**Breast cancer during pregnancy - a prospective and retrospective observational study (GBG-20 / BIG02-03)**

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**Abstract**

**Background:** We launched an international registry to increase our limited understanding of breast cancer diagnosed during pregnancy.

**Methods:** Patients with primary diagnosis of breast cancer during pregnancy (BCP) were eligible. The primary endpoint was the foetal health after delivery. Secondary endpoints included obstetrical outcome, breast cancer characteristics and therapy, and long-term outcome of mother and infant.

**Findings:** From April 2003-December 2012, 447 eligible patients were registered, 413 patients with early breast cancer. At the time of diagnosis the median gestational age was 24 weeks. 48% received chemotherapy during pregnancy with a median of 4 cycles. 90% received an anthracycline, 7·6% CMF and 7% a taxane. More women received a taxane-free regimen when chemotherapy was started during pregnancy (57% vs. 45%; p=0.0236). Birth weight was affected by chemotherapy exposure after adjusting for gestational age (ANCOVA test p=0·0179). Premature deliveries <35th week of gestation were frequent and more common if chemotherapy was started after delivery (26·5% vs. 20·2%). 38 (9·8%) of 386 infants had side effects, malformations, or new-born complications reported further referred to as an event; 30/191 (15·7%) infants born below 37th week gestation and 8/195 (4·1%) infants born in the 37th week or later (p=0·0001). Dystocia was more frequent in women starting chemotherapy during pregnancy (7.8% vs. 1.8%; p=0.012). Estimated 5-year disease-free survival was not affected by chemotherapy start during pregnancy (61% vs. 64%; adjusted HR 0·784, p=0·278).

**Interpretation:** Based on these data of breast cancer patients we confirm that BCP can be treated as in non-pregnant women without jeopardizing the infant. We need to underscore the importance of a term delivery. Premature deliveries, obstetrical and neonatal complications are common and need to be managed by multidisciplinary teams.

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**Introduction**

Breast cancer diagnosed during pregnancy (BCP) is rare, accounting for less than 1% of breast cancers.[[1]](#endnote-1) The incidence is increasing probably due to the fact, that women in western countries postpone their pregnancies and with increasing childbearing age the probability of developing breast cancer rises as well.[[2]](#endnote-2),[[3]](#endnote-3) In 2006 about 57.000 women were diagnosed with breast cancer in Germany of whom only 4% were 39 years or younger.[[4]](#endnote-4) Due to the low incidence and in spite of increasing literature evidence-based management of BCP is not possible as the majority of information is based on small cohorts. A pubmed search for last 15 months with the terms “breast cancer” and “pregnancy” revealed 36 hits dealing with diagnostic, therapy, or survival of pregnancy associated breast cancer (PABC) which includes also women diagnosed with breast cancer up to one year after delivery. Only 10 publications were based on individual patient cohorts with a size of 22–99 patients. In 1999 Berry et al.[[5]](#endnote-5) published a series of 24 pregnant breast cancer patients treated during pregnancy using a standardized protocol at the MD Anderson Cancer Center which was updated in 2006.[[6]](#endnote-6) This first report formed the basis for the first international recommendations on breast cancer during pregnancy and was the stimulus for a more structured method of collecting data in breast cancer during pregnancy.[[7]](#endnote-7)

We launched the registry in 2003 to investigate BCP in a more systematic way with respect to the infant and the mother and to prove the hypothesis that breast cancer treatment during pregnancy is safe for mother and child and BCP should therefore be treated as closely as possible to non-pregnant breast cancer. A second similar initiative though with registration of all cancers was initiated in Belgium. Overall, these prospective observational studies will increase the level of evidence from 3a to 2b and improve our treatment recommendations.[[8]](#endnote-8),[[9]](#endnote-9)

**Patients and Methods**

The German Breast Group (GBG) launched a multicentre registry cohort study for breast cancer during pregnancy in 2003 which was internationalized via the Breast International Group (BIG) and other international collaborations. All patients diagnosed with breast cancer during pregnancy were eligible for registration independent of outcome of the pregnancy and treatment of breast cancer. The data were collected with a paper based case report form that was accessible on the website of the German Breast Group ([www.germanbreastgroup.de/pregnancy](http://www.germanbreastgroup.de/pregnancy)) to all interested and collaborative groups and sites. In addition groups were asked to provide their data.[[10]](#endnote-10) Patients could be registered retrospectively if diagnosed prior to the initiation of the registry in April 2003 and prospectively if the diagnosis was made thereafter. In the same time frame though independent from the German initiative, an international online registry for all cancers diagnosed during pregnancy was initiated in Belgium (www.cancerinpregnancy.org). The observational studies were approved by the ethics committee 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 in dependence of gestational age. The primary objective of the study was the outcome of the infant for up to four weeks after delivery. Secondary objectives were the gestational complications of the mother, stage and biological characteristics of breast cancer, breast cancer therapies (systemic treatment and type of surgery), diagnostic procedures (palpation, ultrasound, mammogram and magnetic resonance imaging (MRI)) as well as long term outcome of the infants and the mother.

