The UK Breast Cancer in Pregnancy (UKBCiP) Study. Incidence, diagnosis, management and short-term outcomes of breast cancer first diagnosed during pregnancy in the United Kingdom: A population-based descriptive study.

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ABSTRACT

Objectives: To estimate the incidence of breast cancer diagnosed during pregnancy in the UK, to describe its management and short-term outcomes for mothers and babies.

Design: A population-based descriptive study using the UK Obstetric Surveillance System (UKOSS).

Setting: All UK consultant-led maternity units.

Participants: All cases of breast cancer diagnosed first during pregnancy, between 1st October 2015 and 30th September 2017, with 84 confirmed cases analysed. Women with breast cancer diagnosed before pregnancy or with a recurrence were excluded.

Method: Prospective case identification through monthly UKOSS mailings.

Main outcome measures: Incidence of breast cancer arising for the first time in pregnancy, maternal mortality, severe maternal morbidity, perinatal mortality and severe neonatal morbidity.

Results: The incidence found was 5.4/100,000 maternities (95% CI 4.37, 6.70). Nine women (11%) had an IVF pregnancy. During pregnancy, 30 women (36%) underwent surgery and 37 women (44%) received chemotherapy. Three women had major maternal morbidity during pregnancy. Two women died and there were two perinatal deaths.

Conclusions: The incidence of breast cancer arising in pregnancy in the UK is similar to that reported in other countries. The higher proportion of IVF pregnancies among these women diagnosed with breast cancer during pregnancy needs further investigation. With caveats, the management followed that outside pregnancy, but there was considerable variation in practice. Although the short-term outcome was in general good for mothers and babies, a larger prospective study is required. It is often possible to avoid exposing the baby to iatrogenic prematurity.

Funding: BCUHB

Keywords: Breast cancer, pregnancy, incidence.

TWEETABLE ABSTRACT:

UK study estimates new breast cancer incidence in pregnancy = 5.4/100,000 maternities, but was higher if IVF.

INTRODUCTION

Breast cancer is the most common malignancy in the UK, accounting for almost one third (30%) of cancers in women in England[1], Wales[2], Scotland[3] and Northern Ireland[4].

The incidence of breast cancer rises with age. That many women are delaying pregnancy until later in life may lead to an increasing incidence of breast cancer arising for the first time in pregnancy. Births to women aged 40 or over have increased by 9.5% between 2006-07 and 2017-18 in England.[5] Studies elsewhere have identified an increasing trend in the incidence of breast cancer during pregnancy, for example, in Sweden between 1963 and 2002.(1)

Pregnancy-associated breast cancer is defined as breast cancer diagnosed during pregnancy or lactation up to 12 months postpartum. Some studies include those cases diagnosed up to 5 years after delivery, even though breast cancer during pregnancy and after delivery appear to be two different entities, with different behaviour and outcomes.(2–6) Hence, the estimated incidence of Breast Cancer Associated with Pregnancy (BCAP) ranges from 1/3,000 to 1/10,000 pregnancies, depending on study population and definition used.(1,7–9) Cases diagnosed during pregnancy are estimated to be 18 to 33% of these.(1,7–9) Based on this observation the incidence of breast cancer diagnosed for the first time during pregnancy can be estimated in other countries to range from 2.4 to 7.8 cases per 100,000 births (1,7–9) but this has not estimated for the UK previously.

The aim of this study was to identify cases of breast cancer diagnosed during pregnancy, a period of time when diagnosis, staging and treatment can be challenging for women, their families and clinicians. An objective was that these data could inform clinical discussions with women and their families in order to co-produce management decisions that must account for optimal maternal therapy as well as fetal wellbeing, in what is a rare situation for both clinicians and patients.

METHODS

All newly diagnosed cases of breast cancer during pregnancy in the United Kingdom were reported through the UK Obstetric Surveillance System (UKOSS) in women who delivered their babies or had a termination of pregnancy or miscarriage between 1st October 2015 and 30th September 2017. We excluded women whose breast cancer had been diagnosed before pregnancy or who had a recurrence of previously diagnosed disease.

