Oncological management and pregnancy outcomes in women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients.

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Abstract

Background

The effect of the increased awareness of the potential to treat cancer during pregnancy is currently unknown. The International Network on Cancer, Infertility and Pregnancy (INCIP) registers the incidence and maternal, obstetrical, oncological and neonatal outcome of cancer occurring during pregnancy. In this INCIP study, we aimed to describe the oncological management and the obstetrical and neonatal outcomes of patients treated in the last 20 years and evaluate their changes over time. Further, we evaluated associations of malignancy type and treatment with obstetrical and neonatal outcomes.

Methods

This descriptive cohort study involved data from pregnant patients with cancer registered by all 37 centres (from 16 countries) participating in the INCIP registry. Oncological, obstetrical and neonatal outcome data of consecutive patients diagnosed with primary invasive cancer during pregnancy between 1996 and 2016 were retrospectively and prospectively collected. We analysed changes over time with log-binomial regression. We used multiple logistic regression to analyse preterm pre-labour rupture of membranes (PPROM) and/or contractions, small for gestational age (SGA), and neonatal intensive care unit (NICU) admission. In these models, malignancy type, six chemotherapeutic agents (alkylating, anthracyclines, antimetabolite, taxanes, platinum, and any other agent), and abdominal and/or cervical surgery were the key covariates, prespecified confounding variables were time period of diagnosis, age at diagnosis, diagnosis in 3rd pregnancy trimester, and systemic disease. The INCIP registry is registered with ClinicalTrials.gov (NCT00330447), and is ongoing.

Findings

1170 patients were included. Breast cancer was the most common malignancy (n=462, 39%). 779 patients (67%) received treatment during pregnancy. Every five calendar years, treatment during pregnancy increased by 10% (95% CI 5 to 15). This increase was mainly related to an increase of chemotherapeutic treatment by 31% every five calendar years (95% CI 20 to 43). Overall, 995/1089 singleton pregnancies ended in a live birth (88%) of which 429 (48%) ended preterm. Every five calendar years, 4% more live births (95% CI 1 to 6), and 9% less iatrogenic preterm deliveries (95% CI 2 to 16) were reported. Our data suggested a relationship between platinum-based chemotherapy and SGA (odds ratio 3·12, 95% CI 1·45 to 6·70), and between taxanes and NICU admission (odds ratio 2·37, 95% CI 1·31 to 4·28). NICU admission was suggested to depend on malignancy

type, with gastro-intestinal cancers having highest risk (odds ratio vs. breast cancer 7·13, 95% CI 2·86 to 17·7) and thyroid cancers having lowest risk (odds ratio vs. breast cancer 0·14, 95% CI 0·02 to 0·90). Unexpectedly, the data suggested that abdominal and/or cervical surgery was related to a lower NICU admission rate (odds ratio 0·30, 95% CI 0·17 to 0·55). Other associations of treatment and malignancy type were less clear.

Interpretation

Over the years, we observed that more patients with cancer during pregnancy received antenatal treatment, especially chemotherapy. Our data indicate that patients with antenatal chemotherapy exposure may have an increased risk to develop pregnancy related complications, specifically SGA and NICU admission. We therefore recommended involving hospitals with obstetrical high care units in the management of these patients.

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Introduction

Based on several national-wide studies, the incidence of cancer during pregnancy is estimated to be one in 1000 pregnancies.[1-3] Breast cancer, haematological cancer, cervical cancer and melanoma are the most commonly diagnosed malignancies during pregnancy.[4,5] Awareness of this subject has increased the number of cohort studies on maternal and foetal outcome in these women.[4,5] These studies focused on overall maternal and obstetrical outcome, but their population size or follow-up is limited.

In 2010, our group published the first epidemiologic data on cancer during pregnancy based on the registry of the International Network on Cancer, Infertility and Pregnancy (INCIP).[4] Few years later, Amant et al.[6,7] published two prospective follow-up studies of children with antenatal chemotherapy exposure. They found no clinical difference in neurocognitive and cardiac development between the treatment and the control group. In both groups, preterm delivery was the main risk factor for paediatric developmental problems up to three years of age.[7] These studies showed reassuring results on the neonatal and infant outcome up to three years and strengthened the overall idea that oncological treatment in pregnancy is feasible. However, the effect of antenatal chemotherapy on secondary malignancies or fertility later in life is still not known. Antenatal exposure to cancer treatment, and especially chemotherapy, was associated with a higher proportion of small-for-gestational-age (SGA) children in some studies,[4,6,8,9] while others did not find such an association.[2,10] Also, several studies described an increased preterm delivery rate in patients with cancer during pregnancy.[2,4,8] Nevertheless, these studies were often small and could not identify which patients with cancer in pregnancy are at risk for negative obstetrical or neonatal outcome.

The aim of this study is to describe the oncological, obstetrical and neonatal data of the INCIP registry and to evaluate changes in obstetrical management and neonatal outcome over the last 20 years. We hypothesized that over the years more patients were treated during pregnancy, which might have influenced the obstetrical and/or neonatal outcome. Further, we investigated whether type of malignancy or treatment modalities might be related to adverse obstetrical or neonatal outcomes within the group of patients with cancer during pregnancy. We hypothesized that chemotherapy during pregnancy might have resulted in a higher number of adverse outcomes. We were particularly interested in the following outcome measures because they were relatively common: preterm prelabour rupture of membranes (PPROM) and/or preterm contractions, SGA and neonatal intensive care unit (NICU) admission. See Appendix, page 3.