Weight, height, haematology, Apgar scores at 5 and 10 minutes, hair loss, and signs of infection were captured with direct questions. All other events could be reported as free text at the discretion of the reporting physician. Follow-up was collected annually.

The main analysis was performed according to the following groups: early breast cancer vs. patients diagnosed with metastases; prospective vs. retrospective data collection, patients with chemotherapy during pregnancy vs. patients without chemotherapy during pregnancy (i.e. patients receiving no chemotherapy at all and patients receiving chemotherapy after delivery).

Data were collected into a MS SQL Server database. Evaluation of the data was performed using SAS version 9.2 under SAS Enterprise Guide 4.3. The main analysis is descriptive. All percentages are valid percentages (excluding missing values). Fisher´s exact test (for binary parameters), χ2-test (for parameters with 3 or more categories) and Wilcoxon test (for continuous parameters) were used to compare between groups. All percentages are valid percentages. To explore the influence of gestational week and intrauterine exposure to chemotherapy/number of chemotherapy cycles on birth weight, ANCOVA (Analysis of Covariance) and linear regression were correspondingly used. Kaplan Meier method was used to estimate the median disease-free (DFS) and overall survival (OS) and a Cox proportional-hazards model to estimate the hazard ratio and 95% confidence intervals. The significance level was set to ≤ 0·05 (two-sided).

**Results**

Between April 2003 and December 2011, the cut-off date for this analysis, 447 eligible patients were registered from seven European countries. For more details see the flow diagram. In 299 patients diagnosis has been made after the start of the registry and data were collected prospectively. A further 148 patients had their diagnosis before start of the registry and data were collected retrospectively.

**Baseline Characteristics**

The median age of the women was 33 years (range 22-51). The median gestational age at diagnosis was 24 (range 5 to 40) weeks with 41·6% of patients being diagnosed with breast cancer during the second trimester.

Baseline and tumour characteristics are outlined in table 1. Patients who received chemotherapy during pregnancy had significantly more often T4 tumours (11·6 vs. 3·6%; p=0·0053) and tended to have more nodal involvement (62·7% vs. 54·1%; p= 0·109) compared to those receiving chemotherapy after delivery. No difference between these two groups was observed regarding hormone-receptor and HER2 status.

Diagnosis during pregnancy was guided by ultrasound in 83·2%, mammography in 51·2%, and MRI in 15·5%.

**Treatment**

Patients with early breast cancer were treated by breast conserving surgery in 50·8%. The rate was 47·5% in patients treated before and 52·5% in the patients treated after 2003 (p=0.37). Breast conservation was performed in 45·4% of 197 patients starting chemotherapy during pregnancy and in 54·4% of 171 patients receiving no chemotherapy during pregnancy was given (p=0·095).

In total, 1187 chemotherapy cycles were given, 745 (62·7%) of these cycles during pregnancy. The patients received a median of 4 cycles (range 1-8) during pregnancy. 90·4% (178) received an anthracycline during pregnancy. 15 (7·6%) patients received CMF (all before 2003) and 14 patients (7·1%) received a taxane during pregnancy (9 docetaxel and 5 paclitaxel), of whom also 11 received an anthracycline. Overall 77 (39·1%) of all patients with early breast cancer received a taxane as part of their (neo-)adjuvant chemotherapy, but the majority of patients received the taxane after delivery. Significantly more women were treated with a taxane-free regimen (59·9% vs. 47·3%; p=0·0209) if the decision was taken to start chemotherapy during pregnancy. TAC and dose-dense ETC were only given after delivery. Platinum was given only after delivery to 9 (2·4%) patients. None of the patients received trastuzumab, endocrine therapy, or radiotherapy during pregnancy (Table 3).

