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Treatment of cancer during pregnancy with monoclonal antibodies: a real challenge

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"Managing cancer during pregnancy lacks a standardized approach. The fact that anticancer therapy needed to treat the mother could exert serious adverse effects on the developing fetus calls for the development of tailored strategies for these patients."

The diagnosis of cancer during the course of pregnancy is a relatively rare clinical situation. Cancer complicates approximately one out of 1000 pregnancies, with an estimated 6000 new cases diagnosed in the USA every year [1]. This incidence is expected to increase given the rising trend of postponing pregnancy to later in life. Breast and cervical cancers are the most commonly diagnosed tumors during pregnancy, followed by melanoma, lymphoma and leukemia [2].

Managing cancer during pregnancy lacks a standardized approach. The fact that anticancer therapy needed to treat the mother could exert serious adverse effects on the developing fetus calls for the development of tailored strategies for these patients [3]. In general, chemotherapeutic agents are the most widely used in managing cancer patients, including those diagnosed during pregnancy. The rule of thumb is to avoid administering chemotherapy during the first trimester of gestation as it increases the risk of spontaneous abortion, fetal death and major congenital malformations [4]. The fetus is especially vulnerable to malformations when exposed to chemotherapy during the period of organogenesis (weeks 2–8 after conception), with the risk reaching as high as 20% [1,2,4]. Starting in the second trimester (i.e., weeks 12–14), drugs like anthracyclines, vinca-alkaloids and alkylating agents have been shown to be generally safe, with a risk of congenital anomalies highly comparable to that of the general population [5,6]. However, long-term data remain insufficient.

Monoclonal antibodies (mAbs) are increasingly used for the management of several tumor types. However, there is limited experience assessing the reproductive and developmental toxicities of these agents in experimental models. In addition, the predictive value of human application of these tests have been questioned [7]. Furthermore, the relatively recent incorporation of mAbs into routine clinical practice and the brief period of postmarketing experience limit our knowledge and understanding about the safety of these agents when given to pregnant cancer patients.

Transplacental transfer of mAbs

Five major classes of antibodies constitute human humoral immunity; however, the human placenta seems to be impermeable to all classes except IgG [8]. IgG is further classified into four subclasses: IgG1, IgG2, IgG3 and IgG4. As most of the IgG in the fetus is of maternal origin, its concentration in the fetus reflects transport from the mother [9]. Of note, the currently available mAbs are mostly of the IgG1 subclass [10].

Keywords: cancer • monoclonal antibody • pregnancy • reproductive toxicity • transplacental transfer

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Owing to their nature as large hydrophilic molecules with a molecular mass exceeding 100 kDa, mAbs cannot be transported across the placenta by simple diffusion. They require active transport across the placental barriers via a specific receptor-mediated mechanism [11]. IgG transplacental transport is regulated by the syncytiotrophoblast and the fetal capillary endothelium [12]. The process is initiated via binding of the Fc portion of the IgG to the Fc receptor in the syncytiotrophoblast [13].

The Fc receptor is hardly detectable before the 14th week of gestation, suggesting that materno–fetal transfer of IgG during the first trimester is minimal [14]. This is further supported by the fact that, during the first trimester, there is an additional layer of cytotrophoblast, which is initially broken by week 14–16 of gestation [15]. The fetal IgG concentration starts to rise smoothly until week 18, with a sharp increase in total IgG levels observed between weeks 22 and 26 of gestation. It is important to point out that Gurevich and colleagues have detected IgG transfer into embryonic tissue as early as week 4 of gestation, but no real quantification has been made [16], which suggests that concentrations were probably very low [15].

Safety of mAb administration during pregnancy

In all animal species used for testing developmental toxicities, fetal exposure to IgG has been found to be very low during organogenesis [15]. As discussed earlier, transplacental transfer of IgG tends to build up over time, and this increase continues such that the neonate is born with an IgG concentration similar to or sometimes higher than that of the mother [15].

