The effect of maternal malignancy on fertility, pregnancy, and neonatal outcomes

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LUND UNIVERSITY

DOCTORAL DISSERTATION

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The aim of this thesis is to investigate whether a malignant disease in women increases the risk of fertility disturbances, pregnancy and delivery complications and also of adverse birth outcomes among their infants.

By linkage between six national health registers, we obtained data for all children born in Sweden 1994-2011 and their mothers including information on malignancy diagnosis, method of conception (natural/ART), pregnancies, and health outcomes of the infants.

In Papers I- III we studied the outcomes after a malignancy diagnosis of more than one year before delivery. We found increased risks of fertility disturbance and some pregnancy and delivery complications among these women. We also saw an increased risk of preterm birth and low birth weight among their infants and as a result of this an increased risk of neonatal morbidity. No increased risk of malformation was found after a history of malignancy. However, an increased malformation risk was seen after IVF and previous maternal malignancy.

In Paper IV the focus was on women and their infants with a malignancy close to or during pregnancy. We observed a high incidence of prematurity and neonatal morbidity, especially when the malignancy was diagnosed during the second and third trimesters. An increased risk was also seen of relatively mild malformations after maternal malignancy within six months prior to pregnancy or during the first trimester.

In conclusion, it is important that these women receive adequate information about potential risks but also reassurance from clinicians who provide counseling. During their pregnancies additional surveillance is possibly required.

Key words: Malignancy, Pregnancy complications, Prematurity, Congenital malformations, IVF

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To my family

“Knowledge is power”

Francis Bacon

Content

List of original papers

This thesis is based on the following original papers. They are referred to in the text by their Roman numerals. The papers are appended at the end of the thesis. Reprints are made with the permission from the publisher.

I. **Sabeti Rad Z**, Friberg B, Henic E, Rylander L, Ståhl O, Källén B, Lingman G. Deliveries after malignant disease before pregnancy: maternal characteristics, pregnancy and delivery complications. *Journal of Adolescent and Young Adult Oncology*. 2016; 5:240-7.

II. **Sabeti Rad Z**, Friberg B, Henic E, Rylander L, Ståhl O, Källén B, Lingman G. Characteristics of the offspring of women with a history of malignancy, excluding congenital malformations. *Journal of Obstetrics and Gynaecology Canada*. 2016; 38:1037-1044.

III. **Sabeti Rad Z**, Friberg B, Henic E, Rylander L, Ståhl O, Källén B, Lingman G. Congenital malformations in offspring of women with a history of malignancy. *Birth Defects Research Part A: Clinical and Molecular Teratology*. Doi: 10.1002/bdra.23584. [Epub ahead of print]

IV. **Sabeti Rad Z**, Friberg B, Henic E, Rylander L, Ståhl O, Källén B, Lingman G. Prematurity and neonatal outcome including congenital malformations after maternal malignancy within six months prior or during pregnancy. *Submitted*.

Abbreviations

AOF	Acute ovarian failure
ART	Assisted reproductive technology
AYA	Adolescent and young adult
ASD	Atrial septal defect
BMI	Body mass index
CI	Confidence interval
CP	Cerebral palsy
CNS	Central nervous system
ESMO	European Society for Medical Oncology
ET	Embryo transfer
GnRH	Gonadotropin-releasing hormone
Gy	Gray
HER-2	Human epidermal growth factor receptor 2
HPV	Human papilloma virus
ICD	International Classification of Diseases
ICSI	Intracytoplasmic sperm injection
IVF	In vitro fertilization
LBW	Low birth weight
LMP	Last menstrual period
MBR	Medical Birth Register
OD	Oocyte donation
OR	Odds ratio
PDA	Patent ductus arteriosus
PROM	Premature rupture of the membranes
PPROM	Preterm premature rupture of the membranes
PTB	Preterm birth
Q-IVF	Assisted Reproduction National Quality Register
RR	Risk ratio
SGA	Small for gestational age
TTP	Time to pregnancy
VSD	Ventricular septal defect

Papers I-IV at a glance

Paper	Title	Aim	Subjects	Main Results
I	Deliveries after malignant disease before pregnancy: maternal characteristics, and delivery complications.	To evaluate subfertility, pregnancy and delivery complications in women with a history of malignancy compared with all other women in Sweden who gave birth during 1994-2011.	3931 women with 7176 deliveries. A total number of 1 032 251 women with 1 746 870 deliveries in Sweden during 1994-2011.	An increased risk of subfertility, use of IVF, some delivery complications, and rate of cesarean section was observed.
II	Characteristics of the offspring of women with a history of malignancy, excluding congenital malformations.	To study the characteristics of offspring born to women with a history of malignancy, in the same cohort as mentioned above.	7315 infants born to women with a history of malignancy (31 stillborn) with a total of 1 780 112 (6186 stillborn) infants being born in Sweden during this period.	An increased risk of preterm birth, low birth weight, and neonatal morbidity was detected but no increased risk of intrauterine or postnatal death.
III	Congenital malformations in offspring of women with a history of malignancy.	To compare congenital malformations in offspring of women with a history of malignancy with all other offspring, in the same cohort as mentioned above.	Among 7284 live-born infants to women with a history of malignancy, 204 relatively severe malformations were found. A total of 1 773 926 infants with 47081 relatively severe malformations.	No general increase in malformation rate was found after a history of malignancy. An increased malformation risk was seen after IVF and previous maternal malignancy.
IV	Prematurity and neonatal outcome including congenital malformations after maternal malignancy within six months prior or during pregnancy.	To study infants born 1994-2011 to women with a malignancy diagnosed within six months prior to last menstrual period (LMP) up to delivery.	802 infants of 790 women with a malignancy within six months prior to LMP up to delivery with a total of 1 743 559 infants of 1 015 935 women.	A high incidence of prematurity was observed in this group, mostly due to induced preterm delivery with an increased risk of neonatal morbidity. Also an increased risk of malformations was seen in infants of women with a malignancy diagnosed within six months prior to LMP or during the first trimester.

Background

Introduction

Having survived a malignancy has been suggested to strengthen the importance and the value most cancer survivors place on future parenthood (Schover, 2005; Schmidt *et al*., 2016). At the same time, they are often worried about the impact of malignancy and its treatment on their future fertility, pregnancy and the health risk of their potential infants. They are of great need of adequate information from health care providers (Schover, 2005; Reinmuth *et al*., 2008; Schmidt *et al*., 2016).

The loss of fertility for younger women has been suggested to be almost as painful as the confrontation with malignancy itself (Surbone *et al*., 1997; Schover, 2005). Through the combination of earlier detection and improved treatment of malignancies, survival after childhood and adolescent and young adult (AYA, 15-39 years of age) malignancy has increased during the last decades. For several malignancies, a five-year survival rate has reached 81% among childhood patients (0-14 years at diagnosis) and 87% among AYA patients (Gatta *et al*., 2009; Madanat-Harjuoja *et al*., 2010; Haggar *et al*., 2014). Although the incidence of some malignancies, such as breast cancer shows an increasing trend among young adults in Europe, improvements in diagnostic methods leading to earlier detection and improved treatment of malignant diseases during the last decades have increased survival rates (Edwards *et al*., 2005; Karim-Kos *et al*., 2008; Torre *et al*., 2016). The improved cancer survival rates have increased the focus on long-term quality of life, including maintenance of fertility (Levine *et al*., 2015). Pregnancies have become more prevalent in this group and the issue of long-term effects of malignancy and its treatment on women's pregnancy has therefore also increasingly come into focus. Malignancies and their treatments may affect fertility, outcome of pregnancy and the health of the offspring of these women.

At the same time childbearing has become increasingly delayed, especially in industrialized countries (Matthews *et al*., 2009). According to a review article by Schmidt *et al*. (2016) a substantial proportion of women with malignancy are at reproductive age. This trend combined with the fact that the rate of malignancy increases with age results in an increased risk of malignancy occurring during pregnancy (Gziri *et al*., 2012; Han *et al*., 2013a).

Previous studies indicate that despite the fact that fertility preservation methods for women have come to focus during the past years in clinical oncology, only a minority of patients of reproductive age has been referred to fertility specialists and has undergone fertility preservation before the start of oncological treatment (Geue *et al*., 2014; Schmidt *et al*., 2016). Following the recommendations of the American and European societies of clinical oncology, health care providers are supposed to inform patients about fertility-related issues soon after diagnosis and before the start of oncological treatment. During recent years various efforts to preserve fertility in these girls/women have been made. A classical method is embryo cryopreservation before oncological treatment and performance of embryo transfer (ET) after cancer recovery. In the last few years, oocyte cryopreservation has also become a clinical method. Although successful pregnancies have been reported after ovarian tissue cryopreservation, this method is still considered as experimental in most countries (Anderson *et al*., 2015; Kim *et al*., 2016). Ovarian suppression with gonadotropin-releasing hormone (GnRH) has been used but the question regarding its effectiveness is still not resolved (Loren *et al*., 2013; Peccatori *et al*., 2013; Kim *et al*., 2016).

Oocyte donation (OD) is another possibility, which is legal in Sweden since 2003, solely on the basis of medical indication and is only performed in university clinics. The total number of oocyte donations in Sweden up to, and during 2011 was limited (Assisted Reproduction National Quality Register, Q-IVF).

The number of women who underwent fertility preservation with ET after recovery before 2011 is as far as we know small.

Malignancy before pregnancy

In 2016 Luke *et al*. showed in a large population-based study that women with a malignancy within five years and six months before using assisted reproductive technology (ART) were less likely to become pregnant and to have a live birth compared to women without a malignancy who have undergone ART. In particular, this was seen after specific cancer diagnoses such as breast cancer and all gynecological cancer (cervix, uterus, other female genitalia, ovary, vagina, and vulva). They discussed the possibility that this may be associated with the cancer process itself, the cancer therapy, or a combination of both factors.

Fertility

Infertility is defined as an inability to reach a pregnancy after more than one year of attempts of conception.

Previous studies have shown an increased risk of infertility and premature ovarian failure in cancer survivors (Sklar *et al*., 2006; Green *et al*., 2009; Barton *et al*., 2013; Levine *et al*., 2015). Strong associations have been demonstrated with cancer therapies such as surgical resection of reproductive structures, high-doses of pelvic radiation or radiation to the brain, and use of chemotherapeutic agents (especially alkylating agents).

Chemotherapy and/or radiotherapy can diminish the ovarian reserve (Green *et al*., 2009; Mörse *et al*., 2013). Uterine radiotherapy is known to affect reproductive function independently of the ovarian effect (Barton *et al*., 2013; Teh *et al*., 2014). Radiation to the brain can affect the hypothalamic-pituitary-gonadal axis (Pfitzer *et al*., 2014; Levine *et al*., 2015).

Most previous studies on fertility among cancer survivors concern childhood malignancy (Sklar *et al*., 2006; Green *et al*., 2009; Johnston *et al*., 2009; Barton *et al*., 2013).

Ovarian reserve

By the time of birth, the human ovary has a limited number of oocytes. They reach their maximum number at around 5-6 months gestational age, when there are approximately seven million primordial follicles. Each primordial follicle consists of an immature oocyte in meiotic arrest surrounded by a few granulosa cells (somatic cells). At birth, this number has been reduced to approximately 1-2 million. During childhood the number of oocytes decline and only around 300,000 are present at menarche, and fewer than 500 will be ovulated. Primordial follicles are continuously being recruited out of the resting pool and activated to grow, however only one oocyte matures and is ovulated each cycle. The majority of follicles are lost through the process by atresia (Johnston *et al*., 2009; Morgan *et al*., 2012).

Premature ovarian failure

Premature ovarian failure is defined as menopause before the age of 40 years. Women who lose ovarian function and entry into menopause during oncological treatment or shortly after completing the therapy are classified as having acute ovarian failure (AOF). The accelerated depletion of ovarian reserve caused by cancer treatment is a significant mechanism through which they cause menopause (Chemaitilly *et al*., 2006; Levine *et al*., 2015). The age of the women at treatment is therefore a key factor, due to the fact that older women have a smaller ovarian reserve at the start of treatment. Menopause occurs once the number of remaining

follicles is below a certain threshold of approximately 1000 (Johnston *et al*., 2009; Morgan *et al*., 2012).

