"First trimester placental growth factor and soluble fms-like tyrosine kinase 1 are significantly related to PAPP-A levels"

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Treatment of breast cancer during pregnancy: an observational study

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Summary

Background Little is known about the treatment of breast cancer during pregnancy. We aimed to determine whether treatment for breast cancer during pregnancy is safe for both mother and child.

Methods We recruited patients from seven European countries with a primary diagnosis of breast cancer during pregnancy; data were collected retrospectively if the patient was diagnosed before April, 2003 (when the registry began), or prospectively thereafter, irrespective of the outcome of pregnancy and the type and timing of treatment. The primary endpoint was fetal health for up to 4 weeks after delivery. The registry is ongoing. The study is registered with ClinicalTrials.gov, number NCT00196833.

Findings From April, 2003, to December, 2011, 447 patients were registered, 413 of whom had early breast cancer. Median age was 33 years (range 22–51). At the time of diagnosis, median gestational age was 24 weeks (range 5–40). 197 (48%) of 413 women received chemotherapy during pregnancy with a median of four cycles (range one to eight). 178 received an anthracycline, 15 received cyclophosphamide, methotrexate, and fluorouracil, and 14 received a taxane. Birthweight was affected by chemotherapy exposure after adjustment for gestational age (p=0·018), but not by number of chemotherapy cycles (p=0·71). No statistical difference between the two groups was observed for premature deliveries before the 37th week of gestation. 40 (10%) of 386 infants had side-effects, malformations, or new-born complications; these events were more common in infants born before the 37th week of gestation than they were in infants born in the 37th week or later (31 [16%] of 191 infants *vs* nine [5%] of 195 infants; p=0·0002). In infants for whom maternal treatment was known, adverse events were more common in those who received chemotherapy in utero compared with those who were not exposed (31 [15%] of 203 *vs* seven [4%] of 170 infants; p=0·00045). Two infants died; both were exposed to chemotherapy and delivered prematurely, but both deaths were thought not to be related to treatment. Median disease-free survival for women with early breast cancer was 70·6 months (95% CI 62·1–105·5) in women starting chemotherapy during pregnancy and 94·4 months (lower 95% CI 64·4; upper 95% CI not yet reached) in women starting chemotherapy after delivery (unadjusted hazard ratio 1·13 [95% CI 0·76–1·69]; p=0·539).

Interpretation Although our data show that infants exposed to chemotherapy in utero had a lower birthweight at gestational age than did those who were unexposed, and had more complications, these differences were not clinically significant and, since none of the infants was exposed to chemotherapy in the first trimester, were most likely related to premature delivery. Delay of cancer treatment did not significantly affect disease-free survival for mothers with early breast cancer. Because preterm birth was strongly associated with adverse events, a full-term delivery seems to be of paramount importance.

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Introduction

Breast cancer diagnosed during pregnancy is rare, contributing to less than 1% of breast cancers in Europe.[1] The incidence of breast cancer during pregnancy is increasing, likely due to women in high-income countries having children at an increasingly older age, with the probability of developing breast cancer increasing with age.[2,3] In 2006, about 57 000 women were diagnosed with breast cancer in Germany, of whom only 4% were aged 39 years or younger.[4] Because of the low incidence of breast cancer during pregnancy and despite an increasing number of studies, evidence-based management of breast cancer during pregnancy is not possible because most information is based on small cohorts. In 1999, Berry and colleagues[5] published a series of 24 patients with breast cancer treated during pregnancy using a standardised protocol at the MD Anderson Cancer Center (Houston, TX, USA), which was updated in 2006.[6] This report formed the basis for the first international recommendations on breast cancer during pregnancy and was the stimulus for a more structured method for the collection of data in breast cancer during pregnancy.[7]

We launched the Breast Cancer During Pregnancy Registry in 2003 to systematically investigate breast cancer during pregnancy, assessing the outcome of mothers and their infants. We aimed to test the hypothesis that breast cancer treatment during pregnancy is safe for mother and child, and that

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For the **case report form** see http://www.germanbreastgroup.de/pregnancy

For the **Belgian international online registry** see http://www.cancerinpregnancy.org

pregnant patients with breast cancer should, therefore, be treated as similarly as possible to non-pregnant patients with breast cancer. A second similar initiative that registered patients with all cancers during pregnancy was initiated in Belgium.

Methods

Study design and patients

The German Breast Group (GBG) launched a multicentre registry cohort study for breast cancer during pregnancy in April, 2003, which was expanded to other countries (the Netherlands, UK, Poland, Italy, and Czech Republic) in April, 2009, via the Breast International Group (BIG) and other international collaborations (115 centres). All patients diagnosed with breast cancer during pregnancy were eligible for registration, independent of outcome of the pregnancy and the type and timing of breast cancer treatment (no age restrictions). The data were collected with a case report form, which is available online. Also, Belgian and UK groups were asked to provide data partly published.[8,9] Patients could be registered retrospectively if they were diagnosed before the initiation of the GBG registry in (April, 2003) and prospectively if their diagnosis was made thereafter. In the same timeframe, although independent from the German initiative, an international online registry for all cancers diagnosed during pregnancy was initiated in Belgium. Both observational studies were approved by the ethics committees (University of Frankfurt, Germany, and Leuven University, Belgium) and patients had to give written informed consent for data and biomaterial collection.

The study protocol of the GBG provided a treatment algorithm for breast cancer that was dependent on the patient's gestational age. The primary objective of the study was the outcome of the infant for up to 4 weeks after delivery. Secondary objectives were gestational complications of the mother, stage and biological characteristics of breast cancer, breast cancer treatments (systemic treatment and type of surgery), diagnostic procedures (palpation, ultrasound, mammogram, and MRI), and long-term outcome of the infant and the mother.

Weight, height, haematology counts, Apgar scores at 5 min and 10 min, hair loss, and signs of infection were recorded with direct questioning at birth and at 4 weeks after birth. All other events were reported as free text at the discretion of the reporting physician. Follow-up was obtained from annual visits to a physician. Metrics such as height, weight, and any abnormalities were obtained. Information about the decision-making process (ie, induced *vs* spontaneous abortion or delivery) was not collected. Follow-up is ongoing.