UKOSS collects information on specific rare events occurring during pregnancy from all obstetric units in the UK. The reporters submit monthly returns for the current list of conditions including if this is a zero value, notifying UKOSS when

[1] https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/previousReleases

[2] http://www.wcisu.wales.nhs.uk/home

[3] https://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics

[4] http://www.qub.ac.uk/research-centres/nicr/

[5] https://digital.nhs.uk/data-and-information/publications/statistical/nhs-maternity-statistics/2017-18

an event has occurred (in this case the diagnosis of breast cancer in pregnancy). UKOSS staff send a data collection form for completion by the reporter. The data collection form was approved and refined by the UKOSS National Steering Committee[6]. In addition, we notified oncologists around the UK in order to gain their assistance with completion of information on oncological diagnosis and management. No identifiable data were included. Ethics committee approval was obtained (REC 14/WA/1267, IRAS project ID 165517). BCUHB sponsored and funded the study.

Information requested included maternal demographics and details of the current and past pregnancies, BRCA (BReast CAncer) gene mutation status, details of the diagnosis and staging when known. Staging, surgical management, chemotherapy use and pregnancy outcomes were collected. Babies were categorised as small for gestational age (SGA) if the birth centile was less than 10th centile. (10)

Incidence rates with 95% confidence intervals (CI) were calculated using national data on maternities as the denominator. Categorical data are summarised as percentages. Continuous data are presented as median, IQR and range. Group comparisons were made using Fisher's exact tests.

RESULTS

A total of 132 cases were reported in the 24-month period. From those, 29 cases were excluded as they did not meet the eligibility criteria and 8 cases were duplicate notifications. The data collection form was not returned in 11 cases, therefore, 84 confirmed cases were available for analysis.

Incidence

The estimated total maternities in the UK during the study were 1,544,700,(11–13) giving an estimated incidence of 5.4 per 100,000 maternities (95% CI [4.37, 6.70]).

Maternal characteristics

Women's characteristics are given in table 1. The median maternal age at diagnosis was 36 (IQR: 33-38, range 26 to 44 years). The median BMI at booking was 25, (IQR: 22-28.5 range 18 to 48). Nine women (11%) had IVF pregnancies.

Data on presentation and diagnosis are given in table 2. Two women were asymptomatic, with their tumours identified at specific screening. The majority of symptomatic women (n=50, 61%) presented solely with a lump. Fourteen women (17%) presented with a lump associated with other breast symptoms: pain, skin changes, discharge or tenderness. The remaining 18 women (22%) presented with different combinations of symptoms but not a lump, including nipple inversion, pain and fullness, skin changes, breast enlargement, discharge from the nipple and erythema. The median duration of symptoms before diagnosis was 3 weeks (IQR: 2-9, range: 0 to 56). (Table 2)

[6] https://www.npeu.ox.ac.uk/downloads/files/ukoss/forms/UKOSS%20Breast%20Cancer%20V1.pdf

The median gestational age at diagnosis was 25 weeks (IQR: 16-33, range 2 to 40 weeks). The diagnosis was made before week 14 in 18 cases (21%), between 14 and 26 weeks in 23 (27%), between 27 and 36 weeks in 32 cases (38%) and after 36 weeks in 5 women (6%). The gestational age at diagnosis was not reported in 6 cases (7%). (Table 2)

Staging and tumour characteristics

Staging investigations performed during pregnancy were reported fully for 76 women and included a variety of modalities and combinations.

Data were available on histology type for 71 women. The histological type was invasive ductal carcinoma in 62(74%), poorly differentiated in 2(2%), invasive lobular carcinoma in 3 (4%) and ductal carcinoma in situ (DCIS) in 2(2%). Metaplastic carcinoma, inflammatory, and invasive ductal and lobular were reported in the remaining cases. (Table 3)

Of the 61 cases where grade was recorded, grade 3 tumors were found in 45 (74%), grade 2 in 15 (25%) and grade 1 in 1 case (1%). (Table 3)

The TNM (Tumour size, lymph Nodes, Metastasis) stage was known for 58 women (Table 3). The clinical size of the tumour at diagnosis was greater than 2 cm in 39 (68%). Just over 1 in 6 women (N=9) had a tumour greater than 5 cm. Using the American Joint Committee on Cancer (AJCC) pathological staging system, 14 (24%) were stage 1, 27 (46%) were stage 2, 13 (22%) were stage 3 and 4 (7%) were stage 4. Of the 58 women that had complete TNM staging 24 (41%) were node negative, 34 (59%) were node positive and 4 (7%) had distant metastasis to liver, and bones. (Table 3)

