Breast Cancer Res Treat (2013) 137:349–357
DOI 10.1007/s10549-012-2368-y

REVIEW

Trastuzumab administration during pregnancy: a systematic review and meta-analysis

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Received: 8 November 2012 / Accepted: 30 November 2012 / Published online: 15 December 2012

Abstract Landmark studies have established trastuzumab in the treatment of HER2-positive breast cancer. The present systematic review and meta-analysis aims to synthesize all available data, so as to evaluate the safety of trastuzumab during pregnancy. This study was performed in accordance with the PRISMA guidelines. All studies that examined the safety of trastuzumab administered during pregnancy, regardless of sample size, were considered eligible. Overall, 17 studies (18 pregnancies; 19 newborns) were included. In 55.6 % of cases, trastuzumab was administered in the metastatic setting. The mean duration of trastuzumab administration was 14.8 weeks. Occurrence of oligohydramnios/anhydramnios (O/A) was the most common (61.1 %) adverse event. 73.3 % of pregnancies exposed to trastuzumab during the second/third trimester were complicated with O/A; the respective rate of pregnancies exposed to trastuzumab exclusively during the first trimester was 0 % ($P = 0.043$). The mean GA at delivery was 33.8 weeks, and the mean weight of babies at delivery was 2,261 gr. In 52.6 % of cases, a healthy neonate was born. At the long-term evaluation, all children without problems at birth were healthy with a median follow-up of 9 months, while four out of nine children facing troubles at birth were dead within an interval ranging between birth and 5.25 months. All children exposed to trastuzumab in utero exclusively in the first trimester were completely healthy at birth. Trastuzumab should not be administered during pregnancy. However, for women who become accidentally pregnant during trastuzumab administration and wish to continue pregnancy, trastuzumab should be stopped and pregnancy could be allowed to continue.

Keywords Breast cancer · Pregnancy · Trastuzumab · Oligohydramnios

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Introduction

Breast cancer in pregnancy is relatively uncommon; it occurs in approximately one out of 3,000–10,000 pregnancies [1]. Pregnancy adds complexity to cancer treatment recommendations; this co-existence may be an important issue for the forthcoming years as more women delay childbirth [2]. In this context, it is important to note that according to the Surveillance Epidemiology and End Results (SEER) Database, approximately 12.1 % of breast cancer cases are diagnosed in women under the age of 44 [3].

Landmark studies have established trastuzumab as standard-of-care in the treatment of HER2-positive breast cancer patients; indeed, addition of trastuzumab to chemotherapy, either in the adjuvant or advanced-disease setting, significantly reduces the risk of relapse and improves overall survival (OS) [4–8]. However, the relatively recent incorporation of this monoclonal antibody into routine clinical practice limits our knowledge and understanding about the safety of this agent. It is worth noting that, according to ESMO and NCCN guidelines, the use of trastuzumab is contraindicated during pregnancy, given the apparent risk of oligo- and/or anhydramnios as

well as the unknown long-term sequelae on the fetus [1, 9, 10]. Moreover, unlike chemotherapy, trastuzumab does not induce amenorrhea [11]; therefore, accidental pregnancy during the administration of trastuzumab is possible if no adequate contraception is used. Accordingly, how should breast cancer patients who had become accidently pregnant during trastuzumab administration be handled and what recommendations can be given?

To our knowledge, this is the first systematic review and meta-analysis of the literature to synthesize all available data emerging from case reports and to evaluate the efficacy and safety of trastuzumab during pregnancy in breast cancer.

Search strategy, data abstraction and statistics

This systematic review was performed in accordance with the PRISMA guidelines [12]. Eligible articles were identified by a search of MEDLINE bibliographic database for the period up to September 19, 2012. The search strategy included 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 addition, we checked all the references of relevant reviews and eligible articles that our search retrieved, so as to identify potentially eligible papers. Language restrictions were not applied; two investigators (FZ and DC), working independently, searched the literature and extracted data from each eligible study.

All studies that examined the efficacy and safety of trastuzumab, when pregnant women were exposed to this agent during pregnancy and reported the relevant frequencies regardless of sample size, were considered eligible for this systematic review. All cases, where therapeutic abortion was scheduled or spontaneous abortion occurred, were excluded from this systematic review. Moreover, reviews were ineligible, while all prospective and retrospective studies, as well as case reports, were eligible for this systematic review. In instances where multiple (overlapping) publications stemming from the same study were identified, the larger size study was included, unless the reported outcomes were mutually exclusive.

For each of the eligible studies, the following data were collected: first author, year of publication, agents, number of patients treated, patient age at diagnosis, TNM stage (according to the latest i.e., 2010 classification [reviewed in (9)]), gestational age (GA) at diagnosis, pathologic type (ductal, lobular, etc.), grade, ER and PR status, c-erbB2 status, GA at first cycle of chemotherapy administration, GA at trastuzumab administration, total dose of trastuzumab administered during pregnancy, GA at delivery, way of delivery (cesarean section (CS), etc.), fetal outcome, weight at delivery, adverse events of chemotherapy during pregnancy, overall survival (OS) in months, progression free survival (PFS) in months.

