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REVIEW

Birth outcome in women with breast cancer, cutaneous malignant melanoma, or Hodgkin's disease: a review

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Background: Data on birth outcome in women diagnosed with cancer before, during, or shortly after pregnancy are very sparse. The purpose of this review was to summarize the existing epidemiologic evidence of the adverse effect of breast cancer, cutaneous malignant melanoma, and Hodgkin's disease on birth outcome.

Methods: The MEDLINE database was used to review the literature systematically. Studies that examined the following outcomes were included: preterm birth, low birth weight, low birth weight at term, stillbirths, congenital abnormalities, male proportion of newborns, and mean birth weight. Studies were grouped according to whether the woman had been diagnosed with the specific cancer before, during, or shortly after pregnancy.

Results: Few data exist on birth outcome in women with breast cancer, melanoma, or Hodgkin's disease. The overall results from the limited number of studies, which included a comparison group for birth outcome, were reassuring. However, for women diagnosed with breast cancer before pregnancy, the only 2 studies that included comparison groups for birth outcome had conflicting results regarding the risk of preterm birth and congenital abnormalities. Furthermore, a recent cohort study of birth outcome in women who were diagnosed with Hodgkin's disease before pregnancy indicated a slightly increased risk of congenital abnormalities among the

Conclusion: Overall, the existing studies offer reassuring results concerning the risks of adverse birth outcome for women diagnosed with breast cancer, melanoma, or Hodgkin's disease before, during or shortly after pregnancy. A limitation of most studies was the imprecise risk estimates caused by the small number of adverse birth outcomes and the lack of results stratified by treatment. Therefore, international collaboration is necessary in the future, to obtain more precise risk estimates for adverse birth outcomes, and to allow stratified analyses according to, for example, treatment.

Keywords: epidemiology, breast cancer, melanoma, Hodgkin's disease, birth outcome

Introduction

In Western countries women often postpone childbearing for personal or professional reasons. The average age of Danish women at their first delivery has gradually increased from 23 years in the 1960s to 29 years in 2008.2 Because the incidence rates of most cancers increase with advancing age³ more women can be expected to be diagnosed with cancer before childbearing, during pregnancy, or shortly after giving birth.

In Denmark, the most common malignancy affecting women of childbearing age is breast cancer, and the second most common one is cutaneous malignant melanoma (excluding nonmelanoma skin cancer).3 Hodgkin's disease, whose incidence peaks in early adulthood and thus also affects women of childbearing age, belongs to cancers

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with a good prognosis. 4 While in previous decades pregnancy in patients with a history of cancer was discouraged,5 currently such pregnancies are treated with more optimism, partly owing to the improved prognosis for several cancers,6 and partly because pregnancies subsequent to breast cancer, for example, do not seem to adversely affect maternal life expectancy.⁷⁻⁹ Because of a growing population of young cancer survivors, however, concerns have been raised about the adverse effects of cancer and cancer therapy on the offspring of the treated individuals.¹⁰ Offspring include those conceived after completion of treatment, and fetuses exposed to cancer therapy in utero. Data on birth outcome in women diagnosed with cancer before, during, or shortly after pregnancy are very sparse. Thus the purpose of this review was to summarize the existing epidemiologic evidence of the adverse effect of breast cancer, cutaneous malignant melanoma, and Hodgkin's disease on birth outcome.

Incidence of breast cancer, cutaneous malignant melanoma, and Hodgkin's disease in women of childbearing age Breast cancer

Breast cancer is the most common female cancer in Denmark with more than 4000 women diagnosed every year (approximately 400 women are younger than 45 years of age at the time of diagnosis).³ The age-standardized incidence rate of breast cancer has almost doubled over the last 4 decades, but this increase is mainly confined to women aged between 45 and 75 years.¹¹ The incidence of breast cancer in pregnancy is unknown, but is estimated to range from 1 in 3000 to 1 in 10,000 pregnancies.¹²

Cutaneous malignant melanoma

For decades, the incidence of cutaneous malignant melanoma has been rising in most white populations around the world. ¹³ In Denmark, the incidence of melanoma for women aged 15 to 34 years increased, on average, by 4.3% annually from 1970 to 1999, ¹⁴ and in recent years, approximately 270 Danish women younger than 45 years have been diagnosed annually with melanoma. ³ It has been estimated that melanoma represents approximately 8% of malignancies diagnosed during pregnancy. ¹⁵

Hodgkin's disease

Hodgkin's disease is characterized by a bimodal age incidence curve, with the first peak in young adults and the second in old-age groups. ¹⁶ While age standardized incidence of Hodgkin's disease has been declining slightly over time, the

true incidence in older age groups has in fact decreased substantially, whilst among young adults in industrialized countries increases have been documented. ¹⁶ In 2000, 29 women younger than 45 years of age were diagnosed with Hodgkin's disease in Denmark. ¹⁷ Hodgkin's disease during pregnancy has a reported incidence ranging from 1 per 100,000 to 1 per 6000 deliveries. ^{18,19}

Definition of birth outcomes

This review focuses on the prevalence of specific birth outcomes for children of cancer patients. It does not examine the risk of spontaneous or induced abortions, or diseases diagnosed later in life. The birth outcomes examined are defined below:

Preterm birth

Preterm birth is defined as delivery before 37 completed weeks of gestation. The time of delivery depends both on the natural course of the pregnancy and on clinical interventions, which may either shorten or prolong gestation. Given this mixture of spontaneous events and effects of medical interventions, the outcome of preterm birth itself is heterogeneous.²⁰

Low birth weight

Low birth weight (LBW) is defined as birth weight of less than 2500 g. Children in this group represent a mix of newborns whose growth is suboptimal, newborns delivered early, and newborns who are small for genetic reasons. ²⁰ As an alternative, some studies use "LBW at term" (defined as birth weight less than 2500 g in those born at least 37 weeks after conception), which suggests that the child remains small despite having had adequate time for growth. ²⁰ The presumption is that a child with LBW at term is likely to be growth retarded.

Stillbirth

In Denmark stillbirth is defined as antepartum or intrapartum fetal death after 22 completed weeks of pregnancy. Before 2004 only fetal deaths after 28 completed weeks of pregnancy were considered stillbirths.

Congenital abnormalities

Congenital abnormalities occur in 3% to 5% of all livebirths.²⁰ However, each individual type of congenital abnormality is rare, with the most common occurring in about 1/1000 live births.²⁰ The etiologic events that generate structural abnormalities typically occur within the first 2 to 8 weeks post-conception, but the recognition of the abnormality may not occur until later in pregnancy (during ultrasound evaluation), at birth, in early childhood, or in adulthood, or the abnormality may never be recognized.

Male proportion of newborns

Approximately 51% of live-born children in Denmark are boys.

Methods

The epidemiologic evidence of the possible adverse effect of maternal breast cancer, melanoma, and Hodgkin's disease on birth outcome was examined via a systematic literature review, including studies published before January 2010.

To review the literature, I searched the MEDLINE database and used the MeSH (Medical Subject Heading) terms "breast neoplasms", "melanoma", and "Hodgkin disease" [MAJR] (Major Topic headings only), respectively, in combination with "pregnancy" [MAJR], limiting the search to include only studies on human females, in English, and with an abstract. More studies were identified through communication with other researchers and by reviewing the reference lists of relevant articles. Studies were classified as case-series, if they reported birth outcome in a cohort of women with cancer without comparing it with the outcome of a comparison group. However, if the authors computed risk estimates for adverse birth outcome in comparison with the general population, the study was classified as a cohort study.

