Trastuzumab Administration During Pregnancy: Un Update

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Abstract

Background

Over than one third (28–58%) of pregnancy-associated breast cancer (PABC) cases are characterized by positive epidermal growth factor receptor 2-positive (HER2) expression. Trastuzumab anti-HER2 monoclonal antibody is still the benchmark treatment of HER2-positive breast tumors. However, FDA has categorized Trastuzumab as a category D drug for pregnant patients with breast cancer. This systemic review aims to synthesize all currently available data of trastuzumab administration during pregnancy and provide an updated view of the effect of trastuzumab on fetal and maternal outcome.

Methods

Eligible articles were identified by a search of MEDLINE bibliographic database and ClinicalTrials.gov for the period up to 01/09/2020; The algorithm consisted of a predefined combination of the words “breast”, “cancer”, “trastuzumab” and “pregnancy”. This study was performed in accordance with the PRISMA guidelines.

Results

A total of 28 eligible studies were identified (30 patients, 32 fetuses). In more than half of cases, trastuzumab was administered in the metastatic setting. The mean duration of trastuzumab administration during gestation was 15.7 weeks (SD: 10.8; median: 17.5; range: 1–32). Oligohydramnios or anhydramnios was the most common (58.1 %) adverse event reported in all cases. There was a statistically significant decrease in oligohydramnios/anhydramnios incidence in patients receiving trastuzumab only during the first trimester (P = 0.026, Fisher’s exact test). In 43.3% of cases a completely healthy neonate was born. 41.7 % of fetuses exposed to trastuzumab during the second and/or third trimester were born completely healthy versus 75.0% of fetuses exposed exclusively in the first trimester. All mothers were alive at a median follow-up of 47.0 months (ranging between 9 and 100 months). Of note, there were three cases (10%) of cardiotoxicity and decreased ejection fraction during pregnancy.

Conclusions

Overall, treatment with trastuzumab should be postponed until after delivery, otherwise pregnancy should be closely monitored.

Background

Pregnancy-associated breast cancer (PABC) is defined as any breast carcinoma diagnosed during pregnancy or during the first postpartum year [1]. It occurs in 1 to 3000 pregnancies while it has been estimated that up to 3% of breast cancers may be diagnosed in pregnant women [1, 2]. The incidence of PABC is also increasing due to advanced maternal age in today’s society. Median age of disease is 33 years (23–47 years), while there is a 2- to 3-fold decreased risk of PABC in women younger than 30 [1]. Interestingly enough, there is an increased incidence (54% – 80%) of estrogen receptor (ER) – negative tumors in pregnancy-related tumors [1]. This is explained by the interference of circulating steroids with the assays used to determine hormonal receptor status or by downregulation of the receptors as a negative feedback effect of estrogen and progesterone upon hormonal receptor expression. However, some studies demonstrated that the percentage of ER-positive pregnancy-associated breast cancers was not significantly different from that of non-pregnant age-matched patients [3, 4]. On the other hand, epidermal growth factor receptor 2-positive (HER2) tumors compose the 28–58% of PABC [3–5]. Although Elledge et al. found 7 out of 12 pregnant patients (58%) to be positive for HER2, Middleton et al. found no difference in the HER2 expression rate (28%) between pregnant and young nonpregnant women [3, 4]. Amant et al. reported an 31.8% incidence of HER2-positive tumors in pregnant women which is consistent with the results provided by Cardonick et al (27%) [6, 7]. Overall, the incidence of HER2-positive tumors was approximately equal to this of patients with breast cancer younger than 35 years old (39%), although it still remains a significant proportion [8].

Treatment of pregnant women with breast cancer represents a clinically challenging case in terms of maternal and fetal safety. Treatment of HER-2 positive PABC relies on the administration of trastuzumab anti-HER2 monoclonal antibody which remains the standard-of-care for all HER2-positive breast tumors. Trastuzumab binds HER2 on the C-terminal portion of domain IV and inhibits HER2 proteolytic cleavage and release of the extracellular domain in breast cancer cells [9]. Cells treated with trastuzumab undergo arrest during the G1 phase of the cell cycle leading to reduced proliferation. Trastuzumab exerts its antitumor activity through antibody-dependent cell-mediated cytotoxicity. However, our knowledge remains limited on the use and safety of trastuzumab during pregnancy because of its cytotoxic nature. Adverse effects of trastuzumab treatment include hematological and gastrointestinal disorders as well as cardiovascular effects that could potentially threaten pregnancy outcome.

