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Case Report

Systematic Review Concerning the Care of Breast Cancer during Pregnancy with a Case Report of Breast Cancer during Triple Gestation

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Abstract

Introduction: Cancer affects 1 woman over 1000 during the gestation of which the most common is the breast cancer. Its management is not yet well defined. The study aim is to carry out a systematic review to help achieve the most optimal management. This literature review will be accompanied by a case report concerning a pregnant with a triple fetus complicated by pre-eclampsia and breast cancer at 28 weeks.

Methods: We performed a systematic review. The potentially eligible studies were identified by searching the United States National Library of Medicine (PubMed) electronic database, from January 2001 through December 2020, using combinations of the following keywords: (breast cancer) AND (pregnancy) more or less (pre-eclampsia). For pre-eclampsia, the research spanned from January 2010 to December 2020. The Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) were used. We examined the retrieved articles and discarded duplicated ones. We also excluded unrelated studies through careful browsing of titles and abstracts of all retrieved publications; studies with an inadequate design, case reports with a low number of participants, and publications in languages other than English were removed.

Results: 5018 articles were found concerning breast cancer during pregnancy and 43 on pre-eclampsia and breast cancer, only 54 were kept.

Conclusion: Diagnostic and extension assessment of breast cancer during pregnancy is like without pregnancy, the treatment is modulated according to gestational age. The surgery is possible during all trimester. Chemotherapy is prohibited during the first trimester. The target therapy and hormonotherapy are not possible during the pregnancy.

Keywords: Breast Cancer; IUGR; Neoadjuvant Chemotherapy; Surgery; Triple Gestation; Triple Negative

Abbreviation: IVF: In Vitro Fertilization**;** HELLP Syndrome: Haemolysis, Elevated Liver Enzyme, Low Platelets Syndrome; SBR: Scarff-Bloom ET Richardson; TNS: Non-Specific Infiltrating Carcinoma**;** IP: Proliferation Index**;** DCIS: Ductal Carcinoma in Situ; IUGR: Intrauterine Growth Restriction; ACR: American College of Radiology; AC: Doxorubicin and Cyclophosphamide; T: Triplet

Introduction

Pregnancy woman cancer affects 1 gestation over 1000, amounting to 700 to 800 women every year. Despites, the breast cancer is the first cancer in pregnancy women, followed by cervical cancer, and the lymphoma [1-3]. The breast cancer prevalence increases, and this can be explained, inter alia, by late pregnancy over 30 years old [4]. The cancer prognosis at equal age and stage is the same than outside pregnancy [1,3,5]. But with the delayed diagnosis due to breast physiological modifications, the pregnancy patient survival is lower than in the overall breast cancer [3,4,6,7]. The medical care is difficult, low standardization, and gestational age and pregnancy progress dependent. Many prospective observational studies are showing the risks and benefits of breast cancer treatment during pregnancy, but there have been very few controlled trials performed. Furthermore, few studies examine multiple pregnancies, specifically triple pregnancies. Lastly, triple negative breast cancers during pregnancy affect 30% of cases [8] and are little studied. We used reviews on breast cancer during the pregnancy complicated pre-eclampsia to enable us to best treat our patient from breast cancer discovery to the treatment during a multiple (triple) pregnancy complicated by a pre-eclampsia in the United States National Library of Medicine (PubMed) electronic database, and accompanied by case report.

Methods

First, we relate our case report. Then, we performed a systematic review to conduct this investigation. Potentially eligible studies were identified by searching the United States National Library of Medicine (PubMed) electronic database, from January 2001 through December 2020, using combinations of the following keywords: breast cancer, pregnancy more or less pre-eclampsia. For pre-eclampsia, the research spanned from January 2010 to December 2020. The Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) were used (Moher et al., 2009). Screening. We examined the retrieved all articles and discarded duplicated ones. We selected articles that help us take patient's care. Additionally, we also excluded unrelated studies through careful browsing of titles and abstracts of all retrieved publications. Additionally, existing review articles for breast cancer during pregnancy were also screened for papers that could have been missed in the search strategy. Exclusion criteria:

- Publications in languages other than English.
- Studies with an inadequate design,
- Case reports with a low number of patients except for lack of something better
- Studies that do not allow us to improve patient care.