The effect of chemotherapeutic agents and radiation on the ovary and uterus

Chemotherapeutic agents act by a range of mechanisms but with particular cytotoxicity to dividing cells. There are different cell types in the ovary. Oocytes and granulosa cells have different vulnerabilities to cytotoxic agents. Most oocytes are dormant in meiotic arrest (non-dividing) within immature follicles, while the granulosa cells of such follicles show a high rate of proliferation. There is however, a bidirectional communication between the oocyte and the granulosa cells and they regulate the growth and maturation of each other. Damage to granulosa cells will therefore result in indirect damage of the oocyte, leading to loss of oocytes and this will diminish the ovarian reserve. However, the oocytes within the growing follicles are metabolically active and therefore more vulnerable (Arnon *et al*., 2001; Johnston *et al*., 2009; Morgan *et al*., 2012).

Another mechanism by which chemotherapy has been suggested to reduce the ovarian reserve, also called the immediate effect, occurs during treatment and induces temporary amenorrhea. This is a result from the loss of growing follicles which is thought to result in an increased recruitment of primordial follicles into the growing pool. Repeated cycles of chemotherapy may therefore reduce the ovarian reserve. However, provided that sufficient primordial follicles remain in the resting pool upon the cessation of treatment, the population of growing follicles will then be replenished, and menstruations are resumed (Meirow *et al*., 2010; Morgan *et al*., 2012).

Among chemotherapies, alkylating agents, including cyclophosphamides, procarbazine and busulfan, are strongly associated with ovarian failure in a dose-dependent manner. The dose threshold is lower the older the women are, since the ovarian reserve diminishes normally with age. AOF occurs in a minority of cancer survivors who have undergone intensive alkylating agent-based treatment (Gracia *et al*., 2012; Levine *et al*., 2015).

The ovaries are also sensitive to radiation therapy. The effect of radiation on ovaries is dose-dependent (Sklar *et al*., 2006; Green *et al*., 2009; Levine *et al*., 2015). According to the American Society of Clinical Oncology, abdominal or pelvic radiation doses >6 Gy (Gray) in adults, >10 Gy in postpubertal girls, and >15 Gy in prepubertal girls are associated with a high risk of infertility (Loren *at al*., 2013; Levine *et al*., 2015).

In 2014 Teh *et al*. have, however, in a review article indicated that even low abdominal radiation doses during childhood can have a negative impact on future fertility with a dose of 4 Gy as a threshold dose, depending on the associated treatment.

Uterine radiotherapy is known to affect reproductive function independently of the ovarian effect by diminishing uterine volume, impairing blood supply, and causing endometrial damage (Barton *et al*., 2013; Teh *et al*., 2014).

Cranial irradiation with a dosage ≥ 30 Gy to the pituitary gland has been suggested to be associated with a high risk of hypogonadotrophic hypogonadism (Pfitzer *et al*., 2014; Vern-Gross *et al*., 2015).

Obstetric and neonatal outcomes

Previous studies on this subject are mostly concerned with survivors of childhood malignancies (Blatt, 1999; Chiarelli *et al*., 2000; Green *et al*., 2002; Signorello *et al*., 2006; Edgar *et al*., 2007; Reulen *et al*., 2009; Green *et al*., 2010; Sudour *et al*., 2010; Signorello *et al*., 2010).

These authors have shown that women who had been exposed to abdominal/pelvic irradiation have an increased risk of preterm delivery and low birth weight among their infants. None of these studies found a statistically significant association between chemotherapy treatment during childhood and an increased risk for preterm birth (PTB) or low birth weight (LBW).

Signorello *et al*. have suggested in 2010 that previous uterine and ovarian irradiation >10 Gy increases the risk of stillbirth or neonatal death. Concerning pre-pubertal girls, irradiation doses as low as 1.00-2.49 Gy significantly increased the risk of stillbirth or neonatal death (but the number of cases was small), with the hypothesis that an immature uterus would be more susceptible to the effects of radiation. Teh *et al*. (2014) have in a review article summarized the literature regarding the effect of radiation to the uterus. According to their summary of current evidence, uterine radiation is associated with a smaller uterine volume. Impaired uterine blood supply, defective endometrial function, and poor uterine distensibility have been suggested as the mechanisms of radiation damage. Impaired uterine blood supply can decrease fetal-placental blood flow and cause fetal growth restriction. Development of myometrial fibrosis which reduces uterine elasticity and volume can lead to preterm labor and delivery. The radiation–induced uterine injury is dose and site dependent but the threshold radiation dose that can damage the uterine cavity to such a degree that pregnancy is not sustainable is according to these authors unknown. However, they recommend that women who have received radiation to the uterus > 45 Gy during adulthood or >25 Gy before menarche should avoid attempting pregnancy.

There are some data on an elevated rate of fetal malposition after flank radiation in childhood. However, premature births were increased in this group (Green *et al*., 2010).

Some studies have also included the effect after AYA malignancy (Clark *et al*., 2007; Mueller *et al*., 2009; Madanat-Harjuoja *et al*., 2010; Haggar *et al*., 2014). Also here the common results of perinatal effects are PTB and LBW.

Haggar *et al*. (2014) studied outcomes of the first completed pregnancies in 1894 female survivors of AYA malignancy and found an increased risk of threatened abortion, gestational diabetes, preeclampsia, postpartum hemorrhage, cesarean section, and maternal postpartum hospitalization >5 days. For the infants an increased risk of PTB, LBW, fetal growth restriction, and low Apgar score (<7) at one minute was found. No increased rate was seen for perinatal death (intrauterine or ≤ 7 days of birth) among offspring of cancer survivors.

In 2010 Madanat-Harjuoja *et al*. studied 1309 first post-diagnosis deliveries in women who were diagnosed with a malignancy between 0-34 years of age and at least 9 months before delivery. They found an increased risk for PTB, especially after germ cell tumors and central nervous system tumors.

In 2009 Mueller *et al*. studied 1898 cancer survivors with a malignancy diagnosis before 20 years of age and their first delivery of a live-born infant. They found no significantly increased risk of diabetes or preeclampsia but a significantly increased risk of PTB and LBW. No increased risk of infant death, congenital malformations or an altered sex ratio was observed, suggesting no increased rate of germ cell mutations.

Clark *et al*. (2007) studied the first pregnancies of 917 women with a previous malignancy at least 10 months before delivery. They found increased rates of PTB, postpartum hemorrhage, and operative delivery (abdominal or vaginal) compared with controls.

Birth outcome in women with previously treated breast cancer

Breast cancer is one of the most common malignant tumors in women and the incidence is increasing, which has been suggested to be due to earlier detection, the increasing prevalence of smoking among females and changing reproductive patterns (Karim-Kos *et al*., 2008; National Board of Health and Welfare, 2011). In 2006 Dalberg *et al*. studied 331 first births following invasive breast cancer. Mean time to pregnancy from the cancer surgery was 37 months. They observed an increased risk of very preterm birth (<32 weeks), LBW, cesarean section, and also a tendency towards an increased risk of malformations among the infants. A meta-analysis of 14 studies by Petráková *et al*. (2016) also showed an increased risk of PTB and LBW among infants of women with previous breast cancer.

Obstetric outcomes after cancer of reproductive organs

The most common reproductive cancer in women below the age of 40 is cervical cancer. There are several studies concerning obstetric and neonatal outcomes after

cervical cancer including Smaldone *et al*., 2010; Mangler *et al*., 2012; Nishio *et al*., 2013; Ebisawa *et al*., 2013; and Robova *et al*., 2014. They have all shown an increased risk of PTB. According to a review article by Mogos *et al.*, (2013) the increased risk found from 13 cervical cancer studies was 48.5%. Also an increased rate of PPROM (preterm premature rupture of membranes < 37 weeks) and cesarean section has been shown (Ebisawa *et al*., 2013; Nishio *et al*., 2013). Smaldone *et al*., in 2010 evaluated the risk for small for gestational age (SGA) and found a significant association with cervical cancer.

The theories that have been proposed as a mechanism behind this are (Mogos *et al*., 2013; Pinborg *et al*., 2015):

1. A shortened cervix that causes a mechanical weakness,
2. A disturbance in the endocervix to develop and maintain the cervical mucus plug during pregnancy. The cervical mucus plug contains high levels of immunoglobulin and phagocytic cells which protect the feto-maternal unit against ascending microbes,
3. Ascending infection with human papilloma virus (HPV).

Mogos *et al*. (2013) also reviewed 16 ovarian cancer studies in the same review as that mentioned above. They did not find any increased rate for PTB. However, a significant number of these studies did not report maturity status for all pregnancies. They only found a small number of studies on uterine cancer which is likely due to the fact that these cases are often treated with hysterectomy.

Obstetric and neonatal outcomes after infertility

There is increasing evidence that infertility, regardless of treatment, is associated with an elevated risk of obstetrical complications and adverse neonatal outcomes (Romundstad *et al*., 2008; Jaques *et al*., 2010; Messerlian *et al*., 2013). Messerlian *et al*. (2013) reviewed literature, published 1974-2011, on the association between infertility in an untreated population (>12 months of trying to conceive) and the risk of PTB, LBW, and SGA. A moderately increased risk of PTB and LBW was reported.

Several studies and reviews have shown that pregnancies resulting from ART are associated with an increased risk of poor obstetric and neonatal outcome, such as PTB and LBW (Schieve *et al*., 2007; McDonald *et al*., 2009; Sunkara *et al*., 2015). The possible reason for this has mainly been related to the underlying infertility itself. However, in 2013 Pinborg *et al*. have in a review article indicated that hormone stimulation or *in vitro* fertilization (IVF) might also have an impact on the increased risk of adverse obstetric and neonatal outcome and more research is required concerning embryo specific epigenetic modifications due to the IVF techniques.

It has been suggested that ovarian aging in women with poor ovarian response is associated with an increased risk of adverse obstetric outcomes. This is thought to be the result of vascular aging and vascular endothelial dysfunction (Bonamy *et al*., 2011; Ludford *et al*., 2012; Phadungkiatwattana *et al*., 2014).

It has also been indicated that an excessive response and high egg numbers following ovarian stimulation might have an association with adverse obstetric outcomes (Pinborg *et al.,* 2013; Sunkara *et al*., 2015).

Maternal cardiac complications after malignancy

Different chemotherapeutic agents are known to induce cardiovascular complications, such as heart failure, myocardial ischemia/infarction, arterial hypertension, thrombo-embolism and arrhythmia. Relatively recent reviews are written on cardiotoxicity effects of oncological treatments (Senkus *et al*., 2011; Schlitt *et al*., 2014; Ewer *et al*., 2015). The most recognized cardiotoxic chemotherapy group is anthracyclines, which are used in a wide variety of malignancies. They can cause acute, subacute and late cardiac damage. The late effect may occur even 10-20 years after treatment. The late effect is clinically the most significant adverse cardiac effect of anthracyclines which can lead to congestive heart failure. Previous studies have suggested an incidence of 26% for heart failure in the anthracycline treated group (Swain *et al*., 2003; Senkus *et al*., 2011; Gziri *et al*., 2012).

Also HER2-targeted agents (used in breast cancer patients with human epidermal growth factor receptor 2+ disease), mostly trastuzumab, are associated with an increased risk of heart failure and asymptomatic decline in systolic function. The risk has been shown to increase when trastuzumab was administered with or shortly after anthracycline treatment (Telli *et al*., 2007).

The risk of cardiotoxicity after radiotherapy to the thorax using a modern procedure is considered to be low, but it is relevant in the long-term survivors who received radiotherapy in the past (Mulrooney *et al*., 2009; Schlitt *et al*., 2014).

Cardiotoxic damage may appear or get worse during pregnancy and delivery due to an increased hemodynamic load on the cardiovascular system during pregnancy. Few studies exist on cardiotoxic effects of cytotoxic drugs resulting in pregnancy complications. In 2016 Hines *et al*. followed 847 female cancer survivors with 1554 pregnancies. In 26 women cardiomyopathy was diagnosed before pregnancy and in eight of them the cardiac function deteriorated during pregnancy. They suggested a careful follow-up during pregnancy of women who have a history of cardiotoxic therapies, even if the treatment was in childhood.

In 2012 Gziri *et al*. have in a review article summarized the knowledge on the cardiovascular effect of chemotherapy treatment during pregnancy. Because of the

increased hemodynamic load on the cardiovascular system during pregnancy and the lack of good data concerning cardiotoxicity of different chemotherapeutic agents during pregnancy, they recommend precautions using chemotherapeutic agents during pregnancy. Pregnant women, exposed to such drugs, should be considered to have an overall increased risk of developing heart failure.