In vivo studies conducted in cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg Herceptin revealed no evidence of harm to the fetus. However, trastuzumab transfer through the placenta has been observed during the early (days 20–50 of gestation) and late (days 120–150 of gestation) pregnancy period [10]. A warning about trastuzumab administration during pregnancy states that administration should be avoided during gestation unless it is mandatory for mother’s health. As for patients with breast cancer that become pregnant while receiving Trastuzumab or within seven months after the last dose, close monitoring is indispensable.

The aim of this systematic review is to provide an updated consensus regarding trastuzumab administration during pregnancy after synthesizing all existing data emerging from case reports and individual cases. We previously conducted a relevant systematic review assessing exposure to trastuzumab during...
pregnancy that was published in 2012 [11]. Since there is new emerging evidence from additional cases during all these years, an updated review of literature would contribute to revision of existing data and reconsideration of current practice.

Methods

This systematic review was performed in accordance with PRISMA guidelines [12]. Eligible articles were identified by a search of MEDLINE bibliographic database and ClinicalTrials.gov for the period up to September 2020. The search algorithm consisted of the following keywords: (breast AND (carcinoma OR carcinomas OR cancer OR cancers OR neoplasm OR neoplasms)) AND (pregnancy OR pregnant OR gestation) AND (trastuzumab OR herceptin). In order to maximize the amount of synthesized information, we meticulously examined the reference lists of the relevant reviews and articles retrieved for potentially eligible papers. Language restrictions were not applied. All studies that examined the efficacy and safety of trastuzumab during pregnancy were eligible for this systematic review, no matter of sample size. All cases where therapeutic or spontaneous abortion occurred were excluded. In addition, articles assessing trastuzumab administration before or after the gestation period were considered ineligible. Eligible studies required the administration of trastuzumab at some point during pregnancy even if treatment commenced prior to pregnancy initiation. Moreover, reviews were ineligible, while all prospective and retrospective studies, as well as case reports, were eligible for this systematic review. In cases where overlapping publications emerging from the same study were identified, the larger size study was included. Two independently working reviewers (FZ and AA) performed the selection of studies and any disagreements were resolved by team consensus.

Data extraction comprised the following: general information (first author's name, study year, journal, title), patient age at pregnancy, patient age at breast cancer diagnosis, histopathological diagnosis, clinical stage at times of disease and pregnancy diagnosis, treatment regimens administered during pregnancy, gestational age (GA) at trastuzumab initiation and withdrawal, gestational age at delivery, way of delivery and birth weight, adverse effects of chemotherapy during pregnancy, fetal and mother outcome. The quantitative synthesis of all the recruited articles was divided in two parts. First, the descriptive statistics regarding the age of breast cancer patients at pregnancy and at BC diagnosis, GA at delivery, GA at breast cancer diagnosis, GA at trastuzumab administration, stage of disease, duration of trastuzumab administration during pregnancy, birth weight of the neonate and way of delivery were calculated. Second, the association between the occurrence of oligohydramnios/anhydramnios and the following parameters was examined: (1) exposure to trastuzumab during the second/third trimester (vs. exclusive exposure during the first trimester), (2) duration of trastuzumab administration (in weeks). Statistical analysis was performed with SPSS 24.0 statistical software.

Results

Figure 1 presents the successive steps of the selection of eligible studies. Overall, the search algorithm recruited 66 articles. Two articles were reviews examining trastuzumab administration during pregnancy [11, 13], while 31 articles were deemed irrelevant. There were 5 additional cases where the patient declined chemotherapy during pregnancy and thus treatment with trastuzumab was withheld until after delivery [14–18]. These articles were not eligible for our study. In a case report by Berveiller et al trastuzumab treatment was not administered during gestation and thus was excluded [19]. One article by Azim H.A. et al reported all pregnancy events in patients enrolled in HERA trial during or after exposure to trastuzumab [20]. There is no detailed information regarding each one case and therefore the study was not included in our analysis. However, this important study is discussed extensively in the discussion section. Two additional articles were retrieved from the thorough search of the reference lists of eligible articles [21, 22]. From the three clinical trials identified in ClinicalTrials.gov only one study was considered eligible (MOTHER trial), although results are not yet published [23]. Taken as a whole, 28 articles were finally included in our systematic analysis (Table I).