Methods

Study design and patients

This was a descriptive cohort study that involves data from pregnant patients with cancer registered by all 37 centres (16 countries) participating in the INCIP registry. The INCIP was established in 2005 to evaluate oncological care and obstetrical, maternal and neonatal outcome in women with cancer during pregnancy (www.cancerinpregnancy.org). The aim was to register consecutive patients both retrospectively and prospectively. Before 2005, all patients were included retrospectively, after 2005 it depended on the date on which a centre started participating to our study. To include retrospective patients in a most consecutive order, hospitals used patient databases to identify all eligible patients within their hospital. Patient data were registered upon written informed consent of the patients. This study was approved by the Ethical Committee of University Hospital Leuven (Belgian number B322201421061).

Patients diagnosed between 01/01/1996 and 10/18/2016 with primary invasive cancer and borderline ovarian cancer during pregnancy, were eligible. Patients with pre-invasive disease or postpartum diagnosis were excluded. Detailed oncologic, obstetric and neonatal data were collected. Diagnosis was made using local standards, but all included histopathological confirmation. We divided our cohort in 3 subgroups according to year of diagnosis: 1996-2004 (group 1); 2005-2009 (group 2); 2010 - November 2016 (group 3). The differentiation between group 1 and 2 was based on the start of our online registration study in 2005, after which most registrations were prospective. The differentiation between group 2 and 3 was based on the publication date of the first INCIP report.

Systemic disease was defined as TNM or FIGO stage IV disease and leukaemia, non-systemic disease was defined as TNM or FIGO stage I to III and all brain cancers. For the variable 'surgery during pregnancy', we only included therapeutic surgical procedures. PPROM was assessed following local protocol and was defined as preterm rupture of membranes without contractions. Perinatal mortality was defined according to the WHO guidelines as the number of stillbirths and deaths in the first week after birth. Major and minor congenital malformations were defined according to Eurocat (www.eurocat-network.eu). Birthweight percentiles were calculated according to the percentile calculator from www.gestation.net (v6·7·5·7(NL), 2014). The included parameters are shown in the Appendix, page 4. Birthweight below the 10^{th} percentile was considered as SGA.
This study is registered as an International Observational Cohort study with ClinicalTrials.gov (NCT00330447) and approval was obtained from all participating centres and authorities. See

http://www.cancerinpregnancy.org/study-protocols for the full study protocol, this manuscript is based on study part I and the primary objective of this study lies within the wider primary objective of the study protocol.

Statistical analysis

No dedicated sample size calculation was performed for this descriptive study. We agreed upon an analysis strategy beforehand, did not adapt this strategy based on obtained results, and fully reported all results. We provide descriptive statistics of oncological, obstetrical, and neonatal information. Then, we analysed the relationship of malignancy type and treatment modalities with obstetrical and neonatal outcomes (PPROM and/or preterm contractions, SGA, and NICU admission) with multiple logistic regression models using Firth bias correction. We stress that these models do not include a control group of patients without cancer, but compare patients with cancer during pregnancy with respect to the presence or absence of different characteristics or exposures. For the obstetrical outcome PPROM and/or preterm contractions, we based the regression analysis on the sample of singleton live births and stillbirths. For the two neonatal outcomes, we based the analysis on the sample of singleton live births only. Both outcome variables and covariates in the models were fully pre-specified. Key covariates in the models were malignancy type, six chemotherapeutic agents (alkylating, anthracyclines, antimetabolite, taxanes, platinum, and any other agent), and abdominal and/or cervical surgery. We added the following potential confounding variables without further data-driven variable selection: time period of diagnosis, age at diagnosis, diagnosis in 3rd pregnancy trimester, and systemic disease. We did not consider interaction terms. Alkylating chemotherapeutic agents were divided into platinum and other alkylating agents due to the relatively higher placenta passage of carboplatin compared to other agents in baboon models and the high placental passage of cisplatin in humans.[11,12] We reported adjusted odds ratios (OR) with 95% confidence intervals (CI) from the multiple logistic regression models. We report p-values to measure the strength of the evidence against the null hypothesis of no relationship, but do not specify an alpha level and hence do not determine statistical significance. For the multiple regression models, we handled missing values for covariates or outcomes using multiple imputation (See Appendix, page 5).[13] As a sensitivity analysis, we compared results based on imputed data with results based on complete case analysis.

For the descriptive analysis and evaluation of changes over 20 years in categorical patient characteristics, outcomes, and treatment modalities, we use univariable log-binomial regression models with year of diagnosis as a continuous predictor. We express results using relative risks (RR) to describe the average change every five calendar years (See Appendix, page 6), together with 95% confidence intervals. For continuous parameters, we

use univariable linear regression with year of diagnosis as continuous predictor, with results expressed as average change every five calendar years. Statistical significance was not determined. For this analysis, we did not impute missing data but rather used available cases. This analysis was prespecified, and was performed and reported for all parameters of interest.

The analysis was performed using R 3·3·1 (www.r-project.org).

Role of the funding source

The financial funders had no role in the study design, data collection, data analysis, interpretation of the data or in writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The trial design is depicted in Figure 1. In total, 1170 consecutive patients were eligible from 37 centres in 16 countries. The distribution of countries with highest accrual was as follows: Belgium (319, 27%), the Netherlands (278, 24%), Italy (179, 15%), Russia (135, 12%) and Czech Republic (100, 9%). Specifications of inclusion are in Appendix, page 7 and 8. An overview of missing values is given in Appendix, page 9 and 10).

Oncological information

Baseline characteristics are shown in Table 1, distribution of malignancies and stage of disease per malignancy are depicted in Figure 2A and 2B, respectively. Seventy-nine percent (893/1125) of patients had non-systemic disease. Forty-five percent (n=490/1098) of patients were diagnosed in the second trimester, whereas 24% in first and 24% in third trimester (Appendix, page 11 for specification per malignancy).