Tumour receptor status is given in table 3. Overall 41 (59%) were ER (+), 24 (35%) were Her2 (+) and 20 (29%) were triple negative (ER, PR, HER2). (Table 3)

Treatment

Data on the use of systemic chemotherapy were available for 79 women. This was administered during pregnancy in 37 (47%), was not recommended in 7 cases (9%) and was delayed until the end of pregnancy in 35 cases (44%). Timing was unknown in 5 cases. Of the 37 women who had chemotherapy during pregnancy, this was neo-adjuvant in 18 (49%) and adjuvant in 17(46%). One woman received palliative chemotherapy for metastatic disease.

The median gestational age at the start of the chemotherapy was 23 weeks (IQR: 19-27.5 range from 13 to 35 weeks).
Of the 18 women diagnosed during the first trimester, 11 had chemotherapy during pregnancy (all of them after 14 weeks), two had chemotherapy after miscarriage and in five cases chemotherapy was considered not indicated. Out of these 18 women, 13 had surgery during pregnancy all of them between 6 and 15 weeks.

Of the 23 women diagnosed during the second trimester, 20 had chemotherapy during pregnancy and 3 had the start of chemotherapy delayed until after delivery. In all three cases the delivery was after 37 completed weeks. In the same

group of women 11 had surgery during pregnancy and 8 had it delayed until the end of pregnancy (in two of these cases the delivery was between 34 and 36 weeks), all the other cases delivered after 37 weeks.

Overall, thirty women out of the 77 with data (39%) had surgery during pregnancy, with 14 undergoing breast conservation surgery and 16 mastectomy. One woman had both procedures during pregnancy. The median gestational age at breast conservation surgery was 17 weeks, ranging from 6 to 34 weeks. The median gestational age at mastectomy was 18 weeks, ranging from 9 to 35 weeks. In 34 women (44%), the surgery was delayed until the end of pregnancy. Of these 34 women, 11 received neo-adjuvant chemotherapy during pregnancy. The reasons for delayed surgery were not collected.

Including the 32 cases known that had axillary clearance during pregnancy, the median number of lymph nodes removed was 12 (IQR: 4.8-17.3 range 2 to 34). From these cases, the median of positive nodes was 1 (IQR: 0-3.3 range: 0 to 16).

Breast cancer was diagnosed in 37 women during the third trimester. Thirty-five of them had induction of labour or prelabour caesarean section, in 50% of the cases before 37 completed weeks (between 32 and 36 weeks). From these women diagnosed during the third trimester, 6 had surgery during pregnancy and 25 had it delayed until the end of pregnancy. Five had chemotherapy during pregnancy and 30 had it delayed until the end of pregnancy.

The systemic regimen most patients received was anthracycline-based chemotherapy (31 out of 37). This was associated with Cyclophosphamide in 26 out of 37 women that received chemotherapy in pregnancy. Taxanes were used in 15 women. The combination more widely used was FEC in 10 women. (Table 4)

Outcomes

There were 81 babies born to the 80 women who continued with pregnancy, with a median gestational age at delivery of 37 completed weeks (IQR: 35-38 range 28 to 41). In total 41% babies were delivered preterm and 59% after 37 completed weeks. All 16 women who gave birth before 36 completed weeks received steroids for fetal lung maturation; two babies died, both prior to 30 weeks. Sixteen babies (20%) were admitted to the neonatal care unit, 13 (81%) because of symptoms directly related to their prematurity. At birth, 11 out of 78 (14%) neonates with known birth weight were classified as small for gestational age (SGA; weight below the 10th centile).(10) Eight of the babies who were SGA were born to the 35 mothers that had chemotherapy, and 3 SGA babies were born to the 39 mothers who did not have chemotherapy during pregnancy. This difference was not statistically significant, 22.8% vs 7.7%, p= 0.142; Fisher's exact test.

Thirty women were induced, 28 of them (93%) for reasons related to their cancer. The mode of delivery was known for 78 of the 80 women continuing pregnancy beyond the second trimester; 37 (47.4%) had pre-labour caesarean section, 21 (57%) after 37 weeks and 16 (43%) preterm. Of the 41 women that were planning a vaginal birth, 27 (66%) had a spontaneous vaginal birth, four (10%) had ventouse birth, three (7%) had a forceps birth, one woman had a breech birth and six women (15%) had an emergency caesarean section after the onset of labour.