We rate the study design according to their methodology using the Oxfords Centre for Evidence-based Medicine's Level of Evidence and Grades of Recommendation (level 1, 2, 3, 4, 5) , with level 1 being based on small, retrospective studies. The quality of each study was assessed according to the study type and the number of participating subjects. Regarding supportive care, we expended the search with hyperemesis gravidum studies or renal failure. Concerning the pre-eclampsia, we expended the research also.

Results

Case report

This case report concerns a 46-years-old woman with a BMI at 30 kg/m2. She is pregnant with multiples (triplets). She does not have an oncological medical history in her family. In January 2020, the patient profited of an IVF with an oocyte donation in Liban. Following this IVF, she got a triple pregnancy, triamniotic, trichorial. At 28 week's gestation, she has been hospitalized in high-risk pregnancy unit, for a premature delivery risk and suspicion of pre-eclampsia. Regarding the foetuses, T1 and T2 had a standard weight on ultrasound at 28 week's gestation. Yet, T3 had a probable vascular origin IUGR with an estimated fetal weight lower than the first percentile. Indeed, T3 had initially a brain sparing effect on Doppler analysis. During hospitalization, she mentioned right breast mass, increasing since the 5th month of pregnancy. Breast cancer screening by mammography results showed an ACR 5 mass of 42 mm at the upper quadrants union, and a second of 10mm in upper outer quadrant with a mildly suspect axillary lymph node. Biopsies by ultrasounds revealed a TNS SBR 3 invasive carcinoma, triple negative, IP 60%, without DCIS, without vascular embolus and peri-nervous sheathing (Figure 2). An extension by PET/CT scan showed none remotely injuries but a not specific mildly hyperactive metabolic right axillary lymph node (Figure 3). Axillary lymph node biopsies were negative. After the patient's pre-eclampsia was deemed stable, a multidisciplinary meeting was had with the French national reference centre (Thonon hospital's RCP) for pregnancy and cancer oncologists, and a decision was made to treat the patient with neo-adjuvant chemotherapy 4 AC (Doxorubicin 50 mg/m2 and Cyclophosphamide 500 mg/m2) every 3 weeks and then 4 courses of Docetaxel. The first chemotherapy agent (AC) was done at 30 week's gestation. The supportive care treatment done was antiemetic aimed with Ondansetron 8 mg on morning and evening, combined with Prednisolone 50 mg at D1 and D2. The chemotherapy was well tolerated. However, a new hospitalization was necessary for a monitoring in front of non-controlled high blood pressure combined with a thrombocytopenia (164 G/L) and an anaemia (haemoglobin at 103 g/L). However, the proteinuria progressive increase. The decision of a caesarean in emergency for a HELLP syndrome at 34 week's gestation + 4 days has been taken. Therefore, the patient delivered 15 days after the first chemotherapy cure. At the fetal level, T1, T3 have a small weight for gestational

age. However, T2 has a normal weight for gestational age. They did not have cytopenia. After a stay of neonatal intensive care, they are well. Concerning J3, he has significant postnatal complications with moderate bronchopulmonary dysplasia, and a little inter-atrial communication both requiring a single monitoring. Breast MRI, after three cures of AC, showed a clear decrease of the mass 25x19x21 mm, and a disappearance of the second mass (Figure 4). In front of this good treatment respond, we decided to implement four Docetaxel cures before surgery (broad lumpectomy combined with an oncoplastic surgery and sentinel node biopsy) which are found in anatomopathological of three residual focus, one of 14 mm of SBR 3 and 2 infracentimetric, IP 10 %, some DCIS, and the excision's shores are healthy but the lower shore is less than 1 mm from the DCIS lesions. Sentinel nodes are negatives. To finish, radiotherapy was performed with the following modalities: irradiation of 50 Gy in 25 fractions with boost on surgical tumorectomy.

