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REVIEW

Tamoxifen and pregnancy: an absolute contraindication?

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Abstract

Purpose Breast cancer is the most common malignancy among young women of reproductive age. Adjuvant treatment with tamoxifen reduces the risk of recurrence in hormone-sensitive breast cancer. However, the use of tamoxifen is considered contraindicated during pregnancy, because of a limited number of case reports demonstrating potential adverse effects on the fetus. The objective of this report is to give a more broad overview of the available data on the effect of tamoxifen exposure during pregnancy.

Methods A literature review was performed using PubMed and the databases of the Netherlands Pharmacovigilance Centre Lareb and of the International Network on Cancer, Infertility, and Pregnancy.

Results A total of 238 cases of tamoxifen use during pregnancy were found. Of the 167 pregnancies with known outcome, 21 were complicated by an abnormal fetal development. The malformations described were non-specific and the majority of cases concerned healthy infants despite exposure to tamoxifen.

Conclusion There seems to be an increased risk of fetal abnormalities when taking tamoxifen during pregnancy (12.6% in contrast to 3.9% in the general population), but the evidence is limited and no causal relationship could be established. The possible disadvantage of postponing or discontinuing tamoxifen for the maternal prognosis is unclear. Patients should be counseled about the use of tamoxifen during pregnancy instead of presenting it as being absolutely contraindicated.

Keywords Tamoxifen · Breast cancer · Pregnancy · Teratogenicity · Fetal toxicity

Introduction

Breast cancer is the most common malignancy in women of reproductive age. In the Netherlands, 5% of the women who are diagnosed with breast cancer are younger than 40 years, which accounts for more than 700 women each year [1]. Because of the rising incidence of breast cancer with age and the trend to postpone childbirth, physicians are increasingly confronted with breast cancer during pregnancy or in nulliparous women who still wish to conceive [2].

The majority of breast cancer patients aged 40 years or less will undergo adjuvant systemic treatment with chemotherapy, to be followed by adjuvant endocrine therapy in patients with hormone receptor-positive disease. The standard adjuvant endocrine treatment consists of tamoxifen for 5 years with the possibility to extend treatment up to 10 years in breast cancer with high-risk features [2]. This endocrine regimen will reduce the absolute risk of recurrence until 15 years with 12% (33.2% vs. 45%) and the mortality risk with 9% (24% vs. 33%) [2, 3].

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Despite the chemotherapy, ovarian function is preserved in a large group of these young patients, which also leaves the possibility to conceive. In patients with a wish to become pregnant, the general advice is to stop treatment with tamoxifen due to its potential teratogenic effect. These women then face the dilemma of choosing between the advised anti-cancer treatment to reduce risk of recurrence and the desire to have children. Others are confronted with an unexpected pregnancy while taking tamoxifen and face the uncertainty of its effect on the fetus. This is one of the reasons why first trimester pregnancies during and after breast cancer treatment are frequently terminated [4].

Postponing pregnancy until the end of adjuvant hormonal treatment will affect women's fertility because of her increased age. It is well known, based on data in healthy women, that changes to conceive above the age of 38 are rapidly decreasing [5]. Moreover, in breast cancer patients, the chances of becoming pregnant may have already been reduced by the preceding chemotherapy, considering previous data showing that the age of menopause occurs years earlier in women who have been subjected to cytostatic treatment. Tamoxifen itself may also contribute to an early menopause [6].

Although there is limited evidence, it is recommended to stop tamoxifen at least 2 months before conception due to the long half-life of its active metabolites. The advice to discontinue tamoxifen is however based on only a few studies, which are referred to by many authors [7–9]. These reports need to be interpreted with caution because of the very low level of evidence and the conclusion should therefore not be blindly copied.

In the present article, an outline of the characteristics and effects of tamoxifen is given to better understand why the drug is thought to have a detrimental influence on the outcome of pregnancies. In addition, a literature search was done to give a current overview of the available data on the effect of tamoxifen exposure during pregnancy, to enable adequate counseling of patients and individualized care.