Regarding the quantitative synthesis (meta-analysis) of the published articles, two sets of calculations were performed. First, the descriptive statistics were calculated regarding age at pregnancy, GA at diagnosis (either at breast cancer diagnosis during a known pregnancy or at the diagnosis of an unknown pregnancy in patients with known breast cancer), GA at chemotherapy initiation, duration of trastuzumab administration, total dose of trastuzumab during pregnancy, GA at delivery, weight of babies at delivery, and follow-up periods.

Second, the association between the occurrence of oligohydramnios/anhydramnios and the following parameters was examined (pregnancy-based analyses): (1) exposure to trastuzumab during the second/third trimester (vs. exclusive exposure during the first trimester), (2) duration of trastuzumab administration (in weeks), (3) administration protocol of trastuzumab (weekly vs. every three weeks) (4) stage of the disease (metastatic vs. non metastatic). Fisher's exact test was performed for cases 1, 3, and 4, and logistic regression was performed for case 2. The respective set of analyses was performed regarding the association of the aforementioned exposure parameters and death of the fetus (fetus-based analyses).

Statistical analysis was performed with STATA 11.1 statistical software (StataCorp, College Station, TX, USA).

Results

The search strategy retrieved 36 articles. Of these articles, 11 were irrelevant and eight were reviews. Checking all the references of relevant reviews and eligible articles, no other studies were included. Therefore, an overall of 17 articles (18 pregnancies; 19 newborns) were eligible for this systematic review [13–29] (Table 1). The aforementioned stages concerning the selection of studies are illustrated in detail in Fig. 1.

Trastuzumab has been administered during pregnancy as a single agent [15, 16, 18–20, 22, 24, 26, 27, 29] or in combination with vinorelbine [14, 25], paclitaxel [23], docetaxel [21], docetaxel and carboplatin [13], and tamoxifen [17, 28]. The mean age of breast cancer patients at pregnancy was 32.3 years (SD: 3.8; median: 32; range 27–38) [13–29]. In 55.6 % of cases, trastuzumab was administered in the metastatic setting [14–16, 18–23, 25], while in the remaining cases, it was administered in the adjuvant setting [13, 16, 17, 24, 26–29]. In all cases specified, invasive ductal carcinoma was diagnosed [13–15, 17, 19, 21, 22, 24–29], while in one case, infiltrative lobular carcinoma co-existed [20]. The tumor was

Table 1 Summary of studies describing the administration of trastuzumab during pregnancy for breast cancer

Author[a]	Treatment during pregnancy	Initial stage at diagnosis	Stage at pregnancy	Age at pregnancy (y)	GA at diagnosis (week)	GA at chemo (week)	GA at trastuzumab (week)	Total dose during pregnancy
Gottschalk et al. [13]	Docetaxel + carboplatin + trastuzumab weekly	TxNxM0	TxNxM0	38	11	14	14–17	8 mg/kg
El-Safadi et al. [14]	Vinorelbine + trastuzumab + ibandronate	IV	IV	32	29	30	30	6 mg/kg
Mandrawa et al. [15]	Trastuzumab	TxN0M0 3 years previously	IV	28	12	NA	Before conception- 27	3,510 mg
Goodyer et al. [16]	Trastuzumab	TxNxM0 3 years previously	IV	33	2nd trimester	NA	2nd trimester- 29	NR
Warraich et al. [28]	Trastuzumab + tamoxifen + goserelin	TxNxM0	TxNxM0	35	7	NA	7–31	3,675 mg
Roberts et al. [29]	Trastuzumab	T2N1M0	T2N1M0	36	17	NA	4–21	NR
Goodyer et al. [16]	Trastuzumab	III	III	38	6	NA	Before conception- 6	NR
Waterston et al. [24]	Trastuzumab	TxN1M0	TxN1M0	30	3	NA	Before conception-3	523 mg
Azim HA Jr et al. [27]	Trastuzumab	T2N1M0	T2N1M0	29	3	NA	Before conception-1	3 mg/kg
Beale et al. [17]	Trastuzumab + Tamoxifen	TxNxM0	TxNxM0	29	23	NA	Before conception- 22	56 mg/kg
Weber-Schoendorfer et al. [18]	Trastuzumab	NR	IV	32	NR	NA	Before conception- 23	NR
Pant et al. [19]	Trastuzumab	T1N1M0 48 months previously	IV	35	14	NA	Before conception- 30	4,200 mg
Witzel et al. [20]	Trastuzumab	T2NxM0 18 months previously	IV	34	23	NA	Before conception- 26	56 mg/kg
Sekar et al. [21]	Docetaxel + trastuzumab	T2N3M0, 1 year previously	IV	28	20	23	23–27	1,385 mg
Shrim et al. [22]	Trastuzumab	TxNxM0, 4 years previously	IV	32	5	NA	Before conception- 24	3,200 mg
Bader et al. [23]	46 Gy (cervical vertebra) with shielding → trastuzumab + paclitaxel	Stage I, 86 months previously	IV	38	17	25	25–28	14 mg/kg
Fanale et al. [25]	Vinorelbine + trastuzumab	T2N1M0, 14 months previously	IV	27	27	27	27–34	18 mg/kg
Watson et al. [26]	Trastuzumab	T2N3M0	T2N3M0	28	23	NA	Before conception- 20	3,480 mg