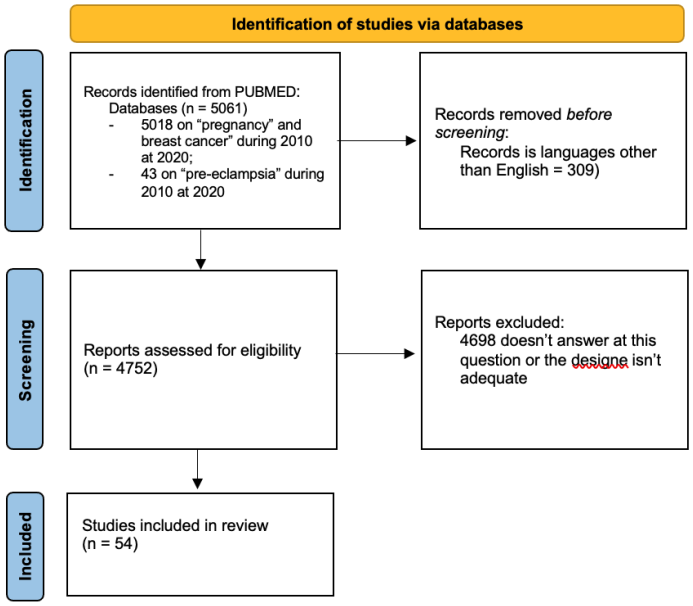

Figure 1: Search strategy flowchart for the inclusion and exclusion of studies concerning "breast cancer and pregnancy" and/or "pre-eclampsia.

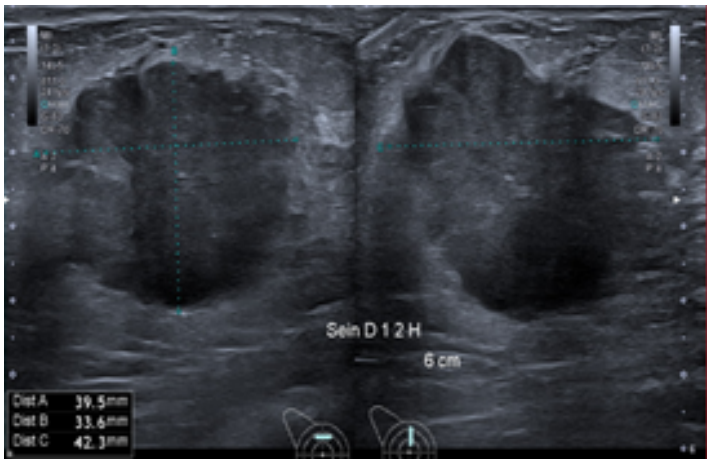

Figure 2: Mammary mass ultrasounds.

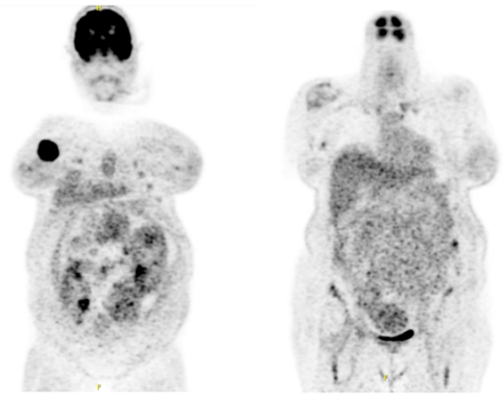

Figure 3: Hyper metabolic mammary mass and metabolic axillary lymph node PET/CT scan.