Congenital malformations

Several studies have addressed the concern that both chemotherapy and radiotherapy have a potential to be mutagenic to germ cells which might then influence fertilization, increase the rate of abortions, or cause malformations in their infants (Byrne *et al*., 1998; Arnon *et al*., 2001; Winther *et al*., 2004). However, the findings of these studies have been reassuring in terms of rate of congenital malformations after a history of maternal malignancy and indicate that the postulated increase in germ cell mutation has not been translated into an increased rate of fetal abnormalities. (Green *et al*., 1991; Blatt *et al*., 1999; Chiarelli *et al*., 2000, Arnon *et al*., 2001; Winther *et al*., 2004; Langagergaard *et al*., 2006; Mueller *et al*., 2009; Green *et al*., 2009; Sudour *et al*., 2010; Haggar *et al*., 2014).

In 2001 Arnon *et al*. have summarized the mutagenic and teratogenic potential of the different modalities of oncological treatment. They suggest different factors may explain why the postulated mutations in germ cells have not been shown to increase fetal malformations. For instance, the mutated oocyte might not be able to get fertilized. If fertilization does occur, dominant lethal mutations may result in an undetected miscarriage at a very early stage. It has also been suggested that some correction mechanism exists within the oocyte. Most previous studies in this subject concern childhood malignancies which may to some extent explain the low frequency of genetic abnormalities in pregnancies which have been established a long time after exposure to chemotherapy or radiotherapy. Pregnancy or only treatment with ART for fertility preservation within six months after chemotherapy treatment is discouraged, to avoid mutagenic damage to the growing follicles (Gougeon, 1996; Arnon *et al*., 2001; Morgan *et al*., 2012).

The risk for genetic diseases in the offspring of cancer survivors after exposure to oncological treatment has also been evaluated (Byrne *et al*., 1998; Boice *et al*., 2003; Winther *et al*., 2004). No association has been found between previous oncological treatment and genetic disease. Genetic disease was defined as a chromosomal abnormality, a single gene defect, or altered sex ratio. However, these studies mostly concerned childhood malignancies.

Congenital malformations after IVF

Several studies have addressed the issue of congenital malformations in pregnancies after IVF treatment and have found a moderate increase in birth defects (Källén *et al*., 2005, 2010; Zhu *et al*., 2006; Davies *et.al*., 2012; Pinborg *et al*., 2013; Heisey *et al*., 2015). However, there is increasing evidence that this finding is mainly due to the underlying infertility. Simpson summarized previous studies in a review article in 2014 and found the overall odds ratio (OR) of 1.30 for birth defects after ART but that subfertility is a major factor, if not the sole explanation of, in ART-related birth defects. It has been concluded in most previous studies that after taking into account subfertility and the age of the woman receiving treatment, it is not clear if there is an increased risk for congenital malformations after IVF (Källén *et al*., 2005; Rimm *et al*., 2011; Davies *et al*., 2012; Simpson *et al*., 2014; Wijers *et al*., 2015).

Malignancy during pregnancy

The rate of a malignancy diagnosis during pregnancy is estimated to 1:1000-2000 (Amant *et al*., 2015).

The most frequent malignancies during pregnancy are breast cancer, melanoma, cervical cancer and hematological malignancies which correspond to the most common malignancy types in this age group of women (Van Calsteren *et al*., 2010a).

According to recommendations from the European Society for Medical Oncology (ESMO), once the diagnosis of a malignancy during pregnancy is confirmed, the patient should be referred to a multidisciplinary team of experts in dealing with such cases. This team should contain beside the oncology team also an obstetrician and a neonatologist. Administration of chemotherapy should be avoided during the first trimester, being the period of organogenesis (Peccatori *et al*., 2013). It is of great importance that the parents receive adequate information and are involved in the decisions. There are some guidelines available for health care practitioners treating pregnant women with a malignancy. These guidelines are mainly based on expert opinions (Han *et al*., 2013b; Amant *et al*., 2014; Loible *et al*., 2015; Lishner *et al*., 2016).

During the last decade, several studies have indicated mostly reassuring results regarding the risks of adverse birth and neonatal outcome among infants born to women who have been treated for malignancy during pregnancy, notably after the first trimester (Langagergaard *et al*., 2006; Cardonick *et al*., 2010; Loible *et al*., 2012; Murthy *et al*., 2014; Amant *et al*., 2012, 2015).

The potential teratogenic effect of oncological treatment during pregnancy depends upon the developmental stage of the fetus at the time of exposure. Exposure during the first two weeks post-fertilization is most likely lethal to the embryo. During the period of organogenesis (post-fertilization week 3-10) damage to any developing organ will most likely lead to major malformations (Arnon *et al*., 2001; Cardonick *et al*., 2004; Amant *et al*., 2015). According to previous reviews the estimated incidence for major malformations among fetuses that have been exposed to chemotherapy during the first trimester is 10-20% (Caliguri *et al*., 1989; Arnon *et al*., 2001; Amant *et al*., 2015). It has been suggested that the significantly lower risk of teratogenesis following oncological treatment than is commonly appreciated is probably due to developmental stage at exposure, the nature of the cytotoxic agent, dose, duration and frequency of drug administration (Arnon *et al*., 2001; Amant *et al*., 2015). It has also been suggested that placenta acts as a barrier and to some degrees protects the fetus. Trans-placental passage of some chemotherapeutic drugs has been studied in animal models and *in vitro* and have indicated lower fetal concentration than in maternal blood. However, these studies have explored the trans-placental passage during second to third trimesters (Grohard *et al*., 1989; Van Calsteren *et al*., 2009, 2010b, 2011). The transfer of chemotherapeutic agents through the placenta depends on maternal pharmacokinetics, placental blood flow, and the physicochemical properties of the drugs (lipid solubility, polarity, molecular weight, and concentration gradient over the placenta). Low molecular weight, lipid soluble, non-ionized drugs pass easily through the placenta (Gziri *et al*., 2012; Dekrem *et al*., 2013; Amant *et al*., 2015).

During the second and third trimester, the damage is suggested to be less extensive since it is after the organogenesis period. However, eyes, gonads, central nervous system (CNS), and the hematopoietic system remain vulnerable to exposure. Obstetric and fetal complications such as premature labor, intrauterine growth restriction, intrauterine death, and maternal and fetal hematopoietic suppression have been reported after prenatal exposure to chemotherapy during the second and third trimester (Dekrem *et al*., 2013). Exposure to chemotherapy are advised against at least during three weeks before delivery in order to avoid drug accumulation in the offspring and problems associated with hematopoietic suppression during delivery (Peccatori *et al*., 2013; Amant *et al*., 2015). Concerning brain development, it has previously been indicated that chemotherapy might have a potentially negative influence, in particular on frontal brain regions which are important for attention, memory, and executive functioning (Mennes *et al*., 2005). There are, however, studies that have not shown this negative influence (Aviles *et al*., 2001; Hahn *et al*., 2006; Amant *et al*., 2012). The sample sizes of these studies are small and except for the study by Aviles *et al*. the follow-up period is not long enough to draw major safety conclusions. Hence, subtle impairments of fetal development, especially

disturbances of neurological maturation, may be difficult to detect at birth and can manifest later in life (Arnon *et al*., 2001; Cardonick *et al*., 2004).

Another concern is the potential effect of chemotherapy on the developing fetal heart which is suggested to be more vulnerable than the adult heart (Gziri *et al*., 2012). Data on this subject is limited and is mainly based on case reports and retrospective studies. Gziri *et al*. (2012) have in a review article suggested that overall chemotherapy treatment during the second and third trimester is relatively safe but direct effects on the fetal heart should be considered. They recommend that the fetal cardiac function should be monitored with ultrasound within one to two weeks after each dose of cardiotoxic medication. After delivery, the newborn should be evaluated for hematologic and cardiac effects.

Concerning radiotherapy, the important factors are fetal dosage, radiation field extension and gestational age. Fetal radiation doses >100 mGy are associated with fetal malformation and mental retardation (Peccatori *et al*., 2013). If the pregnancy is still early and there is an adequate distance between the radiation field and the fetus (with adequate shielding) with a fetal radiation dose <100 mGy, radiotherapy is suggested to be safe in most cases (Amant *et al*., 2015). However, even lower doses have been indicated to cause childhood malignancy or future sterility (Peccatori *et al*., 2013). The recommendation from ESMO is therefore, if possible, to postpone radiotherapy to the postpartum period (Peccatori *et al*., 2013). According to the recommendation from the American Society of Clinical Oncology (Coccia *et al*., 2014) radiation therapy is contraindicated during pregnancy. However, in rare cases, when it is necessary for controlling maternal cancer, it should be used in low therapeutic doses with adequate uterine shielding to minimize fetal exposure.

A high rate of preterm labor induction with a subsequent high rate of PTB complications have been previously reported in women with a malignancy during pregnancy, in particular during second or third trimesters (Van Calsteren *et al*., 2010a; Han *et al*., 2013a; Vandenbroucke *et al*., 2014). This is done in order to start cancer treatment in the postpartum period. The recommendation from ESMO is targeting full-term delivery (≥ 37 weeks) whenever possible (Dekrem *et al*., 2013; Peccatori *et al*., 2013).

Prematurity

Premature birth is the birth of an infant before 37 weeks of gestational age and is a significant cause of morbidity and mortality. The frequency of preterm birth has been described as 5-9% in many developed countries. It can be divided into three groups: 1. Spontaneous labor with intact membranes. 2. PPROM. 3. Iatrogenic preterm delivery for maternal or fetal indications (Goldenburg *et al*., 2008). Due to

progress in the medical management of premature neonates the mortality of these infants has dramatically declined over the past decades. Improved survival has raised the concern for a high rate of morbidity (Bastek *et* al., 2008; Boyle *et al*., 2013; Glass *et al*., 2015). The complications of preterm birth are well-studied and include those shown in Table 1 and also early neonatal death (0–6 days), neonatal death (0–27 days), and infant death (0–364 days) (Morken *et al*., 2007; Bastek *et al*., 2008; Glass *et al*., 2015).

Table 1:
Groups of prematurity complications

System	Complications
Cardiac, respiratory	Bradycardia/apnea, need for respiratory assistance, infant respiratory distress syndrome, chronic lung disease
CNS	Intraventricular hemorrhage, periventricular leukomalacia, seizures, cerebral palsy, cognitive developmental delay
Gastrointestinal	Hypoglycemia, feeding problems, necrotizing enterocolitis, reflux
Hematology	Hyperbilirubinemia, sepsis
Eye	Retinopathy of prematurity, visual impairment
Ear	Hearing impairment

The question of whether or not spontaneous and iatrogenic preterm birth should be distinguished in studies of the etiology of prematurity has been raised before (Savitz *et al*., 2005; Morken *et al*., 2007). A population-based study by Morken *et al*. (2007) showed different outcomes among infants born after spontaneous and iatrogenic premature delivery. In their study the risk for respiratory distress syndrome was significantly higher among infants born after iatrogenic delivery at all preterm gestational weeks. Bronchopulmonary dysplasia, gastrointestinal complications and retinopathy of prematurity seemed also to be associated with iatrogenic rather than spontaneous PTB but with differences of significance during different preterm gestational ages. Cerebral palsy (CP) was more associated with spontaneous preterm birth than with iatrogenic preterm birth.

Malignancy after pregnancy

The association between pregnancy complications and adverse birth outcomes and long-term risk for maternal cancer has been previously studied by some authors but is still controversial. Some perinatal factors are suggested to be associated with altered gestational hormones and may therefore influence subsequent maternal cancer risk, in particular breast and ovarian cancer which are known to be hormone dependent (Melbye *et al*., 1999; Innes *et al*., 2004; Mucci *et al*., 2007). These studies have shown that PTB, especially extreme prematurity (<32 weeks) is associated

with an elevated risk of later breast or ovarian cancer. It has been hypothesized that this is due to the hormonal milieu of a pregnancy. Mammary cells proliferate during the last few weeks of the first and during the second trimester of pregnancy and differentiate during the third. Extreme prematurity has been suggested to increase breast cell proliferation due to high estrogen levels (Melbye *et al*., 1999; Innes *et al*., 2004). For ovarian cancer, the hypothesis is progesterone deficiency and that progesterone has a protective effect. During pregnancy, progesterone levels increase with gestational age. Women with preterm births have a pregnancy with a relative deficit of progesterone compared with term birth (Mucci *et al*., 2007).

