (Maternal and fetal survival following surgery and chemotherapy of endodermal sinus tumor of the ovary during pregnancy: a case report)	25	The mother is disease free after 33 months
60 (Endodermal sinus tumor of the ovary associated with pregnancy)	25	The mother remains disease free
61 (Metastatic Sertoli-Leydig cell tumor of the ovary during pregnancy treated by BV-CAP chemotherapy)	19	The mother remains free for 22 months
62 (Oat cell carcinoma of the uterine cervix in a pregnant woman treated with cis-diamminedichloroplatinum)	25	The patient remains disease free for 9 months

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Preclinical studies

Paper	Species	Chemotherapeutic agent	Dose	Outcome
Eliesen GAM et al.	Placental villous tissues	Crizotinib	1 µM, 10 µM and 100 µM	Fully inhibited tissue viability.
		Sunitinib malate	1 µM, 10 µM and 100 µM	Fully inhibited tissue viability.
		Cisplatin	1 mM	Reduced tissue viability to 21-17%.
		Carboplatin	1 µM, 10 µM and 100 µM	Reduced tissue viability to 65-47%.
		Doxorubicin	1 µM, 10 µM and 100 µM	100 µM reduced tissue viability to 16-12%.
		Paclitaxel	1 µM, 10 µM and 100 µM	Moderately affected tissue viability.
		Imatinib	1 µM, 10 µM and 100 µM	Reduced tissue viability to 31-26%.
		Gefitinib	1 µM, 10 µM and 100 µM	Reduced tissue viability to 28-24%.
Hassan MS et al.	Rats	Cisplatin	Intraperitoneally 5 mg/kg.b.wt	Foetal weights were reduced. Increased chances of Foetal dwarfs which, may show s/c haemorrhages, skeletal abnormalities, or foetal death.
		N-acetyl-l-cysteine	Oral 200 mg/kg daily	

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Hassan MS et al.	Sprauge-Dawley rats	Cisplatin	0.5 mg/kgb wt	Visceral abnormalities, skeletal abnormalities. Severe pathological alterations.
Podratz JL et al.	Mice	Cisplatin	1, 5, 10, and 50 µg/ml cisplatin	Mice were sensitive to cisplatin. Shorter neurites were observed.
Furukawa S et al.	Rats	Cisplatin	2 mg/kg/day during gestational days 11-12	Foetal mortality rates were increased to 65 %. Foetal weights were decreased. Placental weights were decreased. Increases in apoptosis was discovered.
Mu XF et al.	Mice	Cisplatin	N/R	Caused a reduction in cells. Blocked cells before the next S phase.
Hao S et al.	Guinea pigs	Cisplatin	1.5 mg/kg bw	Induced hearing loss. This occurred by the activation of caspase-3.
Al-Saleh E et al.	Placentae	cisplatin	100 µL	Cisplatin transport rates averaged 0.97, 0.97, 0.96, 0.97 and 0.99 times the antipyrine reference value.
Ognio E et al.	Mice	Cisplatin	8 or 12 mg/kg	Higher volumes caused foetal death. Caused growth restriction. Dose-dependency caused varying foetal survival.

				Skeletal anomalies were observed.
Náprstková I et al.	Chick embryos	Cisplatin	0.03 and 0.3 microg	Dose dependent increase in renal malformations. Impairment to the vascular network.
Gerschenson M et al.	Rats	Cisplatin	15 mg/kg bw	Severe toxicity was observed within the kidneys. Activities of OXPHOS complexed II and IV were decreased. Damage to the mitochondria was mild.
Pascual MJ et al.	Rats	Cisplatin	N/R	Accumulated in foetal tissues in the kidney, lung and heart.
Jirsová K et al.	Rats	Cisplatin	10 microM	The lowest concentration cause neurite outgrowth alteration at 10 microM. Cisplatin was discovered after 72 hours.
Giurgiovich AJ et al.	Patas monkeys	Cisplatin	5.3 mg/m^2	DNA adducts were observed in foetal adrenal, brain, heart, kidney, liver, skin, spleen and thymus. Mitochondrial DNA adducts were high in the foetal liver, brain and kidney.
Giurgiovich AJ et al.	Rats	Cisplatin	5 or 15 mg/kg bw	Extensive DNA adducts formed in the brain and liver mitochondria in foetal rats.

Giurgiovich AJ et al.	Rats	Cisplatin	5, 10 or 15 mg/kg bw	DNA damage in foetal rat tissues such as the kidney, lung and the brain
Diwan BA et al.	Rats	Cisplatin	5 mg/kg bw	Renal cell adenomas were identified. Kidney tumours were more common. Frank cell carcinomas were identified. Tumours of the central nervous and peripheral nervous systems were recorded.
Shamkhani H et al.	Placenta Patas monkeys	Cisplatin	Exposed to 200 mg/m^2 cisplatin	Elevated levels in the placenta and high adduct levels in the brains of the foetus that survived the treatment.
Diwan BA et al.	Mice	Cisplatin	7.5 mg/kg bw	High incidences of papilloma's were observed in offspring. Development in thymic lymphomas, lung tumours and kidney lesions in offspring.
Köpf-Maier P et al.	Mice	Cisplatin	2.5, 5, 10 or 20 mg	Dose reduction of the number of foetuses in the litter, a decrease in foetal weight and skeletal malformations.most foetal internal organs were without anomalies.
Köpf-Maier P et al.	Mice	Cisplatin	20 mg/kg	Elevated level of necrosis began with chromatin

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				condensation and fragmentation of the cytoplasm.
Keller KA et al.	Rats	Cisplatin	0.3, 1.0, 2.5 or 3.0 mg/kg	No increase in embryo lethality. Increase in growth reduction but no malformations were observed.
Köpf-Maier P	Mice	Cisplatin	N/R	Lesser amounts of radioactivity were detected 10, 11 and 12 days after treatment. DDP may pass the placenta after placenta maturity.