The studies listed in Tables 1, 2, and 3 were selected according to these criteria: studies of birth outcome in women who were diagnosed with breast cancer, melanoma, or Hodgkin's disease at *any* time before pregnenancy (including childhood), during pregnancy, or within 2 years after delivery were included. I selected only studies that examined preterm birth, LBW (or LBW at term), stillbirths, congenital abnormalities, male proportion of newborns, and/or mean birth weight. I excluded studies that reported overall risks of adverse birth outcome for survivors of different cancers combined. In addition, I excluded reviews, case-reports, case-series, and comments from the tables. However, given that the overall evidence on the topic is sparse, there are some references to case-series in the text.

Results

Below is a summary of the existing epidemiologic evidence of the adverse effect of maternal breast cancer, melanoma, and Hodgkin's disease on birth outcome. The studies of birth outcome in women with, respectively, breast cancer, melanoma, and Hodgkin's disease (Tables 1, 2, and 3) were selected according to the inclusion criteria described under Methods. No case-control study fulfilled the inclusion criteria.

Birth outcome in women with breast cancer

Data on birth outcome in women diagnosed with breast cancer before pregnancy are very sparse. Small case series have reported births of healthy children to women who became pregnant after being diagnosed with breast cancer.^{21,22} The only 2 studies with a comparison group for birth outcome that have been published, however, had conflicting results on the risk of preterm birth and congenital abnormalities after breast cancer (Table 1).23,24 In a registry-based cohort study from Sweden, Dalberg et al examined 331 births from 1973 to 2002, to women who were diagnosed with breast cancer before pregnancy.²⁴ Dalberg et al found that a large majority of these births were free of adverse events, and reported no increased risk of stillbirth or reduced birth weight for gestational age. However, the study also reported an increased risk of very preterm birth (<32 weeks) (odds ratio [OR] = 3.2; 95% confidence interval [95% CI]: 1.7–6.0) and LBW (<1500 g) (OR = 2.9; 95% CI: 1.4–5.8) and an increased risk of congenital abnormalities (OR = 1.7; 95% CI: 1.1-2.5) among children of breast cancer survivors, compared with the general population. The increased risk of congenital abnormalities was seen especially in the births occurring in 1988 to 2002 (OR = 2.1; 95% CI: 1.2-3.7), which the authors explained by an increased use of chemotherapy in younger patients. The study, however, had no data on the treatment of women with breast cancer. In contrast, a nationwide Danish cohort study of 216 newborns of women diagnosed with breast cancer before pregnancy found no increased risk with respect to preterm birth, LBW at term, stillbirth, and congenital abnormalities as well as mean birth weight, compared with the outcomes of 33,443 births from unaffected mothers, and with results unaltered by stratification by a treatment variable.²³ As suggested by Dalberg et al the different results in the Swedish and the Danish cohorts may be caused by different degrees of misclassification of the outcome variables between the registries or differences in the use of adjuvant radiotherapy or systemic treatments after breast cancer.

The Danish cohort study also observed an 8-fold increased risk of preterm delivery among 37 women diagnosed with breast cancer during pregnancy, which reflected a higher rate of elective early delivery, probably to allow an early start to cancer therapy. After adjustment for gestational

Table I Studies of birth outcome in women with breast cancer

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Comparison group from 9 months not specified preceding delivery until 12 months after delivery Comparison: Births by cancer free pregnancy and birth women matched by 442 births of county of mother's within 2 years after for gestational age county of mother's within 2 years after for gestational age residence delivery DOR for preterm birth, and calendar period of LBW at term, stillbirth, and CAs women matched by 442 births of PORs for CAs and mean time of birth and by women diagnosed BW were also adjusted county of mother's within 2 years after for gestational age	NSA		Comparison:	who were diagnosed			CAs = none
ergaard 1943–2002 Cohort study 37 births of women Yes, maternal age, parity, POR for preterm birth, Comparison: diagnosed during and calendar period of LBW at term, stillbirth, Births by cancer free pregnancy and birth women matched by 442 births of PORs for CAs and mean time of birth and by women diagnosed BW were also adjusted county of mother's within 2 years after for gestational age residence delivery	2001		Comparison group	from 9 months			$OR_{\text{very LBW}} = 2.0 (95\% \text{ CI: } 1.0-4.1)$
delivery ergaard 1943–2002 Cohort study 37 births of women Yes, maternal age, parity, POR for preterm birth, Comparison: diagnosed during and calendar period of LBW at term, stillbirth, Births by cancer free pregnancy and birth and CAs women matched by 442 births of PORs for CAs and mean time of birth and by women diagnosed BW were also adjusted county of mother's within 2 years after for gestational age residence delivery			not specified	preceding delivery			OR _{preterm birth} = 2.2 (95% CI: 1.7–2.8)
Delivery Generated 1943–2002 Cohort study 37 births of women Yes, maternal age, parity, POR for preterm birth, Comparison: diagnosed during and calendar period of LBW at term, stillbirth, Births by cancer free pregnancy and birth and CAs and CAs and mean time of birth and by women diagnosed BW were also adjusted county of mother's within 2 years after for gestational age residence delivery				until 12 months after			
Comparison: diagnosed during and calendar period of LBW at term, stillbirth, Births by cancer free pregnancy and birth and CAs women matched by 442 births of PORs for CAs and mean time of birth and by women diagnosed BW were also adjusted county of mother's within 2 years after for gestational age residence delivery	Langagergaard	1943–2002	Cohort study	delivery 37 births of women	Yes. maternal age. parity.	POR for preterm birth.	Women diagnosed during pregnancy:
Births by cancer free pregnancy and birth and CAs women matched by 442 births of PORs for CAs and mean time of birth and by women diagnosed BW were also adjusted county of mother's within 2 years after for gestational age residence delivery	et al ²³		Comparison:	diagnosed during	and calendar period of	LBW at term, stillbirth,	POR = 8.1 (95% CI: 3.8–1.7)
women matched by 442 births of PORs for CAs and mean time of birth and by women diagnosed BW were also adjusted county of mother's within 2 years after for gestational age residence delivery	Denmark		Births by cancer free	pregnancy and	birth	and CAs	(10 of 12 preterm deliveries were induced)
women diagnosed BW were also adjusted within 2 years after for gestational age delivery	2006		women matched by	442 births of	PORs for CAs and mean		POR _{1 RAV at Februs} = 5.3 (95% CI: 0.6–5.1)
mother's within 2 years after for gestational age			time of birth and by	women diagnosed	BW were also adjusted		$POR_{CA_s} = 0.5 (95\% \text{ Cl: } 0.1-3.6)$
delivery			county of mother's	within 2 years after	for gestational age		Stillbirths: none
Proportion of male newborns 49% vs 52% in cont difference = -3.4% (95% CI: -20 ; 13).			residence	delivery			Mean BW = $2948 \text{ g vs } 3472 \text{ g in controls.}$
difference = -3.4% (95% CI: -20 ; 13).							Proportion of male newborns 49% vs 52% in controls,
							difference = -3.4% (95% CI: -20 ; 13).

Women diagnosed within 2 years

after delivery:

POR_{preterm birth} = 1.4 (95% CI: 1.0–2.0) POR_{LBW at term} = 1.4 (95% CI: 0.7–2.8) POR_{CAs} = 1.1 (95% CI: 0.6–1.8)

Stillbirths: none

Proportion of male newborns 53% vs 51% in controls Mean BW = 3471 g vs 3466 g in controls.

difference = 2.5% (95% CI: -2.2; 7.2)

age, there was a 240 g reduction (95% CI: -404; -76) in mean birth weight for newborns of women diagnosed with breast cancer during pregnancy. Furthermore, the study showed a tendency towards an increased risk of preterm birth for 442 women diagnosed with breast cancer within 2 years after delivery.²³ The study found no increased risk of stillbirth or congenital abnormalities in women diagnosed with breast cancer during pregnancy or within 2 years of delivery.