Of all 1170 patients, 779 (67%) received treatment during pregnancy, of which 574 received a single treatment modality (74%) and 205 a combination of different treatment modalities (26%) (Table 2; Appendix, page 12). Surgery was the most common therapy in patients with thyroid cancer, ovarian cancer or melanoma. Chemotherapy was the most common treatment modality in patients with lymphoma or breast cancer. The majority of patients with cervical or brain cancer were not treated during pregnancy (respectively 56% and 52%). Specification of the different chemotherapeutic agents given during pregnancy can be found in Table 1. Combination regimens consisting of more than one chemotherapeutic agent were registered in 351/423 (83%)

patients. Abdominal and/or cervical surgery was performed in 149 patients. Sixty-nine percent (98/143) of these patients had stage I disease and for 70% (104/149) surgery was the only treatment modality performed during pregnancy.

Obstetrical information

Of all 1142 pregnancies with known obstetrical outcome, 25 (2%) ended in a miscarriage and 113 (10%) were terminated. Sixty-two percent (64/103) of terminations were performed in the first trimester, 38% (n=39/103) in the second trimester. For 10 patients, GA at termination was unknown. Main reasons for termination were start of oncological treatment or poor maternal prognosis (77%), unwanted pregnancy (10%), and foetal anomalies (4%). Information on differences in number of terminations per period of diagnosis and malignancy type can be found in Appendix, page 13. Of the ongoing pregnancies, there were 27 twin pregnancies and 1 triplet pregnancy. Five (<1%) patients died during pregnancy. For the obstetrical outcomes, only data from singleton live births and stillbirths are reported and is summarized in Table 3.

Of the 969 ongoing singleton pregnancies, seven (1%) intra-uterine fetal deaths and seven (1%) perinatal deaths were reported, see Appendix, page 14 for detailed information on these cases. All other 955 pregnancies (99%) ended in a live birth. Preterm delivery rate was 48% (429/887, excluding 68 cases with missing GA at birth). Eighty-eight percent (373/425) of preterm deliveries was iatrogenic. PPROM and/or preterm contractions (98/969, 10%) was the most reported obstetrical complication (Appendix, page 15). From all these patients, 52 patients actually delivered spontaneously before 37 weeks (53%).

Neonatal outcome

For neonatal outcomes, only data from singleton live births are reported. Percentages of missing data in singleton live births are presented in Appendix, page 16. Birth weight percentiles were calculated in 796/955 (83%) singleton live births for which birth weight and GA at delivery were known (Appendix, page 16). Data on all neonatal outcomes stratified by different variables are shown in Appendix, page 17. 167/796 children (21%) were SGA. Information on neonatal intensive care unit (NICU) admission was available for 720/955 (75%) children, with an admission rate of 41% (298/720). NICU admission was mainly prematurity related (249/298, 84%). The presence of congenital malformations was reported in 32/721 (4%) live born singletons, with 17 (2%) minor and 15 (2%) major malformations (2·5-3% major malformations are reported in general population[14]). Three other pregnancies were terminated because of foetal anomalies (hydrocephalus, trisomy 21 and

unspecified major malformations). Anomalies did not differ between the different treatment modalities. (Appendix, page 19)

Association of malignancy type and treatment modalities with adverse obstetrical or neonatal outcomes

Here we describe results for the key variables (malignancy type, administration of chemotherapeutic agents, and abdominal and/or cervical surgery). Full results of the multiple logistic regression models, including associations for the prespecified potential confounders (age at diagnosis, period of diagnosis, trimester at diagnosis, and systemic disease), can be found in Table 4. Model coefficients and standards errors can be found in the Appendix, page 20.

The multiple regression model for SGA provided support for a relationship between chemotherapy and SGA, in particular for platinum-based chemotherapy (OR 3·12, 95% CI 1·45-6·70). Other agents like non-platinum alkylating chemotherapy or taxanes may also be related (OR>2), but results were more uncertain. Malignancy type and abdominal and/or cervical surgery had a weak relation with SGA (Table 4; Appendix page 21).

For NICU admission, there appears to be a strong independent association with malignancy type: gastro-intestinal cancers had the highest admission rates (OR 7·13 vs. breast cancer, 95% CI 2·86-17·7), thyroid cancer to the lowest (OR 0·14 vs. breast cancer, 95% CI 0·02-0·90) (Appendix page 22). There was again support for an association between chemotherapy and NICU admission, in particular for taxanes (OR 2·37, 95% CI 1·31-4·28). Finally, the data suggested that abdominal and/or cervical surgery was related to a lower NICU admission rate (OR 0·30, 95% CI 0·17-0·55).

For PPROM, the least common of the three investigated complications with 98 registered instances, results were largely inconclusive for all variables (Table 4; Appendix page 23). This was the least common of the investigated outcomes, resulting in high standard errors (Appendix, page 20). The relationship between chemotherapy and PPROM is in line with our hypothesis, with OR>2 for the platinum and non-platinum based alkylating agents.

The sensitivity analysis based on complete cases provided highly similar results (Appendix, page 24).

Changes over 20 years

Specification of descriptive statistics per time period, and analysis of change over time is given in Appendix page 25. An overview of the most important changes per period can be found in Figure 3. Every five calendar

years, there was an increase of 10% in the number patients who received treatment during pregnancy (RR 1·10, 95% CI 1·05 to 1·15). Also, every five years, 31% more patients received chemotherapy during pregnancy (RR 1·31, 95% CI 1·20 to 1·43), and only 1% less patients underwent surgery (RR 0·99, 95% CI 0·92 to 1·07). Radiotherapy became less frequent and targeted therapy more frequent, but these modalities were uncommon in general. Every five years, we observed an increase of 2·6 days (95% CI -1·1 to 6·3) in the GA of the last chemotherapy cycle given during pregnancy.