Author[a]	Pathological type, grade	ER, PR, c-erbB2 status	GA at delivery	Fetal outcome	Weight at delivery (gr)	Way of delivery	AE during pregnancy	OS mo	PFS mo
Gottschalk et al. [13]	IDC + DCIS	ER (+), PR (+), c-erbB2 (+)	33	Dystrophic premature neonate at birth.	N/A (< 3rd percentile)	CS	Anhydramnios, intrauterine growth restriction, fetal renal insufficiency	>5.9	>5.9
El-Safadi et al. [14]	IDC, grade 3	ER (−), PR (−), c-erbB2 (+)	33	Healthy at 12 months.	1,990	CS	Anhydramnios	>13	>13
Mandrawa et al. [15]	IDC	ER (−), PR (−), c-erbB2 (+)	37	Transient tachypnoea at birth. Healthy at 28 months.	3,060	Vaginal	Oligohydramnios	>52.25	2.75
Goodyer et al. [16]	NR	ER (−), PR (−), c-erbB2 (+)	29	Respiratory distress syndrome at birth. Minimal tightness of the left Achilles tendon at 36 months.	1,220	CS	None	>36	>2

Table 1 continued

Author[a]	Pathological type, grade	ER, PR, c-erbB2 status	GA at delivery	Fetal outcome	Weight at delivery (gr)	Way of delivery	AE during pregnancy	OS mo	PFS mo
Warraich et al. [28]	IDC, grade 3	ER (+), PR (+), c-erbB2 (+)	34	Dead within 40 min at birth.	NR	NR	Anhydramnios, fetal severe pulmonary hypoplasia and atelectasis.	>14.25	>14.25
Roberts et al. [29]	IDC, grade 3	ER (−), PR (−), c-erbB2 (+)	37	Mild transient tachypnoea.	3,200	Vaginal	Decline of cardiac ejection fraction (week 17-postdelivery).	>9.25	>9.25
Goodyer et al. [16]	NR	ER (−), PR (−), c-erbB2 (+)	39	Healthy at 24 months	2,940	Vaginal	1 of 2 viable fetal sacs	>24	>24
Waterston et al. [24]	IDC, grade 2	ER (−), PR (−), c-erbB2 (+)	NR	Healthy at birth.	NR	Vaginal	None	>9.25	>9.25
Azim HA Jr et al. [27]	IDC, grade 3	ER (−), PR (−), c-erbB2 (+)	39	Healthy at 14 months.	3,550	CS	None	>46	>46
Beale et al. [17]	IDC, grade 3	ER (+), c-erbB2 (+)	31	Twin A: chronic lung disease and renal failure. Dead from respiratory arrest at 0.25 months. Twin B: creatinine elevation and respiratory distress syndrome at birth. Healthy at 0.25 months.	1,590 and 1,705	CS	Oligohydramnios, non reassuring cardiotocography	>14	>14
Weber-Schoendorfer et al. [18]	NR	NR	27	Multiple prematurity related problems at birth. Non-optimal perfusion of the kidneys on the 3rd day. Dead at 4 months.	NR	CS	Oligohydramnios	>8.25	>8.25
Pant et al. [19]	IDC, grade 2/3	ER (−), PR (−), c-erbB2 (+)	32	Healthy at 60 months.	1,810	NR	Oligohydramnios	>129.5	NR
Witzel et al. [20]	IDC + ILC, grade 2	ER (+), PR (+), c-erbB2 (+)	27	Respiratory failure, strong capillary link syndrome, persisting infections, necrotizing enterocolitis. Dead at 5.25 months.	1,015	CS	Oligohydramnios and vaginal bleeding	>37.25	>1
Sekar et al. [21]	IDC, grade 2	ER (−), PR (−), c-erbB2 (+)	36	Healthy at birth.	2,230	CS	Anhydramnios	>16	>4
Shrim et al. [22]	IDC, grade 3	ER (−), PR (−), c-erbB2 (+)	37	Transient tachypnea at birth. Healthy at 2 months.	2,600	CS	Asymptomatic low ejection fraction (weeks 18, 24)	>100	>22
Bader et al. [23]	NR	ER (−), PR (+), c-erbB2 (+)	32	Signs of bacterial sepsis (hypotension, transient renal failure, respiratory failure, positive laboratory findings. Healthy at 3 months.	1,460	CS	Anhydramnios, fetal renal failure	>16.75	>7.75
Fanale et al. [25]	IDC, grade 3	ER (−), PR (−), c-erbB2 (+)	34	Healthy at 6 months.	2,580	Vaginal	None	>18.75	>3
Watson et al. [26]	IDC, grade 3	ER (−), PR (−), c-erbB2 (+)	37	Healthy at 6 months.	2,960	Vaginal	Anhydramnios and small fetal bladder (23 weeks)	>16.5	>16.5