Overall, 30 patients and 32 fetuses were exposed to trastuzumab during pregnancy [21, 22, 32–41, 24, 42–49, 25–31] Table I. Trastuzumab was administered during pregnancy as a monotherapy regimen in most cases [22, 25, 45–48, 27, 28, 31, 32, 34, 36, 42, 43] or in combination with pertuzumab [24], vinorelbine [26, 35], paclitaxel [21, 49], docetaxel [33, 39], docetaxel and carboplatin [44], taxotere [29, 30, 37], tamoxifen and lapatinib [40], docetaxel and cyclophosphamide [38], doxorubicin and cyclophosphamide and paclitaxel [41] and also concurrently with brain RT in one case [40]. The mean age of patients at pregnancy was 31.1 years (SD: 3.96; median: 31.5; range 23–38) [21, 22, 32–37, 39, 42–44, 24, 46–49, 25–31], while the mean age at breast cancer diagnosis was 29.9 years (SD: 4.21; median: 30.0; range: 22–38) [20, 21, 31–37, 39, 42, 43, 22, 44–46, 48, 49, 24–30]. In more than half of cases, trastuzumab was administered in the metastatic setting [21, 24, 40–42, 45, 47–49, 25–27, 31–33, 35, 39], while in the remaining cases it was administered in the adjuvant setting [22, 28, 44–46, 29, 30, 34–37, 42, 43].

Evaluating available histologies, invasive ductal carcinoma (IDC) was diagnosed in all known cases [21, 22, 33–37, 39, 41–44, 24, 46, 48, 25–27, 29–32], while in one case invasive lobular carcinoma (ILC) co-existed [32]. The tumor was estrogen receptor (ER) - positive in 23 % of the cases [25, 29, 30, 32, 37, 44] and progesterone receptor (PR) - positive in 20,8% of the cases [22, 25, 37, 44, 49]. Breast cancer was human epidermal growth factor receptor 2 (HER2) – positive in all included cases [21, 22, 32–41, 24, 42–49, 25–31].

The mean duration of trastuzumab administration during gestation was 15.7 weeks (SD: 10.8; median: 17.5; range: 1–32) [24, 25, 34–37, 39, 41–45, 26, 46–49, 27–33]. Overall, 23.3 % of patients were exposed to trastuzumab during all trimesters of pregnancy [25, 27, 30–32, 42, 43]. Importantly, 20.0 % of patients with breast cancer were exposed to trastuzumab exclusively during the first trimester [22, 34, 40, 45, 46] while trastuzumab was also administered during the second or third trimester in 80.0 % of the cases [21, 24, 33, 35–39, 41–44, 25, 45, 47–49, 26–32].

Oligohydramnios or anhydramnios was the most common (58.1 %) adverse event reported in all cases [22, 24, 35, 36, 41–44, 47, 49, 25–27, 29–33]. Only one of the six cases (16.7%) of trastuzumab exposure exclusively during the first trimester of gestation was complicated with oligohydramnios or anhydramnios. In contrast, seventeen out of 24 pregnancies (70.8 %) where trastuzumab was administered during the second or/third trimester were complicated with oligohydramnios or anhydramnios. The difference was statistically significant (P = 0.026, Fisher's exact test). The trend pointing to a positive association...
between the duration of trastuzumab treatment and the development of oligohydramnios or anhydramnios did not reach statistical significance (OR = 1.05, 95 % CI: 0.96–1.14, increment: one week, P = 0.316).

In 67.9 % of cases, delivery was performed via a cesarean section [21, 22, 40, 42–49, 25, 26, 29, 30, 32, 33, 37, 39], while in nine pregnancies (32.1 %) there was a vaginal delivery occurred [27, 28, 31, 34–36, 38, 41, 45]. The mean gestational age at delivery was 34.6 weeks (SD: 3.26; median: 35.4; range: 27–39) [22, 25, 35–44, 26, 45–49, 27–33], whereas the mean birth weight at delivery was 2,371 gr (SD: 771.2; median: 2,490; range: 1,015–3,820) [22, 25, 36–39, 42, 43, 45, 46, 48, 49, 26–28, 30–33, 35].

In thirteen cases (43.3 %), a completely healthy neonate (thirteen out of 32 neonates) was born [21, 25, 41, 45, 46, 26, 31, 33–37, 39]. In the remaining cases, neonates presented with: renal agenesis/hypoplasia (2 cases) [24, 47], mild transient tachypnoea (three cases) [27, 28, 48], respiratory distress syndrome (six cases) [22, 38, 42, 43, 45, 49], respiratory failure (two cases) [29, 32], renal failure (three cases) [29, 47, 49], transient respiratory failure and elevated creatinine (one case) [29], severe pulmonary hypoplasia (one case) [30], capillary leak syndrome and necrotizing enterocolitis (one case) [32], pulmonary hypertension and persistence of arterial canal (one case) [42], prematurity-related disorders (two cases) [44, 47], conductive hearing loss and mild hypotonia/hyperreflexia (one case) [45], bacterial sepsis (one case) [49] and cardiorespiratory arrest (one case) [22].