Tamoxifen

Tamoxifen is a non-steroidal selective estrogen receptor modulator. In breast tissue, it has an anti-estrogenic effect due to competitive binding to estrogen receptors (Fig. 1). In other tissues, tamoxifen can have an estrogen agonistic effect, e.g., causing stimulation of the endometrium with

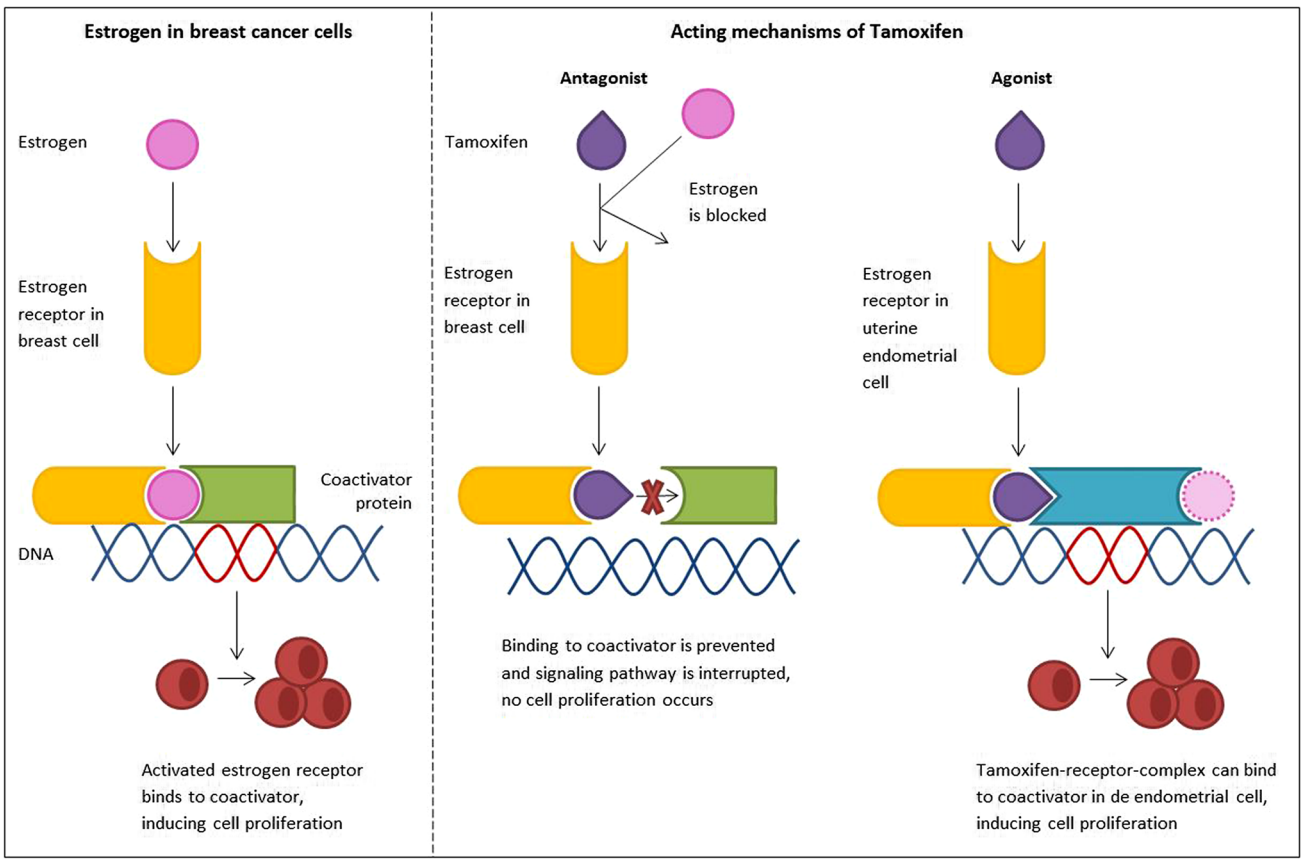


Fig. 1 The different mechanisms of action of tamoxifen in relation to estrogen and its receptor

subsequent increased risk of endometrial cancer, inhibition of bone resorption in postmenopausal women, and a decrease in total and LDL cholesterol levels [10].