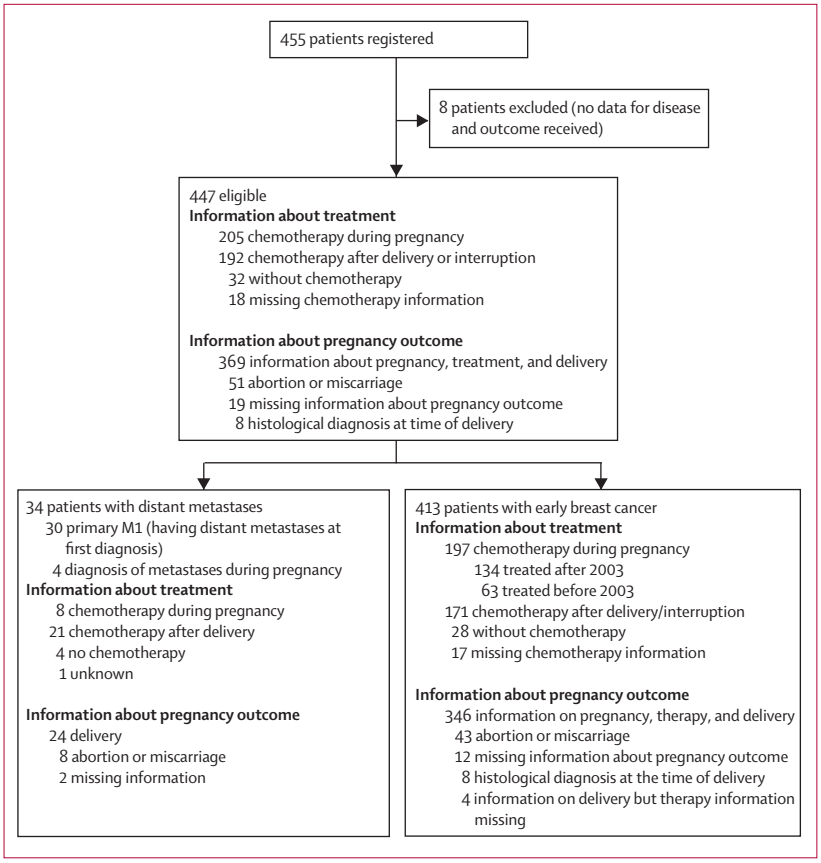

Figure 1: **Profile of patient cohort**

Statistical analysis

The main analysis was descriptive. All percentages excluded missing values. We used Fisher's exact test (for binary parameters), χ^2 test (for parameters with three or more categories), and Wilcoxon test (for continuous parameters) to do between-group comparisons. We used analysis of covariance (ANCOVA) to explore the effect of gestational week and intrauterine exposure to chemotherapy on birthweight, and linear regression to explore the effect of gestational week and number of chemotherapy cycles on birthweight. We constructed Kaplan-Meier survival curves to estimate the median disease-free survival (DFS) and overall survival and used a Cox proportional-hazards model to estimate the hazard ratio and 95% CI. Two sided p values of 0·05 or less were deemed significant. Data were collected into an MS SQL Server database. We used SAS (version 9.2 under SAS Enterprise Guide 4.3) for all statistical analyses.

Role of the funding source

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

Results

Between April 1, 2003, and Dec 31, 2011, the cutoff date for this analysis, 447 eligible patients were registered

	All patients (N=447)	M0 patients (N=413)	M0 patients with chemotherapy (N=368)	M0 patients with chemotherapy during pregnancy (N=197)	M0 patients with chemotherapy after delivery (N=171)
Age (years; median [range])	33 (22–51)	33 (22–51)	33 (23–51)	33 (25–43)	34 (23–51)
Tumour stage					
T1	86 (20%)	83 (21%)	66 (18%)	32 (17%)	34 (20%)
T2	217 (50%)	203 (51%)	186 (52%)	96 (51%)	90 (54%)
T3	92 (21%)	82 (21%)	78 (22%)	40 (21%)	38 (23%)
T4a–c	25 (6%)	23 (6%)	20 (6%)	18 (10%)	2 (1%)
T4d	11 (3%)	9 (2%)	8 (2%)	4 (2%)	4 (2%)
Data missing	16	13	10	7	3
Nodal status					
Negative	181 (42%)	176 (44%)	150 (41%)	72 (37%)	78 (46%)
Positive	252 (58%)	229 (57%)	213 (59%)	121 (63%)	92 (54%)
Data missing	14	8	5	4	1
Histological tumour type					
Ductal or other	419 (97%)	390 (97%)	351 (98%)	188 (98%)	163 (98%)
Lobular	14 (3%)	11 (3%)	8 (2%)	4 (2%)	4 (2%)
Data missing	14	12	9	5	4
Grading					
G1	10 (3%)	10 (3%)	8 (2%)	3 (2%)	5 (3%)
G2	87 (22%)	78 (21%)	73 (22%)	34 (19%)	39 (25%)
G3	296 (75%)	280 (76%)	257 (76%)	143 (79%)	114 (72%)
Data missing	54	45	30	17	13
ER/PgR-status					
Negative for both ER or PgR	214 (52%)	203 (53%)	185 (54%)	99 (54%)	86 (54%)
Positive for ER, PgR, or both	197 (48%)	180 (47%)	159 (46%)	86 (47%)	73 (46%)
Data missing	36	30	24	12	12
HER2 status					
Negative	226 (64%)	214 (65%)	197 (65%)	101 (64%)	96 (66%)
Positive	126 (36%)	113 (35%)	108 (36%)	58 (37%)	50 (34%)
Data missing	95	86	63	38	25
Triple negative	118 (31%)	115 (33%)	109 (34%)	55 (32%)	54 (37%)
Gestational week at diagnosis (median [range])	24 (1–40)	24 (1–40)	24 (1–40)	20 (1–36)	30 (1–40)
Trimester at diagnosis					
First trimester	81 (19%)	76 (19%)	60 (17%)	31 (16%)	29 (18%)
Second trimester	178 (42%)	170 (43%)	160 (45%)	132 (68%)	28 (17%)
Third trimester	169 (40%)	152 (38%)	137 (38%)	31 (16%)	106 (65%)
Unknown	19	15	11	3	8
Gestational week at chemotherapy start (median)	..	..	..	24	NA

Data are n (%), unless otherwise stated. ER=oestrogen receptors. PgR=progesterone receptors. NA=not applicable.