These findings corroborate the results of 2 earlier cohort studies of birth outcome in women with breast cancer diagnosed during or shortly after pregnancy (Table 1).18,25 In these studies, however, the authors did not distinguish between birth outcome in women diagnosed with breast cancer during pregnancy and women diagnosed shortly after pregnancy. Smith et al identified 423 cases of breast cancer diagnosed from 9 months preceding delivery until 12 months after delivery over a period of 6 years in California.¹⁸ After adjusting the analyses for maternal age, the authors reported an OR of 2.2 (95% CI: 1.7-2.8) for preterm birth, and an OR of 2.0 (95% CI: 1.0-4.1) for very low birth weight. The study concluded that the data were consistent with an obstetric practice involving elective early delivery for cancer patients. Likewise, a historical cohort study of 118 women, who were pregnant within 9 months before or 3 months after their first treatment for breast cancer, reported a higher proportion of preterm births among offspring of women with breast cancer compared with controls, mainly because elective cesarean sections were done more often to allow earlier start to cancer therapy.²⁵ In that study, only 2 stillbirths and no congenital abnormalities were observed. The authors also reported a lower mean birth weight after adjustment for gestational age.

Three case-series of 24, 28, and 29 pregnant breast cancer patients, respectively, have reported that chemotherapeutic treatment in the second and third trimester caused no congenital abnormalities or other complications, except for intrauterine growth retardation (IUGR) in 1 case.^{26–28}

Only 1 study examined the sex ratio among newborns and found no substantial differences in proportions of boys born to breast cancer patients compared with cancer-free mothers.²³ Thus, the findings did not corroborate a theory of psychological stress²⁹ (caused by a cancer diagnosis) or potential mutagenic exposure (from chemotherapy or radiation)³⁰ reducing the male proportion of newborns. These findings are in line with earlier studies that examined the sex ratio for newborns of childhood cancer survivors and found no significant alterations.31-33

Abbreviations: BW, birth weight; CAs, congenital abnormalities; CI, confidence interval; GA, gestational age; LBW, low birth weight; OR, odds ratio; POR, prevalence odds ratios; RR, relative risk; SGA, small for gestational age

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Table 2 Studies of birth outcome in women with cutaneous malignant melanoma

Author	Period of	Design	Number	Adiustment	Relative effect	Results for birth outcome
	5	:0	3			
Country	cancer				estimates	
year	diagnosis					
CMM diagnosed	CMM diagnosed before pregnancy					
Langagergaard	1970-2002	Cohort study	620 births	Yes, maternal age,	POR for preterm birth,	POR _{monotoners} kind, = 1.1 (95% CI: 0.8–1.6)
et al ³⁴		Comparison:	by women	parity, and calendar	LBW at term, stillbirth,	POR _{1, BAV} at February 11 (95% CI: 0.6–2.0)
Denmark		births of cancer free	with previous	period of birth	and CAs	POR _{CA} = 1.2 (95% CI: 0.8–2.0)
2007		women matched by	melanoma	Mean BW was		Stillbirths: none
		time of birth and by		also adjusted for		No difference in mean BW
		county of mother's		gestational age		Proportion of male newborns $= 53.2\%$ vs
		residence				51.7% in controls, difference = 1.5% (95% CI: -2.5; 5.5)
CMM diagnose	CMM diagnosed during or shortly after pregnancy	after pregnancy				
Ravid et al ³⁶	Not stated, but	Cohort study	18 births of	Yes, maternal age	οZ	Lower mean birth weight $(P = 0.15)$
Canada	over a period	Comparison: births	women diagnosed	(by matching)		No difference in mean GA ($P = 0.53$)
9661	of 30 years	by aged-matched	during pregnancy			Mean birth weight $= 3036$ g vs 3392 g in controls
		women				Mean GA = 39.5 wk vs 40.1 wk in controls
						Stillbirths = 5.6% $CAs = 5.6$
O'Meara et al ³⁵	6661-1661	Cohort study	149 births by	Yes, maternal age	OR for preterm birth	Women diagnosed during pregnancy:
USA		comparison:	women diagnosed	and race	and LBW	OR = 0.8 (95% CI: 0.3–1.8)
2005		births by melanoma	during pregnancy			OR $= 0.9 (95\% \text{ CI: } 0.5 - 1.6)$
		free women	and 263 births by			Stillbirths: none
			women diagnosed			Women diagnosed within 12 months after delivery:
			within 12 months			No increased risk of LBW and preterm birth
			after delivery			Stillbirths: none
Langagergaard	1970-2002	Cohort study	88 births by	Yes, maternal age,	POR for preterm birth, LBW	Women diagnosed during pregnancy:
et al ³⁴		Comparison:	women diagnosed	parity, and calendar	at term, stillbirth, and CAs	POR POR (95% CI: 0.03–1.5)
Denmark		births of cancer free	during pregnancy	period of birth		POR _{I RAV or February} = 0.6 (95% CI: 0.1–4.5)
2007		women matched by	and 351 births by	PORs for stillbirth		$POR_{CA_s} = 0.6 (95\% \text{ Cl: } 0.2-2.7)$
		time of birth and by	women diagnosed	and mean BW was		Stillbirths: none
		county of mother's	within 2 years of	also adjusted for		Higher mean BW (difference = 88 g (95% CI: -18; 194).
		residence	delivery	gestational age		Proportion of male newborns = 56.8% vs 51.9% in
						controls, difference = 4.9% (95% CI: -5.5; 15)
						Women diagnosed within 2 years after delivery:
						POR preserve birth = $0.9 (95\% \text{ CI: } 0.5-1.5)$
						$POR_{LBW, at rerm} = 0.9 (95\% CI: 0.4-2.2)$
						POR _{stillbirth} = 4.6 (95% CI: 1.7–12.3)
						$POR_{CAs} = 1.1 (95\% CI: 0.6-2.0)$
						No difference in mean BW
						Proportion of male newborns = 58.4% vs 51.9% ,
						difference = 6.5% (95% CI: 1.3; 12)
		-		-		

Abbreviations: BW, birth weight; CAs, congenital abnormalities; CI, confidence interval; CMM, cutaneous malignant melanoma; GA, gestational age; LBW, low birth weight; OR, odds ratio; POR, prevalence odds ratio; RR, relative risk; SGA, small for gestational age.