NA not applicable, *NR* not reported

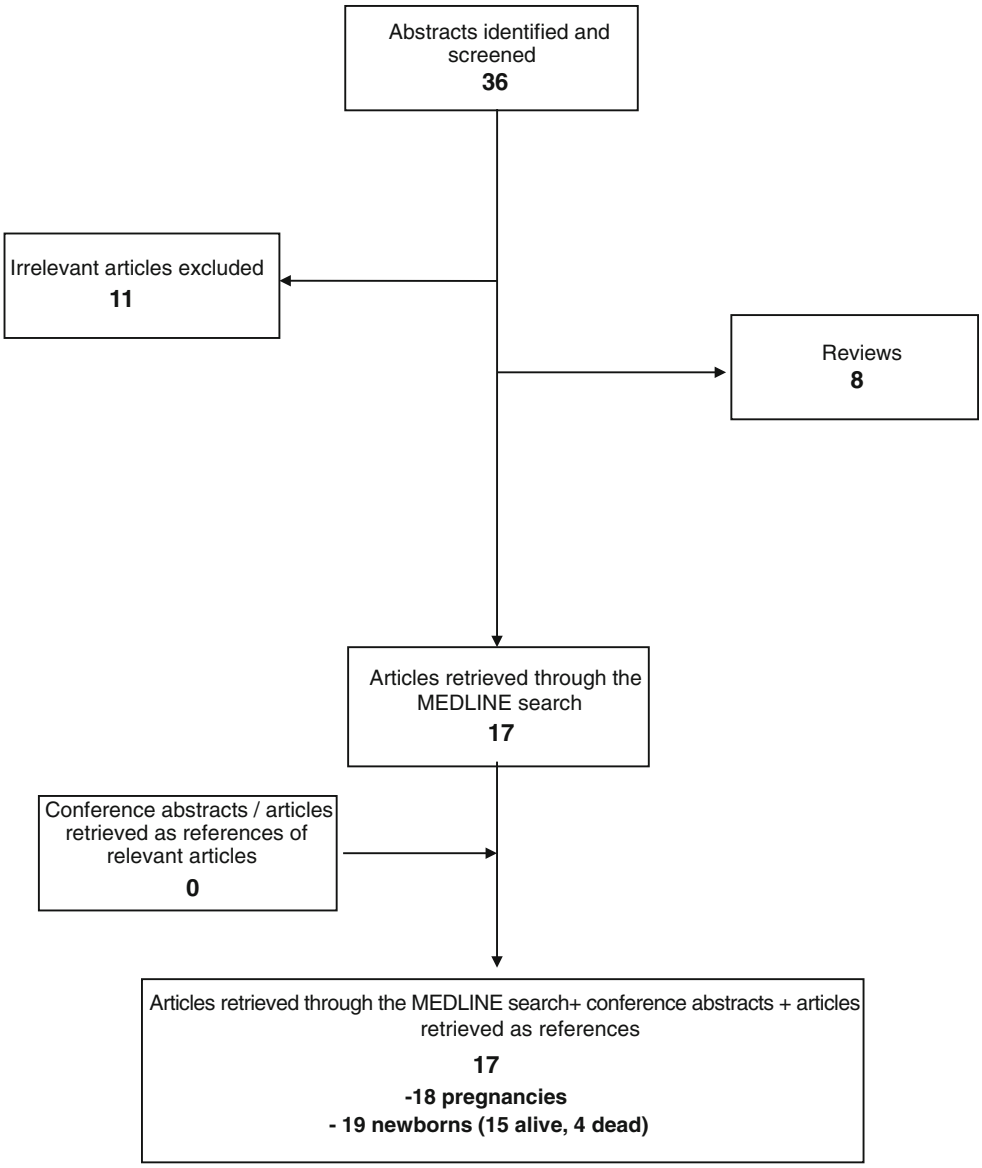

Fig. 1 Stages of the search strategy

hormone- receptor- positive in 29.4 % of the cases [13, 17, 20, 23, 28], while c-erbB2 was overexpressed or amplified in all of the cases [13–29]. The mean GA at diagnosis (at breast cancer diagnosis during a known pregnancy or at the diagnosis of an unknown pregnancy in patients with known breast cancer) was 15.0 weeks (SD: 8.7; median: 15.5; range: 3–29), while the mean GA at chemotherapy administration was 23.8 weeks (SD: 6.1; median: 25; range: 14–30) [13–29].

The mean duration of trastuzumab administration was 14.8 weeks (SD: 11.2; range: 1–31) [13–29]. Moreover, according to the data provided, the mean total dose of trastuzumab administered during pregnancy was 2,853 mg (SD: 1,355; median: 3,480; range: 523–4,200) [15, 19, 21, 22, 24, 26, 28]. 83.3 % of the pregnancies were exposed to trastuzumab during the second/third trimester [13–23, 25, 26, 28, 29], while 16.7 % of them had been exposed exclusively during the first trimester [16, 24, 27].

Oligohydramnios/anhydramnios were the most common (61.1 %) adverse events (AE) [13–15, 17–21, 23, 26, 28]. Eleven out of 15 pregnancies (73.3 %) exposed to trastuzumab during the second/third trimester were complicated with oligohydramnios/anhydramnios; the respective rate among pregnancies exposed to trastuzumab exclusively during the first trimester was 0 % (0/3). The difference was statistically significant ($P = 0.043$, Fisher's exact test) (Fig. 2). The trend pointing to a positive association between the duration of trastuzumab administration and the presence of oligohydramnios/anhydramnios did not reach statistical significance (OR = 1.07, 95 % CI: 0.97–1.19, increment: one week, $P = 0.175$).