Of note, 41.7 % (10 out of 24) of fetuses exposed to trastuzumab during the second and/or third trimester were born completely healthy [21, 25, 41, 45, 46, 26, 31, 33–37, 39] in contrast with 75.0% of fetuses exposed exclusively in the first trimester [34, 45, 46]. However, the sizeable numerical statistical significance was not achieved (P = 0.311; Fisher's exact test). Once again, the trend pointing to a negative association between the duration of trastuzumab administration and the delivery of a completely healthy neonate did not reach statistical significance (OR = 0.921, 95 % CI: 0.85–1.00, P = 0.061).

As far as maternal outcome is concerned, all patients with breast cancer were alive at a median follow-up of 47.0 months (ranging between 9 and 100 months), while only two patients relapsed during follow-up according to existing data. It should be noted that there were three cases (10%) of cardiotoxicity and decreased ejection fraction during pregnancy [21, 28, 48].

Detailed information of all eligible studies is provided in Table 1.

Discussion

PABC is a rare but complex entity which demands multidisciplinary management. Amant et al. reported similar survival rates between pregnant patients with breast cancer and the matched non-pregnant population, despite the preceding belief that PABC is associated with a poor outcome [6]. The finding that survival rates of pregnant BC patients are comparable to those of nonpregnant is essential for mother counselling and optimization of PABC management. Breast cancer treatment during pregnancy does not jeopardize maternal prognosis.

Specific guidelines have been developed for PABC treatment. Surgery is not contraindicated during pregnancy and the type of surgery chosen should be based on usual criteria (mastectomy versus breast conserving surgery) [50]. The lack of wound complications in pregnant BC patients supports surgical management of PABC. Despite the concern of milk fistulae development and that of postoperative hematoma due to the hypervascularization of the breasts, there was no apparent increase in surgical complications between pregnant and nonpregnant patients [50].

Chemotherapy should be started after the first trimester and should be stopped 2–3 weeks prior to delivery for a chemotherapy-free interval. The teratogenicity of chemotherapy depends on time of exposure, dose administered and placental transfer. During the first two weeks of pregnancy, spontaneous abortion is more common after chemotherapy treatment, rather than teratogenic effects on the fetus. However, as organogenesis happens from 2nd to 8th gestational week, the embryo is more vulnerable to congenital malformations during this period. The risk of chemotherapy-induced congenital malformations during the 1st trimester is 20%, whereas it declines to 1–2% during the 2nd and 3rd trimester [51–53].

Regarding trastuzumab administration during pregnancy, we report that in approximately two third of cases oligohydramnios or anhydramnios were developed. The risk for intrauterine complications and oligohydramnios/anhydramnios development was minimal in pregnancies were fetal exposure to trastuzumab occurred exclusively during the first trimester (16.7% vs 70.8%; P = 0.026). In addition, a completely healthy neonate was born in 75% of cases that trastuzumab treatment affected only the first trimester in contrast with 41.7% of cases where the fetus was exposed during second and/or third trimester as well, although this association failed to reach statistical significance (P = 0.311; Fisher’s exact test). Our results are consistent with existing knowledge. Fetal exposure to trastuzumab is considered to be low during the first trimester while it gradually increases during the second half of gestation to reach mother levels at delivery [54]. Trastuzumab in an IgG1 monoclonal antibody with a molecular mass that does not permit transport across the placenta via simple diffusion. Active transport of these antibodies require binding to the Fc receptor of the syncytiotrophoblast, however Fc receptor is hardly detectable before the 14th week of gestation. Therefore, placental transfer of trastuzumab during the first trimester is minimal [54]. Antibody transfer to fetal endocrine organs has been reported from 4th to 6th week of development, although concentration was rather low [55]. Indeed, fetuses exposed to trastuzumab exclusively in the 1st trimester tend to be healthy at delivery. This observation is important for the correct consultation of women diagnosed with pregnancy while being on trastuzumab treatment.

US FDA has categorized Trastuzumab as a category D drug due to fetal complications [56]. No congenital malformations or teratogenic effects were reported in our review, apart from some prematurity-related problems [44, 47]. Indeed, animal studies did not reveal any teratogenic effects even at doses up to 25 times the recommended weekly human dose [56].