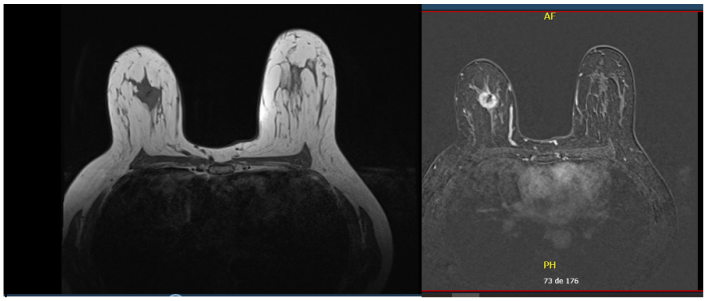

Figure 4: Breast MRI post AC - T2 and FLAIR.

Literature Review

We took multiple studies like 4 meta-analysis, 21 literature reviews, more of 5336 patients followed in cohort, 3 pre-clinical studies, 1 mathematic model, 2 cases reports, 2 expert advices and 1 clinical trial. Review was made, on breast cancer and pregnancy more or less pre-eclampsia (Figure 1). A number of articles were found and were excluded because they are not written in English, or do not answer the question or the design was not adequate. The selection was based on the title, the abstract. The quality of the studies, if we take the 4 groups described by the Oxfords Centre for Evidence-based Medicine's Level of Evidence and Grades of Recommendation, goes from level 5 to level 1, even if that of level 1 is biased because it is based on small, retrospective studies. The rate of breast cancer occurrences increases during pregnancy [1,3]. Features of breast cancer during gestation typically present in middle-aged women from 24-43 years-old and present with a localized grade in 80% to 97% of the patients [2,7-12]. Furthermore, breast cancer has been found to be a hormone-sensitive cancer in 50% to 60% of the patients, a HER2 positive cancer in 30% to 35% of the patients, and triple negative in 30% of the patients. The diagnosis typically occurs around the 19th week of gestation [2,7,8,10-13].

Diagnostic assessment

This review shows there was no fetal or maternal risk regarding the diagnostic assessment tools of MRI, mammography, or breast ultrasound [3,6,7,14-16]. However, the mammography can be difficult given the density of the breasts during pregnancy [11]. Concerning the PET/CT scan, there is a theatrical risk, especially over the long term with a higher leukaemia risk. But the last American Radiology Academic Society recommendations are comforting on this point like other study [14,17]. The most recent publications of Amant et al. reveals that some MRI modalities would do as well as PET scans for lymph node evaluation and presence of secondary locations [15]. CA 15.3 is not used as a biomarker of breast cancer during gestation as it fluctuates during pregnancy [1].

Termination of Pregnancy or Induction

Medically induced abortion is presented as a treatment option during the first trimester of pregnancy. It uniquely depends on the patient's willingness and gestational age. After 36 week's gestation, the delivery is artificially induced. Before 36 week's gestation, the consequences of prematurity are greater than that of neoadjuvant chemotherapy [1].

Surgery

Regarding surgery, it's possible at every trimester of the pregnancy [1,11,18,19]. In many cases, the surgery enforces a sentinel lymph node achievement, which, it is necessary even during pregnancy with a loss of luck if not carried out [10]. According to 2 literature reviews and 485 patients followed in cohort, the sentinel node technic is done with a radioactive tracer and not with patent blue because a theoretical risk of allergic response is high, no other complication was found despite the fact that it passes the blood-placental barrier [3,12,20-23] The surgery risks are mainly found during the first gestation trimester with on/off effect on the pregnancy [1,18].