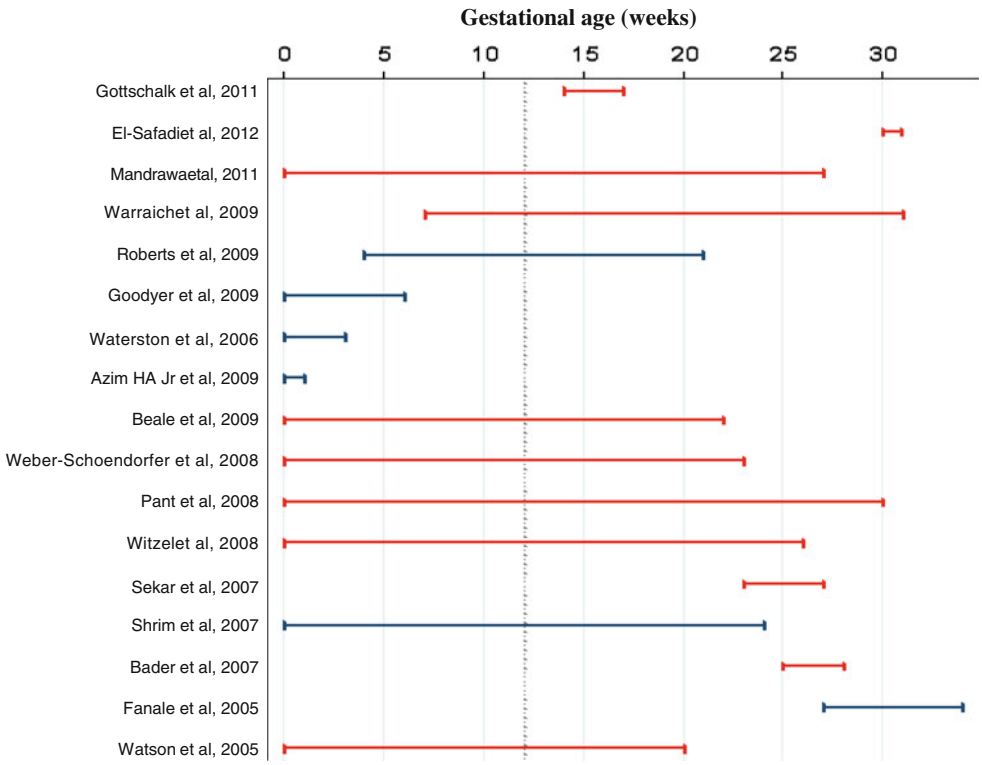

Fig. 2 Duration of trastuzumab administration (GA in weeks). Pregnancies free from oligohydramnios/anhydramnios are depicted blue, whereas pregnancies complicated with oligonydramnios/anhydramnios are depicted red. The grey dotted line presents the limit between the first and second/third trimesters. Although the study by Goodyer [16] was included in the analysis, one case (exposed during or after the second trimester) is not presented in the graph as the exact week of trastuzumab initiation was not disclosed. It should be stressed that each entry in the plot represents one person (pregnancy)

In 62.5 % of pregnancies, a CS was performed [13, 14, 16–18, 20–23, 27], while in six pregnancies (37.5 %), a vaginal delivery occurred [15, 16, 24–26, 29]. The mean GA at delivery was 33.8 weeks (SD: 3.8; median: 34; range: 27–39) [13–29], whereas the mean weight of babies at delivery was 2,261 gr (SD: 787; median: 2,230; range: 1,015–3,550) [13–29].

In slightly over half of cases (52.6 %), a healthy neonate (ten out of 19 neonates) was born [14–16, 19, 21, 22, 24–27]; while, in the remaining cases, the following conditions were noted: mild transient tachypnoea (one case) [29], infant respiratory distress syndrome (one case) [16], lung disease and renal failure (one case) [17], creatinine elevation and respiratory distress syndrome (one case) [17], multiple prematurity- related problems (two cases) [13, 18], respiratory failure, strong capillary link syndrome, persisting infections, and necrotizing enterocolitis (one case) [20], severe pulmonary hypoplasia and atelectasis (one case) [28], and signs of bacterial sepsis (one case) [23]. At the long-term evaluation, all children without problems at birth were healthy with a median follow-up of 9 months (range 0–60 months) [14–16, 19, 21, 22, 24–27], while four out of nine children facing troubles at birth were dead within an interval ranging between birth and 5.25 months [17, 18, 20, 28]. It is worth mentioning that all children exposed to trastuzumab in utero exclusively in the first trimester were completely healthy at birth [16, 24, 27]. In line with those data, 25 % (4/16) of fetuses exposed to trastuzumab during the second/third trimesters died, whereas no deaths were noted among children exposed exclusively during the first trimester; although the sizeable numerical statistical significance was not achieved ($P > 0.999$; Fisher's exact test). Once again, the trend pointing to a positive association between the duration of trastuzumab administration and death of the exposed fetus did not reach statistical significance (OR = 1.18, 95 % CI: 0.96–1.45, increment: one week, $P = 0.125$).