Three types of studies are commonly used to investigate the reproductive toxicity of new agents. The first is the Fertility and Early Embryo Developmental Design (FEED) in which the drug is administered from before mating until implantation. The second is the Embryo-Fetal Developmental (EFD) studies, with administration from implantation to cleft palate closure, while the third is the Pre (peri)- and Post-Natal Design (PPND), with administration from cleft palate closure until weaning. Until 2007, seven mAbs were approved for managing different cancer types. In two of them (ibratumomab, rituximab), no animal reproductive studies were conducted at all, while in another two (alemtuzumab, cetuximab), only repeated dose-toxicity studies were carried out. The preclinical reproductive toxicities of bevacizumab, panitumumab and trastuzumab were better studied; however, the latter is the only drug in which FEED, EFD and PPND were performed [15].

Trastuzumab and rituximab are the only mAbs that were reported to be administered in pregnant cancer patients. Bevacizumab was also used in humans but as a local application in the ophthalmology setting. These agents will be discussed later in more detail. For the remaining mAbs, only data from preclinical models are available. Alemtuzumab, which is a mAb used in managing low-grade lymphomas, showed no reproductive adverse effects in repeated dose-toxicity studies conducted in monkeys [15]. On the other hand, animal models have shown that EGF receptor inhibitors (cetuximab and panitumumab), which are used primarily in managing colon cancer, increase the risk of weight loss and spontaneous abortion when administered during pregnancy [15].

Bevacizumab in pregnancy

Bevacizumab is a mAb that targets VEGF, which is a key regular of angiogenesis, both physiological (e.g., during embryogenesis and skeletal growth) and pathological (e.g., tumor growth) [17,18]. It is mainly used in colon cancer but recent studies have suggested an active role in breast, lung, renal and ovarian cancers [19].

Angiogenesis is a very complex process that plays a critical role in embyrogenesis [18,20,21]. It has been shown that VEGF receptor 2 is crucial for the corpus luteum, which is an endocrinal organ that plays a vital role in supporting pregnancy development [22]. Furthermore, VEGF plays a key role in the production and reabsorption of the amniotic fluid produced by the fetal kidney [23]. Hence, given the diverse effects of angiogenesis in pregnancy and fetal development, inhibiting this process could result in major complications. This was observed in the late 1950s with thalidomide, which was used to treat morning sickness in pregnant women at the time. In the period from 1957 until 1961, this drug resulted in limb deformities in more than 10,000 children [24]. Later, it was found that thalidomide has an anti-angiogenic effect that was proposed as the possible mechanism behind these drastic congenital anomalies [25], which has been described as the 'thalidomide tragedy'.

> "...the relatively recent incorporation of monoclonal antibodies into routine clinical practice and the brief period of postmarketing experience limit our knowledge and understanding about the safety of these agents when given to pregnant cancer patients."

Unsurprisingly, preclinical models have shown serious adverse events when bevacizumab is given during pregnancy [22]. The administration of bevacizumab in pregnant mice resulted in disruption of survival of the pre-existing luteal blood vessels in the ovary and termination of embryonic development [26], in addition to several developmental anomalies [18,20]. This was also observed with sunitinib, which is a small-molecule tyrosine kinase inhibitor targeting several angiogenesis-related proteins [27].

In the clinical setting outside pregnancy, the administration of bevacizumab is associated with an increased risk of hypertension and proteinuria [28]. This is of major concern if encountered during pregnancy as this would increase the risk of developing pre-eclampsia, which could endanger the pregnancy course and compromise maternal and fetal health [29]. To date, there are no reports describing the use of bevacizumab in a pregnant cancer patient. However, a very small population of pregnant patients were exposed to the drug as an intravitreal injection to manage choroidal neovascularization [30–32]. Normal fetal outcomes were reported in some of these cases [30,31], while spontaneous abortion was encountered in at least one case [32]. It is hard to apply this limited information within the oncology context as the dose used in ophthalmology is much lower (range 1–2 mg, vs 5–15 mg/kg in oncology). In addition, the systemic absorption of the intravitreal application is probably also very low. Taken together, systemic administration of bevacizumab or any anti-angiogenic agent should not be considered in managing pregnant cancer patients.