Table 1: **Baseline characteristics**

(figure 1). In 299 patients, diagnosis was made after the start of the registry and data were collected prospectively. A further 148 patients were diagnosed before the start of the registry and their data were collected retrospectively. The median follow-up for DFS and overall survival for the women was 31·5 months (95% CI 21·5–42·3).

Baseline characteristics of participants are shown in table 1. The median age of the women was 33 years (range 22–51) with the median gestational age at diagnosis of 24 weeks (5–40). 178 (42%) women were diagnosed with breast cancer during the second trimester of pregnancy. T4 tumours were more common in patients who received chemotherapy during pregnancy compared with those who had chemotherapy after pregnancy (p=0·0053; table 1). We recorded no other significant differences between these two populations of patients. Diagnosis during pregnancy was guided by ultrasound in 83% (322 of 387 patients), mammography in 51% (198 of 387 patients), and MRI in 16% (60 of 387 patients) of patients (60 patients with imaging type unknown).

182 (51%) of 358 patients with early breast cancer were treated with breast conservation surgery (48% of patients

[57 of 120] treated before registry inception [April, 2003] and 53% of patients [125 of 238] treated thereafter; p=0·37; data missing for 55 patients). For the 396 women with early breast cancer and known chemotherapy treatment, breast conservation surgery was done in 79 (45%) of 197 patients starting chemotherapy during pregnancy (data missing for 23 patients) and in 100 (56%) of 199 patients who started chemotherapy after delivery or received no chemotherapy (data missing for 21 patients; p=0·055).

In total, 1187 chemotherapy cycles were given, 745 (63%) of which were given during pregnancy. Chemotherapy regimens are summarised in table 2. The patients received a median of four cycles (range one to eight) during pregnancy. 178 (90%) of the 197 patients who received chemotherapy during pregnancy received an anthracycline (102 epirubicin, 76 doxorubicin; 10 of the vinca alcaloid-based regimens contained an anthracycline); 15 (8%) patients received cyclophosphamide, methotrexate, and fluorouracil during pregnancy (CMF; all before April, 2003) and 14 (7%) patients received a taxane during pregnancy (nine docetaxel, five paclitaxel), of whom ten also received an anthracycline. Overall, 77 (39%) of 197 patients with early breast cancer received a taxane as part of their adjuvant or neoadjuvant chemotherapy, but most received the taxane after delivery (table 2). Treatment with a taxane-free regimen was more common in women whose chemotherapy was started during pregnancy compared with those whose chemotherapy was started after pregnancy (118 [60%] of 197 patients *vs* 81 [47%] of 171 patients; p=0·021). Combined docetaxel, doxorubicin, and cyclophosphamide and dose-dense sequential epirubicin, paclitaxel, and cyclophosphamide were given only after delivery. None of the patients received trastuzumab, endocrine therapy, or radiotherapy during pregnancy (table 2).

	Chemotherapy after delivery (N=171)	Chemotherapy during pregnancy (N=197*)
A(E)/C	16 (9%)	55 (28%)
FE(A)C	42 (25%)	34 (17%)
AC/EC-taxane	29 (17%)	46 (23%)
FE(A)C-taxane	19 (11%)	19 (10%)
CMF	16 (9%)	11 (6%)
AC/EC-CMF	4 (2%)	4 (2%)
FE(A)C-CMF	0 (··)	1 (1%)
A(E)mono-CMF	3 (2%)	4 (2%)
A(E)mono-taxane	0 (··)	4 (2%)
A(E)mono-taxane-CMF	1 (1%)	0 (··)
A(E)taxane	3 (2%)	0 (··)
A(E)taxane-CMF	1 (1%)	0 (··)
TAC	20 (12%)	0 (··)
dd E-P-C	4 (2%)	0 (··)
TC	1 (1%)	1 (1%)
Vinca alcaloid-based†	0 (··)	13 (7%)
Platinum-containing†	7 (4%)	2 (1%)
Other†	5 (3%)	3 (2%)

A=doxorubicin. C=cyclophosphamide. E=epirubicin. F=fluorouracil. CMF=cyclophosphamide, methotrexate, fluorouracil. T=docetaxel. P=paclitaxel. dd=dose-dense. Parenthesis mean "or" and solidi are "combined with"—eg A(E)/C=doxorubicin or epirubicin combined with cyclophosphamide. Data are n (%). *Not all agents were given during the course of pregnancy. †Some of these regimens contained taxanes.

Table 2: **Chemotherapy regimens**

	All patients (N=447)	M0 patients (N=413)	M1 patients (N=34)	p value*	All M0 patients with known chemotherapy and delivery outcome (N=346)	M0 patients with chemotherapy during pregnancy (N=194)	M0 patients with chemotherapy after delivery or no chemotherapy (N=152)	p value†
Abortion				0·039	..	..	..	
No	382 (88%)	358 (89%)	24 (75%)					
Yes	51 (12%)	43 (11%)	8 (25%)					
Unknown	14	12	2					
Delivery mode				0·077				0·540
Spontaneous	171 (49%)	165 (50%)	6 (26%)		156 (49%)	85 (48%)	71 (51%)	
Operative vaginal delivery	18 (5%)	16 (5%)	2 (9%)		16 (5%)	11 (6%)	5 (4%)	
Caesarean section	162 (46%)	147 (45%)	15 (65%)		146 (47%)	83 (47%)	63 (45%)	
Unknown	31	30	1		28	15	13	
Delivery week (median [range])	36 (23–42)	37 (23–42)	35 (31–40)	0·022	37 (23–42)	37 (31–42)	36 (23–42)	0·478
Premature delivery								
Median birthweight (g [range])	2770 (1070–4295)	2770 (1070–4295)	2415 (1830–3270)		2770 (1070–4295)	2770 (1260–4050)	2770 (1070–4295)	
<37th week	186 (51%)	171 (50%)	15 (65%)	0·196	166 (50%)	89 (47%)	77 (52%)	0·380
<35th week	88 (24%)	78 (23%)	10 (44%)	0·039	77 (23%)	38 (20%)	39 (27%)	0·192
<32nd week	13 (4%)	12 (4%)	1 (4%)		12 (4%)	5 (3%)	7 (5%)	
Data missing	14	13	1		11	6	5	

Data are n (%) excluding missing data, unless otherwise stated. *p value for difference between M0 and M1 patients. †p value for difference between patients who received chemotherapy during pregnancy and those who received chemotherapy after delivery or not at all.