Three women were diagnosed later in pregnancy with metastatic cancer: to liver, thoracic spine and lung. There were two maternal deaths reported. Two additional women had major maternal morbidity during pregnancy or the puerperium, one thought to be directly related to her chemotherapy.

Thirty seven percent of women (27 out of 73 known) breastfed and 19 women had lactation suppression.

DISCUSSION

Main findings

The incidence of breast cancer diagnosed during pregnancy in the UK of 5.4 per 100,000 maternities, is similar to the incidence found in other countries.

The median maternal age was 36, which is the same found in the Prospective Study of Outcomes in Sporadic versus Hereditary Breast Cancer (POSH Breast Cancer Study) in the UK between 2000 and 2008 that included 2956 young women aged 18 to 40 with breast cancer (14), with a similar mean maternal age found in other studies during pregnancy: 35 to 37.(15–18). This may partially explain the observation of a disproportionate number of women with IVF pregnancies, who tend to be older. However, the percentage of IVF pregnancies in the UK for 2015 and 2016 were 2.57% and 2.6%(19) compared to 11% in this study. This observation needs further study. Meanwhile, there needs to be discussion of this potential risk, and special attention be paid to breast symptoms and examination during the antenatal period in these women in particular until the position is clarified.

The high percentage of symptomatic women before diagnosis (97%) is similar to that found in the POSH study (98%) (14) as might be expected outside a screening programme population demographic. In postmenopausal women two thirds of women are asymptomatic at the moment of diagnosis, with diagnosis at an earlier stage during screening. This may contribute to the worse prognosis of young women with breast cancer.(20) Three quarters of cases presented with a breast lump, two thirds on its own and the remainder mostly with a lump and / or other symptoms. These other presentations - such as nipple inversion, pain and fullness, skin changes, breast enlargement, discharge from nipple and erythema - need highlighting to women and midwives, because symptoms are easily dismissed as being part of the normal pregnancy breast changes. This emphasizes the importance of increasing awareness of this diagnosis when discussing breast symptoms at any stage of pregnancy.

Pregnancy often masks symptoms and signs of breast cancer, leading to delayed diagnosis. The interval between the start of symptoms and diagnosis reported here (median 3 weeks IQR: 2-9) is shorter than the median time of 4 weeks (range 1 to 104 weeks) found in the Australian study of Ives,(7) which included postpartum diagnosis, and the mean time of 3.9 months during pregnancy found by Langer et al.(21)

The median gestational age at diagnosis, 25 weeks, had a wide range, similar to findings in smaller studies (17). A large number of women (44%) were diagnosed during the third trimester. Of these 37 women, 35 (95%) had induction of labour

or prelabour caesarean section. In most of them the treatment (surgery or chemotherapy) was delayed until the end of pregnancy with iatrogenic delivery between 32 and 36 weeks in nearly half (49%). This finding could reflect guidelines regarding the safe time of delivery for women receiving chemotherapy to allow both maternal and fetal bone marrow recovery.[7] (22) The effects of granulocyte-colony stimulating factor on treating neutropenia in pregnancy may modify this decision, avoiding iatrogenic prematurity and seems to be safe.(23,24)

The UK confidential enquiry into maternal mortality, Mothers and Babies: Reducing Risk through Audit and Confidential Enquiries (MBRRACE-UK) have recently reported on a subset of the cases identified through the UKOSS reporting system as part of this UKBCiP study, with direct access to anonymised patient records for assessment. This suggests new guidance: In general, early delivery to avoid delays in chemotherapy should not be recommended. For women diagnosed with breast cancer in the third trimester, the risk-benefit is likely to favour both mother and baby if a woman can receive at least two cycles of chemotherapy prior to a term (39-40 week) birth. (25)

Overall we found that women were more likely to be induced (57% vs 39%) or undergo elective caesarean section (47% vs 15%) when compared to the general population in England. (26)