The affinity of natural estrogens for the estrogen receptor is much higher than that of tamoxifen. However, the affinity of the active metabolites of tamoxifen, endoxifen, and 4-OH-tamoxifen, is much higher than that of tamoxifen itself and stronger than of the circulating estrogens. The CYP3A4 and CYP2D6 enzymes, which are expressed in the liver, are required for the formation of these active metabolites. Due to their long half-life of 14 days, it takes approximately 6 to 8 weeks for complete elimination of tamoxifen and its metabolites from the circulation [10, 11].

Over time, tamoxifen has had several opposite indications. It was developed as a contraceptive agent, but it turned out to stimulate follicle growth, making it an alternative to clomiphene for ovulation induction in subfertile women. However, in these subfertile patients, a higher than expected occurrence of spontaneous abortion was noted in some studies [12–14], although in most studies the miscarriage rate did not increase [4, 15]. Next, the agent was used together with misoprostol to induce abortion, but tamoxifen was shown not to have an additional value to misoprostol [16].

The main mechanism of action of tamoxifen is related to its binding capacity to the estrogen receptor. The estrogen receptor has both genomic (nuclear-initiated steroid signaling) and non-genomic (membrane-initiated steroid signaling) activities (Fig. 2). These two signaling pathways are activated when estrogen binds to its receptor. It thereby regulates a variety of physiological processes [17, 18].

Through its genomic activity, the estrogen receptor acts as a ligand-dependent transcription factor and regulates expression of multiple genes. These genes encode proteins that regulate growth and angiogenesis, for example, insulin-like growth factor 1 receptor (IGFR) and vascular endothelial growth factor (VEGF) that directly promote cell proliferation and survival. The antitumor effects of tamoxifen are related to the inhibition of the expression of these estrogen-regulated genes by counteracting the above-mentioned effects of estrogen [17–19].

The non-genomic pathway is independent of gene transcription and can, in response to estrogen, activate kinase and phosphorylation cascades, resulting in nuclear transcriptional activity and thereby complement the genomic actions of estrogen receptor [17].

Tamoxifen and pregnancy

The effect of tamoxifen on gene transcription and translation is mostly investigated in breast cancer cells, but given the effect it has on other organs, it can be expected that tamoxifen interferes with processes in these organs as well. The