The most common fetal complication observed in our study was oligohydramnios or anhydramnios during second or third trimester. This is a result of EGFR receptor blockade in fetal renal epithelium by trastuzumab, where EGFR receptors are highly expressed [57]. Indeed, EGFR binding affinity in human fetal kidney between 6 and 11th GA week is 4–5 times greater than in normal renal tissue. This abundance of EGFR binding sites in fetal kidney falls rapidly in the
postnatal period to low levels observed in adult renal epithelium [57]. EGF increases DNA synthesis in human fetal kidney cells, while anti-EGFR antibody leads to the opposite result. Therefore, trastuzumab attenuates the important role of EGFR receptors in fetal renal cell proliferation and nephrogenesis resulting in the aforementioned cases of oligo-/anhydramnios, fetal renal failure [29, 47, 49] and renal agenesis [24, 47] reported in our study. In addition, even in the presence of normal kidneys, this receptor blockade leads to decreased urinary output and empty fetal bladder visualization. Another explanation of the trastuzumab-induced oligohydramnios is the decreased expression of vascular endothelial growth factor (VEGF). VEGF regulates amniotic fluid production and absorption via modulation of the rate of intramembranous absorption of amniotic fluid by both passive and nonpassive mechanisms [58]. Trastuzumab downregulates VEGF expression and may affect the amniotic fluid level.

Another possible mechanism of trastuzumab-mediated reduction of amniotic fluid may be through altering the function of aquaporins, a family of cell membrane water channels responsible for intramembranous fluid exchange in various tissues as proposed by Sekar and Stone [33]. More specifically, Aquaporin-3 is expressed in placenta, chorion, and amnion and regulation of its expression may contribute to amniotic fluid homeostasis [59]. Moreover, it was shown that Aquaporin-8 and Aquaporin-9 levels were significantly decreased in amnion and increased in placenta in fetuses suffering from oligohydramnios, further supporting the effect of aquaporins in amniotic fluid levels [60].

Whatever the mechanism, there is increased evidence that oligohydramnios induced by trastuzumab are reversible upon discontinuation of treatment [25, 27, 29]. The mean half-life elimination time for trastuzumab weekly schedule is 6 days (range: 1–32 days) and for the 3-week schedule 16 days (range: 11–23 days) [53]. This may indicate the time required for recovery of oligo-/anhydramnios after trastuzumab treatment. Moreover, it has been shown that the risk of oligo/anhydramnios is analogous to the duration of exposure to trastuzumab during pregnancy. Trastuzumab exposure for a relatively short period does not seem to substantially affect the pregnancy outcome. In contrast, a more prolonged period of exposure is associated with increased risk of fetal harm. In our study, there was a trend to a positive association between the duration of trastuzumab treatment and the development of oligohydramnios or anhydramnios, although not statistically significant (OR = 1.05, 95 % CI: 0.96–1.14, increment: one week, P = 0.316).

Berveiller et al reported one case of ectopic cervico-isthmic pregnancy while on trastuzumab treatment [19]. ErbB2 is required embryo implantation process [61]. On days 1–4 ErbB2 mRNA is expressed in uterine epithelial cells, while on days 6–8 the mRNA was accumulated in both implantation and interimplantation sites [61]. Given the crucial role of HER2 in embryo implantation process, it could be postulated that trastuzumab was responsible for the incidence of this ectopic pregnancy.

Azim et al explored the effect of previous or concurrent trastuzumab administration on pregnancy outcome based on data emerging from HERA trial, one of the largest Phase III trials evaluating trastuzumab treatment in the adjuvant setting [20]. Azim et al reported that 25% of pregnancies that occurred while on trastuzumab treatment resulted in spontaneous abortions. In consistence with our results, no congenital anomalies were reported in the study. However, there were also no cases of oligohydramnios or anhydramnios recorded in the study. The study demonstrated that women that conceived after a period of 3 months after trastuzumab cessation had an uneventful pregnancy, a finding that contributes significantly to the existing knowledge [20]. Of note, results from the very interesting MOTHER trial are anticipated [23].

Conclusions

Overall, medical oncologists encounter the dilemma of choosing between the optimal therapy for the mother and survival of the fetus. Considering that trastuzumab is equally effective when administered within six months from breast cancer diagnosis, it may be delayed until after delivery [62]. However, if trastuzumab administration is inevitable as in the case of metastatic disease, close monitoring of both mother and the fetus is required.

Abbreviations

PABC
pregnancy-associated breast cancer
HER2
human epidermal growth factor receptor 2
FDA
Food and Drug Administration
PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analyses
GA
Gestational Age
BC
breast cancer
AE
adverse event
IDC
invasive ductal carcinoma
ER
Estrogen receptor
PR
Progesterone receptor
ILC
invasive lobular carcinoma
DCIS
Ductal Carcinoma in Situ
LNs
Lymph Nodes
Gr
Grade
LVEF
Left ventricular ejection fraction
CHF
Congestive Heart Failure
EGFR
epidermal growth factor receptor
ErbB2
Erb-B2 Receptor Tyrosine Kinase 2
VEGF
vascular endothelial growth factor
RT
Radiation Therapy
IUGR
intrauterine growth restriction
RDS
respiratory distress syndrome
PROM
premature rupture of membranes
CPAP
Continuous positive airway pressure
SCN
Special Care Nursery
IgG1
immunoglobulin G1
CI
Confidence Interval
OR
Odds ratio
SD
Standard deviation
NR
Not reported