Concerning infant birth weight, Innes *et al*. (2004) showed a tendency towards a reduced risk for breast cancer among women who gave birth to an infant >4500g in their first pregnancy. They explained that this may be due to the fact that a substantial proportion of these women had gestational diabetes and they suggested that this condition may have reduced estrogen levels during pregnancy. However, Bukowski *et al*. (2012) have shown the opposite result. They found an increased breast cancer risk later in life in women whose first infant had a high birth weight, independently of the mother's own birth weight and breast cancer risk factors. Their hypothesis was that these women were more likely to have had high estrogen activity and free insulin-like growth factors concentrations which may be associated with breast cancer development. Jeffreys *et al*. (2011) have, however, not found any association between insulin-like growth factors and breast or cervical cancer.

Grisaru-Granovsky *et al*. (2015) have studied the association between very low birth weight (<1500g) and subsequent maternal malignancy. They found an increased risk for all sites of malignancies with the highest risk for gastrointestinal cancer while hematological malignancies, ovarian, and breast cancers showed a weaker correlation. The incidence was age-related. Besides maternal age the authors discussed other environmental factors such as smoking and alcohol which might have an association with preterm birth and with malignancy later in life. Like other studies they lacked validated data on these additional risk factors and also on maternal co-morbidities.

Bellamy *et al*. (2007) have not found any association between pre-eclampsia and future maternal cancer, in a review article.

A review article by Tong *et al*. (2014) concluded that the association between gestational diabetes mellitus and some maternal cancer later in life is inconclusive.

Aims of the thesis

The overall aim of this thesis is to investigate the effect of malignancy on women's fertility, pregnancy and health outcomes among their infants. In Papers I-III the objective was to study the impact of a maternal malignancy at least one year before delivery. In Paper IV we aimed to investigate the impact of maternal malignancy six months prior to last menstrual period (LMP) or during pregnancy.

Women with deliveries more than one year after a malignancy:

Maternal characteristics including signs of fertility disturbance (Paper I). Pregnancy complications and diagnoses (Paper I), cardiac complications (present text).

Neonatal outcomes, including congenital malformations (Paper II-III).

Women with malignancies just before or during pregnancy:

Premature delivery, infant congenital malformations (Paper IV).

Women with malignancies within 10 years after delivery:

Pregnancy complications, preterm delivery, congenital malformations (present text).

Material and Methods

Subjects

This thesis is based on all children born in Sweden between 1994 and 2011 and their mothers. The data are based on six national registers in order to identify maternal malignancy, deliveries and the infants born.

In the first three studies, we evaluated the impact of maternal history of malignancy on pregnancy, including fertility disturbances, delivery and also on birth outcomes among their infants. Thus, a child was considered to have a maternal history of malignancy if the mother was first diagnosed with a malignancy at least one year before the child's birth. In the fourth study we examined the outcomes after a maternal malignancy diagnosed between six months prior to LMP and the date of delivery.

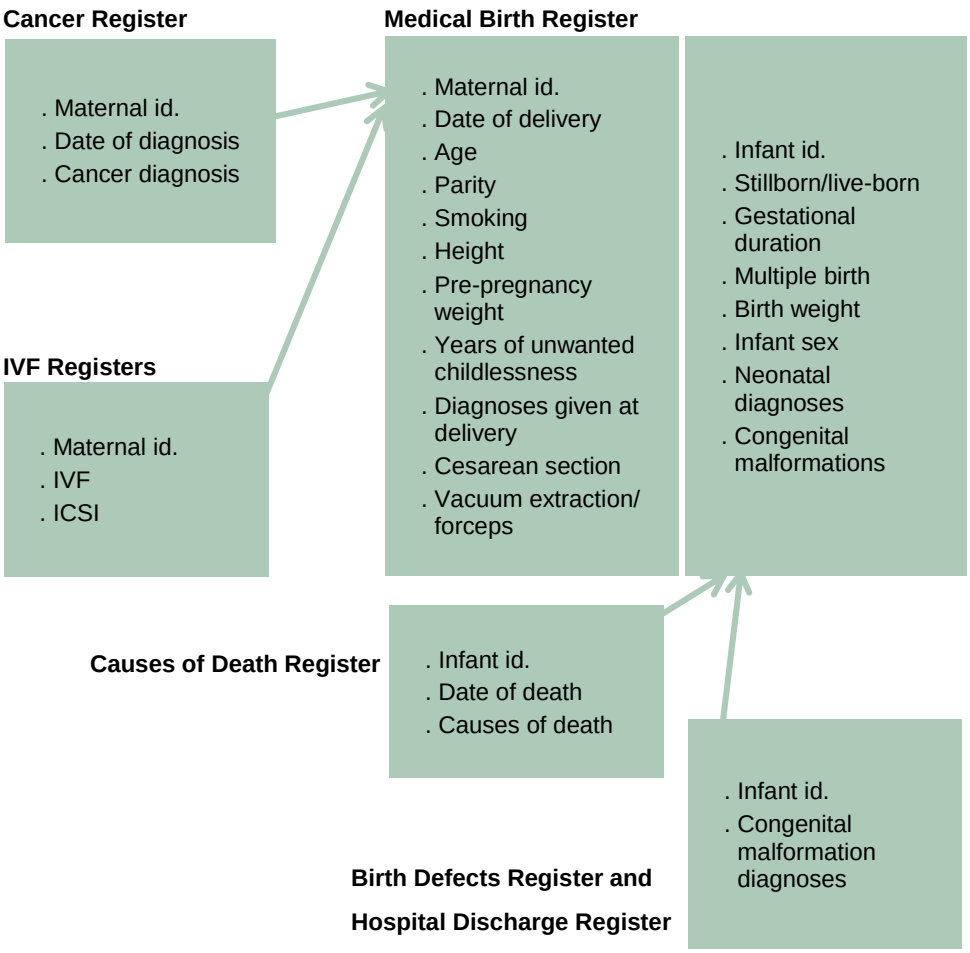
We have also studied in this cohort the association between pregnancy and neonatal complications with maternal malignancy within 10 years after delivery. This has not been published. It will be described here together with some further supplementary material. The studied material will therefore be described in three parts: malignancy at least one year before delivery, malignancy just before and during pregnancy, and malignancy after delivery.

Methods

The Swedish National Registers

The six national registers which have been used and linked together in order to identify and characterize maternal malignancy and their offspring are summarized in Figure 1. All these registers use the unique social security number which every person living in Sweden possesses. The National Board of Health and Welfare replaced these social security numbers with unique but unidentifiable numbers which were subsequently used for further linking between the registers.

Figure 1: National registers



The Medical Birth Register (MBR): Women who gave birth during the years 1994-2011 were identified. The register contains data on the mothers and infants born in Sweden with 1-2% missing (National Board of Health and Welfare, 2003). The register gives information on maternal characteristics and diagnoses and on infant neonatal characteristics (see Figure 1). Information on smoking, pre-pregnancy weight, height, and years of unwanted childlessness (Time to Pregnancy, TTP) in MBR were obtained from midwife interviews in early pregnancy, usually around

week 10-12. Information on the survival of the infants was linked from the national Causes of Death Register up to and including 2013.

The Medical Birth Register contains information on infant malformations from the pediatric examination of the newborn. These data were supplemented with information from the Birth Defects Register and from the Hospital Discharge Register (National Board of Health and Welfare, 2004). The children were followed in the Hospital Discharge Register until one year of age.

The IVF-Registers: Information on IVF was obtained from special registers, based on data reported from all IVF clinics in Sweden. Between 1994 and 2006, all IVF and intracytoplasmic sperm injection (ICSI) treatments leading to a delivery were reported to the National Board of Health and Welfare (Källén *et al*., 2005). Between 2007 and 2011 similar information was obtained from a new IVF register run by the IVF clinics (Q-IVF). The only information used in this study was that IVF had been performed and whether it was a standard IVF or ICSI.

The Cancer Register: This register dates back to 1958 at the National Board of Health and Welfare and reporting to it is mandatory from multiple sources. The analysis included all reported malignant diagnoses 1958-2011 (Barlow *et al*., 2009). Cervical cancer *in situ* is not included in the analysis. The cancer register does not contain information on treatments, but specific diagnostic groups were expected to have received specific treatments. Skin cancers are for instance typically only treated with surgery, whereas hematological malignancies are likely to have been treated with chemotherapy.

Data and diagnoses

Malignancy diagnoses were divided into subgroups based on International Classification of Diseases, ICD-7. The distribution of subgroups of malignant diseases is shown in Table 2. More detailed information is presented in Papers I and III.

Table 2:
Malignacy subgroups

Subgroups of malignancy
I. Respiratory, digestive, urinary tract cancer
II. Skin cancer
III. Breast cancer
IV. Eye and nervous system cancer
V. Bone and soft tissue malignancy
VI. Hematological malignancy
VII. Ovarian cancer
VIII. Cervix cancer
IX. Thyroid cancer
X. Other malignancies

The following pregnancy and delivery diagnoses were studied in Paper I (Table 3). Cesarean section and vacuum extraction or forceps are marked in MBR. For pregnancy diagnoses during 1994-1996 ICD-9 was used and for the years 1997-2011 ICD-10.

Table 3:
Pregnancy and delivery diagnoses

Diagnoses	ICD 9	ICD10
Gestational diabetes	648.8	O24.4
Preeclampsia	642.4-642.7	O14-O15
Premature rupture of membranes	658.1	O42
Placenta previa	641.0-641.1	O44
Placental abruption	641.2	O45
Placenta retention	666.2, 667	O72.2, O73
Bleeding before delivery	641.3-641.9	O46
Bleeding during delivery	-	O67
Bleeding after delivery	666	O72

Cardiovascular complications were also studied, though not described in Paper I. The code for diseases of the circulatory system complicating pregnancy, childbirth or puerperium were selected and supplemented with codes for common cardiac complications of chemotherapeutic agents (Table 4).

Table 4.
Cardiac diagnoses

Cardiovascular diagnoses	ICD-9	ICD-10
Circulatory system complicating pregnancy, childbirth or puerperium	674.0	O994
Heart failure	428, 429.9	I50
Cardiomyopathy	425	I42, O903
Cardiac arrest	427.5, 668.1	I46, O754
Paroxysmal tachycardia	427.1-3	I47

The following neonatal conditions were studied in Paper II:

Preterm/very preterm birth (in most cases pregnancy duration was based on results of second trimester sonography but when absent, other sources were used (National Board of Health and Welfare 2003, page 24). Using these sources in a hierarchical order, the best available estimate of gestational age for each infant was determined. Low birth weight (<2500g) and very low birth weight (<1500g) were based on actual birth weight. Small for gestational age (SGA, <-2 SD) and large for gestational age (LGA, >2 SD) were determined from sex and parity specific graphs (Källén 1995). Low Apgar score was defined as five minutes Apgar score <7.

The neonatal conditions based on ICD diagnoses are given in Table 5.

Table 5:
Neonatal diagnoses studied in Paper II

Neonatal diagnoses	ICD9	ICD10
Intrauterine asphyxia	768	P20
Birth asphyxia	769, 770 (excl 770.7)	P22-P23
Chronic respiratory conditions	770.7	P27
Intracerebral non-traumatic hemorrhage	772.1, 772.2	P52
Jaundice	774	P58,P59
Hypoglycemia	775.6	P70.3-P70.9
CNS-symptoms	779.0-779.3	P90-P92

Congenital malformations were identified from ICD-diagnoses. In order to limit the congenital malformations to relatively severe ones, the following common, less serious and variably registered malformations were excluded: preauricular tags, patent ductus arteriosus (PDA) in preterm infants, single umbilical artery, tongue tie, undescended testicle, hip (sub)luxation or unstable hip, and hemangioma. The remaining cases, which are called “relatively severe malformations”, mainly correspond to what is usually called major malformations.

Induced abortions because of prenatally identified malformations are reported to the National Board of Health and Welfare but without patient identification, therefore it is not possible to link these cases with the cancer register.

The neonatal morbidity diagnoses that were studied in Paper IV are listed in Table 6.