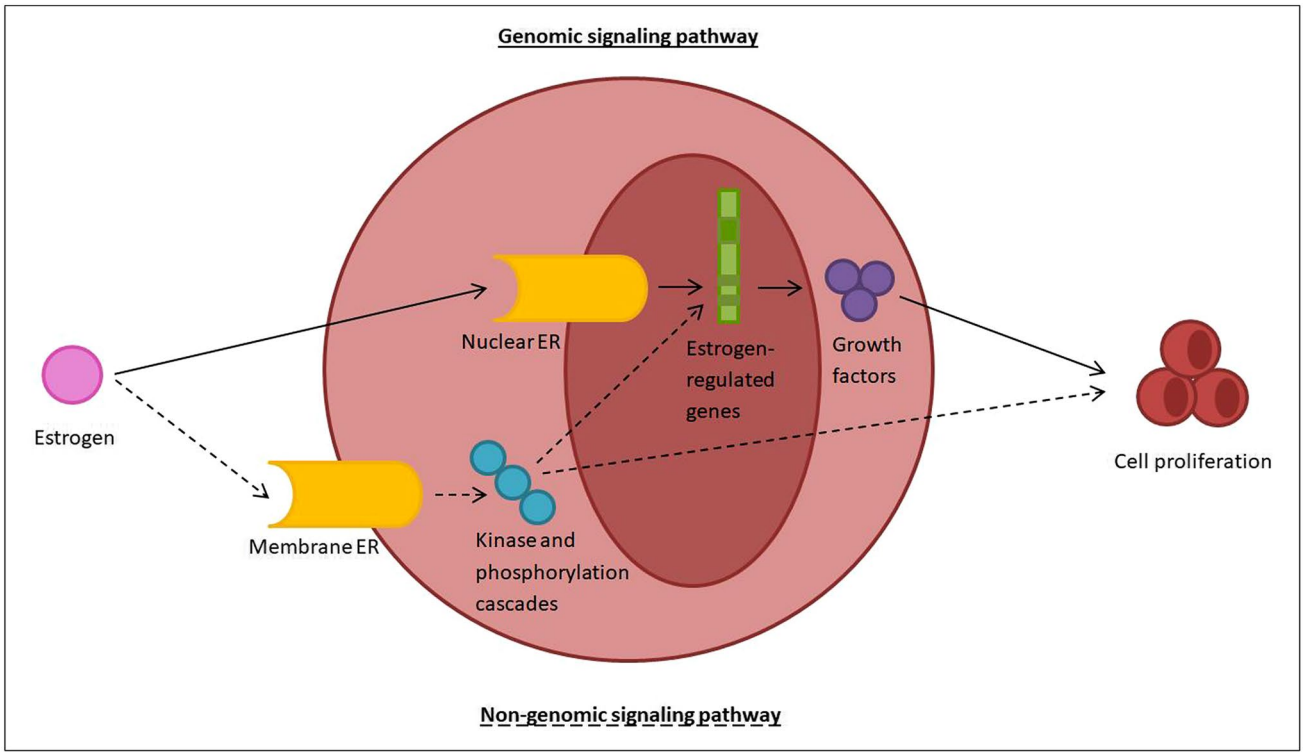


Fig. 2 Genomic and non-genomic actions of estrogen via the nuclear estrogen receptor (ER) and membrane-associated estrogen receptor

effects of tamoxifen during pregnancy occur on three levels: the fetus, the placenta, and the pregnant mother.

Since gene transcription and translation is essential during pregnancy, tamoxifen is believed to interfere with the rapidly growing and developing fetus [20]. However, the mixed estrogenic and anti-estrogenic effects of tamoxifen are species-, tissue-, and even cell-specific, which makes it difficult to predict its exact effect in pregnancy [10].

Besides its presumed direct effect on the growing fetus, tamoxifen is thought to interact with the development and function of the placenta. Levels of progesterone and human chorionic gonadotropin have been shown to be lower during tamoxifen use in cultured placental villus tissue, indicating that tamoxifen could have an inhibitory effect on the secretory function of the placenta [21]. In addition, defective development of uterine spiral arteries and hypoplasia of the metrial gland, the outermost layer of the maternofetal interface, was observed in rats [22].

In the mother, the use of tamoxifen leads to stabilization or even increase in the number of estrogen receptors. Since estrogen receptor expression appears to be down-regulated in early pregnancy and does not seem to increase until term, tamoxifen can interact with this physiological process [23]. The clinical consequences of this potential interference are unknown.

Estrogens play an important role during pregnancy and delivery. The balance between the effects of estrogen and progesterone is essential for pregnancy maintenance and the onset of labor. Estrogen controls uterine growth, cervical ripening, and uterine contractility [24]. Tamoxifen is known to have an estrogen agonist effect on uterus and ovaries instead of an anti-estrogen effect, which might limit its interference with these processes because of the already high estrogen levels during pregnancy. However, the concentration of estrogens is not a reliable measure of the expected biological activity of tamoxifen. Since tamoxifen seems to be as effective in premenopausal women, with their much higher estrogen levels, as in postmenopausal women, the increasing estradiol levels during pregnancy might not influence the activity of tamoxifen and vice versa.

Animal studies

Concerns about the use of tamoxifen during pregnancy are mainly based on animal studies that showed various fetal toxicities. Although tamoxifen will seldom be initiated in the first trimester, inadvertent pregnancy can occur leading to exposure in early pregnancy. In reproductive studies reported by the manufacturer, no teratogenicity was observed in rats, rabbits, and marmosets [25]. However, exposure of tamoxifen during early pregnancy resulted in an increased abortion rate in pregnant marmosets and rabbits [25, 26].

When administered after the first trimester, tamoxifen has been shown to induce dose-related toxic changes in the developing genital tract in a few animal studies [27–31]. These changes involved trophic effects on the uterus and vagina similar to those caused by estrogens. Abnormalities in sexual differentiation of female offspring have been observed [32]. The chemical structure of tamoxifen has similarities to that of diethylstilbestrol (DES), which is known to cause genital tract anomalies and increase risk of clear cell carcinoma of the vagina and cervix in humans. In mice and rats, abnormalities induced by tamoxifen were in most cases comparable to those seen after administration of DES, including vaginal adenosis and uterine hypoplasia [32–35].