Table 3: **Obstetrical outcome**

Women diagnosed with distant metastases were more likely to have a discontinuation of pregnancy during the first trimester (miscarriage or abortion) than were women who were diagnosed without distant metastases (p=0·039, table 3). Pregnancy was discontinued in 18 (13%) of 144 patients before 2003 (data missing for four patients) and in 33 (11%) of 289 patients after 2003 (data missing for ten patients). We recorded no statistically significant difference in the rates of premature delivery—before the 37th week of gestation—between those who were recruited before 2003 and those who were recruited thereafter (56% *vs* 48%; p=0·15). We recorded no significant difference in the frequency of premature delivery between patients with or without distant metastases or between patients given or not given chemotherapy during pregnancy (table 2, figure 2).

In total, participants gave birth to 386 liveborn babies (374 patients continued with pregnancy after diagnosis, eight patients were diagnosed at birth, seven women had twins, three babies were stillbirths). Information about chemotherapy was missing for 13 women, thus 373 newborn babies were available for the comparison with (n=203) or without (n=170) chemotherapy during pregnancy (both the early stage and metastatic patients). Birthweight of infants exposed to chemotherapy in utero (median 2765 g [range 1260–4050]) was much the same as those without exposure (median 2758 g [1070–4295]) without adjustment for gestational age. Median weight 4 weeks after delivery in infants exposed to chemotherapy in utero was 3590 g (1795–9190) compared with 3375 g [2500–5365] in infants without such exposure. After adjustment for gestational age, birthweight at delivery was affected by chemotherapy exposure (ANCOVA test p=0·018), but not by number of chemotherapy cycles (linear regression p=0·71). Birthweight was less than the 10th percentile in 15 infants (9% of 175 infants) exposed to chemotherapy and in five infants (4%) of 139 infants not exposed to chemotherapy (p=0·10; figure 2, appendix). Median birthweight was not different when analysed by exposure to type of anthracycline (epirubicin 2735 g [1270–3970] and doxorubicin 2810 g [1260–4050]; p=0·23). Median birthweight of the 14 infants exposed to taxanes in utero (2713 g [1435–3800]) did not differ from the birthweight of all other babies. We recorded no significant difference in the frequency of intrauterine growth restriction or retardation between fetuses exposed to chemotherapy and those without exposure (p=0·069; table 4).

We recorded no differences between babies who were exposed to any chemotherapy in utero and those who were not in height, Apgar scores, haemoglobin concentration, leucocyte counts, thrombocyte counts, and alopecia, at the time of birth as well as at 4 weeks after delivery. Nor did we record a difference in the proportion of infants (for whom we had data) not discharged with their mother in these two populations (34% [50 of 147] patients *vs* 41% [47 of 116]; p=0·30).