Chemotherapy

Many oncological treatments are suitable during the pregnancy according to 4325 patients followed in cohort, 13 reviews. Under this literature, the Anthracyclines and the Cyclophosphamide are interesting with a positive benefit/risk ratio [1,24]. These chemotherapies have low molecular weight, are lipophilic, so could get through placental barrier [15,18,25]. Besides, the pharmacokinetics of cytotoxic products changes during the pregnancy [3,11,26]. Chemotherapies are recommended from 14 until 36 week's gestation [3,15]. The found adverse effects of the Anthracyclines are various according to the pregnancy age. During the first trimester, an ON/OFF effect is observed [24]. The literature shows during the third trimester at the fetal level a pancytopenia risk when the chemotherapy is given in the 2 weeks before the delivery, and perinatal infectious complications requiring a neutropenia treatment at the birth [3,27]. However, to date the literature doesn't find fetal cardiac toxicity [1,3, 24,28]. Concerning the Anthracycline choice and the association with another chemotherapy molecule, the benefit/risk ratio would be the same for the Doxorubicin and the Epirubicine [1,24]. However, the toxicity would be higher regarding the Daunorubicine and the Idarubicine [27]. The Association by FAC or FEC (Doxorubicin or Epirubicine, and Cyclophosphamide) are usable during the second and the third trimester with a lower risk for the fetus and the mother [1,2,18,29]. In the literature, the Cyclophosphamide is mainly used in the breast cancer during pregnancy. Its toxicity is increased during the first semester [1,2]. The platinum chemotherapy use option is raised. The literature shows with this use IUGR, cytopenia but no fetal malformation with a dose from 25 to 75 mg/m2 [2,30]. This can be explained by the fact that a low proportion is going in the blood fetal flow [25]. Carboplatin could have a lower toxicity than Cisplatin concerning a risk of ototoxicity [3,15]. In view of this risk, Amant et al. recommends, if using platinum salt during pregnancy, to do an ORL follow-up [15]. Docetaxel is well tolerated during pregnancy. To this day, no fetal malformation and only few cytopenia is found, but less frequent than with other chemotherapy families [1]. This would be explained by a drug under-dosing due to the fear to use chemotherapy products during the pregnancy [31], and especially by a distributing volume physiological increase during the pregnancy [26]. Nevertheless, others studies find a IUGR risk and an entry increase in neonatology at the birth with this drug [1,2,31,32]. Besides, the toxicity profile

would be better with weekly treatment cycle at the mother's level [33]. Loibl et al. note a preference to Paclitaxel over Docetaxel due to the decreased likelihood of placental barrier crossing [3]. In general, the National Toxicology Program reports an increase in malformations with a prevalence of 14% if chemotherapy is used in the first trimester, while from the 2nd trimester the prevalence of malformation is 3%, which is not higher than in the general American population, like other studies [3,11,13,15,18,28]. This would be confirmed on imaging (MRI), with brain areas identical to the general population at 18 months [34]. On the long-term, the literature shows only few examples of chemotherapy adverse effects [1]. In some cases, it wouldn't have a difference on the intellectual development between children were born at a same gestational age [11,28,35-38]. The intellectual capability leading factor is the prematurity [35,37,38]. However, the prematurity is often inducted with these pathologies, due to the fear of chemotherapy-incurred risks for the fetus. All of these points lead to the hypothesis that it would be better to leave the gestation as it is with the chemotherapy, instead of stopping it [2,35,37]. However, according the Amant et al.'s, a higher diastolic pressure and a lower velocity in interventricular septal is found 36 months after the birth during a cardiovascular examination in children having received antenatal chemotherapy with for the majority, the Anthracycline. However, with these observations, they cannot conclude to a pathologic cardiac ultrasound [35]. In the studied case, one of the foetuses had an IUGR, but prior to the chemotherapy. Besides, the only chemotherapy cure don't inflect the growth path of one of the fetuses. This is certainly due to the delivery speed after the first chemotherapy cure. The chemotherapy during the first trimester of gestation increases the fetal complications which generally are miscarriages and birth defects [1,3,11,15,18,38,39]. The IUGR, premature membrane (chorioamnionitis) breaking, and prematurity occurrence are increased and especially inducted by the chemotherapy [1,2,3,30,35,40].

Hormonotherapy

The literature shows a teratogenic and fetotoxic risk with the use of hormonotherapy, requiring a 2-month washout period before delivery, most notably seen with Tamoxifen [11,18,19,41-43].

Targeted therapy

The targeted therapy is no recommended during the pregnancy. There are few studies on this subject because the observed side effects during its use are important throughout a pregnancy. The Bevacizumab would increase the pre-eclampsia risk as would suggest the study on pre-eclampsia physiopathology [44,45]. The Trastuzumab displays at the fetal level a kidney toxicity, sepsis risk, but above all an oligohydramnios and anamnios prevalence increase with a risk of respiratory distress [3,31,45-47].