Moreover, when exposed to tamoxifen after the first trimester, fetal toxicity such as intrauterine growth restriction, abortions or fetal deaths, and premature delivery was common in some species [22, 25].

However, some of these animal studies used dose levels much higher than those used in humans. In addition, there are several studies that did not confirm an increased incidence of fetal abnormalities in the offspring of experimental animals [26, 36, 37]. Due to these conflicting results, the clinical implications of the findings from animal reproduction studies are still uncertain.

Nevertheless, based on the pharmacological characteristics of tamoxifen and the above-mentioned animal studies, the assumption that tamoxifen exerts a negative effect on the developing fetus and placenta is plausible.

Methods

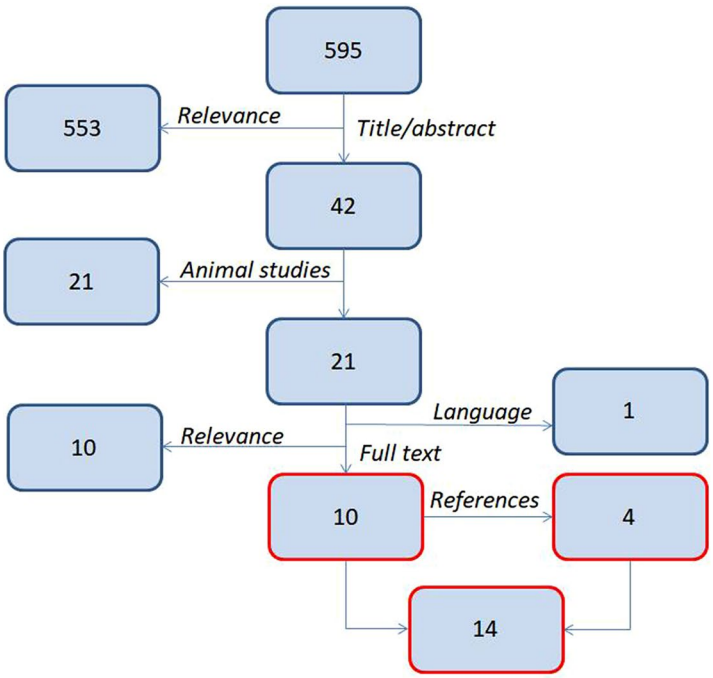
We designed a literature review to describe a case series with the aim to assess the consequences of the use of tamoxifen during pregnancy on the developing fetus. A secondary goal was to determine whether there is a difference in effect per trimester.

A literature search was performed using the electronic biomedical publication database PubMed to identify relevant articles. Additionally, the database of the Netherlands Pharmacovigilance Centre Lareb and the database of the International Network on Cancer, Infertility and Pregnancy (INCIP) were consulted.

In the search strategy, keywords resembling tamoxifen and synonyms of pregnancy, fetus, or teratogenicity were used to identify potential articles of interest (see legend of Fig. 3). There were no limitations used in the search regarding date or language.

First, all titles and abstracts of the retrieved articles were screened for relevance. After this first selection, the following exclusion criteria were applied: (1) studies not meeting our research question (2) animal studies. Second, the full text articles were reviewed. Articles were included in the

Fig. 3 Search strategy



Search: 4-10-2018
Syntax: (tamoxifen[Title/Abstract]) AND ((((((((((pregnancy[Title/Abstract]) OR pregnant[Title/Abstract]) OR gestation[Title/Abstract]) OR gestational[Title/Abstract]) OR fetal[Title/Abstract]) OR fetus[Title/Abstract]) OR foetus[Title/Abstract]) OR congenital[Title/Abstract]) OR teratogenic[Title/Abstract]) OR teratogenicity[Title/Abstract])

review if they met the following inclusion criteria: (1) full text available in English or Dutch (2) study reporting on the research question of this review. Third, the reference lists of all included studies were screened for the identification of additional studies. The search strategy is shown in Fig. 3.

Results

The search retrieved 595 articles. After applying the inclusion and exclusion criteria and screening the reference lists, a total of 14 articles were considered eligible for our review. The database of Lareb and INCIP contained both two additional cases.