**Declarations**

**Ethics approval and consent to participate**

Not applicable

**Consent for publication**

Not applicable

**Availability of data and materials**

Data supporting our findings can be found in PubMed bibliographical database and ClinicalTrials.gov website. Links providing these data are listed below:

https://pubmed.ncbi.nlm.nih.gov/25853260/

https://www.wjpmr.com/home/article_abstract/1874

https://pubmed.ncbi.nlm.nih.gov/30110018/

https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0035-1559647

https://pubmed.ncbi.nlm.nih.gov/22381111/
Competing interests

MAD has received honoraria from participation in advisory boards from Amgen, Bristol-Myers-Squibb, Celgene, Janssen, Takeda. FZ has received honoraria for lectures and has served in an advisory role for Astra-Zeneca, Eli-Lilly, Merck, Novartis, Pfizer, and Roche. The remaining authors declare no conflict of interest.

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Author’s contributions

AA and CS searched the literature and wrote the first draft of the manuscript. KA conducted the statistical analysis. EZ and BG contributed to manuscript drafting. FZ and MAD critically revised the manuscript for important intellectual content. All the authors have read and approved the final manuscript. FZ is the corresponding author and guarantor of the review.

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| Author                        | Treatment during pregnancy | Pathological type, Grade | Stage at Pregnancy | Age at BC diagnosis | Age at pregnancy | GA at trastuzumab | GA at delivery | Delivery | Fetal outcome                  |
|-------------------------------|----------------------------|--------------------------|--------------------|---------------------|------------------|-------------------|----------------|----------|--------------------------------|
| Yildirim et al. 2018 (9)      | Trastuzumab, Pertuzumab    | IDC, ER: -, PR: -, HER2: + | IV (liver, lung bone) | 22                  | 23               | Prior to pregnancy – 20th GA week | Not delivered | -        | Elective abortion               |
| Rasenack et al. 2016 (10)     | Trastuzumab                | IDC, ER: -, PR: -, HER2: + | IV (retroperitoneal, supraclavicular, mediastinal, left hilar, upper abdominal LNs) | 25                  | 29               | Prior to pregnancy – 24th GA week, 29th GA week | 35th + 5 week | Cesarean section | Healthy at 3273g birth, Apgar 7/9/9 |
| Safadi et al. 2012 (11)       | Trastuzumab, Vinorelbine   | IDC scirrhous, ER: -, PR: -, HER2: + | IV (bone)          | 32                  | 32               | 30th GA week | 33rd + 5 week | Cesarean section | Healthy at 1990g birth, Apgar 8/9/9 |
| Mandrawa et al. 2011 (12)     | Trastuzumab                | IDC, ER: -, PR: -, HER2: + | IV (brain)         | 25                  | 28               | Prior to pregnancy – 27th GA week (9 doses in total, 3510 mg) | 37 weeks | Vaginal delivery | Healthy at 2.3060 g, Birth weight, Tachypnoea newborn |
| Roberts et al. 2010 (13)      | Trastuzumab                | IDC, ER: -, PR: -, HER2: + | T2N1M0             | 36                  | 36               | 4th GA week to 21st GA week | 37 weeks | Vaginal delivery | Healthy, 3200g weight, Mild Tachypnoea Newborn, ant 24 hours |
| Beale et al. 2009 (15)        | Trastuzumab, Tamoxifen     | IDC, ER: -, HER2: +, Gr3 | TxNxM0             | 28                  | 29               | Prior to pregnancy – 22nd week, already received 9 doses of trastuzumab | 31 + 6 weeks | Cesarean section | Twin A: 159g, 5/8/9, Intubation minutes for failure, Chor failure and disease, Dea respiratory of c months |
| Smith et al. 2009 (16)        | Trastuzumab, Tamoxifen, Goserelin | IDC, ER: +, HER2: +, Gr3 | TxNxM0             | 35                  | 35               | 7th GA week – 31st week | 37 weeks | Cesarean section | Severe pulmonary hypoplasia, aplectasis, 2 weight, 5 months  |
| Pant et al. 2008 (17)         | Trastuzumab                | IDC, Gr2/3, ER: -, PR: -, HER2: + | IV (lung)          | 30                  | 32               | Prior to pregnancy – 30th week, total dose 4200 mg | 32 + 1 week | Vaginal delivery | Healthy at 5 Normal Apgar 1810g birth |