Every five years, there were 4% more live births among singletons (RR 1·04, 95% CI 1·01 to 1·06), 7% fewer preterm live births (RR 0·93, 95% CI 0·86 to 0·99), and 9% fewer iatrogenic preterm live births (RR 0·91, 95% CI 0·84 to 0·98). In line with the declining number of preterm deliveries, every five years, NICU admissions decreased with 9% every five years (RR 0·91, 95% CI 0·83 to 0·99). The occurrence of SGA increased 16% every five years (RR 1·16, 95% CI 0·99 to 1·35). We observed a 3% decrease in PPROM and/or preterm contractions every five years (RR 0·97, 95% CI 0·80 to 1·18).

Discussion

Our data suggested a relationship between platinum-based chemotherapy and SGA, and between taxanes and NICU admission. NICU admission was suggested to depend on malignancy type. Unexpectedly, the data suggested that abdominal and/or cervical surgery was related to a lower NICU admission rate. Other associations of treatment and malignancy type were less clear. Over 20 years, we observed an increased number of pregnancies ending in a live birth that coincide with cancer together with an increase of 31% every five years in patients treated with chemotherapy during pregnancy (Appendix, page 25). In line with the increasing chemotherapy rates over the years, SGA also increased with 16% every five calendar years. These results strengthen the recommendation to involve hospitals with obstetrical high care units in the management of pregnant cancer patients with these risk factors. The complexity of dealing with two patients at once stresses the need for a multidisciplinary approach.

The reason for the observed increased rate of chemotherapy during pregnancy in combination with an increase of live births may be attributed to changing treatment regimens during the period of registration in combination with reassuring results on antenatal chemotherapy exposure. Since 1996, 25 cohort studies including more than 50 patients were published on the subject of cancer during pregnancy with a focus on obstetrical outcome

(Appendix, page 26). In summary, a high rate of preterm birth was observed, but the relation between SGA and cancer treatment during pregnancy remained inconclusive. Several studies describe a reassuring foetal outcome after chemotherapy during pregnancy. No congenital, neurologic or psychologic abnormalities were detected in children antenatal exposed to chemotherapy.[7,15,16] These reassuring fetal, neonatal and infant outcome up to three years, together with the similar maternal survival rates compared to non-pregnant women diagnosed and treated for cancer, are potential factors for the increase of cancer treatment over time as observed in our analysis.

The current study confirms the high overall prematurity rate (48%) in patients with cancer during pregnancy, as published by several previous cohort studies (Appendix, page 26). Preterm birth is related to an increased risk of perinatal morbidity and mortality, and neurodevelopmental impairment later in life. There is a direct correlation between a lower GA at delivery and negative outcome.[17] Lu et al.[8] observed an increased risk of neonatal mortality in patients with cancer during pregnancy (IRR 2·7, 95% CI 1·3 to 5·6), which was caused by prematurity in 89% of the cases. Our study found inconclusive results on the association between antenatal chemotherapy exposure and PPROM and/or contractions. As for other risk factors for spontaneous premature delivery, we hypothesised that patients undergoing abdominal and/or cervical surgery would be at greater risk of PPROM and/or preterm contractions. Our multiple regression analysis did not support such an effect. It may be explained by the high number of stage I disease (69%) and surgical therapy only (70%) in this group of patients, as these patients have no potential risk factors for adverse obstetrical or neonatal outcome.[18,19] We observed a decline of the preterm birth rate during the registration period of 7% every five calendar years, which was mainly attributed to the lower iatrogenic prematurity rate. This decline may be attributed to the tendency to continue chemotherapy longer during pregnancy to postpone delivery for the benefit of the child. Although, we realize that the effect of 2·6 days (95% CI -1·1 to 6·3) every five years is not strong. This may be explained by the fact that reassuring results on antenatal chemotherapy were published only a few years ago and that the follow-up in this cohort is not long enough to fully evaluate this change.

The tendency to treat more patients with chemotherapy during pregnancy may also have adverse consequences. We reported an increased incidence of SGA. Preterm birth, perinatal morbidity and mortality in the first weeks and cardiovascular and metabolic diseases later in life are more frequently seen in these children.[20,21] Several studies have highlighted an increased rate of SGA in children from patients with cancer during pregnancy (Appendix, page 26). Still, influences of supportive medication, stress and malnutrition cannot be excluded.

We hypothesized a relationship between systemic disease and SGA, for which our analysis provided mild support. In these patients, nutritional state besides other factors, such as general condition, fatigue and circulating

cytokines, may be compromised compared to patients with localized malignancy, irrespective of the treatment given.

Our study further suggests a relationship between chemotherapy, mainly platinum-based agents, and SGA, as hypothesized. Several reasons may contribute to such a relationship. Chemotherapeutic agents have several toxic properties of which some cause direct damage to the DNA or interfere with DNA replications (e.g. alkylating agents, antimetabolites). These direct DNA damage might influence the placental development and its blood supply towards the fetus. Additional indirect effects of chemotherapy (induction of vasculopathy or inflammation), or the maternal illness itself (associated with malnutrition, anaemia, and high maternal stress) may further contribute to restricted foetal growth.[22-24] Besides the impact of chemotherapy on foetal growth, the maternal age has an additional impact, but also influences of supportive medication, stress and malnutrition can e contributively.

Fortunately, the lower birth weights in chemotherapy-exposed children recover, with normal values for weight, height, and head circumference in the first months of childhood.[6,7]

In pregnant patients with cancer, it is important to recognize obstetrical and neonatal risks associated with cancer and its treatment modalities. The tendency to avoid preterm deliveries by cancer treatment during pregnancy needs to be balanced against an increased risk of SGA children. The short- and long-term risks of SGA are important to consider, nevertheless the risk of preterm birth is also of great importance. More long-term research comparing the risks in these two groups is necessary.