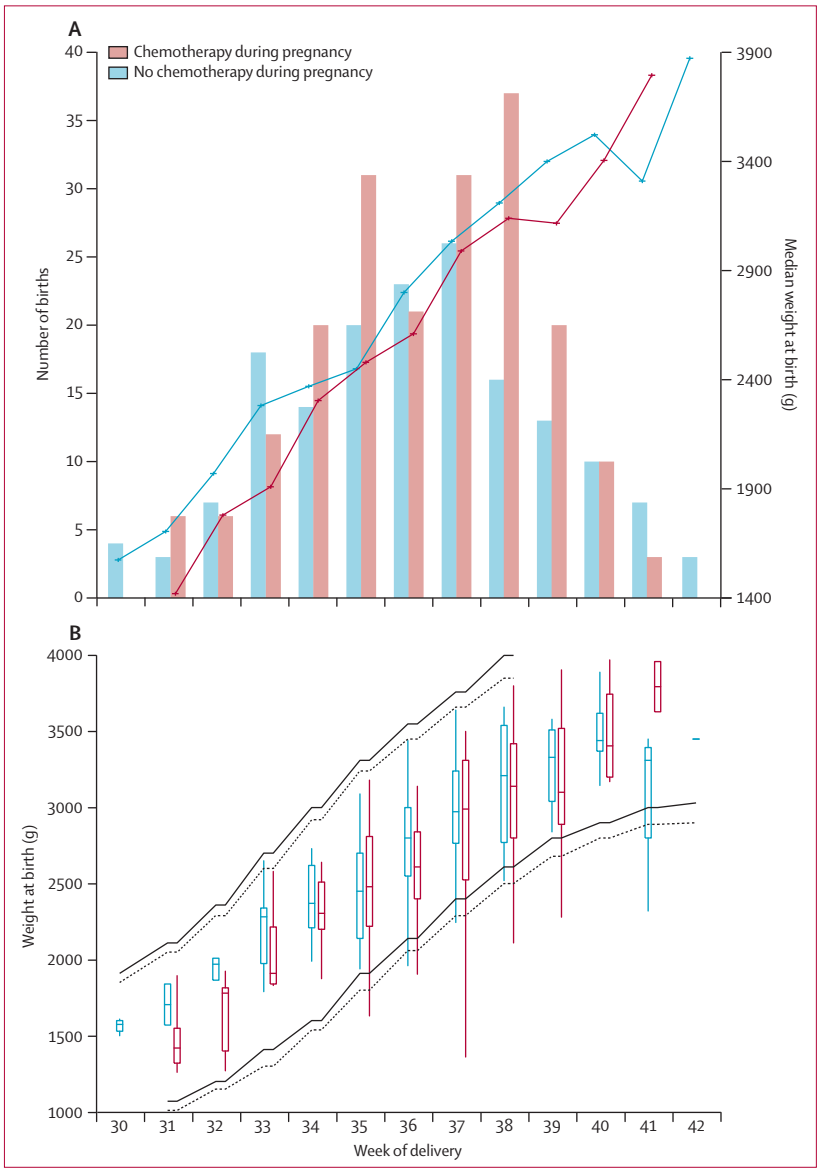

Figure 2: **Median birthweight, by exposure to chemotherapy in utero and week of delivery**
N=373 (203 with chemotherapy exposure in utero, 170 without). (A) The lines show median birthweight and the bars show number of births. (B) Box-plots show median birthweight in the study population, with bars showing IQRs; lines show 10th and 90th percentile birthweight (dashed lines for girls and solid line for boys) for pregnancies without cancer involvement in the general population (data from reference 10).

Overall, we recorded side-effects, malformations, or newborn complications (hereafter referred to as events) in 40 (10%) of 386 liveborn infants; events were more common in infants born before the 37th week of gestation than they were in infants born in the 37th week or later (31 [16%] of 191 infants *vs* nine [5%] of 195 infants; p=0·0002). Of the 373 infants for when we have information on maternal treatment, events were more common in infants exposed to chemotherapy than for infants not exposed [31 [15%] of 203 infants *vs* seven [4%] of 170 infants; p=0·00045; figure 3). Two infants died; both were exposed

See **Online** for appendix

	No chemotherapy during pregnancy (N=164)	Chemotherapy during pregnancy (N=179)	p value
Any obstetrical complication			
No	149 (91%)	148 (83%)	0·027
Yes	15 (9%)	31 (17%)	
Gestational diabetes			
No	163 (99%)	177 (99%)	1·00
Yes	1 (1%)	2 (1%)	
Pre-eclampsia			
No	163 (99%)	177 (99%)	1·00
Yes	1 (1%)	2 (1%)	
Hypertension			
No	164 (100%)	178 (99%)	1·00
Yes	0 (··)	1 (1%)	
Oligohydramnios			
No	164 (100%)	176 (98%)	0·249
Yes	0 (··)	3 (2%)	
Cervical insufficiency			
No	164 (100%)	176 (98%)	0·249
Yes	0 (··)	3 (2%)	
Placenta insufficiency			
No	164 (100%)	177 (99%)	0·499
Yes	0 (··)	2 (1%)	
Placenta haematoma			
No	164 (100%)	178 (99%)	1·00
Yes	0 (··)	1 (1%)	
Solution placentae			
No	164 (100%)	178 (99%)	1·00
Yes	0 (··)	1 (1%)	
Bleeding			
No	163 (99%)	175 (98%)	0·374
Yes	1 (1%)	4 (2%)	
Vasa praevia			
No	164 (100%)	179 (100%)	NA
Congenital abnormality (pregnancy termination)			
No	164 (100%)	179 (100%)	NA
Intrauterine growth restriction			
No	163 (99%)	172 (96%)	0·069
Yes	1 (1%)	7 (4%)	
Chorioamnionitis			
No	163 (99%)	179 (100%)	0·478
Yes	1 (1%)	0 (··)	
Spontaneous abortion (included in pregnancy interruptions)			
No	160 (98%)	179 (100%)	0·051
Yes	4 (2%)	0 (··)	
Spontaneous abortion of one twin			
No	164 (100%)	178 (99%)	1·00
Yes	0 (··)	1 (1%)	
Premature labour			
No	161 (98%)	169 (94%)	0·090
Yes	3 (2%)	10 (6%)	
Premature rupture of the membrane			
No	164 (100%)	174 (97%)	0·062
Yes	0 (··)	5 (3%)	
Fetal distress			
No	163 (99%)	177 (99%)	1·00
Yes	1 (1%)	2 (1%)	
Stillbirth			
No	162 (99%)	178 (99%)	0·608
Yes	2 (1%)	1 (1%)	
Pyelonephritis			
No	164 (100%)	179 (100%)	NA
Cholestasis			
No	163 (99%)	179 (100%)	0·478
Yes	1 (1%)	0 (··)	
Pruritus			
No	163 (99%)	179 (100%)	0·478
Yes	1 (1%)	0 (··)	

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Data are number of women (%). NA=not applicable. *Data was not available for 35 women who did not have chemotherapy during pregnancy and for 18 women who had chemotherapy during pregnancy.

Table 4: **Obstetrical complications in women with early breast cancer with and without chemotherapy during pregnancy (n=343)***

to chemotherapy and were delivered prematurely (figure 3). One of these infant's death was related to a diagnosis of trisomy 18 (Edwards' syndrome); the other infant (who died from necrotising enterocolitis) was exposed to two cycles of fluorouracil, epirubicin, and cyclophosphamide and weighed 1895 g at delivery in the 31st week of gestation (80th percentile). Both deaths were deemed to be unrelated to chemotherapy exposure. Malformations were reported in nine (2%) of 386 infants (eight in infants exposed to chemotherapy). Five events (four after exposure to chemotherapy) were reported beyond 4 weeks after delivery: night terrors, acute respiratory distress syndrome (ARDS; in two infants), speech impairment measured at 6 years old, and motor neuropathy.