The Prospective Study of Outcomes in Sporadic versus Hereditary Breast Cancer (POSH Breast Cancer Study) although not directly comparable, provides context outside pregnancy, because the demographics overlap with this UKBCiP study. Breast cancer was found to present at a more advanced stage in pregnancy, with higher node involvement and grade of tumour. The tumour size at diagnosis was more commonly greater (above 2 cm in 68% in vs 52% of cases and above 5 cm in 15% vs 7% in pregnancy and outside pregnancy respectively). Node involvement was greater (59% vs 50%) as were metastases 7% vs 2.5%). Histological grade may be higher in pregnancy (grade 1, 1% vs 6%; grade 2, 18% vs 32.9% and grade 3, 53% vs 59%). The finding of invasive ductal carcinoma in 84% of cases is similar to that found by other authors. (7,16–18,21,26) Despite 2/3 (68%) being diagnosed as stage II or III, most women do well in the short term.

The finding that 59% of women with newly diagnosed breast cancer in pregnancy are oestrogen receptor (ER) positive compares to 66% in the POSH study, with triple negative tumours present in 29% and 20% of women respectively.

Although, in England overall for the period 2016-17 7.9% of babies were preterm (25) and in Scotland 6.5%,(12) the preterm delivery rate of 41% is less that reported by Amant et al in an international collaborative study of 311 cases of breast cancer diagnosed during pregnancy (49.6%). Smaller case series report higher figures for preterm delivery; Gomez-Hidalgo in 11 cases found that 54.6% of the neonates were preterm (14) and Framarino-dei-Malatesta in 54.5% including 22 women.(16) Outcome data suggesting that the fetus does relatively well even when exposed to several maternal chemotherapy regimens. Amant et al concluded in her study in 2015 that prenatal exposure to maternal cancer with or without treatment did not impair the cognitive, cardiac, or general development of children in early childhood. Prematurity was correlated with a worse cognitive outcome, but this effect was independent of cancer treatment.(27)

[7] **https://academic.oup.com/annonc/advance-article/doi/10.1093/annonc/mdz228/5552554**

MBRRACE also note that variation around the practice of staging may have led to unnecessarily extensive surgery.(25)

The safety of current chemotherapy regimens during pregnancy is well documented and the treatment of breast cancer during pregnancy should adhere to that of non-pregnant woman. Most patients received anthracycline-based chemotherapy. (31 out of 37) This was associated with Cyclophosphamide in 26 out of 37 women that received chemotherapy in pregnancy. Taxanes were used in 15 women. The combination more widely used was FEC in 10 women.

It seems that later delivery (for the fetus), giving appropriate chemotherapy in pregnancy and aiming for vaginal delivery are all reasonably safe. In a situation that is psychologically distressing for a woman and her family, the creation of 'normality' in relation to the birthing experience can be hugely important to their well-being and future perception.

Strengths and limitations

This is the first national, prospective study of breast cancer diagnosed during pregnancy in the UK, finding its incidence, management and short-term outcomes. The study raised awareness of the rare condition of breast cancer in pregnancy among UK obstetricians and oncologists during the 2 years of the UKOSS data collection.

UKOSS data relies on the reporting of monthly cases and a certain amount of under-reporting may occur, hence the use of a 95% confidence interval has been included with our estimate of incidence.

Data collection forms were returned for 4 women who had a miscarriage or termination of pregnancy, but the UKOSS reporting system tends to become more complete for women after the first trimester (because some women will present to gynaecological or private facilities outside the obstetric service) and thus this will not be a true reflection of what may be happening in early pregnancy.

The incidence estimate reported here must be considered a minimum estimate for several reasons. UKOSS is a system that involves all consultant-led maternity units in the UK, but some women diagnosed with breast cancer during pregnancy could have chosen to undergo termination of pregnancy before reaching these maternity units. Additionally, although we wrote to clinical oncology units and contacted patient support groups such as Mummy's Star to raise awareness of the study, the anonymised nature of UKOSS reporting precludes the study team from having women's details, for example through self-reporting, to cross-check with reporting units specifically to ensure their details had been included in the study. Currently, pregnancy data are not included in most cancer registries; therefore these data cannot be used to enhance case ascertainment.

CONCLUSIONS:

The incidence of breast cancer arising in pregnancy in the UK is 5.4 / 100,000 maternities. The relatively high number of IVF pregnancies needs further investigation, as this may not be related to increased age alone. This study confirms late

presentation, with diagnosis at a more advanced stage, highlighting the need for education of women and those who care for them about breast symptoms in pregnancy.