Table 3 Studies of birth outcome in women with Hodgkin's disease

y 52 births by 29 women with a history of Hodgkin's grade disease bopulation study bordlings in the bopulation study bopulation the come in the disease and by wives of oppulation with previous Hodgkin's disease study with childhood histor: T29 births by women with a history of Hodgkin's disease and by wives of Oppulation of Hodgkin's disease study and the hildhood histor: T29 births by women with childhood history of Hodgkin's disease study and by county with previous hodgkin's disease hatched by time with previous hodgkin's disease hatched by time who were pregnant no age-matched earlier than 9 months exposed to and no later than ogenic drugs treatment treatment	Author	Period of	Design	Number	Adjustment	Relative effect	Results for birth outcome
Spirits disease diagnosis 1966–1986 Cahort study 1970–1986 Comparison C	Country	cancer	1			estimates	
glain's disease diagnosed before pregnancy Spinits by twee of earling of bit outcome in the latent outcome in the expension of birth and by county of the latent outcome in the late	Year	diagnosis					
ret al ¹⁸ 1966–1986 Cohort study 1970–1991 Cohort study a liablings disease diagnosed during or shortly after per et al ¹⁸ 1970–2002 Cohort study liablings and education li	Hodgkin's disease di	agnosed before	pregnancy				
res ³ Eirth outcome history of Hodglon's sibilings in sibilings cet al ³ 1966–1986 Cohort study with previous Hodglon's disease Birth outcome in the Gonort study of Hodglon's disease Cohort study of Hodglon's disease Cohort study of Hodglon's disease Cohort study of Birth outcome in sibility of Births by women with a history of Hodglon's disease Cohort study of Birth outcome in sibility of Births by women with the Birth outcome in sibility of Births by women with the Birth outcome in sibility of Gonort study and by county of Gonort study after pregnant of Gonort study after pregnancy or study after pregnancy or study after pregnancy or study on the gonore pregnant or study after pregnancy or study after pregnancy or study or by contracting or short study after pregnancy or study or study after pregnancy or study after pregnancy or study or study or study or study or study after pregnancy or study or study after pregnancy or study after pregnancy or study or stu	Holmes and	1944-1975	Cohort study	52 births by	No	Š	No overall increase in risk of abnormal birth
Birth outcome history of Hodglan's in siblings disease Comparison: With previous Brith outcome in the Hodglan's disease Comparison: With previous Brith previous Brith outcome in the Hodglan's disease Comparison: With previous Hodglan's disease Comparison: With previous Hodglan's disease Birth outcome in the disease and by wives of general population I I men with a history of Hodglan's disease Comparison: With outcome in siblings Hodglan's disease Brith outcome in siblings Hodglan's disease Darrity, and calendar Brith outcome in siblings Hodglan's disease Darrity, and calendar Brith outcome in siblings Hodglan's disease Darrity, and calendar Brith outcome in siblings Hodglan's disease Darrity, and calendar Brith outcome in siblings Hodglan's disease Darrity, and calendar Brith outcome in siblings Hodglan's disease Darrity, and calendar Brith outcome in siblings Hodglan's disease Darrity, and calendar Brith outcome in siblings Hodglan's disease Darrity, and calendar Brith outcome in siblings Hodglan's disease Darrity, and calendar Brith outcome in siblings Hodglan's disease Darrity, and calendar Brith outcome in siblings Hodglan's disease Darrity, and calendar Brith outcome in siblings Hodglan's disease Darrity, and calendar Brith outcome in siblings Hodglan's disease Darrity, and calendar Brith outcome in siblings Hodglan's disease Darrity, and calendar Briths by generated by time Hodglan's disease Darrity, and calendar Briths of age-matched Darrity Brith Brith Brith and Brith Statem. Births of age-matched Darrity and Darrity Brith Br	Holmes ³⁹		Comparison:	29 women with a			outcome (stillbirth and CA combined) ($P = 1.00$)
in siblings disease low et a 1966–1966 Cohort study Comparison: with previous state and propulation in the previous the previous that the previous study comparison: with previous disease and by where of comparison in the previous that the previous the previous that the previous	NSA		Birth outcome	history of Hodgkin's			No increased risk associated with radiotherapy
ret al ¹⁹ 1966–1986 Cohort study (with previous and before at al ¹⁸ 1970–1981 Comparison: with previous set al ¹⁸ 1970–1991 Cohort study (with previous and before al ¹⁸ 1970–1986 Cohort study (comparison: and before al ¹⁸ 1970–1986 Cohort study (cohort study (c	1978		in siblings	disease			alone $(P = 0.25)$
1966–1986 Cohort study 15 births by women No RR for LBW							Increased risk of abnormal birth outcome
1966–1986 Cohort study 15 births by women No RR for LBW							associated with radiotherapy and chemotherapy combined ($P = 0.047$)
Comparison: Held outcome in the general population Glow et al ¹⁸ 1970–1991 Cohor study Ref for preterm birth, and by county after pregnancy Gomparison: Hodgkin's disease Burth outcome in siblings Burth outcome in siblings Gomparison: With childhood Burth outcome in siblings Gomparison: With childhood Burth outcome in siblings Hodgkin's disease Gomparison: With childhood Burth outcome in siblings Hodgkin's disease Gomparison: With childhood Burth outcome in siblings Hodgkin's disease Gomparison: With previous Period of birth and by county of mother's residence getstational age. Gomparison: With previous Period of birth and by county of mother's residence Burth outcome of birth and by county of mother's residence Gomparison: With previous Period of birth and by county of mother's residence Burths by cancer free Hodgkin's disease Ab birth by 48 women Yes, maternal age. PoR for preterm Period of birth, and CAs Adjusted for of birth and by county of mother's residence Burths of age-matched by time Comparison: Women exposed to Burths so age-matched by time Comparison: Women exposed to Burths so age-matched by men Comparison: With previous Burths by 48 women Ab birth so age-matched by time Comparison: Women exposed to Burths and by county of mother's residence Burths of age-matched by time Comparison: Women exposed to Burths of age-matched by time Comparison: With previous Ab Burths of age-matched by time Comparison: With previous Age (by matching) Burths of age-matched by time Comparison: Women exposed to Burths of age-matched by time Comparison: Women exposed to Burths of age-matched by time Comparison: With previous and to later than and by county Age (by matching) Burths of age-matched by time Comparison: When the regional of age (by matching) Burths of age (by matching) Burths of age (by matching) Burths of age (by matching) Comparison of birth and by county Comparison of birth and by county Age (by matching) Comparison	lanov et al ³⁷	9861-9961	Cohort study	15 births by women	°Z	RR for LBW	RR = 2 5 (95% CI: 0.3–9.0)
general population diow et al ⁸⁸ 1970–1991 Conhort study Comparison: In et al ⁸⁸ 1970–1991 Comparison: Compari	USA		Comparison:	with previous			CAs: none
general population dow et al ³⁸ 1970–1991 Cohort study RR for preterm birth, Comparison: Birth outcome in the disease and by wives of general population in the disease and by wives of general population Reflect by with previous Hodgin's disease Birth outcome in the disease and by wives of Birth outcome in sibilings Reflect still birth	1992		Birth outcome in the	Hodgkin's disease			
Allow et alia 1970–1991 Cohort study 49 births by 16 women No Comparison: with previous Hodgkin's disease and by wives of general population 1 Immer with a history of Hodgkin's disease net alia 1970–1986 Cohort study 729 births by women No No Comparison: with childhood Birth outcome in siblings Hodgkin's disease with childhood Birth outcome in siblings Hodgkin's disease of agreemental age. POR for preterm vitch hildhood Birth outcome in siblings Hodgkin's disease Comparison: with previous parity, and calendar birth, LBW at term, Birth and by county of hotgkin's disease diagnosed during or shortly after pregnancy of births by 48 women Newer pregnant no Births of age-matched by time adjusted for the cet alia 1958–1984 Cohort study who were pregnant no age (by matching) Births of age-matched by time artier than 9 months women exposed to before and no later than nonteratogenic drugs at months after than 9 months in pregnancy treatment in pregnancy are pregnant treatment.			general population				
Comparison: with previous Hodgkin's lin newborn and between of general population I I men with a history of Hodgkin's disease of Cohort study Comparison: with critical oct all of 1970–1986 Cohort study Sergard et all of 1970–2002	Swerdlow et al ³⁸	1970–1991	Cohort study	49 births by 16 women	No	RR for preterm birth,	$RR_{\text{preterm}} = 0.88 (95\% \text{ CI: } 0.32-2.46)$
Birth outcome in the disease and by wives of general population or et al ⁴⁴ 1970–1986 Cohort study Comparison: Table et al ⁴⁶ 1970–1986 Cohort study Comparison: Relice at al ⁴⁶ 1970–1986 Cohort study Comparison: Birth outcome in siblings Abdgin's disease use and education or Comparison: Birth outcome in siblings Abdgin's disease use and education with childhood and birth and burth study and previous parity, and calendar birth, LBW at term, and the country of mother's residence of birth and by country of mother's residence and a perity of mother's residence and a perity of mother's residence and no later than 9 months women exposed to before and no later than nonteratogenic drugs 3 months after their first in pregnancy arreatment in pregnancy and previous and procured	ž		Comparison:	with previous Hodgkin's		LBW, and male sex	RR _{LBW} = 1.58 (95% CI: 0.52–4.26)
general population I men with a history of Hodgkin's disease comparison: with childhood Burth outcome in siblings erello et al ⁴⁰ 1970–1986 Comparison: Burth outcome in siblings Hodgkin's disease Burth outcome in siblings Hodgkin's disease Burth outcome in siblings Hodgkin's disease Hodgkin's disease Burth outcome in siblings Women matched by time Of burths by Adwomen Hodgkin's disease Hodgkin's disease Burth outcome Ab births by 48 women Yes, maternal age, Burth, LBW at term, Burth outcome Ab births by 48 women Yes, maternal No Ab births of age-matched earlier than 9 months women exposed to before and no later than nonteratogenic drugs 3 months after their first in pregnancy treatment	9661		Birth outcome in the	disease and by wives of		in newborn	$RR_{\text{male sex}} = 0.91 \text{ (95\% CI: 0.52-1.59)}$
n et al ¹⁴ 1970–1986 Cohort study 729 births by women Yes, maternal age, RR for stillbirth Comparison: With childhood Smoking, alcohol Birth outcome in siblings Hodgkin's disease Use and education No Comparison: With childhood Safabirths by women Yes, maternal age, POR for preterm Birth outcome in siblings Hodgkin's disease Hodgkin's disease Birth outcome in siblings Hodgkin's disease POR for preterm Birth sourcer free Hodgkin's disease POR for preterm Women matched by time Hodgkin's disease POR for preterm Births by cancer free Hodgkin's disease Abo birth and by county Abo births by 48 women Births of age-matched Who were pregnant no Births of age-matched Pofith and nonteratogenic drugs Births of age-matched Pofith and no before and no later than In pregnancy Interament In the prednancy In the force and no later than In the prednancy In the first of age-matched In the prednancy In the force and no lat			general population	II men with a history			Stillbirths: none