Oligohydramnios/anhydramnios was noted in 33.3 % (1/3) of pregnancies exposed to weekly administration of trastuzumab [13, 16, 25]; the respective percentage regarding administration at 3-week intervals was 76.9 % (10/13) [14, 15, 17–22, 24, 26–28], and the difference did not reach statistical significance ($P = 0.214$, Fisher's exact test). Similarly, the percentage of death among offsprings did not differ between the two administration protocols, although no deaths were noted in the weekly administration group (0/3 vs. 4/14, $P = 0.541$, Fisher's exact test). Stage of disease did not seem to affect the incidence of oligohydramnios/anhydramnios (the latter was noted in 4/8 pregnancies among non-metastatic cases vs. 7/10 pregnancies among metastatic cases; $P = 0.630$, Fisher's exact test). Similarly, the frequency of death in the offspring was not associated with stage (2/9 fetuses born by women with non-metastatic cancer died vs. 2/10 fetuses born by women with metastatic cancer; $P > 0.999$, Fisher's exact test).

With regard to the maternal outcome, according to the data provided, all breast cancer patients were alive at a median follow-

up of 16.6 months (ranging between 5.9 and 129.5 months), while only one patient relapsed during follow-up.

Detailed information of all eligible studies is provided in Table 1. The qualitative interpretation and the critically detailed evaluation of the individual eligible studies are provided below, in the discussion section.

Discussion

The optimal management of pregnant women with breast cancer is not well-established; the main concern is the effect of the drugs on the developing fetus and long-term implications in offspring born after in utero exposure to ant-cancer drugs. This meta-analysis, synthesizing systematically all available data, shows that there is a higher incidence of oligohydramnios and/or anhydramnios when trastuzumab is used beyond the first trimester.

The most striking observation of this systematic review pertaining to trastuzumab administration during pregnancy is that all children exposed to trastuzumab in utero exclusively during the first trimester of pregnancy were completely healthy without any evidence of congenital malformations [16, 24, 27]. Indeed, the occurrence of oligohydramnios/or anhydramnios was confined to pregnancies exposed during the second or third trimesters. These results are in great contrast to chemotherapy where the risk of inducing malformations secondary to exposure during this period is around 20 % [30–32]. This is possibly attributed to the poor trans-placental transfer of the monoclonal antibody early during pregnancy. In accordance with our finding, Pentsuk et al. [33] have shown that fetal exposure to trastuzumab is very low during the first trimester, and increases during the second half of gestation reaching a drug concentration at birth similar to that of the mother. This is attributed to the large molecular size of trastuzumab which requires active transport across the placental barrier via a specific receptor-mediated mechanism that is not active early in gestation [10, 34].

Moreover, another interesting observation of our meta-analysis pertains to the trend toward increased incidence of oligohydramnios and/or anhydramnios as duration of trastuzumab administration was longer, which however did not reach formal significance. In this context, it is worthwhile mentioning that the examination of trastuzumab total dose was not completely possible as only seven studies reported the necessary data. Oligohydramnios seems to be reversible in stopping the agent [13, 15, 17, 26] with good outcomes observed in the majority of pregnancies. Oligohydramnios and/or anhydramnios are severe complications, usually associated with abnormal fetal outcomes, such as intrauterine growth retardation, post-maturity syndrome, lung hypoplasia, soft tissue deformities, and fetal distress in labor [35, 36]. Although the mechanism of oligohydramnios or anhydramnios is not fully understood, one hypothesis relates to the role of epithelial growth factor (EGF) receptor in fetal kidney development [37]. Blocking EGF receptors with trastuzumab may impair kidney function, and therefore, decrease amniotic fluid production; amniotic fluid is made from fetal kidneys after month 4 and by maternal blood during the first trimester. So, if indeed trastuzumab blocks the EGFR on fetal kidneys, then it may well explain the increased risk of oligohydramnios in the second and third trimesters. Nevertheless, EGF and HER2 receptors are also expressed in high amounts in human placenta; however, data concerning their exact spatial and temporal localization particularly at the implantation site are sparse [38].

Despite the well known potential for inducing cardiotoxicity in adults, there has been no reported case of fetal cardiotoxicity; however, the limited follow-up period of children should be taken into consideration. It is obvious that confirmation of this observation from additional cases and longer follow-up periods are more than warranted.

According to the Food and Drug Administration, trastuzumab is classified as a pregnancy category B drug; studies in cynomolgus monkeys showed no harm to the fetus. However, these studies did reveal placental transfer of trastuzumab in monkeys (reviewed in [10]). Furthermore, in a murine knockout model, investigating deletion of the *Her-2/neu* gene was fatal to embryos at an early gestational age due to cardiac and neural dysfunction [39]. It is difficult, however, to extrapolate from such knockout studies to human embryos, as molecular process of trastuzumab action is different.

In the majority of the included cases, trastuzumab was not combined with anti-hormonal treatment, given that anti-hormonal therapy is forbidden during pregnancy [13–29]. Moreover, in some cases, trastuzumab was administered as monotherapy when pregnancy occurred [15, 16, 18–20, 22, 24, 26, 27, 29]; in these cases, trastuzumab had been previously given in combination with chemotherapy. Subsequently, the physicians had stopped chemotherapy but trastuzumab was continued (to complete one year in the adjuvant setting or until disease progression in the metastatic setting, given the patients' clinical benefit).