To our knowledge, this cohort is the largest cohort on cancer in pregnancy. This study adds to the identification of patients at high risk for obstetrical and neonatal complications. However, limitations to this study need to be addressed. First, we observed missing data for the neonatal outcomes. This can be attributed to the participating hospitals, of which some are either specialized in oncology or obstetrics and perinatology, leading to lack of either oncological or obstetrical and neonatal information. Due to the necessity to report obstetrical complications when observed, but no explicit mention of the absence of complications, it is possible that the occurrence of obstetrical complications is underreported. Second, since we only documented sampling data from our online database registered on a voluntary basis by the participating centres of INCIP including retrospectively included cases, the incidences of the different tumour types and percentages of the treatment modalities given during pregnancy may also differ from these in the worldwide pregnant population. Although all participating centres however acknowledged to have registered all their consecutive cases rigorously, some selection bias for retrospectively included cases cannot be excluded. Third, a common issue in observational

studies is the presence of confounding, in our case between treatment and patient or tumour characteristics. Fourth, due to the rarity of cancer in pregnancy and the changes in cancer treatment over the last years, we encountered small group sizes for some malignancies and treatment modalities of which subgroup analysis was not possible.

The observation of increased SGA with chemotherapy exposure needs further research. In our study percentiles were calculated at birth, not knowing if there is a specific decrease seen from start of chemotherapy. However, the measurement of foetal weight percentiles accurately during pregnancy is difficult, since it is dependent on the observer, and there are no foetal charts available worldwide which include ethnic and gender differences and the impact of the parental weight and height.

Further research on placental pathophysiology and the effect of specific chemotherapeutic agents, as well as increasing the number of patients in the small subgroups of rare tumour types and treatment modalities, are needed to provide all patients confronted with cancer during pregnancy the best tailor made management plan optimize both obstetrical and neonatal outcome. Participation to the online registry (incipregistration.be) is recommended in order to accomplish this goal.

Research in context

Evidence before this study

We searched PubMed on 03/30/2017 for articles on cohorts of patients with cancer during pregnancy describing obstetrical and oncological outcome published between 01/01/1996 and 12/31/2016, using the following keywords: pregnancy, cancer, tumour, neoplasm, pregnancy outcome and neonatal outcome. The search was restricted to publications in English. A review of references from appropriate articles was done to identify additional studies. This resulted in a large number of articles on cancer before or after pregnancy but not specifically during pregnancy. After selection by abstract and full-text, a total of 71 studies including from n=9 to n=984 patients. A cohort was considered large and was included if it contained 50 or more patients. This has led to a total of 25 articles describing either obstetrical and/or neonatal outcome. No articles on management changes were published. Nine cohorts described the complete group including all sort of malignancies, 5 described breast cancer during pregnancy, 4 haematological cancers, 3 melanoma and 1 cervical cancer, 1 ovarian cancer, 1 thyroid cancer. Overall, 23 studies reported risk or rates of prematurity; 12 found an increased

rate or risk of prematurity in cancer in pregnancy and 4 studies did not find an increase. Neonatal outcome was reported to some extent in all studies. One study found an increased rate or risk of neonatal mortality, while 10 did not find such an increase. Increased risk of NICU admission was found in 1 study, while 3 found no such increase. Overall SGA was specified in 22 articles and was increased in 5 articles, while 13 studies did not find an overall increased risk of SGA. None of the studies found an increased rate or risk of congenital anomalies.

Added value of this study

To our knowledge, this is the largest cohort describing both detailed information on clinical management and obstetrical and neonatal outcome. The multiple regression analysis suggested that antenatal chemotherapy may increase the risk of neonatal complications. For SGA, mainly platinum-based chemotherapeutic agents appeared influential. Also, this is the first study evaluating the changes in clinical management and obstetrical and neonatal outcome over years. It appears that during the last 20 years more mothers to be were treated with chemotherapy during pregnancy, resulting in more live births and less prematurity. This observation is indicative of an increased knowledge and awareness about cancer treatment during pregnancy.

Implications of all available evidence

Our study suggests that over the years, oncological treatment during pregnancy increased and prematurity rates decreased. Less prematurity adds to a better neonatal and long-term paediatric outcome. However, the use of chemotherapy during pregnancy may cause neonatal complications like SGA and NICU admission. The long-term paediatric outcome needs to be assessed in more long-term follow-up studies of these children. With the suggested risk factors from our study, it is possible to assess pregnant cancer patients better and refer these obstetrical high risk patient to an academic hospital, where close surveillance in a multidisciplinary setting is provided. Here, paramedical support, psychological guidance and breastfeeding information additionally contribute to an optimal approach.

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Ethical approval

This study was approved by the ethics committee of the University Hospitals Leuven and by every participating centre when needed.

Declaration of interests

Prof. Van Calsteren reports grants from University Hospitals Leuven during the conduct of this study. The other authors declare no conflicts of interest.

Contribution of authorship

FA designed the study. JdH, MV, KVC and FA were involved in the gathering and interpretation of the data and vouch for the data. JdH, MV, KVC, BVC and FA were involved in analysis of the data. All other authors were involved in the gathering of the data. The first draft of the manuscript was written by JdH, MV, KVC, CL and FA, all other authors revised the manuscript for the final draft. All authors agreed with the submitted manuscript.

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Table 1. Patient characteristics.