net al ⁴⁴ 1970–1986 Cohort study Authorid cet al ⁴⁶ 1970–1986 Cohort study Sanchings Hodgkin's disease Use and education No				of Hodgkin's disease			Minor/major CAs: not different from general
net al ⁴⁴ 1970–1986 Cohort study 729 births by women ret al ⁴⁴ 1970–1986 Cohort study Comparison: with childhood smoking, alcohol smoking, alcohol surplings Hodgiri's disease use and education No Comparison: with childhood service and self-size and education siblings and color study and calendar parity, and calendar birth, LBW at term, ark Comparison: with childhood service and birth outcome in siblings Hodgiri's disease Gonor study Comparison: with childhood service and birth and calendar birth, LBW at term, and calendar birth, LBW at term, and birth by canner free Hodgiri's disease of distribution of finith and by county of mother's residence of finith spy 48 women are al ¹⁹ 1958–1984 Cohort study who were pregnant no age (by matching) Births of age-matched earlier than 9 months after their first in pregnancy treatment in pregnancy treatment							population
Birth outcome in siblings Hodgkin's disease use and education Comparison: Sergaard et al ¹² 1970–1986 Cohort study and color study and claim of birth study and claim of birth and by concerned by time of birth and by county of mother's residence at al and birth of comparison: Skin's disease diagnosed during or shortly after pregnancy da Births of age-matched by time and by county of mother's residence and no later than a properties and properties and properties and properties are tall? Births of age-matched earlier than 9 months women monteratogenic drugs amonths after their first in pregnancy and pregnancy	Green et al ⁴¹	1970–1986	Cohort study	729 births by women	Yes, maternal age,	RR for stillbirth	$RR_{\text{stillbirth}} = 1.6 (95\% \text{ CI: } 0.64-4.03)$
Birth outcome in siblings Hodgkin's disease use and education No Comparison: Birth outcome in siblings Hodgkin's disease Gengaard et al ⁴² 1970–2002 Comparison: Birth outcome in siblings Hodgkin's disease Gomparison: Birth outcome in siblings Hodgkin's disease Comparison: Birth outcome in siblings Hodgkin's disease Comparison: Birth outcome in siblings Hodgkin's disease Hodgkin's disease diagnosed during or shortly after pregnancy er et al ¹⁹ 1958–1984 Cohort study da Birth outcome in siblings Hodgkin's disease An Mean BW was also adjusted for agus agus adjusted for agus attained by county of mother's residence Comparison: who were pregnant of gestational age Comparison: who were pregnant on age (by matching) Births of age—atthed Comparison: who were pregnant on age (by matching) Births of age—atthed Comparison: who were pregnant on later than nonteratogenic drugs 3 months after their first in pregnancy treatment	NSA		Comparison:	with childhood	smoking, alcohol		
rello et al ⁴⁰ 1970–1986 Cohort study 337 births by women No No Comparison: with childhood Birth outcome in siblings Hodgkin's disease Yes, maternal age, POR for preterm Birth by cancer free Hodgkin's disease Yes, maternal age, POR for preterm Births by cancer free Hodgkin's disease PoR for preterm Births by cancer free Hodgkin's disease PoR for preterm Births by cancer free Hodgkin's disease PoR for preterm Births by cancer free Hodgkin's disease PoR for preterm Births by cancer free Hodgkin's disease PoR for preterm Births by cancer free Hodgkin's disease PoR for preterm Births by cancer free Hodgkin's disease PoR for preterm Births by county At births by 48 women Yes, maternal No Births of age-matched Cohort study At births by 48 women Yes, maternal No Births of age-matched Cohort study Before and no later than Births of age-matched Before and no later than Births of age-matched Cohort study Births of age-matched Before and no later than Births of age-matched Cohort study Births of age-matched Cohort study Births of age-matched Before and no later than Births of age-matched Cohort study Births of age-matched Cohort stu	2002		Birth outcome in siblings	Hodgkin's disease	use and education		
gergaard et al ¹² 1970–2002 Cohort study Birth outcome in siblings Hodgkin's disease Comparison: Birth outcome in siblings Hodgkin's disease Comparison: Births by cancer free Hodgkin's disease of birth and by county of mother's residence da less as diagnosed during or shortly after pregnancy er et al ¹⁹ 1958–1984 Cohort study da Births of age-matched who were pregnant no age (by matching) Births of age-matched who were pregnant no age (by matching) and in pregnancy treatment with childhood Barth bugkin's disease Aba Mean BW was also adjusted for adjusted for age-tatin 9 women Yes, maternal age, POR for preterm parity, and cAs Mean BW was also adjusted for age-tatin's tudy Ab births by 48 women Yes, maternal No age (by matching) Births of age-matched earlier than 9 months women exposed to before and no later than nonteratogenic drugs in pregnancy treatment	Signorello et al ⁴⁰	1970–1986	Cohort study	337 births by women	No	Νο	Proportion $_{pretern\ birth} = 19.2\%\ vs\ 12.5\%\ in\ siblings$
Birth outcome in siblings Hodgkin's disease gergaard et al ¹² 1970–2002 Cohort study Comparison: Birth sy cancer free Hodgkin's disease women matched by time of birth and by county of mother's residence gkin's disease diagnosed during or shortly after pregnancy at a light soft age-matched earlier than 9 months women exposed to before and no later than nonteratogenic drugs are serial in pregnancy treatment Birth outcome in siblings Hodgkin's disease With previous parity, and calendar birth, LBW at term, parity, and calendar birth, LBW at term, stillbirth, and CAs adjusted for adjusted for gestational age Births of age-matched earlier than 9 months women exposed to before and no later than nonteratogenic drugs 3 months after their first in pregnancy treatment	NSA		Comparison:	with childhood			Proportion $_{LBW} = 5.9\%$ vs 4.2% in siblings
gergaard et al ⁴² 1970–2002 Cohort study 192 births by women very maternal age, Comparison: with previous parity, and calendar birth, LBW at term, Births by cancer free Hodgkin's disease women matched by time of birth and by county of mother's residence gestational age gestational age women returned by time of birth and by county of mother's residence gestational age gestational age gestational age Hodgkin's disease diagnosed during or shortly after pregnancy cer et al ¹⁹ 1958–1984 Cohort study who were pregnant no age (by matching) who were pregnant no age (by matching) age in pregnancy treatment reatment in pregnancy and pregnancy treatment	2006		Birth outcome in siblings	Hodgkin's disease			Proportion _{SGA} = 9.0% vs 9.2 in siblings
Births by cancer free Hodgkin's disease parity, and calendar birth, LBW at term, Births by cancer free Hodgkin's disease women matched by time of birth and by county Igkin's disease diagnosed during or shortly after pregnancy er et al. Births of age-matched women pregnant no Births of age-matched earlier than 9 months women exposed to before and no later than nonteratogenic drugs 3 months after their first in pregnancy treatment Births of age-matched earlier than 10 months after their first in pregnancy treatment Births of age-matched before and no later than nonteratogenic drugs 3 months after their first in pregnancy age (by matching) age (by mat	Langagergaard et al ⁴²	1970–2002	Cohort study	192 births by women	Yes, maternal age,	POR for preterm	POR Breesm birth = 1.1 (95% CI: 0.6–2.0)
Births by cancer free Hodgkin's disease period of birth stillbirth, and CAs women matched by time of birth and by county of mother's residence et al. 1958–1984 Cohort study Comparison: who were pregnant no Births of age-matched earlier than 9 months women exposed to before and no later than nonteratogenic drugs 3 months after their first in pregnancy treatment study adjusted for treatment still bright still bright study adjusted for an adjusted for adjuste	Denmark		Comparison:	with previous	parity, and calendar	birth, LBW at term,	$POR_{LBW at rerm} = 0.6 (95\% Cl: 0.2-2.6)$
Mean BW was also adjusted for gestational age 40 births by 48 women Yes, maternal No who were pregnant no age (by matching) earlier than 9 months before and no later than 3 months after their first treatment	2008		Births by cancer free	Hodgkin's disease	period of birth	stillbirth, and CAs	POR _{stillbirth} = $2.0 (95\% \text{ CI: } 0.3-15.4)$
adjusted for gestational age 40 births by 48 women Yes, maternal No who were pregnant no age (by matching) earlier than 9 months before and no later than 3 months after their first treatment			women matched by time		Mean BW was also		$POR_{CAs} = 1.7 (95\% Cl: 0.9-3.1)$
40 births by 48 women Yes, maternal No who were pregnant no age (by matching) earlier than 9 months before and no later than 3 months after their first treatment			of birth and by county		adjusted for		No difference in mean BW
40 births by 48 women Yes, maternal No who were pregnant no age (by matching) earlier than 9 months before and no later than 3 months after their first treatment			of mother's residence		gestational age		Proportion of male newborns $= 50\%$ vs 51.3% in
40 births by 48 women Yes, maternal No who were pregnant no age (by matching) earlier than 9 months before and no later than 3 months after their first treatment							controls, difference -1.3% (95% CI: -8.4; 5.8)
1958–1984 Cohort study 40 births by 48 women Yes, maternal No Comparison: who were pregnant no age (by matching) Births of age-matched earlier than 9 months women exposed to before and no later than nonteratogenic drugs 3 months after their first in pregnancy treatment	Hodgkin's disease di	agnosed during	or shortly after pregnancy				
Comparison: who were pregnant no age (by matching) Births of age-matched earlier than 9 months women exposed to before and no later than nonteratogenic drugs 3 months after their first in pregnancy treatment	Lishner et al ¹⁹	1958-1984	Cohort study	40 births by 48 women	Yes, maternal	No	No difference in mean BW ($P=0.7$), mean GA
Births of age-matched earlier than 9 months women exposed to before and no later than nonteratogenic drugs 3 months after their first in pregnancy treatment	Canada		Comparison:	who were pregnant no	age (by matching)		(P = 0.3), or stillbirths $(P = 0.08)$
before and no later than 3 months after their first treatment	1992		Births of age-matched	earlier than 9 months			Mean BW = 3325 g vs 3371 g in controls
3 months after their first treatment			women exposed to	before and no later than			Mean $GA = 39.7$ wk vs 40.0 in controls
treatment			nonteratogenic drugs	3 months after their first			Preterm births = 3.4%
CAs = 3.2%			in pregnancy	treatment			Stillbirths = 5.0%
							CAs = 3.2%