These individual cases and the included studies, which consist of case reports and reviews of case reports, are categorized depending on the tamoxifen exposure during gestation and are shown in Tables 1, 2, and 3.

Four cases with congenital abnormalities after tamoxifen use have been reported. A case report by Berger et al. describes an infant born at 32 weeks of gestation with a Pierre Robin sequence, who was exposed to tamoxifen and ramelteon during the first 6 weeks of pregnancy [7]. Ramelteon has been shown to cause fetal structural abnormalities in animal studies. The gestational diabetes reported in this case also was an additional risk factor. Therefore, it cannot be stated with certainty that the Pierre Robin sequence was caused by tamoxifen. Cullins et al. published a case of a premature newborn with Goldenhar syndrome, characterized by congenital craniofacial defects [8]. Tamoxifen was used until delivery at 26 weeks of gestation. The mother, however, also used cocaine and marijuana during the first trimester of pregnancy and underwent a bone scan, all of which are potentially toxic. Again, a causal relationship between tamoxifen and Goldenhar syndrome remains unclear. In 1997, Tewari et al. described a premature female infant born with an ambiguous genitalia after use of tamoxifen during the first 20 weeks of pregnancy [9]. Additionally, the literature database of Lareb contained an abstract by Grandvuillemin et al. presenting a case of a 43-year-old woman with an unexpected pregnancy discovered at 16 weeks of gestation, after which tamoxifen was withdrawn [38]. For maternal reason, a medical abortion was done, revealing a female fetus with an enlarged clitoris. This is likely to be caused by tamoxifen, considering its mechanism of action described above.

In contrast to the above-mentioned cases, several case reports have described the delivery of healthy infants despite exposure to tamoxifen in utero during the first trimester [18, 39–42] or after the first trimester [22, 43, 44]. These reports are presented in Tables 1 and 2, respectively.

Table 1 Tamoxifen exposure during first trimester

Source	*N* of patients	Tamoxifen exposure	Pregnancy outcome	Other factors
INCIP	2	First trimester Until 4 weeks	Spontaneous abortion at 10 weeks No congenital anomaly, at term	
Lareb	2	Until 8 weeks Until 10 weeks	No congenital anomaly, at term Induced abortion	
Berger and Clericuzio [7]	1	Until 6 weeks	Pierre Robin sequence, clubfoot, acetabular, and sacral dysplasia Prematurity (32 weeks)	Use of Ramelteon Gestational diabetes Preeclampsia
Jyoti et al. [18]	1	Until 7 weeks	No congenital anomaly, at term	
Braems et al. [20]	37	First trimester	2 live births with congenital anomalies, 2 elective terminations with fetal defects, 6 spontaneous abortions, 6 live births without congenital anomalies, 4 elective terminations without fetal defects or unknown, 17 unknown	
Koca et al. [39]	1	Until 4 weeks	No congenital anomaly, at term	Use of zoladex
Koca et al. [40]	2	Until 6 weeks Until 4 weeks	No congenital anomaly, at term Induced abortion	
Öksüzoglu and Güler [41]	1	First trimester	No congenital anomaly	
Koizumi and Aono [42]	2	First trimester	No congenital anomalies, at term	Use of bromocriptine

Table 2 Tamoxifen exposure after first trimester or during all pregnancy

Source	*N* of patients	Tamoxifen exposure	Pregnancy outcome	Other factors
Cullins et al. [8]	1	Until 26 weeks	Goldenhar syndrome, prematurity (26 weeks)	Use of cocaine/cannabis and bone scan < 6 weeks
Tewari et al. [9]	1	Until 20 weeks	Ambiguous genitalia (clitoris hypertrophia), induced prematurity (29 weeks)	
Braems et al. [20]	15	After first trimester	2 live births with congenital anomalies, 1 elective termination with fetal defects, 8 live births without congenital anomalies, 1 elective termination without fetal defects or unknown, 3 unknown	
	10	During all pregnancy	1 live birth with congenital anomaly (Cullins et al. [35]), 8 live births without congenital anomalies, 1 elective termination without fetal defects or unknown	
Isaacs et al. [23]	1	Until 31 weeks	No congenital anomaly, induced prematurity (31 weeks)	Radiotherapy < 8 weeks
Grandvuillemin et al. [38]	1	Until 16 weeks	Enlarged clitoris, medical abortion	
Ishizuka et al. [43]	1	Until 25 weeks	No congenital anomaly, at term	Use of zoladex
Andreadis et al. [44]	1	Until 28 weeks	No congenital anomaly, prematurity (35 weeks)	Use of bisphosphonates