With the exceptions that chemotherapy should not be given in the first trimester and the use of HER-2 targeted therapies avoided, the management of these women should be the same as in non-pregnant women. Standard chemotherapy can be safely delivered during pregnancy with good fetal outcomes overall. It is often possible to avoid exposing the baby to iatrogenic prematurity.

Co-ordinated multidisciplinary working between obstetricians, breast surgeons and oncologists is essential to ensure optimal management.

A larger prospective study is required that would allow longer term follow up, but needs individual patient consent. Meanwhile, adding pregnancy status to the cancer UK registries would yield more information about treatment and outcomes.

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Ethics committee approval Wales Research Ethics Committee 5. 15th January 2015 REC 14/WA/1267, IRAS project ID 165517.

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Contribution of authorship: PB conceived the study and was the Chief Investigator, overseeing the R&D approvals process, study design and submission for approval to UKOSS. He had extensive input into all drafts of the manuscript. He acts as the guarantor for the study and work submitted. CH developed the study protocol and was the principal investigator, liaising with UKOSS and the health board R&D department, who sponsored the study. She was responsible for day-to-day conduct of the study, collating results, chasing outstanding data collection forms and verifying data. She has initiated each revision of the manuscript. She is the corresponding author. AB has provided statistical advice on study design and data validation; he performed the statistical analysis. He has been involved with multiple revisions of the manuscript. JJ was instrumental in planning and design of the oncology sections of the study questionnaire. She has been involved with multiple revisions of the manuscript. MK gave advice and helped to plan the submission for UKOSS, providing feedback on data collection and analysis. She has revised the manuscript at several key moments to guide the final version to its current form.

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Table 1. Characteristics of women

Characteristic	Median (IQR*, range) or No of women (%)
Age at diagnosis	36 (33-38, 26-44) N= 84 (100%)
26 – 30	14 (17%)
31-35	30 (36%)
36-40	33 (39%)
41-45	6 (7%)
Missing	1 (1%)
Body mass index (BMI) (kg/m^2)	25 (22-28.5, 18 to 48) N=84 (100%)
<20	5 (6%)
20-25	44 (52%)
26-30	22 (26%)
31-35	8 (10%)
36-40	4 (5%)
>40	1 (1%)
IVF pregnancy?	
Yes	9 (11%)
No	75 (89%)
Known to have BRCA mutation?	
Yes	3 (4%)
No	69 (82%)
Missing	12 (14%)

*IQR = interquartile range

Table 2. Presentation at diagnosis

Characteristic	Median (IQR*, range) or No of patients (%)
Gestational age at diagnosis (weeks)	25 (16-33, 2 to 40) N= 84 (100%)
<14	18 (21%)
14 - 6	23 (28%)
27 - 36	32 (38%)
37 - 40	5 (6%)
Missing	6 (7%)
Symptoms	
Asymptomatic	2 (2%)
Symptomatic	76 (91%)
Missing	6 (7%)
Lump only	50 (60%)
Lump with or without other symptoms	70 (83%)
Pain / tenderness with or without other symptoms	13 (16%)
Skin changes / nipple inversion with or without other symptoms	10 (12%)
Other symptoms	2 (2%)
Clinical size of tumour at diagnosis (mm)	26 (20-40, 7 to 120) N= 84 (100%)
≤ 20	14 (17%)
30 – 50	37 (44%)
> 50	6 (7%)
Missing	27 (32%)
Interval from symptoms to diagnosis (weeks)	3 (2-9, 0 to 56) N= 84 (100%)
0 - 4	45 (53%)
5 - 9	10 (12%)
10 – 14	8 (9%)
15 – 19	1 (1%)
20 – 24	1 (1%)
>24	5 (6%)
Missing	10 (18%)