**Obstetrical outcome**

Of the 447 eligible patients; 14 had missing information on delivery status. Pregnancy was discontinued preterm (miscarriage or abortion) in 51 (11·8%) patients. This was significantly more frequent in women diagnosed with than without distant metastases (25% and 10·7%, respectively p=0·039). Pregnancy was discontinued in 12.5% before and in 11.4% after 2003. Median gestational age at delivery was 36 (range 23 to 42) weeks. Premature delivery before the 35th gestational week was more common in patients with distant metastases (56·5% vs. 37·1%; p=0·077) and numerically more frequent in early breast cancer patients not starting chemotherapy during pregnancy (26·5 vs. 20·2%; p=0·192). (Table 2) (Figure1A)

**Health status of the infants**

We here report on 386 alive new-borns (7 twins). Data on 373 new-borns with known exposure were available for the comparison with (N=203) or without (N=170) chemotherapy during pregnancy. Birth weight of infants exposed to chemotherapy in utero (median 2765g [range 1260 to 4050g]) was comparable to those without exposure (median 2758g [range 1070 to 4295]) without adjusting for gestational age. Weight four weeks after delivery was in median 3590g [range 1795 to 9190g] with compared to 3375g [range 2500 to 5365g] without chemotherapy exposure. Birth weight was significantly affected by chemotherapy exposure (ANCOVA test p=0·0179) but not by number of chemotherapy cycles (linear regression P=0·71) after adjusting for gestational age (Figure 1 and Suppl Figure 1). Median birth weight (2713g [range 1435 to 3800g]) of the 14 infants exposed to taxanes in utero was not different from the overall results.

There were no differences in height, Apgar scores, haemoglobin level, leucocytes, thrombocytes, and alopecia of the new-borns at the time of birth as well as four weeks after delivery in infants with or without chemotherapy exposure. Infants were not discharged with their mother in 34·0% when exposed and in 40·5% when not exposed to chemotherapy (p=0·30).

Overall, 38 (9·8%) of 386 infants had side effects, malformations, or new-born complications reported, further referred to as an event; 30/191 (15·7%) infants born below 37th week of gestation and 8/195 (4·1%) infants born in the 37th week or later (p=0·0001). 29 (14·3%) infants exposed to chemotherapy and 7 (4·1%) infants unexposed to chemotherapy were reported with an event (p=0·0008) (Figure 2). Two infants died, both were exposed to chemotherapy and delivered prematurely. One death occurred related to the diagnosis of trisomy 18; the other death occurred due to necrotizing enterocolitis in an infant exposed during pregnancy to two cycles of 5-fluorouracil, epirubicin, cyclophosphamide (FEC)) and weighing 1895g at delivery in the 31st week of gestation. Malformations were reported in 7 1.8% of 386 infants. Only 7 events (6 after exposure to chemotherapy) were reported beyond four weeks after delivery: pavor nocturnus, Möbus Syndrome, ARHDS (2 times), craniosynostosis, speech impairment, and motoric neuropathy.

**Maternal outcome**

In total 65 (19·0%) women with early breast cancer and known systemic therapy had side effects or obstetrical complications reported further referred to as an event irrespective of the relation to chemotherapy or pregnancy, 48 (26·8%) with chemotherapy during pregnancy and 17(10·4%) without (p<0·001). Typical obstetrical complications (including three stillbirths) were reported in 46 (13·4%) of the women; 31 (17·3%) in women with chemotherapy during pregnancy and 15 (9·1%) in women without chemotherapy during pregnancy (p=0·027) (Suppl Table 1). Dystocia defined as preterm labour or premature rupture of the membrane (PROM) was reported in 14 (7·8%) women receiving chemotherapy during pregnancy and in 3 (1·8%) women not receiving chemotherapy (p=0·012).

In early breast cancer patients the median disease-free survival was 76·3 months and the median overall survival is not yet reached. There was no significant difference in disease-free as well as overall survival rate in patients who started chemotherapy during pregnancy compared to those who started chemotherapy after delivery. (Figure 3) The median disease-free survival was 70·6 months (95% CI [62·1, 105·5]) in women starting chemotherapy during pregnancy and 94.4 months (95% CI [64.4, +∞]) in women starting chemotherapy after delivery (unadjusted HR 1·13; [95%CI 0·761- 1·69] p=0·539). Regression analysis of prognostic variables (age, T-stadium, nodal status, hormone receptor status) and application of chemotherapy during pregnancy confirmed that tumour stadium and nodal-status but not chemotherapy application during pregnancy significantly affected disease-free (adjusted HR for chemotherapy 0·784, p=0·278) and overall survival (adjusted HR for chemotherapy 0·864, p=0·656) (Table 4).