Radiotherapy

Radiotherapy is going to be display to the patient but out of the pregnancy. During gestation, the radiotherapy is feasible up to the second trimester with a lead apron. But it must be note that higher doses that 100-200 mGy at the fetal level would increase the malformation and mental retardation risks [1,3,48]. However, these doses are not delivered during a radiotherapy. The recommendations report a possible increased risk of leukemia [3]. From the second trimester, this kind of treatment has to be performed after the delivery to not exceed a lead-time of 6 months between the surgery and the radiotherapy. A longer lead-time would increase the recurrence risk with a Recurrence/month of 1.11 [1.04-1.19] according to the meta-analysis [49]. However, regarding the performance of radiotherapy, the literature is not unanimous because a recent literature review reports that it can be performed until the end of the 2nd trimester without major fetal risk in breast cancer [50]. Further, in a Luis et al.'s review, no fetal effect is found from the use of radiation therapy during pregnancy for the treatment of mediastinal or cervical cancers [51].

Support Care

According to the literature, antiemetic are safe to use during pregnancy with some exceptions. They are mainly studied for Hyperemesis Gravid arum [53]. To treat nausea and vomiting the anti-dopamine D2 activity as the Metoclopramide exist without contraindication during the pregnancy. On the other hand, Ondansetron, an anti-serotonin 5HT(2H) medication, is not recommended before 10 weeks of gestation due to a discrepancy between studies that indicate a possible fetal malformation risk [54-56]. The Anti-NK1, Aprepitant, is also not recommended before 10 weeks of gestation due to a lack of data on this subject [53]. Regarding the growth factors, the Erythropoietin was not studied to be prescribed in a context. Data are small with a possible safety [3,57]. In relation to the G-CSF, effects are uncertain, and a little bit studied. Some studies show a possible oligoamnios and an insignificant increase of the newborn temporary respiratory distress. These adverse effects are found in a study where the growth factors are indicated in chronic neutropenia [31,58].

Pre-eclampsia

Regarding the pre-eclampsia, development of this disease was expected in front of many risk factors as its age, the medically assisted reproduction, and the triple gestation [59]. The lack of the pre-eclampsia prevalence increase in case of chemotherapy is highlighted, int

an section for a HELLP syndrome at 36 WA but in this patient, pre-eclampsia appears after the 2 cycles of chemotherapy [60]. In addition, Del Gobbo et al. show that performing chemotherapy during pregnancy increases the risk of the presence of vascular and morphological alterations in the placenta, but without clinical

repercussions in these 23 cases [62]. Lastly, the literature does not show statistical link between breast cancer and pre-eclampsia [63].