Characteristic	Result
All patients, n=1170	
Age at diagnosis in years	
Median (IQR)	32 (29-36)
Range	16-53
Missing, n	13
Period of diagnosis	
1996 – 2004	257 (22)
2005 – 2009	376 (32)
2010 – 2016	537 (46)
Trimester of diagnosis, n (%)[a]	
Pregnant during treatment	76 (7)
First trimester	266 (24)
Second trimester	490 (45)
Third trimester	266 (24)
Missing	72
Parity at diagnosis, n (%)	
Nulliparous	486 (44)
Multiparous	625 (56)
Missing	59
Stage of disease	
Local or regional	893 (79)
Systemic[b]	232 (21)
Missing	45
Treatment received during pregnancy, n (%)[c]	
No treatment during pregnancy	391 (33)
Surgery	454 (39)
- Abdominal/cervical surgery	149 (33)
Chemotherapy[d]	429 (37)
- Anthracyclines	328 (78)
- Alkylating (excl. platinum)	292 (69)
- Antimetabolite	108 (26)
- Taxanes	84 (20)
- Platinum	74 (18)
- Other	97 (23)
- Missing	6
Radiotherapy	29 (3)
Targeted therapy	33 (3)
Other therapy	52 (4)
All singleton live & still births, n=969	
Adverse obstetrical outcome	
PPROM and/or preterm contractions	98 (10)
All singleton live births, n=955	
Adverse neonatal outcome	
Small-for-gestational-age	167/796 (21)
Neonatal intensive care unit admission	298/720 (41)

PPROM, preterm prelabour rupture of membranes

[a] Stratification per malignancy group can be found in the Appendix, page 11.

[b] Systemic disease was defined as TNM or FIGO stage IV disease and leukaemia, non-systemic disease was defined as TNM or FIGO stage I to III and all brain cancers.

[c] Patients with multiple treatment modalities during pregnancy are placed in all applicable groups, hence percentages add up to more than 100. Stratification per malignancy group of the different treatment combinations given during pregnancy is shown in Appendix, page 12.

[d] Combination regimens consisting of more than one chemotherapeutic agent were registered in 83% of the patients.

Table 2. Overview of different treatment modalities per malignancy for all 1170 patients. Patients with multiple treatment modalities during pregnancy are placed in all applicable groups.

	Total	No treatment	Surgery	Chemotherapy	Radiotherapy	Targeted and hormonal therapy[a]	Other therapy[b]
	n	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Breast	462	116 (25)	225 (49)	248 (54)	12 (3)	7 (2)	-
Cervix	147	83 (56)	32 (22)	37 (25)	2 (1)	-	-
Lymphoma	113	41 (36)	8 (7)	66 (58)	4 (4)	18 (16)	-
Ovarian	88	23 (26)	64 (73)	21 (24)	-	-	-
Leukaemia	68	22 (32)	-	23 (34)	1 (1)	7 (10)	15 (22)
Gastro-intestinal	49	19 (39)	21 (43)	16 (33)	-	-	-
Melanoma	46	12 (26)	33 (72)	-	2 (4)	-	-
Thyroid	37	7 (19)	30 (81)	-	1 (3)	-	-
Brain	21	11 (52)	10 (48)	1 (5)	1 (5)	-	-
Other	139	57 (41)	31 (22)	17 (12)	6 (4)	1 (1)	37 (27)
Total	1170	391 (33)	454 (39)	429 (37)	29 (2)	33 (3)	52 (4)

[a] Targeted and hormonal therapy include rituximab n=18, imatinib n=7, trastuzumab n=3, tamoxifen n=3, lorlatinib n=1 and trastuzumab + pertuzumab n=1.

[b] Other therapies include interferon n=52.

Table 3. Obstetrical outcome, stratified by malignancy for all singleton pregnancies with known obstetrical outcome, n=1089/1107, 98%).

	Total	Miscarriage	TOP	Still birth[a]	Live birth < 37 weeks	Live birth ≥ 37 weeks	Live birth GA Unknown	Maternal death during pregnancy
Malignancy	n	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Breast cancer	428	6 (1)	26 (6)	1 (<1)	184 (43)	182 (43)	28 (7)	1 (<1)
Cervical cancer	140	2 (1)	21 (15)	2 (1)	72 (51)	37 (26)	6 (4)	-
Lymphoma	107	-	8 (8)	3 (3)	48 (45)	45 (42)	3 (3)	-
Ovarian cancer	83	3 (4)	3 (4)	-	21 (25)	53 (64)	3 (4)	-
Leukaemia	64	5 (8)	6 (9)	2 (3)	26 (41)	25 (39)	-	-
Gastro-intestinal cancer	47	2 (4)	4 (9)	2 (4)	29 (62)	8 (17)	1 (2)	1 (2)
Melanoma	43	-	2 (5)	-	3 (7)	34 (79)	3 (7)	1 (2)
Thyroid cancer	37	-	4 (11)	-	1 (3)	32 (87)	-	-
Brain cancer	19	-	2 (11)	-	9 (47)	6 (32)	-	2 (11)
Other malignancies	121	2 (2)	19 (16)	4 (3)	37 (31)	36 (30)	23 (19)	-
Total	1089	20 (2)	95 (9)	14 (1)	430 (40)	458 (42)	67 (6)	5 (1)

TOP, termination of pregnancy; GA, gestational age;

[a] Still births consisted of 7 intra-uterine deaths, 7 perinatal deaths.

Table 4. Multivariable analysis of the most common obstetrical and neonatal complications. For preterm prelabour rupture of membranes (PPROM)/preterm contractions, we analysed singleton stillbirths and live births (n=969), for the neonatal complications we analysed singleton live births (n=955). We handled missing data using multiple imputation.