Trastuzumab in pregnancy

Trastuzumab is a humanized IgG1κ mAb that targets HER2, which is overexpressed in approximately 20% of patients with breast cancer. In this disease subset, the *HER2* oncogene is considered the main driving force for tumorogenesis and these patients have a very poor prognosis [33]. The addition of trastuzumab to chemotherapy, whether in the early or advanced-disease settings, significantly reduces the risk of relapse and improves overall survival and thus it is considered a cornerstone in managing patients with HER2-positive breast cancer [34,35]. Trastuzumab is classically given in combination with chemotherapy in the advanced setting, but either concurrently or sequentially to chemotherapy for a total duration of 1 year in the (neo)-adjuvant setting. Unlike chemotherapy, it does not induce amenorrhea [36], therefore, accidental pregnancy during the course of trastuzumab is possible if adequate contraception is not used.

> "The most striking observation was the significant diminution of the amniotic fluid volume … which was encountered in more than 50% of cases exposed to trastuzumab during pregnancy."

HER2 plays a pivotal role in embryonic cardiac development and acts as an important recovery pathway when the heart is exposed to stress [37,38]. Data from the clinical setting have shown that trastuzumab significantly increases the risk of congestive heart failure, reaching up to 4% when administered in the adjuvant setting [39].

To date, a total of 15 breast cancer patients have been reported to have been exposed to trastuzumab during pregnancy [40–53]. In four cases, the patients elected to receive trastuzumab following the first trimester (i.e., the period of organogenesis) [42,43,45,51]. The remaining cases unintentionally became pregnant during the course of trastuzumab. Despite the fact that the majority of patients were exposed to the drug during the first trimester, no congenital anomalies were reported at all. No cardiac events or anomalies were encountered either; nevertheless, very few cases reported long-term follow-ups for the newborns. The longest follow-up was 5 years for a baby who was exposed during intrauterine life to trastuzumab throughout the whole pregnancy, with no delayed cardiac anomalies reported [48].

The most striking observation was the significant diminution of the amniotic fluid volume (oligohydramnios or anhydramnios), which was encountered in more than 50% of cases exposed to trastuzumab during pregnancy. Oligohydramnios significantly increases the risk of fetal morbidity and mortality as it predisposes to pre-term delivery. Out of eight cases who developed oligohydramnios, four neonatal deaths were reported secondary to premature delivery, which was complicated by respiratory and renal failure [46,49,52,53]. This has been mainly attributed to the inhibitory effect of trastuzumab on HER2, which is highly expressed on the fetal kidney responsible for amniotic fluid production [54].

Oligohydramnios seemed to be reversible on stopping trastuzumab, with good outcomes observed in these pregnancies. Patients who were exposed to trastuzumab for more than one trimester (i.e., prolonged exposure) were associated with the highest risk of complications, while those who got pregnant during drug administration and discontinued the drug once pregnancy was diagnosed did not seem to be at a considerable risk [40,50,51].

Three possible scenarios could be faced in which pregnant breast cancer patients require trastuzumab:

- Pregnant woman diagnosed with HER2-positive metastatic breast cancer: these patients should be offered chemotherapy starting in the second trimester and trastuzumab could be postponed until delivery. In case trastuzumab is urgently needed to induce faster tumor shrinkage, we would propose administering it on a weekly basis with weekly monitoring of the amniotic fluid volume for a maximum period of one trimester, unless signs of oligohydramnios were encountered;
- Pregnant woman diagnosed with HER-positive adjuvant breast cancer: these patients should be offered chemotherapy during pregnancy starting in the second trimester and trastuzumab should be postponed until delivery. Available evidence outside pregnancy confirms that trastuzumab is very effective after 4–6 months of adjuvant chemotherapy [34]. Hence, there is no need to expose the pregnant woman to the potential hazard of trastuzumab in this case;
- A woman diagnosed with HER2-positive adjuvant breast cancer who unintentionally became pregnant during the course of trastuzumab: this is a tricky situation, however, unlike chemotherapy, it appears that early brief exposure to trastuzumab is not associated with the high risk of malformations observed with chemotherapy. As discussed earlier, transplacental studies suggest very low IgG fetal concentration during the first trimester. In this setting, trastuzumab should be stopped and we believe that pregnancy could be allowed to continue without promotion for abortion for those patients who are willing to preserve their pregnancy. Only three patients were reported to adopt this approach with no pregnancy complications observed at all [40,50,51]. There are ongoing efforts to collect the pregnancy events observed in the large adjuvant trastuzumab studies (~10,000 randomized patients) to better define the complications observed when patients unintentionally became pregnant during the course of therapy.