| Witzel et al. 2008 (18)       | Trastuzumab                | IDC, ER: -, PR: -, HER2: +, Gr2 | IV (lung, brain)   | 29                  | 31               | Prior to pregnancy – 27th GA weeks (9 cycles in total, total dose 56 mg/kg) | 27 weeks | Cesarean section | Severe respiratory distress and capillary leak necrotizing e 1015 g birth, Apgar 8/7/6, to multiple o at 5 months |
| Sekar and Stone 2007 (19)     | Trastuzumab, Docetaxel     | IDC, ER: -, PR: -, HER2: +, Gr2 | IV (lung, brachial plexus) | 25                  | 28               | 23rd GA week – 27th GA week (docetaxel 380 mg total dose, 1385 mg trastuzumab total dose) | 36 + 2 weeks | Cesarean section | Healthy at 1960 g birth weight |
| Author                  | Treatment during pregnancy | Pathological type, Grade | Stage at Pregnancy | Age at BC diagnosis | Age at pregnancy | GA at trastuzumab | GA at delivery | Delivery       | Fetal outcome                          |
|------------------------|----------------------------|-------------------------|--------------------|---------------------|------------------|-------------------|----------------|----------------|----------------------------------------|
| Waterston and Graham (2006) (20) | Trastuzumab               | IDC, Gr2, ER: -, PR: -, HER2: + | II (TxN1M0)       | 30                  | 30               | Prior to pregnancy – 3rd GA week, total dose 523 mg during pregnancy | Term            | Vaginal delivery | Healthy at delivery                      |
| Fanale et al. 2005 (21) | Trastuzumab, Vinorelbine  | IDC, Gr3, ER: -, PR: -, HER2: + | IV (liver)         | 26                  | 26               | 27th GA week – 34th GA week | 34 + 5 weeks | Vaginal delivery | Healthy at delivery, Apgar score 6     |
| Watson et al. 2005 (22) | Trastuzumab               | IDC, ER: -, PR: -, HER2: + | T2N3M0             | 28                  | 28               | Prior to pregnancy – 20th GA week | 37.5 weeks | Vaginal delivery | Healthy at delivery, Birth weight 2960, Apgar score 6 |
| Berwart et al. (2020)   | Trastuzumab, Tamoxifen    | Left: IDC, ER: +, PR: +, HER2: + Right: IDC, ER: +, PR: +, HER2: - | T2N0M0             | 31                  | 32               | Prior to pregnancy – 16th GA week | 38 weeks | Cesarean section | Healthy at delivery, Birth weight 3820, Apgar score 6 |
| Safi et al. (2019) (24) | Trastuzumab, Docetaxel, Cyclophosphamide | NR | NR | NR | NR | 3d trimester | 36 weeks | Vaginal Delivery | Mild Respira 2380 g birth, Apgar score 8/8/9 |
| Aktoz et al. 2020 (25)  | Trastuzumab, Docetaxel    | IDC, ER: -, PR: -, HER2: + | IV (liver)         | 37                  | 37               | 22nd – 34th GA week (5 cycles) | 35 + 3 weeks | Cesarean section | Healthy at delivery, Birth weight 8/8/9 |
| Lambertini et al. 2019 (26) | Trastuzumab, Brain RT | Patient 3: Trastuzumab, Brain RT Patient 4: Trastuzumab, Lapatinib, Tamoxifen (12 patients) | NR | NR | NR | Median:33 (30.0-36.5) | Patient 1,2: Prior to pregnancy – 3 months prior to pregnancy Patient 3,4: 1st trimester | Patient 3: Cesarean section 3 Cesarean sections/1 vaginal delivery/1 missing | 7/12 (58.3%) abortion No spontaneous abortions Median birth 3145g (2880 Apgar 8–9/9) |
| Shlensky et al. 2017 (27) | Trastuzumab, Doxorubicin, Cyclophosphamide, Paclitaxel | IDC, ER: -, PR: -, HER2: + | IV | NR | NR | 15th GA week | 33 | Vaginal delivery | Healthy, Normal weight, 5min score > 7 |
| Andrade et al. 2016 (28) | Trastuzumab               | IDC, ER: -, PR: -, HER2: +, Gr2 | III (T3N2M0)      | 31                  | 32               | Prior to pregnancy – 27th GA week and then 28th -31st GA week (11 cycles in total, 4400 mg total dose) | 32 + 2 weeks | Cesarean section | Respiratory syndrome/P infection, 16 weight, Apgar 39, Pulmonary hypertension of the arteria Low creatinin (6.1 ml/min) 7 years old |
| Pianca et al. 2015 (29) | Trastuzumab               | IDC, ER: -, PR: -, HER2: +, Gr2 | T2N0M0             | 30                  | 31               | 2d trimester – 28th GA week (2 cycles in total) | 37th week | Cesarean section | 2735g birth, Apgar 4/8/0 delivery, Hea years old |
