

**THE FETAL TOXICITY OF TRASTUZUMAB (HERCEPTIN) DURING A TWIN PREGNANCY IN BREAST CANCER: ABOUT A CASE****\*Dr. K. Diakité, N. Bouzid, S. Zabroug, M. Darfaoui, H. Eddaoualline, N. Ismaili, I. Lalya A. Elomrani, R. Belbaraka and M. Kouchani**

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**ABSTRACT**

Breast cancer is the most common solid cancer during pregnancy. Management is a clinical problem because of the fetal risk in case there is an indication for multidrug therapy and the delay in management with a risk of progression during pregnancy. Trastuzumab remains indicated in patients expressing Trastuzumab receptors. The fetal toxicities reported to date are mainly oligohydramnios, respiratory disorders with spontaneous abortion risks. We report the case of a twin pregnancy patient who was exposed to trastuzumab as an adjuvant during her first trimester of pregnancy.

**KEYNOTES:** Pregnancy, Trastuzumab, breast cancer.**INTRODUCTION**

Breast cancer is the most common cancer in women during pregnancy. The most common histological type is the invasive ductal, which accounts for 70-80% of cases.<sup>[1]</sup> However, breast cancer can reach both sexes even if it is rare in men.

Since the 1980s, the treatment of breast cancers has revolutionized with the discovery of HER1 4 receptors, specifically the HER2 (Human epidermal growth factor receptor 2) receptor. Trastuzumab is a humanized agent, a monoclonal antibody that acts on the HER-2 receptor. This targeted therapy is overexpressed in about 20-30% of breast cancers.<sup>[2]</sup> Trastuzumab is prescribed as a neo-adjuvant, after surgery during radiation therapy or in metastatic situations. It is used in mono chemotherapy or in combination with other chemotherapy drugs, if indicated. It is administered every 3 weeks for 1 year in an adjuvant setting with good monitoring of the ventricular ejection fraction,<sup>[1]</sup> after all three cures. Since trastuzumab is not known to cause amenorrhea,<sup>[3]</sup> and given the increasing tendency to delay pregnancy later in life,<sup>[4]</sup> women of childbearing potential could become pregnant during or after exposure to trastuzumab. We report the case of a pregnant woman who received Trastuzumab during the first trimester of a twin pregnancy.

**CLINICAL CASE**

A pregnant woman consults for a right breast nodule, she is 32 years old and mother of 3 children. The

mammogram revealed a nodule located in the superoexternal quadrant of 1.5 cm classed as BIRADS 4. An excisional biopsy made revealing invasive ductal carcinoma of grade II SBR. The patient refused any treatment wishing to complete her pregnancy. She returns after delivery with a Mammography coupled to ultrasound of the right breast showing two suspicious lesions of the right breast BIRADS 5. The patient had a mastectomy and axillary dissection with the anatomopathological examination objectifying a piece of mastectomy of 315 grams and measuring 16 x12x3 cm covered with a skin flap of 13x9cm. The indurated nipple, infiltrating ductal carcinoma, SBR II with intraductal component of large intermediate (20%) associated with Paget's disease plus retro-mamellar extension, five (5) ganglia positive out of 19 removed. PT4N2aMx. Hormonal receptors were negative and the HER 3+ receptor negative. The extension assessment was normal. The therapeutic protocol was an adjuvant chemotherapy consisting of 3 cures of fluorouracil epirubicin and cyclophosphamide plus three (3) cures of docetaxel Trastuzumab followed by Trastuzumab every 3 weeks for a total duration of 18 cycles. She had her first cure of Trastuzumab at a dose of 460mg C2-C18: 350mg. Also, a radiotherapy on the wall at a dose of 50 Gy with axillary and supraclavicular irradiation at the dose of 46 Gy.

At the sixteenth cure of Trastuzumab, the patient reported a delay in the menstrual cycle.

A pelvic ultrasound showed a twin pregnancy of 10 weeks of amenorrhea.

She consults at four months of the last course of trastuzumab with an abdominopelvic ultrasound showing a twin pregnancy of 19 weeks of amenorrhea + 2 days.

Childbirth was caused at 33 weeks of amenorrhea for fetal distress and oligoamnios, the two infants of different sex were born of 1,45kg for the boy and 1,55 for the girl. They remained in the service of neonatal resuscitation for respiratory assistance. The Boy died at ten (10) days for respiratory failure and the girl at 40 days by cardiopulmonary arrest.

## DISCUSSION

Few studies have addressed the issue of fetal toxicities in pregnant patients exposed to Trastuzumab during breast cancer management.

Beale and al,<sup>[5]</sup> reported on 19 pregnancies including 13 exposed from the first trimester and 6 between the second and third trimester. Trastuzumab was administered in single chemotherapy on 11 pregnancies and 8 in poly chemotherapy (including 2 cases associated with hormone therapy). In this study, only one pregnancy termination was performed during the first trimester due to an ectopic pregnancy. No minor congenital malformations have been reported.

Balder and al,<sup>[6]</sup> also reported a case of transient renal failure in an infant with trastuzumab in combination with paclitaxel.

Cases of respiratory and renal insufficiency have been reported in a few infants. Weber and al.<sup>[7]</sup> A case of death of a newborn by multiple organ failure,<sup>[8]</sup> Incidents like oligohydramnios and anhydramnios during the second and third trimester.<sup>[7,8]</sup>

After these various reported cases comes the HERA trial,<sup>[9]</sup> which is a large randomized phase III clinical trial in which patients with HER2-positive breast cancer were randomized to receive 1 or 2 years of trastuzumab. This study included 3 groups formed by patients who contracted pregnancy during and over.

At 3 months after exposure to trastuzumab, another group at 3 months after the last cure of Trastuzumab and the third group of patients not exposed to trastuzumab. It should be noted that the administration of trastuzumab was stopped in group 1 to continue the pregnancy. In this trial, spontaneous abortion was common in Group 1 patients, as in the other groups, there were no cases of congenital abnormality or oligohydramnios.

## CONCLUSION

The effect of trastuzumab on pregnancy in patients treated for breast cancer is still incomplete. The main

effects most documented are spontaneous abortion, and oligohydramnios. We reported the case of a twin pregnancy exposed to trastuzumab whose 2 infants died of cardiorespiratory insufficiency.

Considering the foregoing, further trials will be needed to shed some light on the mechanism of action of trastuzumab on the fetus.

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