**Discussion**

This is the largest prospective data collection based on 455 patients with breast cancer diagnosed during pregnancy. We did not include patients with diagnosis of breast cancer within one year after the end of pregnancy as we wanted to address specific clinical challenges related to the exposure of treatment to the pregnant women and the foetus. Breast cancer diagnosed within the year following delivery has been reported to be more aggressive than disease without time relationship to pregnancy but can be treated according to standard recommendations.1

Our study shows that women with BCP tend to be delivered preterm, 49·6% before completing the <37th week (general definition of prematurity) and 22·8% before 35th week (according to guidelines for BCP). This is lower than the rate reported previously in an unselected cancer in pregnancy population.[[11]](#endnote-11) It is higher than expected in the group receiving chemotherapy during pregnancy, because it is advised to treat until completed 35th week to allow for a pause prior to delivery.[[12]](#endnote-12) However, we observe a trend for fewer preterm deliveries over time. An increased awareness of the possibility to give chemotherapy during pregnancy may explain this observation. In the general population about 10-15% of infants are born preterm (<37th week of gestation).[[13]](#endnote-13),[[14]](#endnote-14) Preterm deliveries are more common if the decision was taken to start chemotherapy after delivery. Morbidity and mortality in new-borns is directly related to gestational age at delivery.14,[[15]](#endnote-15) This is an important clinical message since the decision to deliver the foetus preterm is frequently deliberately (iatrogenic) taken. In contrast to other publications, infants exposed to chemotherapy in utero tend to have a lower birth weight at the same gestational age than infants not exposed to chemotherapy, which was not affected by the amount of chemotherapy given.11 More complications were reported in the group of infants exposed to chemotherapy than in the group not exposed to chemotherapy. But, the majority of complications were reported in the group delivered prematurely. Considering the type of complications, it seems that these were mostly related to premature delivery or malformations rather than chemotherapy exposure. In the German quality control statistics the morbidity in preterm infants is around 9%.13 The rate of malformations is not different from the general population.13 Data suggest that long term morbidity after chemotherapy exposure in utero is not increased.[[16]](#endnote-16),[[17]](#endnote-17) Although the placenta filters cytotoxic agents, important variations in transplacental passage among drugs have been observed in animal models.[[18]](#endnote-18),[[19]](#endnote-19) Preterm labour/PROM is significantly more common when chemotherapy was given during pregnancy without resulting in more preterm deliveries. The reasons are manifold namely, physical or psychological stress, infections, or a still unknown underlying mechanism of the cytotoxic agent itself.[[20]](#endnote-20) Oxidative stress as one of the proposed pathophysiological mechanism of preeclampsia, can also be induced by cytotoxic agents.[[21]](#endnote-21) However, preeclampsia was not more frequently reported when chemotherapy was applied during pregnancy.

Patients who received chemotherapy during pregnancy presented more often in advanced stage of disease and were more often treated with mastectomy. Grading, hormone receptor status, and HER2-status, reflecting breast cancer biology, are comparable between the two groups. However, there seems to be a higher rate of patients with triple negative, HER2-positive, and grade 3 tumours in this cohort compared to recent data of breast cancer in young women below 41 years reported from a single institution.[[22]](#endnote-22) None of our immunohistochemical data are centrally confirmed.[[23]](#endnote-23) The DFS is in line with previously reported results in young women.[[24]](#endnote-24) The survival was not significantly different in the two groups of patients who received the chemotherapy during pregnancy or thereafter, indicating that chemotherapy given during pregnancy is effective despite an altered pharmacokinetic during pregnancy.[[25]](#endnote-25),[[26]](#endnote-26) If chemotherapy was started during pregnancy patients were less likely to receive a taxane or a regimen following current standards.[[27]](#endnote-27) Most guidelines for breast cancer still do not recommend taxanes during pregnancy.8,12,27 However, the reported complications of the infants if taxanes were given during pregnancy did not differ from those of other cytotoxic agents. Data generated in baboon models demonstrate that taxanes are hardly detectable in the foetus.[[28]](#endnote-28),19 In addition, taxanes have been proven to add efficacy independent from nodal status and are proposed as part of (neo)adjuvant treatment even during pregnancy.12,27,[[29]](#endnote-29),[[30]](#endnote-30)

A matched-pair analysis on a subset of these patients treated with modern-type chemotherapy is currently being undertaken to reveal the prognosis of BCP if treated according to actual guidelines compared to non-pregnant women.

This study has several strengths and limitations. A large number of cases have been collected in different countries in a joint effort using the same case report form. But the majority of patients were included from Germany and Belgium/Netherlands where treatment strategies are similar. The majority of cases were reported prospectively. Given the multicentric and observational nature of the study we cannot reduce missing information and exclude that that there might be a reporting bias in favour of the group unexposed to chemotherapy in utero. If 1% of breast cancers are diagnosed during pregnancy, at least 500 cases per year should have been reported in Germany alone. Birth weight, height, hair, blood count, and Apgar scores, alopecia were captured directly whereas any other observations were reported spontaneously. We did not collect information on concomitant medication. Long term effects, e.g. long term cardiac assessments have not been captured in a systematic way.