Table 6:
Neonatal morbidity diagnoses studied in Paper IV

Neonatal diagnoses	ICD9	ICD10
Intrauterine/birth asphyxia, respiratory diagnoses	768-770	P21-P22,P24-P28
Sepsis	771.8	P36
Intracranial non-traumatic hemorrhage	772	P52
Gastrointestinal bleeding	772.8-9	P54
Hypoglycemia	775.6	P704
Necrotizing enterocolitis	777.5	P77
CNS-symptms, incl seizures and feeding problems	779.0-3	P90-P92

Statistical analyses

Risk estimates were mainly based on OR with women without previous malignancy as reference. Adjustment for potential confounders was made either with the Mantel-Haenszel method or with multiple logistic regression. In most analyses, we have a large control group which makes it more beneficial to use Mantel-Haenszel method. The Mantel-Haenszel method consists of a series of strata of 2x2 tables, one for each situation of confounding. One needs to have data from the non-exposed individuals in every 2x2 stratum. If this is not the case, the stratum cannot be used and information is lost. The risk for this to happen is very small when dealing with large control groups as we mostly did in our studies. In logistic regressions the control value for each case is estimated from a regression which usually is linear but could be polynomial. The disadvantage of logistic regression is that in order to use the method correctly, a well-modeled regression is required which may sometimes be difficult to construct. We have used it in analysis within the group of women with a malignancy when the numbers are limited.

In most cases adjustment was made for year of birth, maternal age (5-year groups: <20, 20-24, etc. up to ≥40), parity (1,2,3, ≥4, where parity 1 is the first infant born by the mother), smoking (unknown, none, <10 cigs/day, ≥10 cigs/day), body mass index (BMI) calculated from pre-pregnancy weight and height (unknown, <18.5, 18.5-24.9, 25-29.9, 30-34.9, ≥35). Data on smoking were missing in approximately

5% and on BMI in approximately 12%. In Mantel-Haenszel analyses missing data for smoking and/or BMI were treated as separate strata, in logistic regressions they were excluded.

When the number of outcomes after maternal cancer was low (notably congenital malformations), the expected number was estimated from the large background material with adjustments as above and risk ratios (RR) were presented with exact 95% confidence intervals based on Poisson distributions. Crude rates in different subgroups of malignancies were compared with chi-square analyses. In order to control for the possible effect of dependency between repeated pregnancies, sub-analyses were performed. The results were stratified for parity 1 or 2, which resulted in representation of each woman by only one delivery in each stratum.

Ethical considerations

Ethical approval was obtained from the Regional Ethical Committee, Lund University (2011/750) for the whole project.

All women and infants are anonymous in this study since the National Board of Health and Welfare replaced their social security numbers with unique but unidentifiable numbers.

Results

Malignancy before pregnancy

In Papers I-III the study refers to women with a malignancy at least one year before delivery (Figure 2). We identified a total of 3931 women with 7176 deliveries. The total study cohort consisted of 1 032 251 women with 1 746 870 deliveries and 1780 112 infants.

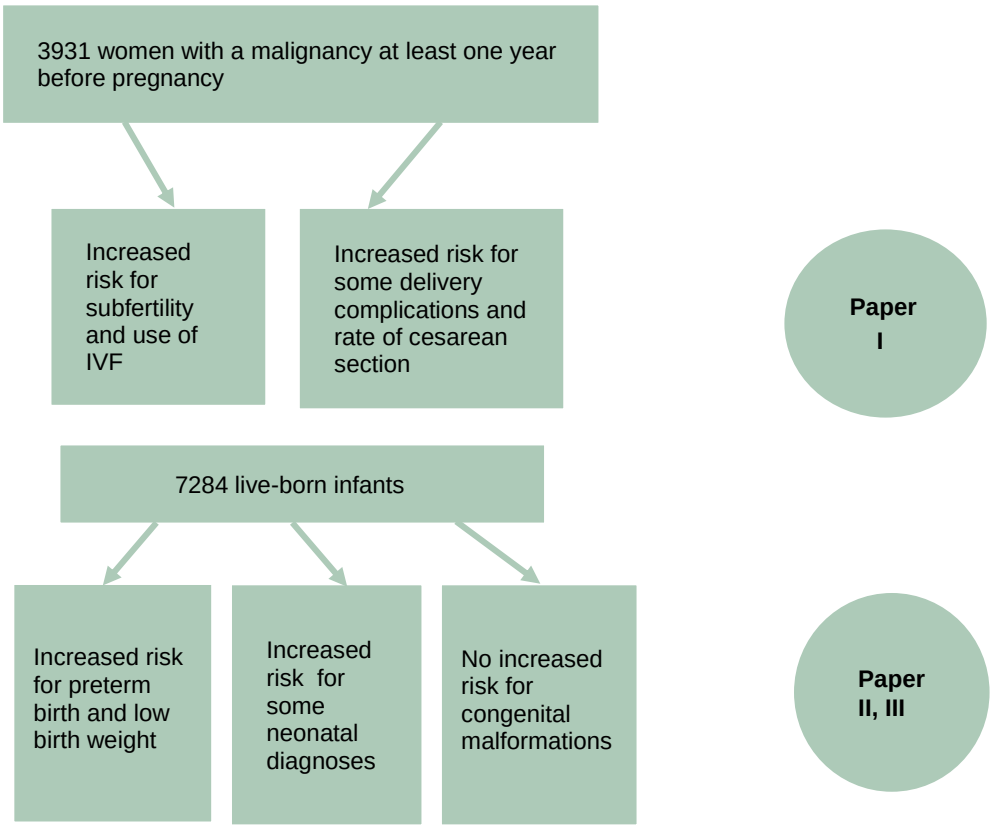


Figure 2:
Schematic diagram of Papers I-III

Fertility disturbance and pregnancy (Paper I)

In the first paper the focus was on the history of fertility disturbance and pregnancies of women with a previous malignancy. Thus, we could only study fertility among women who had achieved a pregnancy. Fertility disturbance was studied as the number of years of unwanted childlessness (TTP) and as the use of IVF. An increased TTP with an adjusted OR of 1.17 (95% CI 1.07-1.28) and use of IVF with an adjusted OR of 1.36 (95% CI 1.21-1.53) was found. There was no significant difference between women who had a malignancy diagnosis before or after the age of 20. The different malignancy subgroups were compared with respect to subfertility and use of IVF and the risk estimates varied significantly. Strong effects were seen after ovarian cancer both on TTP and IVF. Most likely the ovarian cancers were of border-line type. Removal from the analysis of women who had cancers in the genital organs hardly affected the common OR among the remaining malignancies, neither for IVF with an adjusted OR = 1.26 (95% CI 1.11-1.44), nor for TTP with an adjusted OR of 1.15 (95% CI 1.05-1.27).

Concerning pregnancy and delivery complications we also found an increased risk with an adjusted OR of 1.17 (95% CI 1.10-1.24) among women with a history of malignancy. The specific diagnoses with statistically increased risks were: placental abruption, bleeding at delivery, premature rupture of membranes (PROM) and cesarean section. A weaker association was also seen with PPROM which did not reach statistical significance with an OR of 1.07 (95% CI 0.86-1.39). Such complications are associated with subfertility and IVF but exclusion of IVF cases hardly changed the adjusted OR = 1.17 (95% CI 1.10-1.25). There was a significant variability between different malignancy types with the highest OR after cervical cancer and the lowest after ovarian cancer. The increased rate of cesarean sections remained after exclusion of women with a history of cervical cancer.

Oocyte donation (OD) became legal in Sweden in 2003 and only one case was reported before 2007. We evaluated pregnancy and delivery complications before and after January 1st, 2004 and found no significant difference: in 1994-2003 OR = 1.11 (95% CI 1.00-1.22) and in 2004-2011, OR = 1.22 (95% CI 1.12-1.33), p=0.14.

Maternal cardiac complications

Maternal heart complications were not discussed in Paper I.

In order to define cardiovascular complications which could be related to malignancy therapy, we analyzed ICD diagnoses as mentioned in Material and Methods among the total of 1 754 046 women and found 1614 women who had one or more cardiovascular diagnoses. Evaluating characteristics as age, parity, smoking

and BMI and adjusting each variable for all others, maternal age showed a statistically significant trend with an increasing OR with age (Table 7).

Table 7:
Characteristics of women with heart complications during pregnancy. Bold text marks statistical significance.

Variable	Number with known heart problems	Number without known heart problems	OR	95% CI
Maternal age				
<20	16	31 261	0.67	0.41-1.11
20-24	142	246 358	**0.74**	**0.61-0.90**
25-29	440	561 964	1.00	Reference
30-34	553	588 594	1.11	0.98-1.26
35-39	3564	271 134	**1.46**	**1.25-1.69**
40-44	98	50 974	**1.98**	**1.56-2.52**
≥45	9	2197	**4.23**	**(2.27-7.88)**
Parity				
1	705	757 817	1.00	Reference
2	546	642 290	**0.85**	**0.75-0.95**
3	240	245 003	0.93	0.79-1.08
≥4	123	107 322	0.95	0.77-1.17
Smoking				
Unknown	117	95 159	-	-
None	1379	1 484 231	1.00	Reference
<10 cigs/day	80	123 393	0.90	0.72-1.13
≥10 cigs/day	38	52 649	1.08	0.78-1.49
BMI				
Unknown	194	220 556	-	-
<18.5	35	38 976	1.15	0.73-1.81
18.5-24.9	843	969 432	1.00	Reference
25-29.9	365	372 639	**1.21**	**1.05-1.40**
30-34.9	115	115 469	1.26	0.97-1.63
≥35	62	45 360	1.13	0.78-1.62
Total	1614	1 752 432	-	-

Table 8 shows the number of women with heart problems during pregnancy, with or without previous malignancy. Expected numbers were calculated with adjustment for year of delivery, maternal age, parity, smoking and BMI. The numbers are low and the absolute risk for the group "all malignancies" is 24/7152, that is 3 per 1000 and for the malignancy group with the highest risk, hematologic malignancies, 14/ 1244, that is 1 per 100.

Table 8:
RR with 95% CI for cardiac problems during pregnancy associated with previous malignancy. Bold text marks statistical significance.

	Number with heart problems	Number without heart problems	Expected Number	RR	95% CI
No previous malignancy	1590	1 745 280	-	1.00	Reference
All malignancies	24	7152	7.70	**3.12**	**2.00-5.03**
<20 years at diagnosis	12	2234	2.07	**5.80**	**3.00-10.1**
≥20 years at diagnosis	12	4918	5.63	**2.13**	**1.10-3.72**
Respiratory etc.	1	851	0.84	-	-
Skin	1	1561	1.72	-	-
Breast	1	393	0.49	-	-
Eye and CNS	3	985	0.99	3.03	0.62-8.86
Bone and soft tissue	0	330	-	-	-
Hematological	14	1244	1.24	**11.3**	**6.17-18.9**
Ovary	0	273	-	-	-
Cervix	0	321	-	-	-
Thyroid	2	668	0.63	3.17	0.38-11.5
Other	2	526	0.82	2.44	0.30-8.81
All except hematological	10	5908	5.58	1.80	0.86-3.30

We analyzed if the higher risk of cardiac complications after malignancies before the age of 20 could be explained by hematologic malignancies (Table 9). The effect is higher at a hematological diagnosis before the age of 20 than after 20 but the numbers are low and the two RRs do not differ significantly.

Table 9:
RR with 95% CI for cardiovascular problems according to age at diagnosis and hematological malignancies vs. other malignancies. Bold text marks statistical significance.

Maternal age at diagnosis of hematological malginancy	Number with heart problems	Number without heart problems	Expected number	RR	95% CI
<20 years	10	650	0.59	**16.9**	**8.13-31.2**
≥20 years	4	594	0.65	**6.15**	**1.68-15.8**

Neonatal outcomes except malformations (Paper II)

Among a total of 1 780 112 infants in the cohort, 7315 infants were born to women with a history of malignancy, among them 31 were stillborn.

After adjustment for year of delivery, maternal age, parity, smoking and BMI no significantly increased risk for stillbirth was detected, OR = 1.14 (95% CI 0.80-1.62). We also studied the risk for stillbirth when maternal malignancy diagnosis was made less than four years before delivery. There were nine cases with no significantly increased risk (RR = 1.14, 95% CI 0.52-2.16). The remaining part of the study was based on live-born infants of mothers with previous malignancy (n=7284).

We found an increased risk of preterm birth with an OR = 1.50 (95% CI 1.37-1.64) and of low birth weight with an OR = 1.50 (95% CI 1.34-1.68) in these infants and the risk decreased marginally when infants born after IVF were excluded. There was no significant difference in the risk of preterm birth between women who had a malignancy before or after 20 years of age. Excluding all infants with relatively severe malformations among premature infants, no significant difference was seen, OR = 1.59 (95% CI 1.35-1.88).