*IQR = interquartile range

Table 3. Tumour characteristics and staging

Characteristic	**ER (+)**	**ER (-)**	**Total***
	41(49%)	29 (35%)	84 (100%)
Histological grade			
1	0 (0%)	0 (0%)	1 (1%)
2	12 (29%)	3 (10%)	15 (18%)
3	25 (60%)	19 (66%)	45 (53%)
N/A	1 (2%)	2 (7%)	4 (5%)
Missing	4 (9%)	5(17%)	19 (23%)
Histological type			
Ductal	37 (90%)	23 (79%)	62 (74%)
Lobular	1 (2%)	1 (3%)	3 (4%)
Ductal and lobular	1 (2%)	0 (0%)	1 (1%)
Metaplastic	0 (0%)	1 (3%)	1 (1%)
Poorly differentiated	0 (0%)	2 (7%)	2 (2%)
DCIS	2 (5%)	0 (0%)	2 (2%)
Missing	0 (0%)	2 (7%)	13 (16%)
Distribution of cancer			
Localised	26 (63%)	22 (76%)	51 (61%)
Multifocal	11 (27%)	4 (14%)	15 18%)
Missing	4 (10%)	3 (10%)	18 (62%)
PR Status			
Positive	23 (56%)	1 (3%)	25 (30%)
Negative	5 (12%)	26 (90%)	31 (37%)
Missing	13 (32%)	2 (7%)	28 (33%)
HER2 Status			
Positive	15 (37%)	8 (28%)	24 (28%)
Negative	25 (61%)	20 (69%)	45 (54%)
Missing	1 (2%)	1 (3%)	15 (18%)
Pathological T stage			
T1	14 (34%)	6 (21%)	20 (24%)
T2	17 (42%)	11 (38%)	30 (36%)
T3	5 (12%)	6 (21%)	12 (14%)
T4	1 (2%)	2 (7%)	4 (5%)
Missing	4 (10%)	4 (13%)	18 (21%)
N Stage			
N0	14 (34%)	10 (35%)	25 (30%)
N1	10 (25%)	5 (17%)	17 (21%)
N2	3 (7%)	4 (14%)	7 (8%)
N3	3 (7%)	4 (14%)	7 (8%)
Missing	11 (27%)	6 (20%)	28 (33%)
M Stage			
M0	39 (95%)	26 (90%)	68 (81%)
M1	1 (2%)	2 (7%)	4 (5%)
Missing	1 (2%)	1 (3%)	12 (14%)

ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; PR: progesterone receptor.

DCIS: Ductal carcinoma in situ

*ER status unknown for 14 women

CHEMOTHERAPY	Number of cases	GA start median	GA end	GA delivery median	Outcome mother	Outcome neonate
FEC	10	24	33 (not known in 6)	38	No complications	1 NICU: prematurity 34 weeks, 2 cases SGA
EC	6	24.5	28.5 (not known 4)	36	1 urinary infection	3 NICU 1 prematurity, 1 jaundice, 1 GBS infection. 1 case SGA
FEC-T	5	16	32 (not known in 2)	36	1 pericarditis postnatal	1SROM 33 weeks, 2 NICU admissions prematurity, 1 case SGA
EC-D	3	26	33 (not known 2)	38	Extravasation, burn left arm, 1 woman metastatic disease	1 NICU: chest infection, 1 case SGA
DOCETAXEL	2	23	33(not known 1)	37	No complications	1 case SGA
PACLITAXEL AND TRASTUZUMAB	2	32	Not known	40	1 case metastasis, pleural effusion.	1 case SGA 1 case TOP
AC	2	22.5	Not known	32	No complications	1 Delivered at 28 weeks to start Herceptin. Died of sepsis
6 Other combinations. 1 case unknown	7 Each one in one case	13 - 35	26 - 36	28 - 40	In 5 cases no complications. 2 cases worsen condition mother	1 stillbirth 1 admission to NICU for prematurity 1 SGA Other 4 no complications

Table 4: In 9 case the chemotherapy was continued postpartum, but the gestational age at which it was stopped antenatally is unknown.
GA: gestational age. SGA: small for gestational age, includes those cases with a weight at birth below the 10th centile. TOP: Termination of pregnancy.
NICU: Neonatal intensive care unit.
FEC-T: Fluorouracil, Epirubicin, Cyclophosphamide and Docetaxel. **FEC:** Fluorouracil, Epirubicin and Cyclophosphamide. **EC:** Epirubicin, Cyclophosphamide.
EC-D: Epirubicin, Cyclophosphamide, Docetaxel. **ECX:** Epirubicin, Cisplatin, Capecitabine. **AC-TH:** Doxorubicin (Adriamycin), Cyclophosphamide, Docetaxel and Trastuzumab.
AC: Doxorubicin, cyclophosphamide.