**Interpretation**

The majority of our recommendations is still based on small cohort studies or heterogeneous groups and lack comparison with breast cancer patients not treated with systemic therapy during pregnancy. Based on these data of a large cohort of only breast cancer patients we confirm that breast cancer during pregnancy can be treated as in non-pregnant women without jeopardizing the foetal and maternal outcome Particular, we need to underscore the importance of a term delivery. Obstetricians, perinatologists and neonatologists should be included in the multidisciplinary team approach to treat these patients with minimum impairment of foetal health.

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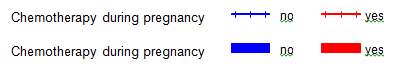
# References

# Figure Legends

**Flow diagram:**

**Figure 1:** **Median birth weight according to week of delivery**

Median birth weight according to week of delivery comparing infants exposed to chemotherapy in utero to those not exposed (n=373).



**Figure 2:** **Events of the newborn reported up to 4 weeks after delivery**

Events of the newborn reported up to 4 weeks after delivery split according to chemotherapy exposure and preterm deliveries defined as deliveries below 37th week of gestation. Respiratory distress combines the following events: continuous positive airway pressure (CPAP), mild (acute respiratory distress syndrome (ARDS), wet lung.

**Figure 3: Survival Curves**

Disease free (A) and overall survival (B) for early breast cancer patients diagnosed during pregnancy. After stratifying for tumour stage and nodal status the log-rank test was as follows: DFS 0·4644; OS: 0·892. In the group of women receiving chemotherapy during pregnancy the estimated 3-year and 5-year DFS rate was 70·2% (95% CI[60·8%, 77·7%]) and 61.1% (95% CI[50.6 %, 69.9%]), respectively. In the group of women receiving chemotherapy after delivery/interruption the estimated 3-year and 5-year DFS rate was 74·3% (95% CI[65·0%, 81·5%]) and 64·4% (95% CI[54·2%, 72·8%]), respectively. The estimated 3-year and 5-year OS rate was 84·9% (95% CI[76·9%, 90·3%]), and 77% (95% CI[67·1%, 84·3%]), respectively, in the group of women receiving chemotherapy during pregnancy. In the group of women receiving chemotherapy after delivery/interruption the 3-year and 5-year OS rate was 87·4% (95% CI[79·3%, 92·5%]), and 82·4% (95% CI[73·1%, 88·8%]), respectively.



# Table legends:

**Table 1: Patient Baseline characteristics**

**Table 2**: **Obstetrical outcome**

**Table 3: Chemotherapy regimen applied if all or parts of chemotherapy was given during pregnancy compared to regimen selected if the therapy was given after delivery**

**Supplemental figure legends:**

**Supplementary figure 1: Impact of number of chemotherapy cycles on birth weight.**

**Supplemental table legends:**

**Supplementary table 1: Obstetrical complications in women with early breast cancer with and without chemotherapy during pregnancy as reported**

**Table 1a: Patient Baseline characteristics**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Characteristic | All patients | M0 patients | M0 patients with chemotherapy | M0 patients chemotherapy during pregnancy | M0 patients chemotherapy after delivery |
|  | N=447 (%) | N=413 (%) | N=368 (%) | N=197 (%) | N=171 (%) |
| Age | 33 (22-51) | 33 (22-51) | 33 (23-51) | 33 (25-43) | 34 (23-51) |
| T Stage |  |  |  |  |  |
| T1 | 86 (20·0) | 83 (20·8) | 66 (18·4) | 32 (16·8) | 34 (20·2) |
| T2 | 217 (50·3) | 203 (50·8) | 186 (52·0) | 96 (50·5) | 90 (53·6) |
| T3 | 92 (21·3) | 82 (20·5) | 78 (21·8) | 40 (21·1) | 38 (22·6) |
| T4a-c | 25 ( 5·8) | 23 ( 5·8) | 20 ( 5·6) | 18 ( 9·5) | 2 ( 1·2) |
| T4d | 11 ( 2·6) | 10 ( 2·3) | 8 ( 2·2) | 4 ( 2·1) | 4 ( 2·4) |
| missing | 16 | 13 | 10 | 7 | 3 |
| Nodal status |  |  |  |  |  |
| negative | 181 (41·8) | 176 (43·5) | 150 (41·3) | 72 (37•3) | 78 (45·9) |
| positive | 252 (58·2) | 229 (56·5) | 213 (58·7) | 121 (62·7) | 92 (54·1) |
| missing | 14 | 8 | 5 | 4 | 1 |
| Histological tumour type |  |  |  |  |  |
| Ductal /other | 419 (96·8) | 390 (97·3) | 351 (97·8) | 188 (97.9) | 163 (97.6) |
| lobular | 14 ( 3·2) | 11 ( 2·7) | 8 ( 2·2) | 4 ( 2·1) | 4 (2·4) |
| missing | 14 | 12 | 9 | 5 | 4 |
| Grading |  |  |  |  |  |
| G1 | 10 ( 2·5) | 10 ( 2·7) | 8 ( 2·4) | 3 ( 1·7) | 5 ( 3·2) |
| G2 | 87 (22·1) | 78 (21·2) | 73 (21·6) | 34 (18·9) | 39 (24·7) |
| G3 | 296 (75·3) | 280 (76·1) | 256 (76·0) | 143 (79·4) | 109 (72·1) |
| missing | 54 | 45 | 30 | 17 | 13 |
| ER/PgR |  |  |  |  |  |
| both ER, PgR negative | 214 (52·1) | 203 (53·0) | 185 (53·8) | 99 (53·5) | 86 (54·1) |
| ER and/or PgR positive | 197 (47·9) | 181 (47·0) | 159 (46·2) | 86 (46·5) | 73 (45·9) |
| missing | 36 | 30 | 24 | 12 | 12 |
| HER2-status |  |  |  |  |  |
| negative | 226 (64·2) | 214 (65·4) | 197 (64·6) | 101 (63·5) | 96 (65·8) |
| positive | 126 (35·8) | 113 (34·6) | 108 (35·4) | 58 (36·5) | 50 (34·2) |
| missing | 95 | 86 | 63 | 38 | 25 |
| Triple negative | 118 (31·3) | 115 (32·9) | 109 (34·1) | 55 (31·8) | 54 (36·7) |