	PPROM/preterm contractions		Small-for-gestational-age		Neonatal intensive care unit admission	
Covariate	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Malignancy		0·16		0·86		<0·0001
Breast cancer	Reference[a]		Reference[a]		Reference[a]	
Cervical cancer	0·74 (0·27-2·04)		0·75 (0·36-1·55)		2·22 (1·19-4·15)	
Lymphoma	1·24 (0·49-3·12)		1·17 (0·52-2·60)		1·04 (0·53-2·04)	
Ovarian cancer	0·60 (0·16-2·30)		0·39 (0·14-1·09)		0·60 (0·26-1·38)	
Leukaemia	2·45 (0·80-7·48)		0·68 (0·23-2·03)		1·27 (0·53-3·03)	
Gastro-intestinal cancer	0·33 (0·06-1·96)		0·80 (0·29-2·22)		7·13 (2·86-17·7)	
Melanoma	0·76 (0·19-3·12)		0·90 (0·29-2·76)		0·36 (0·13-1·04)	
Thyroid cancer	0·52 (0·09-3·12)		0·73 (0·21-2·58)		0·14 (0·02-0·90)	
Other malignancies	0·44 (0·15-1·31)		0·82 (0·36-1·83)		1·42 (0·73-2·75)	
Period of diagnosis		0·69		0·32		0·019
1996-2004	Reference[b]		Reference[b]		Reference[b]	
2005-2009	0·81 (0·44-1·48)		0·77 (0·45-1·31)		0·73 (0·48-1·11)	
2010-2016	0·77 (0·43-1·39)		1·04 (0·63-1·73)		0·55 (0·36-0·84)	
Age at diagnosis (per 5 years)	1·08 (0·86-1·35)	0·53	1·36 (1·11-1·68)	0·0033	0·98 (0·82-1·17)	0·65
Diagnosis in 3rd trimester vs. before	0·64 (0·35-1·15)	0·14	0·78 (0·48-1·27)	0·33	1·13 (0·77-1·65)	0·52
Systemic vs. non-systemic disease	1·43 (0·70-2·92)	0·34	1·86 (1·04-3·33)	0·039	1·14 (0·68-1·93)	0·52
Chemotherapeutic agents		0·056		<0·0001		0·0086[c]
Alkylating (yes vs. no)	2·02 (0·81-5·02)		2·08 (0·88-4·91)		0·88 (0·46-1·70)	
Anthracyclines (yes vs. no)	1·11 (0·42-2·92)		0·50 (0·21-1·22)		1·21 (0·62-2·38)	
Antimetabolite (yes vs. no)	0·89 (0·46-1·71)		1·24 (0·70-2·22)		1·03 (0·60-1·74)	
Taxanes (yes vs. no)	1·11 (0·53-2·33)		2·07 (1·11-3·86)		2·37 (1·31-4·28)	
Platinum (yes vs. no)	2·29 (0·79-6·63)		3·12 (1·45-6·70)		1·66 (0·77-3·55)	
Other (yes vs. no)	1·48 (0·61-3·63)		2·34 (1·04-5·25)		1·63 (0·78-3·38)	
Abdominal/cervical surgery (yes vs. no)	0·42 (0·15-1·16)	0·083	1·31 (0·67-2·59)	0·45	0·30 (0·17-0·55)	<0·0001

[a] We used the largest group as reference category (breast cancer).
[b] We used the first time period as reference category (1996-2004) .
P-values are related to the null hypothesis that all odds ratios to which they refer are 1. For malignancy, these are the odds ratios of all malignancy types vs. breast cancer. For period of diagnosis, these are the odds ratios of each period vs. the first. For chemotherapeutic agents, the p-value refers to the simultaneous association of the administration all six agents with the outcome. All other p-values refer to only one odds ratio.

Figure 1. Flow chart with inclusion process.