No significantly increased risk for multiple pregnancies was observed, OR = 1.16 (95% CI 0.98-1.37).

Only after a history of cervical cancer, an elevated rate of malposition (breech) was found.

Concerning neonatal diagnoses, an elevated risk for birth asphyxia, jaundice, hypoglycemia and low Apgar score was found among infants of women with a history of malignancy. If infants born after IVF were excluded, no significant change in these risks was seen.

The different malignancy forms were compared with respect to prematurity and neonatal diagnosis. An increased risk was seen after eye and nervous system cancer, hematological malignancy, and bone and soft tissue malignancy and the highest risk was seen after cervical cancer (Tables 3 and 7 in Paper II).

When the analysis was divided into preterm and term infants (Table 8, Paper II), no effect on neonatal diagnoses was seen for term births but an effect remained for preterm births. If a further adjustment was made for actual week of gestation among the preterm births, the risk was halved from 1.38 (significant) to 1.18 (not quite significant). It is thus possible but not proved that a residual effect exists, directly due to the malignancy history of the woman.

No significantly increased risk for infant death was seen, adjusted OR = 1.17 (95% CI 0.84-1.64).

Table 10 summarizes the malignancy groups with an elevated risk in Papers I and II.

Table 10:
Malignancy groups with an effect on fertility, obstetric and neonatal outcomes

Malignancy groups	Subfertility	IVF	Obstetric complications	Preterm birth	Neonatal morbidity	SGA
Cervical cancer			X	X	X	
Ovarian cancer	X	X				
Bone and soft tissue malignancy		X	X		X	
Eye and nervous system cancer		X		X	X	X
Hemato-logical malignacy			X	X	X	
Respiratory, digestive, urinary tract	X		X			
Other malignancy	X	X				

Congenital malformations (Paper III)

In Paper III we evaluated the risk of malformations among these infants. Among all infants, a total of 71 954 (4.1%) with any congenital malformation were identified, 47081 (2.7%) were relatively severe. Among 7284 infants born to women with a previous malignancy, 311 (4.2%) had a malformation diagnosis, 204 (2.8%) were relatively severe.

The main finding of the study is that there is no significantly increased risk for any malformations or for relatively severe malformations after a maternal history of malignancy.

Among 19 specific groups of malformations investigated in our study, only unspecified cardiovascular defects were overrepresented in this group of infants. No malformations known to have a definite character of dominant heredity which could indicate DNA mutations were identified. However, five infants showed multiple and apparently unrelated congenital malformations which could have been the result of mutations. Two had syndromes (Moebius with Poland syndrome and Silver Russel syndrome), Table 11. Regardless, no increased risk of conditions known to result from DNA mutations was seen.

Table 11:
Infants with multiple malformations and syndromes

Malformations/ Syndrome	Maternal malignancy
Spina bifida, bladder exstrophy, omphalocele, anal atresia	Breast cancer
Malformation of anterior eye segment. vitreous opacity, atrium septum defect, polycystic kidney	Non-melanoma skin cancer
Choanal atresia, VSD, ASD, scoliosis	Spinal cord tumor
Cleft lip/palate, laryngeal hypoplasia. Unilat.renal hypoplasia/dysplasia	Cervical cancer
Unspecified multiple malformations	Brain tumor
Moebius with Poland syndrome	Malignant melanoma
Silver-Russel syndrome	Thyroid cancer

Analyzing the risk for congenital malformations in relation to IVF and previous maternal malignancy, an increased malformation risk was seen with an OR = 1.98 (95% CI 1.34-2.91) for any malformations and RR = 1.85 (1.08-2.97) for the group of relatively severe ones. Congenital malformations after IVF in absence of previous maternal malignancy also showed an elevated risk with an OR = 1.23 (95% CI 1.18-1.28) for the group of any malformations and OR = 1.31 (95% CI 1.24-1.38) for relatively severe ones. The estimates after IVF and previous malignancy and those after IVF without previous malignancy differed significantly for any malformation but the difference did not reach statistical significance for relatively severe malformations.

No significant difference in the risk of relatively severe malformations was seen between infants of women with malignancy before or after 20 years of age.

We found no significantly increased risk after any specific type of previous maternal malignancy.

Malignancy just before or during pregnancy (Paper IV)

In Paper IV we studied the risks associated with maternal malignancy when diagnosed within six months prior to LMP or during pregnancy.

A total of 790 women with 802 infants were identified. One woman had a stillborn infant.

We found a high rate of prematurity, especially when the mother had a malignancy diagnosed during the second or third trimester, 33% (95% CI 28.6-37.8). Almost all preterm deliveries before 35 weeks were iatrogenically induced, 91%. These premature infants had a significantly higher risk for neonatal morbidity than

premature infants in the control group. After adjustment for year of birth, maternal age, smoking, gestational week and cesarean section, the OR = 2.67 (95% CI 1.86-3.84). Exclusion of multiple pregnancies affected the OR only marginally: 2.72 (95% CI 1.85-3.98). Among these 80 infants 78 had a respiratory diagnosis. Since respiratory complications are increased after cesarean section adjustment was made for cesarean section. Limiting the analysis to the respiratory diagnosis, the adjusted OR increased to 2.92 (95% CI 2.05-4.13).

The number of congenital malformations is low but we found a statistically significant excess of malformations in infants of mothers with a malignancy diagnosis during six months before LMP or during the first trimester. It was based on 28 cases of all malformations with an RR = 1.81 (95% CI 1.20-2.61) and 17 cases of relatively severe ones with an RR = 1.69 (95% CI 1.06-2.71). There was no significant difference in malformation risk if maternal malignancy was diagnosed within three or between three and six months prior to LMP. The increased risk was not due to an excess use of IVF as has been suggested before (Arnon *et al*., 2001).

Malignancy after delivery

We have studied the risk for malignancy within 10 years after delivery. We identified a total of 11 476 women with a malignancy within 10 years after delivery and compared them with 1 015 935 women without a malignancy. We examined the characteristics of these women, such as age, parity, smoking, and BMI. Age and smoking were obviously two variables with an effect on malignancy risk (Table 12).

Table 12:
Maternal characteristics in women with malignancy within 10 years after delivery. OR with 95% CI. Each variable is adjusted for year of delivery and for the other variables. Bold text marks statistical significance

Variable	Number with cancer	Number without cancer	OR	95% CI
Age at delivery				
<20	75	30 962	**0.41**	**0.33-0.51**
20-24	877	243 577	**0.59**	**0.55-0.64**
25-29	3395	553 229	1.00	Reference
30-34	5584	575 948	**1.71**	**1.64-1.79**
35-39	3855	263 277	**2.82**	**2.68-2.96**
40-44	1032	48 985	**4.31**	**4.00-4.65**
≥45	40	2113	**4.33**	**3.22-5.81**
Parity				
1	5187	743 850	1.00	Reference
2	5871	629 468	**1.06**	**1.02-2.10**
3	2599	239 492	0.98	0.93-1.03
≥4	1201	105 281	**0.82**	**0.76-0.88**
Smoking				
Unknown	810	89 811	-	-
0	12223	1 456 452	1.00	Reference
<10	1115	120 690	**1.08**	**1.01-1.15**
≥10	630	51 138	**1.19**	**1.10-1.29**
BMI				
Unknown	2225	215 196	-	-
<18.5	238	38 417	0.86	0.76-0.98
18.5-24.9	8090	914 445	1.00	Reference
25-29.9	3170	365 282	1.00	0.96-1.04
30-34.9	831	113 251	**0.90**	**0.84-0.97**
≥35	304	44 500	0.89	0.79-1.00

Furthermore, we evaluated the association of different pregnancy and delivery complications with maternal future malignancy. Thus, complications such as gestational diabetes, preeclampsia, placenta previa, ablatio placenta, placenta retention, bleeding around delivery, premature rupture of membrane, and cesarean

section/vacuum extraction/forceps were not significantly associated with future maternal malignancy.

We also studied the association between maternal malignancy within 10 years after delivery and neonatal complications, such as preterm birth, low birth weight, low Apgar, intrauterine hypoxia, birth asphyxia, chronic respiratory conditions, intra-cerebral non-traumatic hemorrhage, jaundice, hypoglycemia, and CNS symptoms and maternal malignancy within 10 years after delivery. Only preterm birth and low birth weight showed a moderate but statistically significant increased association with maternal malignancy within 10 years (Table 13) . Adjustment was made for year of delivery, maternal age, parity, smoking and BMI. At maternal malignancy within five years after delivery, the OR for PTB and LBW increased to 1.17 (95% CI 1.06-1.29).

Table 13:
Association between neonatal conditions and future maternal malignancy. Bold text marks statistical significance.

Variabel	With cancer, with diagnosis	With cancer, without diagnosis	Without cancer, with diagnosis	Without cancer, without diagnosis	OR	95% CI
<32 weeks	115	14 471	11 103	1 679 820	1.12	0.93-1.38
<37 weeks	794	13 792	82 003	1 608 920	**1.12**	1.04-1.20
<1500g	102	14 448	9102	1 678 305	1.18	0.97-1.45
<2500g	518	14 032	52 309	1 635 098	**1.12**	1.02-1.22
SGA	373	14 219	38 325	1 653 984	1.04	0.95-1.16

The increased malignancy risk after prematurity and LBW was compared between different malignancy forms. The only two cancer groups that showed a significantly increased risk were cervical cancer with an OR of 1.52 (95% CI 1.25-1.85) and eye and nervous system cancer with an OR of 1.62 (95% CI 1.27-2.05).

We also evaluated the effect of malformations among the infants. No increased risk was seen for any specific malformation except for the group of any chromosomal abnormality (50 infants) where an adjusted OR of 1.38 (95% CI 1.04-1.82) was found. Adjustment was made for year of delivery, maternal age (<20, 20-29 and from 30 for each year until 46), parity, smoking and BMI. An association was also found concerning Down syndrome (36 infants) with an adjusted OR = 1.37 (95% CI 0.99-1.91).

Discussion

While experiencing cancer has been suggested to mainly strengthen the value of parenthood, cancer survivors are often worried about their future pregnancy and the risks for their potential future infants (Schmidt *et al*., 2016). It is of utmost importance to identify risk factors for these girls/women to reduce their suffering in terms of fertility disturbance and better management and surveillance of their pregnancies and for their future infants.

The studies included in this thesis are among the largest available in this field. The strength of these studies is that they are based on national health registers, a fact which excludes recall bias and selective participation. A weakness of these studies is the lack of information regarding specific oncological treatments. This kind of information is not available in the Swedish cancer register. The malignancy diagnoses can be reported to the cancer register from different specialities which makes it difficult to find their detailed medical records. By analyzing specific subgroups of the malignancy diagnoses we have tried to identify diagnoses that are likely to have received a certain type of treatment.

Fertility disturbance and obstetric complications

In line with previous studies, the results of Paper I show an extended time to pregnancy (TTP) and increased use of IVF among women with a previous malignancy. Thus, after adjustment for maternal age, parity, smoking, BMI and year of delivery an increased risk of fertility disturbance was seen and yet women who never succeeded to have a pregnancy were not included in the study. There was a significant difference in the risks for TTP or IVF according to type of malignancy. Patients with skin cancer, unlikely to have received other treatment than surgery, had no increased rate of IVF. In contrast a significantly increased rate was seen in the group of bone and soft tissue malignancy, where the majority of our cohort had sarcomas, and in the group of eye and nervous system malignancies with mostly brain tumors. These two groups are likely to have received treatments with chemotherapy and/or radiation with negative effects on reproductive organs (Barton *et al*., 2013; Teh *et al*., 2014; Levine *et al*., 2015) or brain radiation which can affect

the hypothalamic-pituitary-gonadal axis (Pfitzer *et al*., 2014; Vern-Gross *et al*., 2015).

In accordance with previous studies we found an increased risk of some obstetric complications in women with a history of malignancy (Clark *et al*., 2007; Haggar *et al*., 2014). This effect could not be explained by the increased use of IVF present in this group, since it remained unchanged after the exclusion of IVF cases.

Also here a significant variability was seen between different groups of malignancies which may be related to the previous oncological treatment. The highest OR was seen in women after cervical cancer. It is well known that women who have been treated for cervical cancer have an increased risk of preterm delivery, PPROM, and cesarean section (Ebisawa *et al*., 2013; Nishio *et al*., 2013; Mogos *et al*., 2013). Also for bone and soft tissue malignancy, hematological malignancy, and for the group of respiratory, digestive and urinary tract cancer an increased risk was found. These diseases are often treated with a multimodality approach including chemotherapy and/or radiation.