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apic 2 (continued)						
Author	Period	Design	Number	Adjustment	Relative effect	Results for birth outcome
Country	of cancer				estimates	
Year	diagnosis					
Janov et al ³⁷	9861-9961	Cohort study	10 births by women who	No	RR for LBW	3 premature children with LBW (1 induced
NSA		Comparison:	were pregnant from			preterm delivery)
1992		Birth outcome in the	12 months before diagnosis			$RR_{LBW} = 5.6 (95\% \text{ CI: } 1.2-17.5)$
		general population	until end of treatment			CAs: none
Smith et al ¹⁸	1992–1997	Cohort study	Births by 172 women who	Yes, maternal age	OR for prematurity	$OR_{\text{very IBW}} = 3.6 (95\% \text{ Cl: } 1.5-8.9)$
NSA		Comparison:	were diagnosed from		and very LBW	$OR_{\text{prema turity}} = 2.4 (95\% \text{ CI: } 1.6-3.5)$
2001		Comparison group	9 months before until			A constraint of
		not specified	12 months after delivery			
Langagergaard et al ⁴²	1970–2002	Cohort study	15 births by women	Yes, maternal age,	POR for preterm	Women diagnosed during pregnancy:
Denmark		Comparison:	diagnosed during	parity, and calendar	birth and CAs	$POR_{Dreterm birth} = 26.6 (95\% Cl: 8.5-83.0)$
2008		Births of cancer free	pregnancy and 85 births	period of birth.		(5 of 8 preterm deliveries were induced)
		women matched by time	by women diagnosed	Mean BW was also		$POR_{CAs} = 2.7 (95\% CI: 0.3-22.8)$
		of birth and county of	within 2 years after	adjusted for		LBW at term: none
		mother's residence	delivery	gestational age		Stillbirths: none
						No difference in mean BW
						Proportion of male newborns = 73.3% vs 50.1%
						in controls, difference = 23.2%
						(95% CI: 5.1–45.6)
						Women diagnosed within 2 years after
						delivery:
						POR _{precerm birth} = 1.2 (95% CI: 0.5–2.9)
						$POR_{CAs} = 1.6 (95\% CI: 0.6-4.5)$
						LBW at term: none
						Stillbirths: none
						No difference in mean BW
						Proportion of male newborns = 61.2% vs 51.4% ,
						difference = 9.8% (95% CI: -0.7 ; 20.3)

Abbreviations: BW, birth weight; CAs, congenital abnormalities; CI, confidence interval; GA, gestational age; LBW, low birth weight; OR, odds ratio; POR, prevalence odds ratios; RR, relative risk.