Our observations may be of great importance for women who become accidentally pregnant during trastuzumab administration and wish to continue the pregnancy; in this setting, trastuzumab should be stopped and pregnancy could be allowed to continue without promotion for abortion. However, it should be stressed that no definite conclusion can be drawn given the limited number of observations; clinicians should always advise women to use active contraception while on trastuzumab therapy and up to 6 months following completion of treatment.

As far as trastuzumab administration in the adjuvant setting during pregnancy is concerned, it should be noted

that there is no reason to expose the pregnant HER2-positive woman and the fetus to the potential hazard of the agent. Accumulating data outside pregnancy confirm that trastuzumab is very effective even after 6 months of adjuvant chemotherapy [5]; therefore, the monoclonal antibody could be safely administered after delivery. On the other hand, as far as metastatic HER2- positive breast cancer is concerned, trastuzumab should be avoided and chemotherapy should start from the second trimester. However, in selected cases where the agent may be urgently needed, it would be better to be administered for a short period with careful control of the amniotic fluid, the fetal growth, and the kidney function; in case of signs of oligohydramnios, the agent should be immediately discontinued. Moreover, according to Azim et al. [40], patients who became pregnant after a trastuzumab-free interval of more than 3 months appeared to have normal pregnancy courses and outcomes.

Regarding the limitations of this study, it should be underlined that this meta-analysis is limited to case reports/series, a fact that might bias our findings. More specifically, case series are largely not published unless there is an interesting outcome or adverse event that is surprising to the clinician; hence, a firm conclusion cannot be drawn. Indeed, the term "systematic review" is usually associated with larger sample sizes; nevertheless, in this study, case reports/series were included. Moreover, the adverse effects observed during or after pregnancy cannot be linked directly to trastuzumab in patients who were also exposed to other cytotoxic agents concomitantly [13, 14, 21, 23, 25]. These studies also could overrate the adverse events in second and third trimesters since most of the patients were exposed to cytotoxic agents during the same time period. Hence, it is hard to extrapolate data from these studies and come to a firm conclusion about the impact of trastuzumab on the pregnancy outcome. Therefore, expanding beyond the 18 pregnancies that were included in this meta-analysis, so as to look on a larger scale (medical record reviews and large database studies), might be useful and more than warranted.

In conclusion, it should be stressed that the choice of the best treatment seems limited and may well involve a host of psychologic, ethical, religious, and even legal considerations, as well as medical multidisciplinary decisions. Trastuzumab is related with a high incidence of oligohydramnios and/or anhydramnios when it is used beyond the first trimester. In general, the monoclonal antibody should not be administered during pregnancy; however, if the drug is urgently required, a careful control of amniotic fluid, fetal growth, and kidney function seems more than mandatory.

Acknowledgments FZ is receiving a research grant from HeSMO.

Conflict of interest The authors have declared no conflicts of interest.

References

1. Pentheroudakis G, Orecchia R, Hoekstra HJ et al (2010) Cancer, fertility and pregnancy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 21:v266–v273
2. Mir O, Berveiller P, Ropert S et al (2008) Emerging therapeutic options for breast cancer chemotherapy during pregnancy. Ann Oncol 19:607–613
3. Howlader N, Noone AM, Krapcho M, et al (2011) SEER cancer statistics review, 1975–2008. National Cancer Institute. Bethesda. http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site
4. Gianni L, Dafni U, Gelber RD et al (2011) Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. Lancet Oncol 12:236–244
5. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al (2005) Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 353:1659–1672
6. Untch M, Fasching PA, Konecny GE et al (2011) Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. J Clin Oncol 29:3351–3357
7. Valero V, Forbes J, Pegram MD et al (2011) Multicenter phase III randomized trial comparing docetaxel and trastuzumab with docetaxel, carboplatin, and trastuzumab as first-line chemotherapy for patients with HER2-gene-amplified metastatic breast cancer (BCIRG 007 study): two highly active therapeutic regimens. J Clin Oncol 29:149–156
8. Andersson M, Lidbrink E, Bjerre K et al (2011) Phase III randomized study comparing docetaxel plus trastuzumab with vinorelbine plus trastuzumab as first-line therapy of metastatic or locally advanced human epidermal growth factor receptor 2-positive breast cancer: the HERNATA study. J Clin Oncol 29:264–271
9. NCCN Clinical Practice Guidelines in Oncology (2012) Breast cancer, version 2.2012. www.nccn.com
10. Azim HA Jr, Azim H, Peccatori FA (2010) Treatment of cancer during pregnancy with monoclonal antibodies: a real challenge. Expert Rev Clin Immunol 6:821–826
11. Abusief ME, Missmer SA, Ginsburg ES et al (2010) The effects of paclitaxel, dose density, and trastuzumab on treatment-related amenorrhea in premenopausal women with breast cancer. Cancer 116:791–798
12. Liberati A, Altman DG, Tetzlaff J et al (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 62:e1–e34
13. Gottschalk I, Berg C, Harbeck N et al (2011) Fetal renal insufficiency following trastuzumab treatment for breast cancer in pregnancy: case report und review of the current literature. Breast Care (Basel) 6:475–478
14. El-Safadi S, Wuesten O, Muenstedt K (2012) Primary diagnosis of metastatic breast cancer in the third trimester of pregnancy: a case report and review of the literature. J Obstet Gynaecol Res 38:589–592
15. Mandrawa CL, Stewart J, Fabinyi GC et al (2011) A case study of trastuzumab treatment for metastatic breast cancer in pregnancy: fetal risks and management of cerebral metastases. Aust N Z J Obstet Gynaecol 51:372–376
16. Goodyer MJ, Ismail JR, O'Reilly SP et al (2009) Safety of trastuzumab (Herceptin) during pregnancy: two case reports. Cases J 2:9329