No information was available on oocyte donations or on fertility preservation procedures. However, the number of fertility preservation treatments in Sweden with a subsequent performed ET that could result in pregnancy before 2011 is limited. There is evidence that pregnancies after oocyte donation have an increased risk of complications (Pecks *et al*., 2011; Malchau *et al*., 2013). As oocyte donation became legal in Sweden in 2003, we made separate analyses of pregnancy and delivery complications before and after 2004 without finding any significant difference.

We found no significant differences in fertility disturbances or obstetric complications between women who had a malignancy diagnosis before or after the age of 20. However, concerning fertility disturbances we have only studied women who have achieved pregnancy.

An increased risk of cardiac complications during pregnancy was seen among women with a history of malignancy. It has been described in previous studies, that various chemotherapeutic agents can induce cardiovascular complications (Mulrooney *et al*., 2009; Gziri *et al*., 2012; Ewer *et al*., 2015; Hines *et al*., 2016). In particular, this is true for anthracyclines which are frequently used, e.g., at hematological malignancies, breast cancers, and sarcomas. In our material the highest risk was seen in the group who had a malignancy before the age of 20 and after hematological malignancies which further substantiates previous findings (Senkus *et al*., 2011; Gziri *et al*., 2012). It has been described that the late cardiac damage of anthracyclines can occur even after 10-20 years (Senkus *et al*., 2011). The risk of cardiotoxicity increases when the treatment is combined with radiation,

which is more common among pediatric malignancies, e.g., Hodgkin lymphomas during childhood.

Birth outcomes in the infants

The results of Paper II show no increased risk of stillbirth among infants of women with a history of malignancy, which agrees with previous studies (Signorello *et al*., 2010; Haggar *et al*., 2014). Despite our large material, the number was too small to reveal any specificity between different malignancy types. It has been suggested in a study by Ji *et al*. (2016) that stillbirth was significantly higher among infants that were born within three years after maternal cancer diagnosis. In our data no statistically increased risk was found in this group but numbers were small.

In accordance with previous studies no increased risk was seen for infant death (Mueller *et al*., 2009; Haggar *et al*., 2014).

In agreement with other studies (Edgar *et al*., 2007; Mueller *et al*., 2009; Madanat *et al*., 2010), an increased risk was seen for PTB and LBW and as a consequence of this an increased rate of infant morbidity. It is possible but not proved in our study that previous maternal malignancy could have had some direct effect leading to the increased neonatal morbidity. Still larger studies are needed to evaluate if any effect beyond that caused by prematurity exists.

There is evidence that infertility and use of IVF is associated with an elevated rate of PTB and LBW (Pinborg *et al*., 2013; Sunkara *et al*., 2015). In our study the increased risk of PTB was not due to an excess use of IVF in this group of women. It has been previously suggested that it is not necessarily IVF itself that is associated with an elevated risk of adverse perinatal outcome but rather the underlying condition that causes the use of IVF (Messerlian *et al*., 2015).

The risk of multiple pregnancies did not differ between women with a history of malignancy and other women and was almost unchanged after excluding women who underwent ART.

The highest risk of prematurity and neonatal morbidity was seen after cervical cancer which agrees with previous evidence that there is a high risk of preterm birth in women after cervical cancer and its treatment (Mogos *et al*., 2013). After excluding cervical cancer, a significant variability between different groups of malignancies was seen for prematurity but not for neonatal diagnoses. However, a common increased rate was found, indicating an increased risk for other malignancies as well. An increased risk of preterm birth was seen for eye and nervous system malignancies and for hematological malignancies. Concerning neonatal morbidity, an increased risk was also seen for bone and soft tissue

malignancy, thus three groups of malignancies which to a large extent are treated with chemotherapy or radiation. Concerning SGA, our data showed only an effect among infants of women with a history of eye and nervous system malignancy. The majority in this group were women with previous brain tumors. The risk of PTB, neonatal diagnoses, and SGA was thus significantly increased after malignancies of the eye and nervous system. It has also been shown previously in a Finnish study by Madanat-Harjuja *et al*. (2010) that survivors of CNS tumors had an increased rate of preterm delivery. Fetal growth restriction and PTB has been suggested to be caused by impaired uterine blood supply and reduced uterine elasticity, mostly after abdominal/pelvic radiotherapy (Signorello *et al*., 2006; Teh *et al*., 2014). A hypothetical explanation to this effect among CNS tumors survivors may thus be previous spinal radiation, which can directly affect the uterus. Previous brain radiation can also affect the hypothalamic-pituitary-gonadal axis with a negative effect on ovaries which in turn might affect uterus milieu negatively (Pfitzer *et al*., 2014).

In contrast to the result of Green *et al*. (2002) which showed an excess of fetal malposition after flank radiation, in our material an increased risk of malposition (breech) was only found among women with a history of cervical cancer which is most likely caused by the highly increased PTB in this group. It should be mentioned that in the study of Green *et al*. the rate of prematurity was also elevated which could have caused the increased risk of malposition.

In accordance with Mueller *et al*. (2009) and Haggar *et al*. (2014) we found a normal sex ratio among the infants of women with a previous malignancy. A deficit of male infants among the offspring of women with a previous malignancy could suggest transmission of lethal X-linked mutations.

Congenital malformations

Cancer survivors often fear that their children might be at high risk for birth defects and they are therefore of great need of adequate information about this subject from health care providers (Schover, 2005; Reinmuth *et al*., 2008; Schmidt *et al*., 2016). Most previous studies on this subject concern offspring born to childhood cancer survivors and more studies of survivors treated in adulthood are needed (Green *et al*., 1991; Winther *et al*., 2004; Schover, 2005; Green *et al*., 2009; Sudour *et al*., 2010).

The main results from Paper III are reassuring for women in this situation and further substantiate findings in most previous studies (Langagergaard *et al*., 2006; Green *et al*., 2009; Sudour *et al*., 2010; Haggar *et al*., 2014) that there is no

significantly increased risk of any malformations or of relatively severe malformations after a maternal history of malignancy. The only malformation diagnosis that was overrepresented in this group of infants was unspecified cardiovascular defects. The excess could be due to over-diagnosis because of previous maternal malignancy. Known dominant conditions resulting from DNA mutations (e.g., achondroplasia) did not occur in excess, which agrees with previous studies (Boice *et al*., 2003; Winther *et al*., 2004). The most common chromosome anomaly, Down syndrome showed no increased rate either. Even though this study is one of the largest in this field, much larger studies are needed to evaluate risks of specific and uncommon malformations known to be due to dominant mutations. The malformation risk varied according to type of maternal malignancy but this variation may be random. It can be noted that for two malignancies of the reproductive organs, ovarian and cervical cancer, an increased but not statistically significant malformation rate was seen.

However, if the malignancy occurs within six months prior to pregnancy or during the first trimester, an increased risk was seen (Paper IV) of mainly relatively mild malformations. We did not find any difference if the malignancy occurred within three or six months prior to LMP. One explanation could be a mutagenic effect of oncological treatment on oocytes within the growing follicles before conception, another a teratogenic effect of such treatment during the first trimester which is the main organogenesis period when major malformations arise. Congenital malformations that have been associated with exposure to chemotherapeutic agents during pregnancy are mostly craniofacial and limb abnormalities (Vaux *et al*., 2003). The main defects caused by radiotherapy are microcephaly, mental retardation, cataract, microphtalmia, iridial defects, and skeletal anomalies (Arnon *et al*., 2001). Therefore, if they were only due to the oncological treatment, such specific types of malformations would be expected; however, this was not seen. The numbers are however low. This may be due to a postponement of oncological treatment until after the first trimester or to intensified prenatal diagnosis. It would thus indicate that the clinical management of this situation has been effective in preventing the birth of infants with severe malformations after maternal malignancy. The increased rate of malformations in this group was in our study not due to an increased use of IVF which has been suggested by Arnon *et al*., 2001. When a maternal malignancy was diagnosed during the second and third trimesters (after the organogenesis period), the total malformation rate was not increased which is in agreement with previous studies (Arnon *et al*., 2001; Amant *et al*., 2015). An increased risk of cardiovascular defects was however found, based on 10 cases. Previous studies have addressed the concern that chemotherapeutic agents might have a negative effect on the growing fetal heart (Gziri *et al*., 2012; Amant *et al*., 2015). It is also possible that the presence of maternal malignancy could increase

ascertainment and registration of less conspicuous malformations or that this finding might be a result of multiple testing.

However, one has to consider that disruptions in organogenesis by oncological treatment during the first trimester results in more easily detected findings, such as congenital malformations with the most severe ones detectable already at birth. The effect of oncological treatment during the second and third trimester might be more difficult to detect early and could cause late neurodevelopmental consequences, since the CNS continuous to develop after the first trimester and is sensitive to exposure during the entire period of gestation.

There are concerns that using ART to treat malignancy-related infertility may allow conception to occur with genetically damaged gametes (Arnon *et al*., 2001; Schover 2005). There is increasing evidence that infants born after IVF or ICSI have a moderately increased risk of congenital malformations which is mainly due to the underlying parental infertility (Zhu *et al*., 2006; Källén *et al*., 2005, 2010; Heisey *et al*., 2015; Wijers *et al*., 2015). The results from Paper III are in accordance with previous studies and showed a moderately increased congenital malformation risk after IVF or ICSI among infants born to women without a previous malignancy and the risk was even higher after IVF in infants born to women with a history of malignancy. Two different explanations to this can be discussed. One is that women with a history of malignancy have an increased risk of subfertility and also an increased use of IVF (Paper I). It is possible that this group of women also had a severe genetic damage to their oocytes which could result in an increased risk of malformations. However, scrutiny of the individual malformed cases indicated no such defects. The other hypothetical possibility is that if the risk of malformations in infants born after IVF is due to parental subfertility, it may be more affected by maternal than by paternal subfertility. In our study, the increased risk for subfertility and use of IVF is linked to previous maternal cancer and may mainly be a result of maternal subfertility while in the comparison group of IVF without previous malignancy the subfertility may be equally often due to paternal and maternal subfertility. A support for this idea is that Ståhl *et al*. (2011) found no difference in the malformation rate increase after IVF in the presence or absence of previous paternal malignancy.

Cancer during pregnancy

More and more women are diagnosed with malignancy during pregnancy and choosing the appropriate treatment for a specific patient is a big challenge that requires a multidisciplinary approach (Peccatori *et al*., 2013; Han *et al*., 2013a, Amant *et al*., 2015).

The results from Paper IV show in accordance with previous studies a significantly increased incidence of prematurity (Van Calsteren *et al.*, 2010a; Han *et al.*, 2013a; Vandenbroucke *et al.*, 2014), in particular, when a maternal malignancy was diagnosed during the second and third trimesters (33%). Almost all these premature births are the result of induced delivery (91%), most likely due to an urgency to start maternal malignancy treatment postpartum. It is well-known that prematurity is associated with an increased rate of neonatal morbidity and mortality. The premature infants in our study had a significantly higher risk of neonatal morbidity compared to premature infants without a maternal malignancy, which to a lesser degree are iatrogenically induced. This was true after adjustment for confounders such as week of delivery, cesarean section, maternal age, smoking, and year of delivery. Almost all these premature infants with a neonatal diagnosis, had a respiratory diagnosis. However, no increased risk for SGA was found in this group, as has been previously reported (Van Calsteren *et al*., 2010a). Morken *et al*. (2007) have shown different neonatal outcomes after spontaneous and iatrogenic preterm birth. In their study, infants born after iatrogenically induced delivery had a significantly higher risk of respiratory distress syndrome at all preterm gestational ages, with the strongest effect at gestational age 34-36 weeks. Also gastrointestinal complications (necrotizing enterocolitis), bronchopulmonary dysplasia, and retinopathy of prematurity seemed to be more related to iatrogenic preterm birth than spontaneous preterm birth.

Different explanations to this have been discussed in previous studies. It has been suggested that exposure to inflammation and selected proinflammatory cytokines such as IL-1 before preterm delivery may be beneficial for lung maturation (Kramer *et al*., 2009). Intrauterine infection is a frequent and important mechanism for prematurity. It has been suggested to account for 25-40% of preterm birth. Microbial endotoxins and proinflammatory cytokines stimulate the production of prostaglandins, other inflammatory mediators, and matrix-degrading enzymes. Prostaglandines stimulate uterine contractility, wheras degradation of extracellulär matrix in the fetal membranes leads to PPROM (Goldenburg *et al*., 2008; Philips *et al*., 2014). Kramer *et al*. (2009) have for instance suggested that ureaplasma infection which is one of the major organism associated with severe prematurity, can induce early lung maturation.