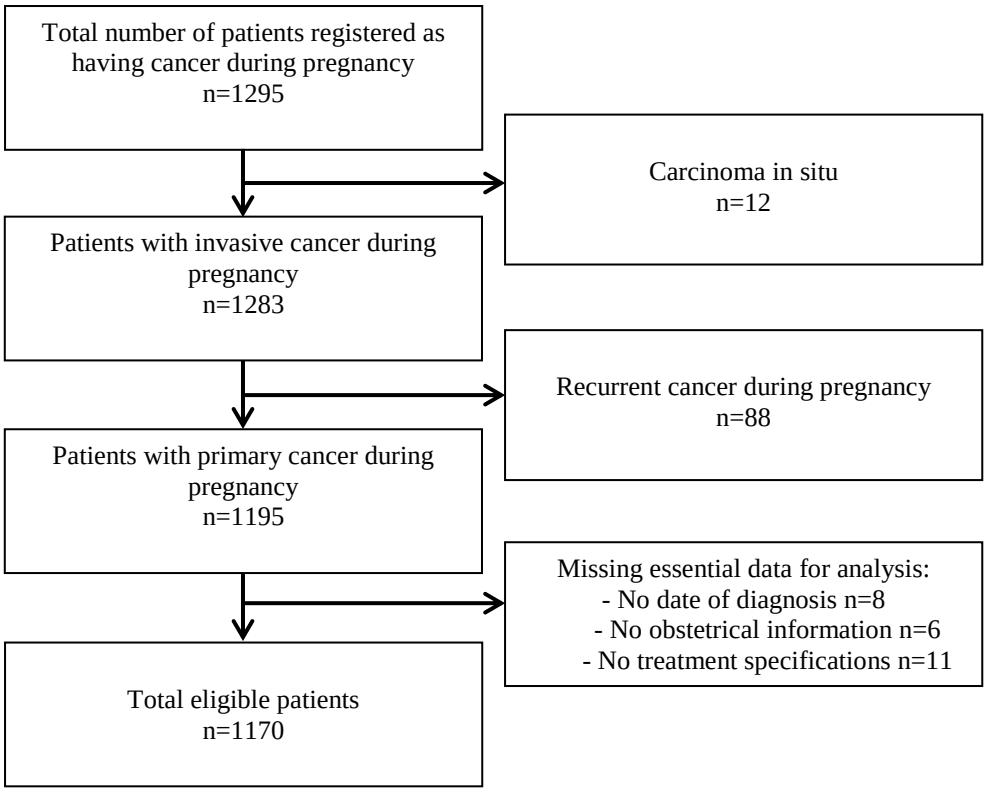
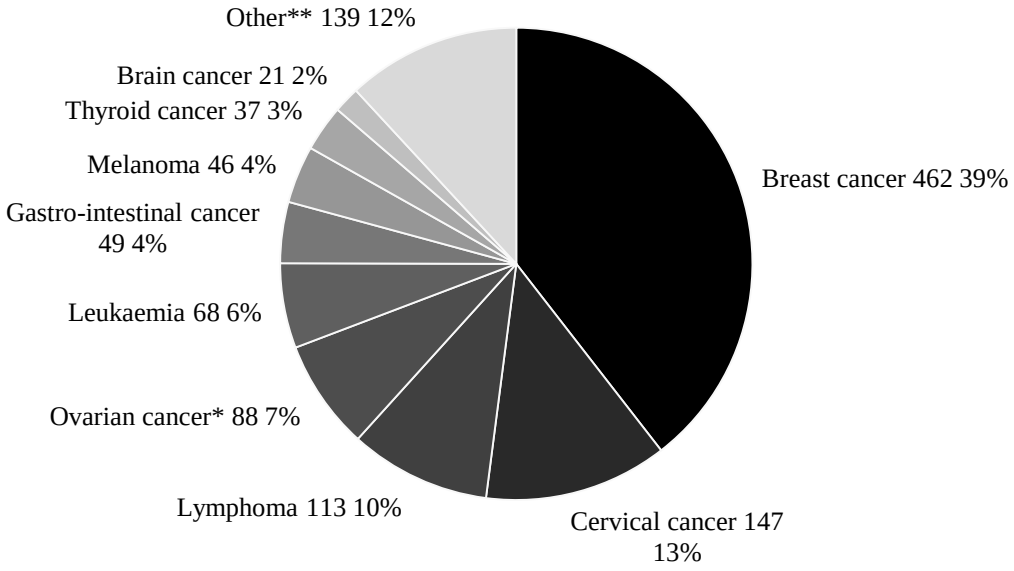
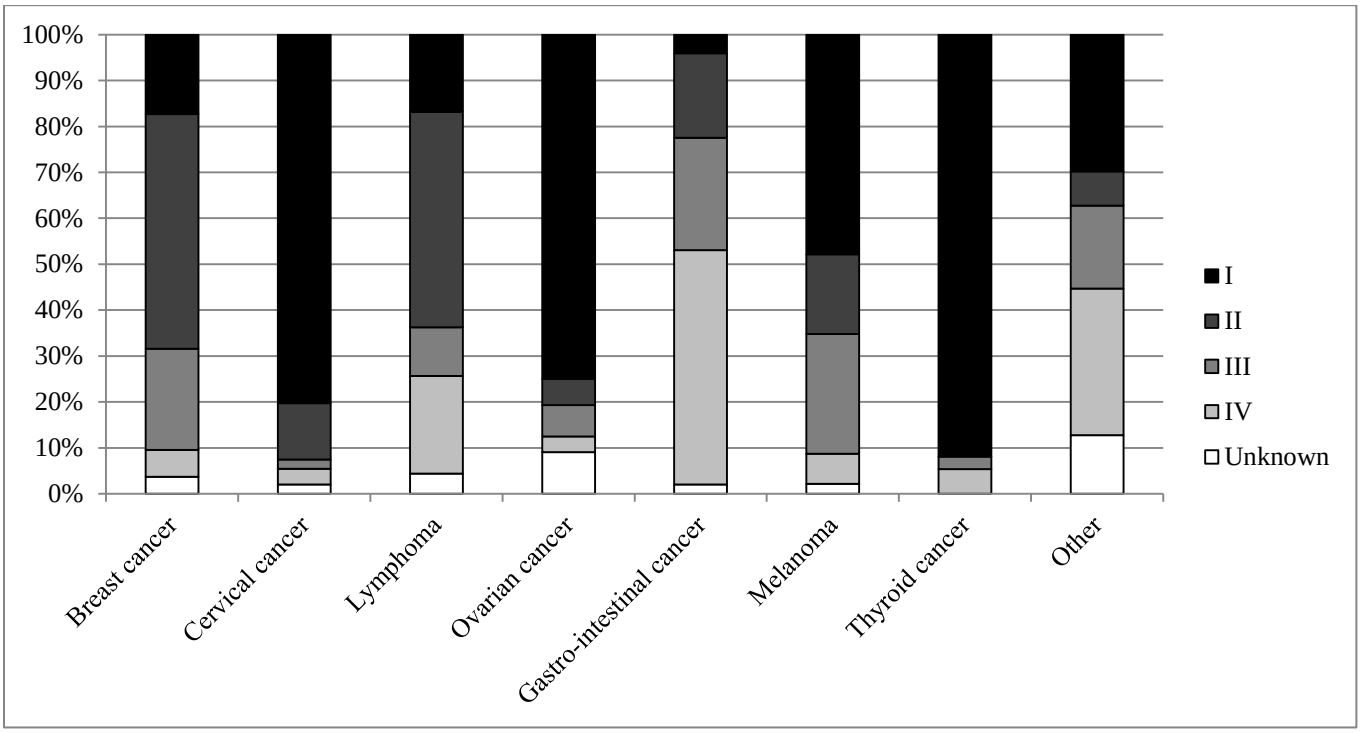


Figure 2. Distribution of malignancies during pregnancy (A) and stage of disease (B) at diagnosis per malignancy. Stage of disease was available for all solid malignancies with TNM or FIGO classification.





* Ovarian cancers include borderline ovarian tumours.

**The group with other malignancies consists of 25 different malignancy types.

Figure 3. Changes in management (A) and obstetrical outcome (B) over 20 years. Management changes are shown for all 1170 patients, obstetrical outcome is shown for all singleton pregnancies.