Table 3 Tamoxifen exposure during pregnancy, trimester unknown

Source	*N* of patients	Tamoxifen exposure	Pregnancy outcome	Other factors
Braems et al. [20]	74	Unknown	6 live births with congenital anomalies, 1 stillbirth with fetal defects, 3 elective terminations with fetal defects, 5 spontaneous abortions, 1 ectopic pregnancy, 11 live births without congenital anomalies, 10 elective terminations without fetal defects or unknown, 36 unknown	
Clark [45]	85	Unknown	No congenital anomalies	

In 1993, a letter in the Lancet stated that 85 women had become pregnant while receiving tamoxifen and that no fetal abnormalities had been reported [45]. These data originate from a trial in which prophylactic tamoxifen was given to healthy women at a high risk of developing breast cancer. Unfortunately, no details were provided about the duration or timing of the tamoxifen use during pregnancy.

Braems et al. conducted a review about the effect of tamoxifen before and during pregnancy [20]. In addition to a literature review, they included cases presented in the safety database of the pharmaceutical company AstraZeneca. This database reported 11 infants with congenital malformations, including the case reported by Cullens et al. [8], out of 44 live births. These congenital malformations included phallic-like clitoris and huge labia, slight clitoral hypertrophy, small degree of labial fusion, vaginal adenoma, idiopathic chylothorax, congenital hand malformation, cleft palate, ear malformation, trisomy 21, and craniofacial defects.

Barthelmes and Gateley also reviewed the evidence for the risk of fetal malformations after tamoxifen exposure during pregnancy [4]. All the cases described in this study are already presented in Tables 1, 2, and 3 and, therefore, this study is not mentioned separately.

In summary, a total of 238 pregnancies during tamoxifen therapy have been reported in the literature. Of the 142 live births documented, 13 infants had a congenital malformation (1:11). When including the pregnancies without live birth but with documented fetal outcome, a total of 21 out of 167 pregnancies were complicated by fetal defects (1:8). However, 71 of the reported 238 pregnancies were not included in this evaluation, since 56 pregnancies had an unknown outcome, 12 spontaneous abortions occurred without known cause, and 2 induced abortions and 1 ectopic pregnancy were reported. So the total incidence of congenital anomalies cannot be assessed adequately based on these findings.

The number of reports on tamoxifen therapy *after* the first trimester was very limited, but one article was found showing three known congenital abnormalities out of 15 pregnancies.

The overall miscarriage rate was 6.7%. However, the accuracy of this percentage may be limited due to unknown data.

Discussion

Physicians generally advice patients with primary breast cancer to stop or not to start tamoxifen during pregnancy. This recommendation is mainly substantiated by adverse effects on the fetus found in animal studies and three of the case reports mentioned in this review [7–9]. Overall, a relatively high incidence of congenital abnormalities is seen after tamoxifen exposure during pregnancy; 12.6% in contrast to 3.9% in the general population [46]. Furthermore, there is a lack of long-term follow-up of the exposed infants. This may be of particular importance since many of the adverse effects seen after exposure to diethylstilbestrol, which has similarities to tamoxifen, only became evident later in life. This is why long-term follow-up of the children exposed to tamoxifen should be stimulated [20].

However, the malformations described in the presented case reports are non-specific and the majority of case reports and case series reported healthy infants despite exposure to tamoxifen. The level of evidence regarding the safety of tamoxifen during pregnancy is obviously low, because it is based on case reports and other retrospective data. This type of study design is prone to reporting bias due to the fact that adverse outcomes are much more likely to be documented. This particularly plays a role in data derived from the safety database of a pharmaceutical company like AstraZeneca, which provided the majority of cases in this overview. Moreover, in retrospective studies, patient-specific factors such as concomitant medication or lifestyle activities are possible confounders. This hampers the confirmation of a causal relationship between tamoxifen and pregnancy outcome.