In conclusion, the overall results regarding the birth outcome among women with breast cancer are reassuring. However, additional studies of birth outcome in women who were diagnosed with breast cancer before pregnancy are needed to resolve the discrepancy between the findings of the Danish²³ and the Swedish²⁴ study.

Birth outcome in women with cutaneous malignant melanoma

A nationwide cohort study from Denmark (Table 2) found no excess risk with respect to preterm birth, LBW at term, stillbirth, and congenital abnormalities among 620 newborns of women who were diagnosed with melanoma before pregnancy or 88 newborns of women who were diagnosed during pregnancy, compared with, respectively, 29,788 and 4180 newborns of cancer free women.³⁴ Furthermore, there was no important difference in mean birth weight or male proportion of newborns between women with melanoma and comparison women. However, the study reported a prevalence odds ratio (POR) of 4.6 (95% CI: 1.7–12.3) for stillbirth among 351 newborns of women, who were diagnosed with melanoma within 2 years after the time of delivery. This finding, which was unexpected, has not been shown by other studies, and may have been a chance finding.

Two other cohort studies have examined birth outcome in offspring of women diagnosed with melanoma during or shortly after pregnancy (Table 2). 35,36 In a hospital-based cohort study of 18 deliveries by women diagnosed with melanoma during pregnancy over a period of 30 years, there were 17 live births and 1 anencephalic stillbirth. 36 The newborns of women with melanoma had a lower mean birth weight than newborns of women without cancer, but there was no difference in mean gestational age. The authors suggested that the differences in birth weight were due to IUGR secondary to the melanoma, its therapies, or its complications. In that study, however, mean birth weights were based on only 9 melanoma-exposed newborns and 9 newborns of age-matched comparison mothers.

In a population-based cohort study, O'Meara et al identified 149 women diagnosed with melanoma during pregnancy and 263 women diagnosed within 12 months after delivery over a period of 9 years in California.³⁵ That study and the Danish study³⁴ were in agreement with respect to the findings of no increased risk of preterm birth or low birth weight among newborns of mothers with melanoma. For women diagnosed during pregnancy, O'Meara and colleagues reported an OR of 0.9 (95% CI: 0.5–1.6) for preterm birth and an OR of 0.8 (95% CI: 0.3–1.8) for LBW,

adjusted for age and race. They found no fetal deaths in the exposed group and no increased risk of adverse birth outcome in women diagnosed with melanoma in the first post partum year. The study did not examine the risk of congenital abnormalities among newborns.

The overall results from these studies show no substantially increased risk of adverse birth outcome for women with melanoma, with the possible exception of an increased risk of stillbirth for newborns of women diagnosed within 2 years of delivery.

Birth outcome in women with Hodgkin's disease

More studies have examined birth outcome in women with previous Hodgkin's disease. Janov et al did not find any substantial increased risk of LBW and no congenital abnormalities among newborns of 15 women with prepregnancy Hodgkin's disease compared with the general population (Table 3).37 Likewise, Swerdlow et al reported no increased risk of preterm birth, LBW, stillbirth, or congenital abnormalities among 49 children of 16 women and 11 men who had previously been treated for Hodgkin's disease compared with the general population (Table 3).³⁸ Another study, which compared 52 births by 29 women previously treated for Hodgkin's disease with births by the women's siblings, found no overall increased risk of congenital abnormalities and stillbirths combined among children of Hodgkin's disease patients. The study also found no association of birth outcome with radiotherapy alone (supra- or infradiaphragmatic), whereas women treated with both chemotherapy and radiation were more likely to give birth to an abnormal child (P = 0.047) (Table 3). The 3 studies, however, were all based on small study populations and did not control for potential confounders.

Recently, a large cohort study of female survivors of childhood cancer found that 19.2% of 337 women with childhood Hodgkin's disease had a preterm birth compared with 12.6% among sibling controls (Table 3).⁴⁰ Another study reported 11 stillbirths among 729 births of female survivors of childhood Hodgkin's disease, corresponding to a relative risk of 1.6 (95% CI: 0.64–4.03) (Table 3).⁴¹ In contrast, a recent Danish cohort study of birth outcome in women with previous Hodgkin's disease found no increased risk of preterm birth and only 1 stillbirth among 192 women, of whom more than 75% had been diagnosed with Hodgkin's disease in adulthood (≥20 years of age at diagnosis) (Table 3).⁴² The results from the Danish study, however, indicated a slightly increased risk of congenital abnormalities among newborns of women with previous Hodgkin's

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disease (POR = 1.7; 95% CI: 0.9–3.1). Furthermore, it was reported, that the POR for congenital abnormalities increased with calendar time of Hodgkin's disease diagnosis (ie, for 1991–2000 the POR was 3.1 (95% CI: 1.4–6.9) compared with POR = 1.0 (reference) for 1970–1980).⁴²

The Danish study also reported increased risk estimates for congenital abnormalities among newborns of women who were diagnosed with Hodgkin's disease during or shortly after pregnancy, but these estimates were based on few outcomes and were therefore imprecise. However, it is important to emphasize that teratogens increase the rate of specific, rather than all abnormalities, and the study was unable to evaluate those.

Two studies reported an increased risk of preterm birth for women diagnosed with Hodgkin's disease during pregnancy, which reflected a higher rate of elective early delivery (Table 3). 18,42 In contrast, a historical cohort study by Lishner et al which included 40 births by women who were pregnant between 9 months before and 3 months after their first treatment for Hodgkin's disease, reported no increased risk of preterm birth or induced deliveries (Table 3). 19 Furthermore, the study indicated no difference in mean birth weight compared with controls, while the proportion of stillbirths was not statistically different from that of the general population. The study reported 1 child with a congenital abnormality born to the only patient treated with chemotherapy in the first trimester.

There was no evidence of any substantial decrease in the male proportion of newborns among women diagnosed with Hodgkin's disease before pregnancy, indicating that earlier treatment for Hodgkin's disease is not a risk factor for early male abortion.⁴²

For newborns of women diagnosed with Hodgkin's disease during pregnancy, there was an increase in the male proportion, compared with newborns of comparison mothers, which was surprising and could have been a chance finding.⁴²

In conclusion, the overall results are reassuring regarding the risks of adverse birth outcome for women with Hodgkin's disease, although the possibility of an increased risk of congenital abnormalities in newborns of women diagnosed with Hodgkin's disease before pregnancy cannot be ruled out.

Discussion

Possible adverse effects of cancer and cancer therapy on birth outcome

When cancer is diagnosed in pregnancy, there is often a conflict between optimal maternal therapy and fetal well-being.⁵ The benefit of the diagnostic work-up, surgery, radiotherapy and chemotherapy must be weighed carefully against the risk to the fetus.¹² Under these circumstances, preterm labor is often induced as soon as the fetus becomes viable, in order to allow amplification of therapy.¹²

The rationale for examining birth outcome in women diagnosed with cancer within a few years after delivery is that pregnancies starting before the diagnosis may be affected by the preclinical cancer. A Swedish study, which compared observed to expected rates of cancer during pregnancy and during the first year after delivery, suggested that diagnosis is often delayed to the postpartum period. ⁴³ A possible explanation for this delay could be that unusual signs and symptoms may be ascribed to the pregnancy rather than the cancer.