17. Beale JM, Tuohy J, McDowell SJ (2009) Herceptin (trastuzumab) therapy in a twin pregnancy with associated oligohydramnios. Am J Obstet Gynecol 201:e13–e14
18. Weber-Schoendorfer C, Schaefer C (2008) Trastuzumab exposure during pregnancy. Reprod Toxicol 25:390–391; author reply 392
19. Pant S, Landon MB, Blumenfeld M et al (2008) Treatment of breast cancer with trastuzumab during pregnancy. J Clin Oncol 26:1567–1569
20. Witzel ID, Müller V, Harps E et al (2008) Trastuzumab in pregnancy associated with poor fetal outcome. Ann Oncol 19: 191–192
21. Sekar R, Stone PR (2007) Trastuzumab use for metastatic breast cancer in pregnancy. Obstet Gynecol 110:507–510
22. Shrim A, Garcia-Bournissen F, Maxwell C et al (2007) Favorable pregnancy outcome following Trastuzumab (Herceptin) use during pregnancy- Case report and updated literature review. Reprod Toxicol 23:611–613
23. Bader AA, Schlembach D, Tamussino KF et al (2007) Anhydramnios associated with administration of trastuzumab and paclitaxel for metastatic breast cancer during pregnancy. Lancet Oncol 8:79–81
24. Waterston AM, Graham J (2006) Effect of adjuvant trastuzumab on pregnancy. J Clin Oncol 24:321–322
25. Fanale MA, Uyei AR, Theriault RL et al (2005) Treatment of metastatic breast cancer with trastuzumab and vinorelbine during pregnancy. Clin Breast Cancer 6:354–356
26. Watson WJ (2005) Herceptin (trastuzumab) therapy during pregnancy: association with reversible anhydramnios. Obstet Gynecol 105:642–643
27. Azim HA Jr, Peccatori FA, Liptrott SJ et al (2009) Breast cancer and pregnancy: how safe is trastuzumab? Nat Rev Clin Oncol 6:367–370
28. Warraich Q, Smith N (2009) Herceptin therapy in pregnancy: continuation of pregnancy in the presence of anhydramnios. J Obstet Gynaecol 29:147–148
29. Roberts NJ, Auld BJ (2010) Trastuzamab (Herceptin)-related cardiotoxicity in pregnancy. J R Soc Med 103:157–159
30. Azim HA Jr, Peccatori FA, Pavlidis N (2010) Treatment of the pregnant mother with cancer: a systematic review on the use of cytotoxic, endocrine, targeted agents and immunotherapy during pregnancy. Part I: solid tumors. Cancer Treat Rev 36:101–109
31. Zagouri F, Sergentanis TN, Chrysikos D et al (2012) Taxanes for ovarian cancer during pregnancy: a systematic review. Oncology 83:234–238
32. Zagouri F, Sergentanis TN, Chrysikos D et al (2012) Taxanes for breast cancer during pregnancy: a systematic review. Clin Breast Cancer [Epub Ahead of print]
33. Pentsuk N, van der Laan JW (2009) An interspecies comparison of placental antibody transfer: new insights into developmental toxicity testing of monoclonal antibodies. Birth Defects Res B Dev Reprod Toxicol 86:328–344
34. Malek A (2003) Ex vivo human placenta models: transport of immunoglobulin G and its subclasses. Vaccine 21:3362–3364
35. Kilpatrick SJ (1997) Therapeutic interventions for oligohydramnios: amnioinfusion and maternal hydration. Clin Obstet Gynecol 40:328–336
36. Vanderheyden T, Kumar S, Fisk NM (2003) Fetal renal impairment. Semin Neonatol 8:279–289
37. Goodyer PR, Cybulsky A, Goodyer C (1993) Expression of the epidermal growth factor receptor in fetal kidney. Pediatr Nephrol 7:612–615
38. Jokhi PP, King A, Loke YW (1994) Reciprocal expression of epidermal growth factor receptor (EGF-R) and c-erbB2 by non-invasive and invasive human trophoblast populations. Cytokine 6:433–442
39. Lee KF, Simon H, Chen H et al (1995) Requirement for neuregulin receptor erbB2 in neural and cardiac development. Nature 378:394–398
40. Azim HA Jr, Metzger-Filho O, de Azambuja E et al (2012) Pregnancy occurring during or following adjuvant trastuzumab in patients enrolled in the HERA trial (BIG 01–01). Breast Cancer Res Treat 133:387–391