**Table 1b: Obstetrical characteristics**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Characteristic** | **All patients** | **M0 patients** | **M0 patients with chemotherapy** | **M0 patients chemotherapy during pregnancy** | **M0 patients chemotherapy after delivery** |
|  | N=447 **(%)** | N=413 **(%)** | N=368 **(%)** | N=197 **(%)** | N=171 **(%)** |
| Gestational week at diagnosis (median) | 24 | 24 | 24 | 20 | 30 |
| trimester at diagnosis |  |  |  |  |  |
| 1st trimester | 81 (18·9) | 76 (19·1) | 60 (16·8) | 31 (16·0) | 29 (17·8) |
| 2nd trimester | 178 (41·6) | 170 (42·7) | 160 (44·8) | 132 (68·0) | 28 (17·2) |
| 3rd trimester | 169 (39·5) | 153 (38·2) | 137 (38·4) | 31 (16·0) | 106 (65·0) |
| unknown | 19 | 15 | 11 | 3 | 8 |

**Table 2:** **Obstetrical outcome**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **All patients**  **N=447** | **M0 patients**  **N= 413** | **M1 patients**  **N=34** | **p-value** | **All M0 patients with known therapy 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 | **n.a.** | **n.a.** | **n.a.** |  |
| no | 382 (88·2) | 358 (89·3) | 24 (75·0) |  |  |  |  |  |
| yes | 51 (11·8) | 43 (10·7) | 8 (25·0) |  |  |  |  |  |
| unknown | 14 | 12 | 2 |  |  |  |  |  |
| **Delivery mode** |  |  |  | 0·077 |  |  |  | 0·540 |
| spontaneous | 171 (48·7) | 165 (50·3) | 6 (26·1) |  | 156 (49·1) | 85 (47·5) | 71 (51·1) |  |
| operative vaginal delivery | 18 ( 5·1) | 16 ( 4·9) | 2 ( 8·7) |  | 16 ( 5·0) | 11 ( 6·1) | 5 ( 3·6) |  |
| caesarian section | 162 (46·2) | 147 (44·8) | 15 (65·2) |  | 146 (47·1) | 83 (46·7) | 63 (45·3) |  |
| 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** |  |  |  |  |  |  |  |  |
| <37th week | 186 (50·5) | 171 (49·6) | 15 (65·2) |  | 166 (49·6) | 89 (47·3) | 77 (52·4) |  |
| <35th week | 141 (38·3) | 128 (37·1) | 13 (56·5) | 0·077 | 77 (22·8) | 38 (20·2) | 39 (26·5) | 0·192 |
| <32nd week | 13 (3·5) | 12 (3·5) | 1 (4·3) |  | 12 (3·6) | 5 (2·7) | 7 (4·8) |  |
| missing | 14 | 13 | 1 |  | 11 | 6 | 5 |  |