For women who retain or regain fertility after cancer treatment, an issue of great importance is their ability to carry a pregnancy to term and give birth to a normal child. Chemotherapy and radiotherapy may affect future pregnancies in cancer survivors by directly affecting the reproductive tract or by causing mutations in germ cells.³⁰ It is therefore important to establish the magnitude of an increased risk (if any) of adverse birth outcomes such as preterm birth, LBW (or LBW at term), stillbirth, and congenital abnormalities.

Possible adverse effects of the cancer itself on birth outcome

Little is known about exact mechanisms whereby maternal cancer may pose risk to a developing fetus. In theory, several factors might influence the fetus if the mother has malignant disease:

- It has been proposed that the cancer may alter metabolism and distribution of hormones and vitamins, some of which are determinants for certain congenital abnormalities.⁴⁴
- Cancer patients have an increased tendency to suffer from febrile illness,⁵ and maternal fever in early pregnancy has been associated with stillbirth⁴⁵ and congenital abnormalities.^{45,46}
- Malnutrition is more frequent in the patients. Maternal undernutrition during pregnancy resulting in reduced transfer of nutrients to the fetus may cause fetal undernutrition and intrauterine growth retardation.⁴⁷ Impaired fetal growth is strongly associated with neonatal morbidity and mortality,⁴⁸ and may also be associated with diseases later in life.⁴⁹
- Psychological stress related to severe life events (eg, a cancer diagnosis) around the time of conception may reduce the male proportion of newborns through differential conception or differential abortion of male embryos.²⁹

Likewise, some studies have reported associations of stress in pregnancy with preterm delivery,^{50,51} and congenital abnormalities.⁵²

Possible adverse effects of specific cancer therapy on birth outcome Surgery

Most surgical interventions can be safely undertaken with minimum risk during pregnancy, although there is almost always some element of maternal–fetal conflict.⁵³

Radiation

Radiation is commonly used for cancer diagnosis and treatment. The fetus is sensitive to ionizing radiation, with the brain being the most sensitive organ. ⁵⁴ During the perimplantation and immediate post-implantation periods, radiation has an all or nothing effect, resulting in either embryonic death or further normal development. Later in pregnancy, radiation may cause congenital abnormalities, IUGR, mental retardation, or childhood cancer. ⁵⁴ As a result, the general recommendation is to postpone radiotherapy until after delivery. ¹² At the same time, births of healthy children after radiotherapy of pregnant women for breast cancer and supradiaphragmatic Hodgkin's disease have been reported (with appropriate shielding of the fetus). ^{19,55–57}

In nonpregnant women of childbearing age, ionizing radiation may damage ovarian function, cause premature ovarian failure, or trigger germ cell mutations, which can lead to congenital abnormalities in future offspring.³⁰

Studies of women exposed to the atomic-bomb radiation and their subsequently conceived offspring have indicated a higher rate of spontaneous abortion, but showed no increase in the risk of major congenital abnormalities compared with the children of women from the general population. ¹⁰ These results corroborate studies of childhood cancer survivors reporting no increased risk of congenital abnormalities or genetic diseases in the offspring of women exposed to pre-gestational radiotherapy. ^{58–61}

It has also been postulated that maternal gonadal exposure to radiation would decrease the male proportion of newborns by inducing recessive sex-linked lethal mutations. ⁶² In addition, women previously treated with high-dose abdominal radiotherapy have been found to have an increased risk of spontaneous abortions, ^{41,63,64} preterm deliveries, ⁴⁰ and LBW infants ^{58,59,63} during subsequent pregnancies. These effects are most likely due to radiation-induced damage to the women's abdominopelvic structures. ^{10,59}

Traditional ways to protect the ovaries against the radiation damage are shielding of the ovaries and, in case of pelvic lymph node irradiation, repositioning of the ovaries out of the irradiation field (oopheropexy). Today, many young patients needing radiotherapy (or chemotherapy) are offered the option of cryopreservation of their ovarian tissue, while recent studies of ovarian tissue autotransplantation offer promising results.

Chemotherapy

A potential teratogenic effect of chemotherapy during pregnancy depends on the agent used, the timing of exposure, the dose, and the characteristics affecting placental transfer.

Use of chemotherapy during the first trimester increases the risk of miscarriage and congenital abnormalities. ²⁶ A review of 139 cases of first-trimester exposure to chemotherapy reported a total of 24 (17%) infants with congenital abnormalities after a single agent exposure, and a prevalence of 25% after combination-agent exposure. ⁶⁷

Chemotherapy during the second and third trimesters may increase the risk of preterm birth, IUGR, and stillbirth. ¹² Furthermore, the central nervous system continues to develop after the first trimester, which makes it sensitive to insults during the entire pregnancy. ¹² While exposure to chemotherapy after the first trimester does not cause macroscopic anatomical defects, it may have long-term subanatomical consequences, for example, by interfering with the neuronal proliferation and migration. ¹² However, a study of late side effects among 84 children whose mothers received chemotherapy, during pregnancy, for hematological malignancies did not show impairments in learning behavior, or neurological abnormalities after a median follow-up of 18 years. ⁶⁸ Given all the evidence, it is generally recommended that chemotherapy is delayed until after the first trimester. ¹²

In nonpregnant women of childbearing age, chemotherapy can adversely affect fertility.⁶⁹ Damage to the ovarian tissue depends on the agent used, the dose, and the age of the patient at treatment.⁷⁰ Furthermore, chemotherapy is potentially mutagenic¹⁰ with animal studies showing that it can cause mutations in oocytes and increase the risk of fetal abnormalities.⁶⁵

Endocrine therapy

The use of anti-estrogenic therapy, such as tamoxifen, in pregnant breast cancer patients has been discouraged because of teratogenic effects seen in animal models. ¹² Direct evidence for teratogenesis in humans is limited, with only isolated reports of rare forms of congenital abnormalities associated with tamoxifen use. ⁷¹

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Conclusions and perspectives

This review summarizes the existing epidemiologic evidence of the adverse effect of maternal breast cancer, melanoma, and Hodgkin's disease on birth outcome. On the whole, existing studies offer reassuring results concerning the risks of adverse birth outcome for women diagnosed with breast cancer, melanoma, or Hodgkin's disease before, during or shortly after pregnancy. However, a limitation of most studies was the imprecise risk estimates caused by the small number of adverse birth outcomes and the lack of results stratified by treatment. Since even countrywide data may be sparse, an international collaboration is required in order to assemble data on a sufficient number of births by women with cancer in order to obtain more precise risk estimates for adverse birth outcomes. Moreover, a larger number of birth outcomes would allow stratified analyses according to, for example, different treatment regimens, stages, and how close in time the cancer diagnosis was to pregnancy. Information on these clinical details could be obtained from hospital medical records and clinical databases.

Very few studies document the long-term follow-up of children exposed to maternal cancer and cancer treatment in utero. ⁶⁸ Maternal cancer may affect not only birth outcome, but also long-term health, as a consequence of intra-uterine programming. Thus, large cohort studies with long term follow-up are needed to evaluate the entire spectrum of adverse effects of cancer or cancer treatment on offspring of the patients.

Disclosure

The contents of this review have previously been included in a PhD thesis.

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