65 (19%) of 343 women with early breast cancer—for whom data were available for obstetrical complications and systemic therapy—had side-effects (obstetrical or non-obstetrical), of which the occurrence was more common in women who received chemotherapy during pregnancy (46 [27%] of 179 women) than it was in those who did not (17 [10%] of 164 women; p=0·0001). Symptoms of preterm delivery including preterm labour and premature rupture of the membrane (PROM), were significantly higher in women receiving chemotherapy during pregnancy compared to those who did not (14 *vs* three [both PROM and preterm labour were reported in one patient], p=0·012). Typical obstetrical complications (including three stillbirths, one in the chemotherapy exposed group) were observed in the group that received chemotherapy during pregnancy although most

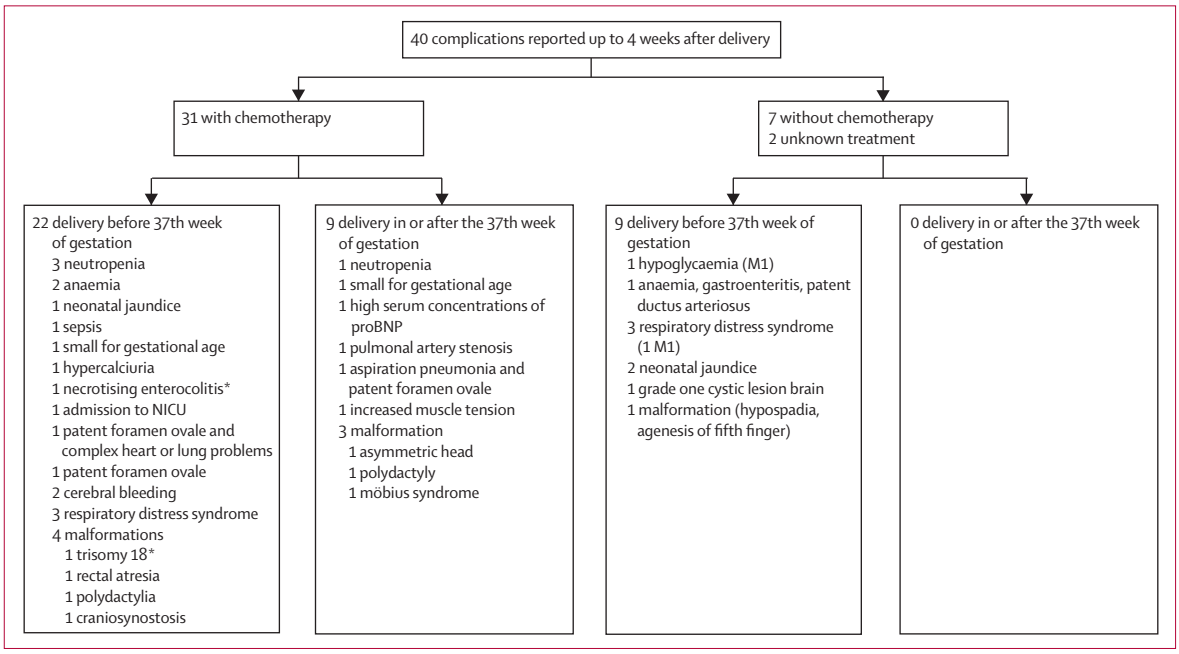

Figure 3: **Adverse events in newborn babies up to 4 weeks after delivery**
Respiratory distress combines the following events: continuous positive airway pressure, mild acute respiratory distress syndrome, wet lung. NICU=neonatal intensive care unit. proBNP=pro-brain natriuretic peptide. *Baby died.

complications do not show a significant difference between the two groups (table 4).

The time from diagnosis to start of chemotherapy was longer when the decision was taken to start chemotherapy after delivery (median 6 weeks [range 0–39] compared with median 4 weeks [0–19] when chemotherapy was started before delivery; p<0·0001). Overall, 26 (6% of 413) women diagnosed with breast cancer before the 28th week of gestation delayed chemotherapy to after delivery (appendix). In patients with early breast cancer, median DFS was 76·3 months (95% CI 64·8–101·3) and the median overall survival is not yet reached. The median DFS was 70·6 months (95% CI 62·1–105·5) in women starting chemotherapy during pregnancy and 94·4 months (lower 95% CI 64·4; upper 95% CI not yet reached) in women starting chemotherapy after delivery (unadjusted hazard ratio 1·13 [95% CI 0·76–1·69]; p=0·539). After stratifying for tumour stage and nodal status the log-rank p value was as follows: DFS 0·4644; overall survival 0·892. We recorded no significant difference between patients with early breast cancer who started chemotherapy during pregnancy and those who started chemotherapy after delivery in DFS (estimated 3-year DFS 70·2% [95% CI 60·8–77·7] *vs* 74·3% [65·0–81·5]; p=0·537) or overall survival (estimated 3-year overall survival 84·9% [76·9–90·3] *vs* 87·4% [79·3–92·5]; p=0·221; figure 4). In the group of women receiving chemotherapy during pregnancy the estimated 5-year DFS was 61·1% (50·6–69·9). In the group of women receiving chemotherapy after delivery or an interruption, estimated 5-year DFS was 64·4% (54·2–72·8). Estimated 5-year overall survival was 77% (67·1–84·3) in the group of women receiving chemotherapy during pregnancy. In the group of women receiving chemotherapy after delivery or interruption, the estimated 5-year overall survival was 82·4% (73·1–88·8).

Regression analysis of prognostic variables (age, T stage, nodal status, hormone receptor status) and application of chemotherapy during pregnancy confirmed that tumour stage and nodal status, but not chemotherapy application during pregnancy significantly affected DFS and overall survival (table 5).

Discussion

We recorded more neonatal and obstetrical events in patients treated with chemotherapy during pregnancy than we did in patients who received no chemotherapy during pregnancy. Infants exposed to chemotherapy during pregnancy had a lower birthweight.