Discussion

During pregnancy, breast cancer should be treated to almost all the recommended treatments except some little specificities (Table 1). The literature shows the possibility of a surgery during a gestation at every trimester but highlights a higher risk of miscarriage during the first trimester. Additionally, the neoadjuvant or adjuvant chemotherapy is feasible, but with a higher risk of fetal mortality during the first trimester. On the other hand, Anthracyclines are noted to show effectiveness without serious fetal or maternal consequences. In this family, the Doxorubicin can be used with a dose lower than 70mg/m² (or the Epirubicine at 100mg/m²), paired with Cyclophosphamide IV, without oral administration. Then Texans can be used, as such as the Paclitaxel, with a weekly administration. Other treatments, such as targeted therapy or hormonotherapy are not recommended during a gestation. Radiotherapy is possible until the 2nd trimester but with protections. The fetal adverse effects are mainly a higher risk of IUGR, cytopenia at the birth, and neonatology admission. Nevertheless, the consequences of prematurity are greater than that of chemotherapy. All these recommendations come from a literature review which itself is mainly based on patient cohorts made up of more or less patients. Therefore, the scientific evidence is low. In addition, there is an extrapolation of certain data excluding pregnancy. The majority of these studies are cohorts therefore studies of weak scientific evidence. In addition, we use several literature reviews, which sometimes use the same sources. According to Oxfords Centre for Evidence-based Medicine's Level of Evidence and Grades of Recommendation, the studies have a level going level 5 to 1. Therefore, we used studies with different level of evidence and different methodological qualities. In addition, the articles selection is based on titles and summaries reading to find out if they answered well to the question. There are also considerable variations in assessment criteria. We have also studied secondary judgment criteria, knowing they do not allow a conclusion by themselves. We sought to collect data on fetal outcomes and adverse events. Regarding support care, the research in PubMed with the following keywords "pregnancy" and "breast cancer" did not allow answering to your question. Therefore, we researched for only a few articles using this drug in other diseases. Thus, we only searched for a few articles using this drug in other diseases. In view of the quality of the articles on anti-emetics, grade 2 according to Oxfords Centre for Evidence-based Medicine's Level of Evidence and Grades of Recommendation, and of case-controls, we decided to stop the study research. On the other hand, concerning growth factors, the level of scientific proof is extremely low, due to the small number and study and their poor quality. About preeclampsia during breast cancer, the literature is few provided. There is very little feedback from experience, cohort or study. In addition, they are of low level of scientific evidence. Concerning our patient, she had cancer with the usual cancer characteristic during the pregnancy. In this case, for the diagnosis and the extension, a breast ultrasound, a mammography and PET/CT scan have been used after a literature review. After, our patient profited during her gestation of a neoadjuvant chemotherapy with Anthracyclines, Cyclophosphamide and Docetaxel like the recommended literature with the benefit/risk ratio. The hormonotherapy question was not raised on this case since the breast cancer is triple negative but the review was necessary. Regarding the back-up care, in this case the patient was treated by corticoids with Prednisolone, Metoclopramide, and Ondansetron. Regarding our patient, her pre-eclampsia development was expected in front of many risk factors as her age, the medically assisted reproduction, and the triple gestation.

Treatment	First Trimester	Second Trimester	Third Trimester
Abortion	Yes	No	No
Induction labor	No	No	Yes from 36 weeks'
	In ESMO Guidelines, review, cohort		
Surgery with GS	Yes, the GS technic with radioactive tracer		
	2 literature reviews and 485 patients followed in cohort		
Chemotherapy	No	Yes until 36 weeks'	
	4325 patients followed in cohort, 13 reviews, 1 pre-clinical study		
Hormonotherapy	No		
	138 patients followed in cohort		
Target therapy	No		
	2 pre-clinical study, 1 expert advice		
Radiotherapy	Yes		No
	3 reviews, 1 mathematic model, 1 expert advice		

Table 1: Summary of treatment.

Conclusion

To conclude, pregnancy should not be a loss of opportunity for the proper management of breast cancer. Despite the complexity of decision-making and patient anxiety, most treatments are possible during pregnancy. More in-depth studies must be conducted to provide a care allowing for maximum efficacy and lowest risk. Concerning the patient in our case report, despite a triple pregnancy and early pre-eclampsia, the neoadjuvant chemotherapy and birth went well. Yet, the chemotherapy treatment could be associated with the pregnancy complication at 32 weeks, requiring an emergency caesarean section. The French national reference centre for cancer and pregnancy was an important support in the decision-making process in this uncommon situation.

Statements and Declarations: Not applicable

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Author's contribution:

- A. BUISSON: protocol/project development, data collection, data analysis, manuscript writing
- E. JACQUET: protocol/project development, data collection, manuscript writing
- A. LAMOTTE: manuscripts proofreading
- A.C. PHILIPPE: manuscripts proofreading
- D. RIETHMULLER: project development, manuscripts proofreading

Compliance with Ethical Standards

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Conflicts of Interest: Alexandre BUISSON, Emmanuelle JACQUET, Anna LAMOTTE, Anne-Cécile PHILIPPE, Didier RIETHMULLER declare no conflict of interest.

Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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