**Table 3: Chemotherapy regimen applied if all or parts of the chemotherapy were given during pregnancy compared to regimen selected if the therapy was given after delivery.**

| Parameter | Parameter value | Chemo after delivery  N= 171(%) | Chemo during pregnancy  N=197(%) | All M0 pts with (neo)adjuvant chemotherapy  N= 368(%) |
| --- | --- | --- | --- | --- |
| Chemotherapy regimen | A(E)/C | 16 ( 9·4) | 55 (27·9) | 71 (19·3) |
|  | FE(A)C | 42 (24·6) | 34 (17·3) | 76 (20·7) |
|  | AC/EC -taxane | 29 (17·0) | 46 (23·4) | 75 (20·4) |
|  | FE(A)C-taxane | 19 (11·1) | 19 (9·6) | 38 (10·3) |
|  | CMF | 16 ( 9·4) | 11 ( 5·6) | 27 ( 7·3) |
|  | AC/EC-CMF | 4 ( 2·3) | 4 ( 2·0) | 8 ( 2·2) |
|  | FE(A)C-CMF | 0 ( 0·0) | 1 ( 0·5) | 1 ( 0·3) |
|  | A(E)mono-CMF | 3 ( 1·8) | 4 ( 2·0) | 7 ( 1·9) |
|  | A(E)mono-taxane | 0 ( 0·0) | 4 ( 2·0) | 4 ( 1·1) |
|  | A(E)mono-taxane-CMF | 1 ( 0·6) | 0 ( 0·0) | 1 ( 0·3) |
|  | A(E)taxane | 3 ( 1·8) | 0 ( 0·0) | 3 ( 0·8) |
|  | A(E)taxane-CMF | 1 ( 0·6) | 0 ( 0·0) | 1 ( 0·3) |
|  | TAC | 20 (11·7) | 0 ( 0·0) | 20 ( 5·4) |
|  | dd E-P-C | 4 ( 2·3) | 0 ( 0·0) | 4 ( 1·1) |
|  | TC | 1 ( 0·6) | 1 ( 0·5) | 2 ( 0·5) |
|  | Vincaalcaloid based | 0 ( 0·0) | 13 ( 6·6) | 13 ( 3·5) |
|  | Platinum-containing | 7 ( 4·1) | 2 ( 1·0) | 9 ( 2·4) |
|  | Other | 5 ( 2·9) | 3 ( 1·5) | 8 ( 2·2) |

AC/EC: doxorubicin(epirubicin)/cyclophosphamide; F: 5-fluorouracil; CMF: cyclophosphamide, methotrexate,5-fluorouracil; T:docetaxel; P:paclitaxel; dd: dose-dense

Table 4: Multivariate analysis for disease free and overall survival

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Parameter | Category | DFS | | | OS | | |
|  |  | HR | 95%CI | p-value | HR | 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 |
| T-stadium | T1-3 | 1 |  |  |  |  |  |
|  | T4 | 5·66 | 3·10, 10·4 | <0·0001 | 4·44 | 2·16, 9·14 | <0·0001 |
| Nodal status | N0 | 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 |  |  |  |  |  |
|  | ER/PgR positive | 0·652 | 0·415, 1·02 | 0·064 | 0·593 | 0·314, 1·12 | 0·106 |

**Supplemantary Table 1: Obstetrical complications in women with early breast cancer with and without chemotherapy during pregnancy as reported (n=396)**