In the general population, about 10–15% of infants are born preterm, which is generally defined as before completing the 37th week of gestation.[11,12] In our study population, 50% of women with breast cancer delivered preterm, with 23% before the 35th week of gestation. However, this proportion of premature deliveries is lower than previously reported in all cancers in another European pregnancy population.[9] In our study population, preterm deliveries were more common if the decision was taken to start chemotherapy after delivery, although most patients reported no additional obstetrical complications. In the group who received chemotherapy during pregnancy, the proportion of preterm deliveries

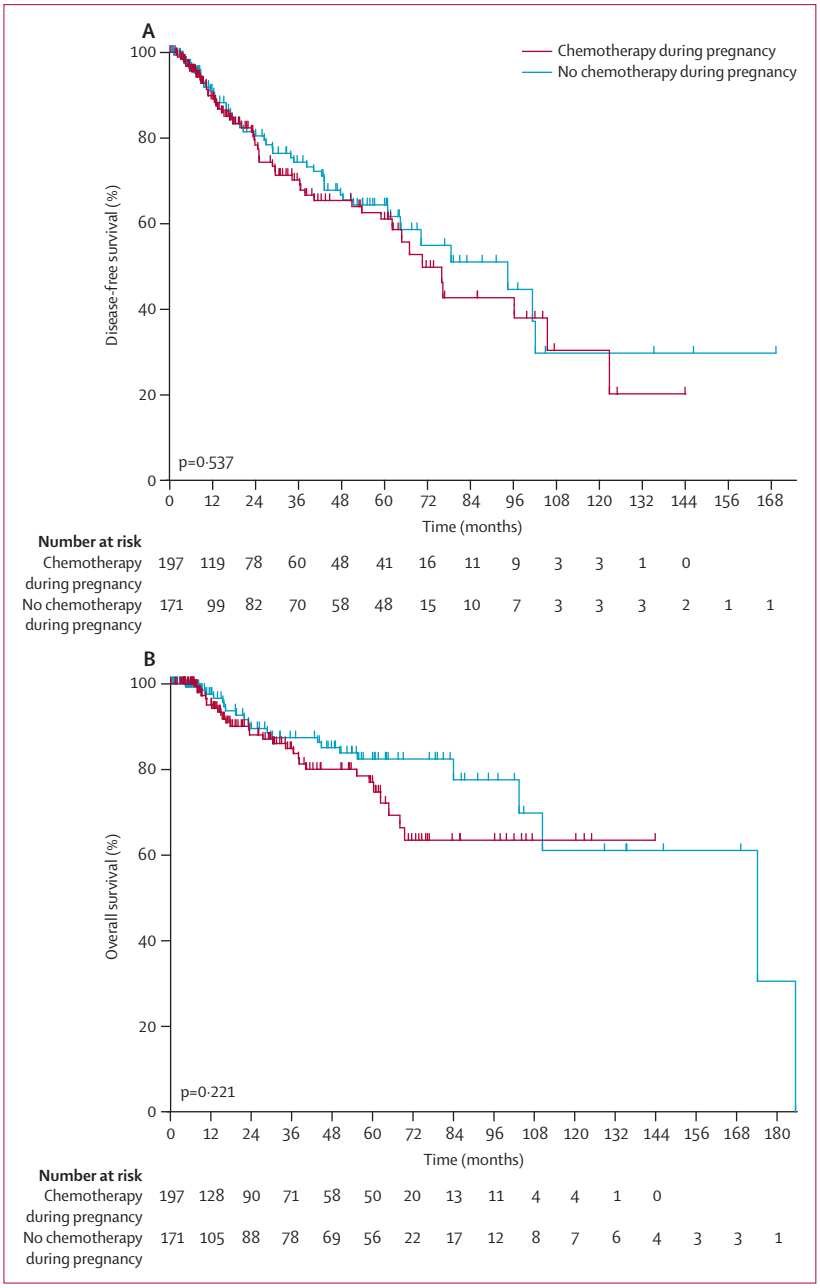

Figure 4: **Disease free (A) and overall (B) survival curves for patients with early breast cancer**
Patients were censored at the date of last follow-up.

was higher than expected because treatment until the completion of the 35th week of pregnancy is advised to allow for a pause in treatment before delivery.[13] However, we recorded a non-significant decrease in the number of preterm deliveries. This finding might be explained by an increased awareness among reporting physicians of the possibility to give chemotherapy during pregnancy, due to the advertisement of the registry and the inclusion of a therapy algorithm into the study protocol and guidelines published by the investigator.

Morbidity and mortality in newborn babies is directly related to gestational age at delivery,[13,14] which is an important clinical message because the decision to deliver the fetus preterm is often taken without medical indication. By contrast with other studies, our findings show that infants exposed to chemotherapy in utero had a lower birthweight at the same gestational age than did infants not exposed to chemotherapy, a finding that was not affected by the amount of chemotherapy given and one that we believe is clinically irrelevant (because such low birthweight would not affect an otherwise healthy baby).[9]

More complications were reported in the group of infants exposed to chemotherapy than in the group not exposed to chemotherapy. However, most complications were reported in babies who were delivered prematurely, irrespective of exposure to chemotherapy. The complications recorded were mostly related to premature delivery or malformations rather than to chemotherapy exposure (none of the children was exposed to chemotherapy during the first trimester and malformations can occur only during that time). In German quality control statistics,[11] morbidity in preterm infants is about 9%.[12] The proportion of malformations in this study is not different from the general population.[12] Data from previous studies suggest that long-term morbidity does not increase if a fetus is exposed to chemotherapy in utero compared with fetuses who do not have this exposure (panel).[15,16] Although the placenta filters cytotoxic agents, important variations in transplacental passage among drugs have been seen in animal models.[17,18] In our study, preterm labour or PROM were more common when chemotherapy was given during pregnancy without resulting in more preterm deliveries. There are several reasons for this finding, including physical or psychological stress, infections, or an unknown underlying mechanism of the cytotoxic agent itself.[19] Oxidative stress, which is one of the proposed pathophysiological mechanism of pre-eclampsia, can also be induced by cytotoxic agents.[20] However, the frequency of pre-eclampsia did not increase when chemotherapy was given during pregnancy. The seemingly high rate of caesarean sections might be explained by the number of preterm deliveries and the recommendation to deliver before the 35th week of gestation, as per guidelines in some countries (eg, Germany). The overall caesarean section rate in Germany is 30% and rises to more than 50% in high-risk subgroups, which is higher than in Belgium or the Netherlands.