Rituximab in pregnancy

Rituximab is a chimeric IgG1κ anti-CD20 mAb that is used to treat B-cell indolent and aggressive non-Hodgkin's lymphoma as well as in the management of some autoimmune diseases. The addition of rituximab to standard chemotherapy in patients with aggressive B-cell lymphoma has been shown to significantly reduce the risk of relapse and improve overall survival, and thus it became the standard of care since 2002 [55]. More recently, the addition of a maintenance course of rituximab following standard therapy has been shown to significantly delay disease progression in patients with follicular lymphoma (median 3.7 years vs 1.3 years; $p < 0.001$) [56]. Thus, more patients are currently considered for prolonged treatment courses with rituximab.

No preclinical reproductive toxicity models have been conducted for rituximab. To date, only seven lymphoma patients were exposed to rituximab during pregnancy; six in combination with chemotherapy [57–62], while rituximab was given as a single agent to the seventh patient [63]. The latter had relapsing follicular lymphoma and was exposed unintentionally to rituximab during the first trimester. The drug was stopped and the pregnancy was allowed to continue. The remaining six patients had different types of aggressive non-Hodgkin's lymphoma and treatment with rituximab was initiated during the second trimester. All seven patients had an unremarkable pregnancy course. In three out of seven neonates, $CD19^+$ B cells were either undetectable or severely decreased at birth or shortly after [59,61,63]. The same was observed in another neonate born to a pregnant woman diagnosed with idiopathic thrombocytopenic purpura and treated with rituximab during pregnancy [64]. The condition was reversible in all cases, with all B-cell levels returning back to normal within 3–6 months. No significant postnatal infections were encountered and subsequent follow-up revealed adequate responses to standard immunization in all four children.

The apparent effect of rituximab on suppressing the B-cell component of the newborns could indeed increase the risk of neonatal infections. The long-half life of this drug could result in observation of this side effect even if the drug was administered early in the pregnancy course and for short periods. However, limited available evidence suggests that it is reversible and does not seem to endanger the neonatal life, provided close monitoring is carried out.

Conclusion

Managing cancer during pregnancy remains a critical clinical situation that forces oncologists, hematologists, obstetricians and neonatologists to make crucial decisions in the absence of strong evidence. The relative rarity of this situation precludes the conduction of large randomized clinical trials and thus decisions will always rely on limited evidence. While some would favor promotion of abortion in these patients, it is important to highlight that abortion is not known to improve their prognosis [1]. Furthermore, from a patient's perspective, social and religious reasons are often a major concern. Thus there is an urgent need to provide some guidance on how to manage these patients, particularly those who are willing to preserve their pregnancy. While we are not yet fully aware of the level of safety of the older chemotherapeutic agents when given during pregnancy, the situation is even more complicated when addressing the safety of novel mAbs recently incorporated in oncology practice. In our opinion, the administration of drugs with antiangiogenic effects such as bevacizumab should be avoided. As for trastuzumab and rituximab, they could be considered but only in particular situations.

> "...fetal exposure during the first trimester appears to be low and hence brief early exposure is unlikely to be associated with a high risk of congenital anomalies..."

It is important to advise cancer patients considered for maintenance therapy with trastuzumab or rituximab to use effective contraception as these drugs do not induce amenorrhea. In case the patient unintentionally got pregnant during the treatment course, she should be informed that the evidence is scarce to make a solid and widely accepted decision. However, based on our current understanding of the physiologic IgG transplacental studies, fetal exposure during the first trimester appears to be low and hence brief early exposure is unlikely to be associated with a high risk of congenital anomalies, which are known to occur with chemotherapy. This does not advocate elective administration of mAbs during this period. However, it calls for reconsideration of the decision of therapeutic abortion for those women who were accidentally exposed to mAbs during this period and are willing to preserve their pregnancy. For patients diagnosed with cancer during the course of pregnancy, if trastuzumab or rituximab are deemed necessary, they should be administered for brief periods with close fetal monitoring as the pregnancy-related risks appear to be related to prolonged drug exposure.

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