| Parameter | Parameter value | No chemo during pregnancy  N(%) | Chemo during pregnancy  N(%) | M0 patients with chemotherapy known and pregnancy outcome known (%) | p-value |
| --- | --- | --- | --- | --- | --- |
| Any obstetrical complication | no | 149 (90·9) | 148 (82·7) | 297 (86·6) | ·027 |
|  | yes | 15 ( 9·1) | 31 (17·3) | 46 (13·4) |  |
|  | missing | 35 | 18 | 53 |  |
| Gestational diabetes | no | 163 (99·4) | 177 (98·9) | 340 (99·1) | 1·00 |
|  | yes | 1 ( 0·6) | 2 ( 1·1) | 3 ( 0·9) |  |
|  | missing | 35 | 18 | 53 |  |
| Pre-eclampsy | no | 163 (99·4) | 177 (98·9) | 340 (99·1) | 1·00 |
|  | yes | 1 ( 0·6) | 2 ( 1·1) | 3 ( 0·9) |  |
|  | missing | 35 | 18 | 53 |  |
| Hypertension | no | 164 ( 100) | 178 (99·4) | 342 (99·7) | 1.00 |
|  | yes | 0 ( 0·0) | 1 ( 0·6) | 1 ( 0·3) |  |
|  | missing | 35 | 18 | 53 |  |
| Oligohydramnios | no | 164 ( 100) | 176 (98.3) | 340 (99.1) | 0·249 |
|  | yes | 0 ( 0·0) | 3 ( 1·7) | 3 ( 0·9) |  |
|  | missing | 35 | 18 | 53 |  |
| Cervical insufficiency | no | 164 ( 100) | 176 (98.3) | 340 (99.1) | 0.249 |
|  | yes | 0 ( 0·0) | 3 ( 1·7) | 3 ( 0·9) |  |
|  | missing | 35 | 18 | 53 |  |
| Placenta insufficiency (NOS) | no | 164 ( 100) | 177 (98.9) | 341 (99.4) | 0·499 |
|  | yes | 0 ( 0·0) | 2 ( 1·1) | 2 ( 0·6) |  |
|  | missing | 35 | 18 | 53 |  |
| Placenta haematoma | no | 164 ( 100) | 178 (99·4) | 342 (99·7) | 1·00 |
|  | yes | 0 ( 0·0) | 1 ( 0·6) | 1 ( 0·3) |  |
|  | missing | 35 | 18 | 53 |  |
| Solution placentae | no | 164 ( 100) | 178 (99.4) | 342 (99.7) | 1·00 |
|  | yes | 0 ( 0·0) | 1 ( 0·6) | 1 ( 0·3) |  |
|  | missing | 35 | 18 | 53 |  |
| Bleeding | no | 163 (99·4) | 175 (97·8) | 338 (98·5) | 0·374 |
|  | yes | 1 ( 0·6) | 4 ( 2·2) | 5 ( 1·5) |  |
|  | missing | 35 | 18 | 53 |  |
| Vasa praevia | no | 164 ( 100) | 179 ( 100) | 343 ( 100) | n.a. |
|  | missing | 35 | 18 | 53 |  |
| Congenital abnormality (pregnancy termination) | no | 164 ( 100) | 179 ( 100) | 343 ( 100) | n.a. |
|  | missing | 35 | 18 | 53 |  |
| Intrauterine growth restriction (IUGR) | no | 163 (99·4) | 172 (96·1) | 335 (97·7) | 0·069 |
|  | yes | 1 ( 0·6) | 7 ( 3·9) | 8 ( 2.3) |  |
|  | missing | 35 | 18 | 53 |  |
| Chorioamnionitis | no | 163 (99·4) | 179 ( 100) | 342 (99·7) | 0·478 |
|  | yes | 1 ( 0.6) | 0 ( 0.0) | 1 ( 0.3) |  |
|  | missing | 35 | 18 | 53 |  |
| Spontaneous abortion (included in preg. interruptions) | no | 160 (97·6) | 179 ( 100) | 339 (98·8) | 0·051 |
|  | yes | 4 ( 2·4) | 0 ( 0·0) | 4 ( 1·2) |  |
|  | missing | 35 | 18 | 53 |  |
| Spontaneous abortion of one twin | no | 164 (100) | 178 (99·4) | 342 (99·7) | 1·00 |
|  | yes | 0 (0·0) | 1 (0·6) | 1 (0·3) |  |
|  | missing | 35 | 18 | 53 |  |
| Premature labour | no | 161 (98·2) | 169 (94·4) | 330 (96·2) | 0·090 |
|  | yes | 3 (1·8) | 10 ( 5·6) | 13 ( 3·8) |  |
|  | missing | 35 | 18 | 53 |  |
| Premature rupture of the membrane (PROM) | no | 164 ( 100) | 174 (97.2) | 338 (98.5) | 0·062 |
|  | yes | 0 (0·0) | 5 (2·8) | 5 (1·5) |  |
|  | missing | 35 | 18 | 53 |  |
| Fetal distress | no | 163 (99·4) | 177 (98·9) | 340 (99·1) | 1·00 |
|  | yes | 1 (0·6) | 2 (1·1) | 3 (0·9) |  |
|  | missing | 35 | 18 | 53 |  |
| Stillbirth | no | 162 (98·8) | 178 (99·4) | 340 (99·1) | 0·608 |
|  | yes | 2 (1·2) | 1(0·6) | 3 (0·9) |  |
|  | missing | 35 | 18 | 53 |  |
| Pyelonephritis | no | 164 ( 100) | 179 ( 100) | 343 ( 100) | n.a. |
|  | missing | 35 | 18 | 53 |  |
| Cholestasis | no | 163 (99·4) | 179 ( 100) | 342 (99·7) | 0·478 |
|  | yes | 1 (0·6) | 0 (0·0) | 1 (0·3) |  |
|  | missing | 35 | 18 | 53 |  |
| Pruritus | no | 163 (99·4) | 179 ( 100) | 342 (99·7) | 0·478 |
|  | yes | 1 (0·6) | 0 (0·0) | 1 (0·3) |  |
|  | missing | 35 | 18 | 53 |  |

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