Lagercrantz *et al*. (1977) showed a high catecholamine concentration in asphyxiated infants and suggested that the stimulating effects of catecholamines on breathing could be of importance for initiation of the breathing in air. They observed, however, that preterm infants responded with less catecholamine secretion during asphyxia compared with full term infants with the explanation that the sympathoadrenal system might not be completely developed in the premature infants.

Previous studies have suggested that oncological treatment with some treatment modification is possible during pregnancy and that premature delivery among these women should be avoided whenever possible (Azim *et al*., 2010; Han *et al*., 2010; Van Calsteren *et al*., 2010a; Gziri *et al*., 2012; Loible *et al*., 2012; Peccatori *et al*., 2013; Amant *et al*., 2015). However, this is a great challenge for the clinicians to evaluate the management and consider maternal and fetal risks. This further emphasizes the importance of these women being referred to a multidisciplinary team of experts.

Cancer after delivery

Among different pregnancy and neonatal outcomes that we have studied, an association was seen between preterm birth and low birth weight with maternal malignancy within 10 years after delivery. Adjustment was then made for some additional risk factors, such as smoking, BMI, and maternal age. Among different malignancy forms only cervical cancer and eye and nervous system cancer showed a significantly increased risk. In Paper II we also found an increased risk of preterm birth and low birth weight after a history of these two cancer forms. We have thus in the same material shown that a history of maternal malignancy increases the risk for preterm birth and low birth weight and on the other hand premature birth and low birth weight increases the risk for future maternal malignancy. Even though both preterm birth and malignancy are multifactorial and their interrelationship can be affected by numerous environmental and genetic factors, this finding in agreement with previous studies indicates some association between preterm birth and later malignancy.

Other cancers of reproductive organs (ovary, breast, uterine) which are also considered to be hormone dependent malignancies showed no significant association.

After adjustment for among other things maternal age, we found an association between any chromosomal abnormality and Down syndrome with a maternal malignancy later in life. This has been suggested in an article by Källén (1988). Various explanations have been discussed, such as mutagen exposure or impaired immunological surveillance. Thus, these two studies suggest that this finding is not a result of multiple testing.

Even though our cohort is one of the largest in this field and we have in the same material also studied malignancy before pregnancy which gives us the possibility to compare these situations, still the results should be interpreted with caution.

Trying to identify women with an increased risk for developing malignancy later in life based on pregnancy-related events is a huge research challenge. Large studies with an analysis that takes into account and makes adjustment for other risk factors (potential confounders) such as smoking, BMI, and maternal morbidity are needed. The results from previous studies have limitations such as lack of validated data on additional risk factors.

Clinical relevance

The results from this thesis substantiate and complement previous studies, thus aiding clinicians who provide counseling to women with a malignancy about the management and surveillance during their current or future pregnancies.

It has previously been shown that these women are often anxious and worried about the impact of malignancy and treatment on their future fertility, pregnancy and health outcomes of their potential infants, especially malformations. Adequate information from health care providers can be of utmost importance for these women and also improve their quality of life.

Even though we have only studied the fertility among women who achieved pregnancy, our results show a fertility disturbance which support the results from previous studies. It is important that these girls (and their parents) / women receive information about the risk of fertility disturbance early and before the start of oncological treatment.

When they do succeed to get pregnant, our results are mostly reassuring. It is important to provide reassurance about the fact that our results in accordance with most previous studies do not show an increased risk of congenital malformations, stillbirth or infant death among infants. However, when malignancy occurs close to and during the organogenesis period of pregnancy, there is an increased risk of malformation, even though our results mainly showed relatively mild ones.

Concerning obstetrics and other neonatal outcomes that we have studied, it is also reassuring for these women that overall births were without adverse events. However, our findings indicate that health care providers should be careful to identify previous malignancy in pregnant women and possibly refer them to special prenatal care.

Cancer survivors with a history of cardiotoxic therapies, particularly with a previous or current subclinical or symptomatic cardiomyopathy should be followed carefully during pregnancy, as has also been shown previously (Hines *et al*., 2016).

The management of pregnancy complicated with maternal malignancy is a huge challenge for clinicians to consider the maternal and fetal risks before inducing preterm birth which may have serious consequences for the infants. Furthermore, larger studies are needed with long term follow up to evaluate the risk of oncological treatment during the second and third trimesters.

Conclusions

In conclusion, Papers I-III have both shown some risks but also reassuring news for women with a history of malignancy. The results further emphasize the importance of adequate information to these women.

- Increased risk of fertility disturbance and use of IVF among cancer survivors who have achieved pregnancy.
- Increased risk of some pregnancy and delivery complications which could not be explained by the increased use of IVF.
- Increased risk of cardiac complications during pregnancy, notably after hematologic malignancies and perhaps more marked at malignancy diagnoses before the age of 20 than after.
- No increased risk of stillbirth or infant death.
- Increased risk of PTB, LBW and as a consequence of this an increased rate of some neonatal morbidity diagnoses.
- No increased risk of malformations in infants born to women with a history of malignancy who achieved pregnancies without IVF.
- Increased risk of malformations in infants of women with a history of malignancy and undergoing IVF, stronger than the general risk increase seen after IVF.

These findings emphasize and reinforce results from previous studies. Namely, that pregnancies in women with a history of malignancy require individual medical assessment with a view to possible extra surveillance, depending on the nature of the previous oncological treatment.

The results of Paper IV have demonstrated:

- The previously shown pattern with a significantly high rate of iatrogenically induced prematurity among women with a malignancy, especially during the second and third trimesters leading to an increased neonatal morbidity. These premature infants had a higher risk of morbidity comparing to infants of mothers without a previous malignancy.
- Increased risk of mainly relatively mild congenital malformations among infants of women with a malignancy diagnosis within six months prior to LMP or during first trimester.

The possible associations with maternal malignancy within 10 years after delivery:

- A moderate but significant association was seen between PTB and LBW with two maternal cancer types within 10 years after delivery: cervical cancer and eye and nervous system cancer.
- After adjustment for among other things maternal age, an association was also seen between any fetal chromosomal abnormality, Down syndrome and maternal malignancy within 10 years.

Future perspectives

It is important to identify risk factors for women with a previous malignancy to reduce their suffering in terms of fertility disturbance and complications during their pregnancy and for their infants, which in turn can affect their quality of life. Even though studies in this thesis are among the largest ones, further large studies are needed with a possibility to also study the oncological treatments given.

Concerning fertility, we have only been able to study fertility among cancer survivors who have achieved pregnancy. There is, however, previous evidence that oncological treatment can have a negative effect on a woman's fertility. Better cooperation between oncologists and fertility specialists are needed to further accelerate the referral of these patients for adequate information about their future fertility and if possible the opportunity to undergo fertility preservation before the start of oncological treatment.

During the past few years in Sweden, different national quality registers of specific malignancies have been created with also information on the oncological treatment given which, as previously mentioned, is missing in the cancer register. These registers will be helpful in future register-based studies, among other things to evaluate the effects of different oncological treatments. They will hopefully further provide clinicians with important information about adverse effects of specific previous oncological treatment on pregnancy and hence result in better surveillance of pregnancies in survivors of different types of malignancy.

Cancer survivors are naturally often worried about their future pregnancies and the risks for their potential future infants. A more comprehensive understanding of the psychosocial aspects of their situation is needed in order to better be able to help them. Support organizations for cancer survivors should continue to increase in number.

Women with a malignancy during pregnancy are faced with difficult decisions and need much support and information from health care. Health care providers should continue work on developing supportive interventions for women with a malignancy during pregnancy. More studies are needed on both the psychosocial effect of experiencing malignancy during pregnancy and also on the effect of oncological treatment during second and third trimesters.

Larger studies are needed to evaluate a possible increase in specific rare malformations caused by dominant mutations.

Identification of women at high risk for developing cancer later in life based on pregnancy-related events remains a research challenge.

A big challenge is to eventually understand a possible direct effect from malignancy itself on the future pregnancy and neonatal risks.

Populärvetenskaplig sammanfattning

Fler kvinnor överlever numera cancer tack vare bättre cancerbehandlingar. För många av dessa kvinnor är det av stor betydelse att kunna bli gravida senare i livet. Flera studier har visat att bevarad fortplantningsförmåga och eventuella risker med barnaskaffande efter genomgången behandling är högt prioriterad hos botade cancerpatienter.

Avhandlingen undersöker påverkan av cancer på kvinnans fortplantningsförmåga, hos kvinnor som har lyckats uppnå graviditet, samt eventuella risker under graviditet, förlossning och även påverkan på avkomman. Vi har undersökt alla barn födda i Sverige mellan 1994 och 2011. Genom att hämta information från olika register har vi identifierat förlösta kvinnor som har haft cancer. I studie I-III har vi inkluderat kvinnor som har haft cancer senast ett år före förlossning. I studie IV har vi koncentrerat oss på kvinnor som har haft cancer inom sex månader före eller under graviditeten.

I den första studien har vi fokuserat på dessa kvinnors fortplantningsförmåga och risker under deras graviditet och förlossning. Resultaten har visat en ökad risk för nedsatt fortplantningsförmåga och ökat behov av att använda provrörsbefruktning. Dessutom har det observerats en viss ökad risk för ett antal graviditets- och förlossningskomplikationer samt ökad risk för att genomgå kejsarsnitt.

I den andra studien har vi analyserat risker för barn till kvinnor med genomgången cancer, både i samband med förlossning och sjuklighet under första levnadsdagarna samt barnadödlighet. Vi har noterat en ökad risk för förtidsbörd, lägre födelsevikt och en del sjuklighet inom första levnadsdagarna hos dessa barn. Studien har inte visat någon ökad risk för barnadödlighet inom denna grupp.

I den tredje studien har vi fokuserat på missbildningsrisken hos barn till kvinnor med genomgången cancer. Ingen ökad risk för missbildning har kunnat påvisas hos dessa barn. Det är känt sedan tidigare att provrörsbefruktning är kopplat till en något ökad risk för missbildning hos barnet. Den risken noterades även i denna studie och risken ökade ytterligare hos barn till kvinnor som både haft cancer och har gjort provrörsbefruktning.

I den fjärde studien har vi undersökt risk för förtidsbörd, sjuklighet under första levnadstiden och missbildningar hos barn till kvinnor som har haft cancer inom sex månader före graviditeten eller under graviditeten. Vi har funnit en kraftigt ökad risk för förtidsbörd med ökad sjuklighet under första levnadstiden hos dessa barn. De flesta av dessa förtidsbörder, framför allt när mammans cancer var diagnostiserad efter tredje graviditetsmånaden, var orsakad av tidig igångsättning, som troligtvis skett på grund av att mamman skulle påbörja cancerbehandling. Hos gruppen som hade fått cancer inom sex månader före graviditeten och under första tre graviditetsmånaderna fanns det dessutom en lätt ökad risk för framför allt mildare former av missbildningar.

Utifrån tidigare data och våra resultat är det av stort betydelse att sjukvården tidigt ger dessa kvinnor information kring negativ påverkan av cancer på deras fortplantningsförmåga. De ska därför tidigt, innan någon behandling startas, remitteras till en fertilitetsläkare för samtal och om möjligt genomgå fertilitetsbevarande åtgärd.

När det gäller konsekvenser under deras graviditet och för deras barn är det framför allt sjukvården som behöver vara observant för vissa ökade risker under dessa kvinnors graviditet för att utifrån de data som finns ta ställning till eventuell extra graviditetsövervakning hos en del av dessa kvinnor. Sammanfattningsvis har studierna ändå visat att för de flesta av dessa kvinnor och deras barn går det bra under graviditeten och sjukvården kan ge dem lugnande besked, framför allt med avseende på missbildningar, vilket dessa kvinnor enligt tidigare studier oftast oroar sig för.

Kvinnor som får cancer under graviditeten möter mycket svåra beslut och handläggning av cancer under en graviditet är en stor utmaning för sjukvården. Att under dessa omständigheter ta de bästa besluten med hänsyn till risker både för mamman och barnet kräver en grupp av experter från olika specialiteter. Kvinnorna behöver mycket stöd och information.

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