| Gottschalk et al 2011 (30) | Trastuzumab, Docetaxel, Carboplatin | IDC, ER: +, PR: +, HER2: +, Gr2 + DCIS | TxNxM0             | 38                  | 38               | 14th GA week – 20th GA week weekly (7 cycles, 4 mg/kg) | 33 + 2 weeks | Cesarean section | Dystrophic p neonate at d weight < 3rd Postpartum development function |
| Author                  | Treatment during pregnancy | Pathological type, Grade | Stage at Pregnancy | Age at BC diagnosis | Age at pregnancy | GA at trastuzumab | GA at delivery | Delivery            | Fetal outcome                  |
|------------------------|----------------------------|--------------------------|--------------------|---------------------|------------------|-------------------|-----------------|-------------------|-----------------------------|
| Azim et al. 2012 (31)  | Trastuzumab (16 patients)  | T NxM0/Non metastatic    | NR                 | NR                  | 32.5 (26–40)     | 40 (39–40)        | NR              | Healthy, Mean birth w (2,940–4,184) Apgar score (9–10) |
| Goodyer et al. 2009 (32)| Trastuzumab (2 patients)   | Patient 1: ER: -, PR: -, HER2: + | Patient 1: IV (pleural effusion) | NR                  | Patient 1: 30    | Patient 1: 29 weeks | Patient 1: Cesarean section | Patient 1: Re distress syndrome, hypertension, N hypertonia a hyperreflexia birth weight, years old with minimal high Achilles tend |
|                        |                            | Patient 2: ER: -, PR: -, HER2: + | Patient 2: III     | NR                  | Patient 2: 36    | Patient 2: 39 weeks | Patient 2: Vaginal Delivery |
|                        |                            |                          |                    |                     |                  |                  |                 |                   | Patient 2: He years old, 29 weight, Even gastroenteritis months |
| Azim et al 2009 (33)   | Trastuzumab                | IDC, ER: -, PR: -, HER2: +, Gr3 | II (T2N1M0)        | 29                  | 30               | Prior to pregnancy - 1st GA week (1 cycle, 6 mg/kg) | 39 weeks | Cesarean section | Healthy at 13550 g birth |
| Schoendorfer et Schaefer 2008 (34) | Trastuzumab | NR | IV (lung) | NR | 32 | Prior to pregnancy - 23rd GA week | 27 + 4 weeks | Cesarean section | Multiple preterm related problems, Dysplastic/h left kidney anomaly, IUGR, congestions, I months |
| Shrim et al 2007 (35)  | Trastuzumab                | IDC, ER: -, PR: -, HER2: +, Gr3 | IV (lung, brain)   | 28                  | 32               | Prior to pregnancy - 24th GA week (3200 mg total dose) | 37 weeks | Cesarean section | Healthy at 2600 g birth Apgar 9/10, tachyphnea of newborn, No |
| Berveiller et al 2008 (36) | Trastuzumab           | ER: -, PR: -, HER2: + | III (T2N2bM0)       | 43                  | 45               | Prior to pregnancy (14 months, 2 mg/kg) | - | - | Voluntary abortion |
| Bader et al 2007 (37)  | Trastuzumab, Paclitaxel   | ER: -, PR: +, HER2: +   | IV (bone mets, spinal cord compression) | 31                  | 38               | 25th – 28th GA week (2 cycles, 14 mg/kg total dose) | 32 + 1 weeks | Cesarean section | Bacterial sepsis transient renal RDS at delivery 1460 g birth Healthy at 3 months |
| Diakite et al. 2019 (41) | Trastuzumab               | IDC, Gr2, ER: -, PR: -, HER2: + | T4N2aMx            | 32                  | 33               | Prior to pregnancy - first trimester | 33d GA week | Cesarean section | Twin A: Respiratory distress, 145 weight, Deat |
| Gupta et al 2014 (42)  | Trastuzumab, Paclitaxel   | (Dexamethazone, RT)  | IDC, Gr3, ER: -, PR: -, HER2: + | IV (brain)          | 24               | Prior to pregnancy - 12th GA week & 3rd trimester – 6 weeks postpartum | 38 weeks | Cesarean section | Apgar 9/9, H months old Maternal LVE decreased, D progression mets/Leptomeningeval spread Death at 6 months postpartum |

NR: Not reported

Table I All eligible studies and case reports of trastuzumab administration during pregnancy in breast cancer patients.