Patients who received chemotherapy during pregnancy were more likely to have presented at an advanced stage of disease than were women who received chemotherapy after pregnancy, and were more often treated with mastectomy. Tumour grading, hormone receptor status, and HER2 status, which show breast cancer biology, were much the same between the two groups (exposure to chemotherapy during pregnancy *vs* no exposure). However, there seemed to be a higher rate of patients with triple-negative, HER2-positive, and grade 3 tumours in our

cohort compared with data for breast cancer in women younger than 41 years reported from a single institution.[21] None of our immunohistochemical data were centrally confirmed.[22] DFS in our study is in line with previously reported results in young women[23] and is much longer than that reported in a US case series.[24] Survival was not statistically different in the two groups of patients who received chemotherapy during pregnancy or thereafter, indicating that chemotherapy given during pregnancy is effective despite an altered pharmacokinetic profile of the agents important for breast cancer treatment during pregnancy.[25,26] Moreover, the adjusted survival analyses indicate that women who received chemotherapy during pregnancy might have a better survival outcome. However, the data should not be over interpreted and certainly do not suggest that initiation of treatment should be delayed. When chemotherapy was started during pregnancy, patients were less likely to receive a taxane or a standard chemotherapy regimen.[27] Most guidelines for breast cancer do not recommend taxanes during pregnancy.[8,11,26] However, the reported complications of the infants if taxanes were given during pregnancy did not differ from those of other cytotoxic agents. Data for baboon and human models show that taxanes are hardly detectable in the fetus.[17,28,29] Furthemore, taxanes add efficacy independent of nodal status and are proposed as part of adjuvant or neoadjuvant treatment even during pregnancy.[10,26,30,31] However, examination of the outcome of patients treated with or without taxanes is beyond the scope of this study.

We are doing a matched-pair analysis on a subset of these patients treated with modern-type chemotherapy to reveal the prognosis of breast cancer during pregnancy if treated according to actual guidelines compared with non-pregnant women.

We did not include patients with a diagnosis of breast cancer within 1 year after the end of pregnancy because we wanted to address specific clinical challenges related to the exposure of treatment to the pregnant woman and the fetus. Breast cancer diagnosed within the year after delivery has been reported to be more aggressive than disease not temporally related to pregnancy, but can be treated according to standard recommendations.[1]

Our study has several strengths and limitations. The main strength is the descriptive information about the obstetric outcome of a large cohort of patients from different countries in a joint effort that used a standardised case report form. Most patients were recruited from Germany, Belgium, and the Netherlands, where treatment strategies are much the same. Some Belgian and UK patients were included in a previously published report.[8,9] However, most cases were reported prospectively, with birthweight, height, hair loss, blood count, and Apgar scores captured directly, whereas any other observations were reported with free text. In view of the multicentric and observational nature of the study, missing data were unavoidable, especially for the follow-up period, and we cannot exclude the possibility that there might be a reporting bias in favour of the group unexposed to chemotherapy in utero (children who were exposed might have been monitored more closely than those who were not). Therefore, we need to interpret the data in relation to malformations or morbidities reported for all deliveries in the general population. With 50 000 newly diagnosed breast cancers a year in Germany, and an incidence of breast cancers diagnosed during pregnancy of 1%, at least 500 should be reported, but fewer are documented per year in Germany. A further limitation to our study is that the tumour characteristics were not balanced between women receiving chemotherapy during pregnancy and after delivery. However, we compensated for this difference by doing an adjusted analysis. Follow-up was short and not

	Disease-free survival		Overall survival	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Chemotherapy during pregnancy				
No	1		1	
Yes	0·784 (0·504–1·22)	0·278	0·864 (0·454–1·64)	0·656
Age (years)	0·979 (0·929–1·03)	0·411	0·953 (0·887–1·02)	0·183
Tumour stage				
T1–3	1		1	
T4	5·66 (3·10–10·4)	<0·0001	4·44 (2·16–9·14)	<0·0001
Nodal status				
N0	1		1	
N+	2·75 (1·60–4·74)	<0·0001	6·57 (2·28–18·9)	<0·0001
Hormone receptor status				
ER/PgR negative	1		1	
ER/PgR positive	0·652 (0·415–1·02)	0·064	0·593 (0·314–1·12)	0·106

ER=oestrogen receptors. PgR=progesterone receptors.

Table 5: **Multivariate analysis for disease-free and overall survival**

Panel: Research in context

Systematic review

We searched PubMed using the terms "breast cancer" and "pregnancy". We restricted our search to studies written in English and published between November, 2010, and April, 2012. We identified 36 studies dealing with diagnos, treatment, or survival of pregnancy-associated breast cancer, which also included women diagnosed with breast cancer up to 1 year after delivery. Only 10 publications were based on individual patient cohorts with a size of 22–99 patients. Most recommendations for the treatment of breast cancer during pregnancy are based on small cohort studies or heterogeneous groups and lack comparison with breast cancer patients not treated with systemic therapy during pregnancy.

Interpretation

On the basis of our findings from this large cohort of patients with breast cancer, and if our findings are substantiated by other studies, breast cancer during pregnancy could be treated as it is in non-pregnant women without putting fetal and maternal outcome at substantially increased risk. We did, however, record more obstetrical and paediatric events in the group treated with chemotherapy during pregnancy, which emphasises the importance of a full-term delivery.

complete, but we will continue to collect data. We did not collect information about concomitant and supportive drug treatment. Long-term effects such as cardiac assessments were not captured in a systematic way but long-term data are being collected continuously to improve the follow-up data for the children.

This large data collection provides a better understanding of breast cancer during pregnancy. The stage of disease and obstetrical health affects treatment decision during pregnancy and the outcome of the infants. Interactions are numerous and cannot yet completely be explained, but data collection is ongoing and should eventually help to understand the complexity even better. Overall, prospective observational studies should increase the level of available evidence and should improve treatment recommendations.[32]

Contributors

All authors except for GvM collected data. SL, SH, GvM, KVC, BVC, VN, and FA analysed and interpreted the data. SL wrote the first draft of the paper. SNH, GvM, KVC, PJW, BVC, VM, VN, and FA reviewed drafts of the paper. All authors approved the final paper.

Conflicts of interest

All authors declare that they have no conflicts of interest.

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