In animal studies with pregnant marmosets and rabbits, administration of tamoxifen after organogenesis resulted in an increase in abortions and premature deliveries [25, 26]. In this report, three spontaneous premature deliveries were described. The miscarriage rate was within normal limits. Unfortunately, there are too limited data to verify the safety of tamoxifen when started in the second or third trimester, although the few data provided by AstraZeneca showed an increased risk of congenital malformations following tamoxifen treatment after the first trimester [20].

Aside from the effect of tamoxifen on the fetus, another relevant question is whether discontinuation or postponement of hormonal therapy worsens the maternal prognosis, in other words the risk–benefit analysis. In 2017, Nye et al. published a retrospective analysis regarding this issue [47]. They included 32 premenopausal women with diagnosis of estrogen receptor-positive breast cancer and subsequent pregnancy and an age- and stage-matched control cohort ($N=29$) without subsequent pregnancy. All patients were offered adjuvant hormonal therapy. In the pregnancy cohort, 19 women (63%) had received endocrine therapy and 23 women (82%) in the control cohort ($P=0.25$). The mean length of endocrine therapy was shorter in the pregnancy cohort (20.9 months, range 0–72 months) than in de control cohort (42.3 months, range 0–120 months; $P=0.008$). Eight women (26%) in the pregnancy cohort experienced breast cancer recurrence compared with four women (14%) in the control cohort ($P=0.34$). The 5-year disease-free survival rate was 84% in the pregnancy cohort compared with 92% in the control cohort ($P=0.69$). The authors concluded that the results did not demonstrate poorer disease-free survival

in women who became pregnant within 5 years after their cancer diagnosis. However, the differences in recurrence are prominent and the fact that it is not significant could easily be explained by the small study sample. Therefore, advocating that it is safe to stop tamoxifen should be done with caution.

Moreover, a study by Hershman et al. showed that early discontinuation and non-adherence to adjuvant hormonal therapy in women with early-stage breast cancer were associated with increased mortality [48], which highlights the importance of adequate counseling of women who are considering to stop adjuvant treatment.

Hopefully, the POSITIVE-trial will provide us with sufficient evidence about the safety and feasibility of interrupting adjuvant endocrine therapy to allow pregnancy [49]. This international multicenter trial started in December 2014 and expects to finish inclusion of the approximately 500 patients in 2028. In the study, patients receive 18–30 months of endocrine therapy. Those with adequate ovarian function can temporarily interrupt endocrine therapy for up to 2 years to allow pregnancy with or without breastfeeding. Afterwards, they are encouraged to resume endocrine therapy for a total course of 5–10 years according to local practice.

In conclusion, data in animal studies and a few human case reports suggest that an increased risk of fetal abnormalities does occur while taking tamoxifen during pregnancy. These findings appear not to be limited to treatment during the first trimester, although evidence is scarce. In clinical studies, no specific congenital anomaly has been associated with the use of tamoxifen and no definite causal relationship can be established between tamoxifen and pregnancy outcome in women with breast cancer due to the lack of sufficient evidence. Moreover, the majority of infants exposed to tamoxifen in utero are healthy, although numbers are small. No data of long-term follow-up are yet available. The possible disadvantages on the maternal prognosis when postponing or stopping the use of tamoxifen are still unclear. These findings may indicate that the use of tamoxifen during pregnancy should be more a matter of shared decision making instead of an absolute no-go. Some women might not want to miss out on the therapeutic benefit of tamoxifen and may be willing to accept the unclear risks for the fetus. Moreover, postponing childbirth after completion of the adjuvant therapy may not be desirable in some cases, since age and previous breast cancer treatment may already lead to reduced chances of becoming pregnant.

When an unexpected but wanted pregnancy occurs during tamoxifen treatment, discontinuation of the adjuvant hormonal therapy still seems to be the safest choice regarding the fetus. Women with the wish to conceive or with an indication to start tamoxifen after the first trimester should be counseled about the uncertainties of tamoxifen exposure in pregnancy and be offered the choice whether to stop or continue treatment, but even better should be stimulated to participate in studies like the POSITIVE-trial.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Not applicable.

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