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Is chemotherapy during the first trimester of pregnancy really safe?

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Dear Editor,

Avilés *et al.*[1] recently reported on the long-term follow-up of 54 children, who were exposed to chemotherapy during the first trimester of pregnancy. The mothers were diagnosed with clinically advanced hematological malignancies requiring urgent treatment and refused abortion procedure or had an excessive risk of death or complication if abortion was performed. After a median follow up of 20.4 to 25.3 years, no adverse events were found in the offspring. No congenital, physical, hematological, neurological, psychological, cardiac, and chromosomal abnormalities were observed. This is a unique and important series, because until now, only case reports have been published on chemotherapy exposure during the first trimester, with a limited follow-up period.

However, when interpreting these results, two key questions remain before solid conclusions can be drawn. First, we lack information that allows us to estimate the risk of teratogenesis including, developmental stage at exposure, dose, duration and frequency of drug administration.[2] Human pregnancy can be divided into three developmental stages: the preimplantation to early postimplantation period (first 2 weeks after conception), the embryonic period of organogenesis (weeks 3 to 8) and the fetal period (week 9 to term). Mutations of pluripotent stem cells in the first 2 weeks after conception are lethal, and continuation of pregnancy depends on the number of surviving stem cells. When enough normal stem cells remain, the pregnancy can continue to develop normally, but with significant cell damage a miscarriage will occur—this is the so-called all-or-nothing phenomenon. The developing embryo is especially vulnerable in the period of organogenesis, and the heart, neural tube and limbs are most easily affected. After week 8, the central nervous system, eyes and genitalia develop further and remain vulnerable.[3] The first trimester is usually defined as the first 12–14 weeks of pregnancy and thus covers the entire implantation and embryogenesis period and a small part of the fetal period.

Second, no congenital malformations were found. The absence of congenital malformations should be interpreted, considering the general background risk of 4.1 to 6.9% for major malformations and 6.5 to 35.8% for minor malformations in children who were not exposed to chemotherapy *in utero*.[4–6] It is well-known that use of chemotherapy during the first trimester increases the risk the risk of major malformations and fetal death.[7] Doll *et al.*[8] reviewed 139 cases and found 25% incidence of malformations after first trimester exposure to chemotherapy for multiagent and 17% for single agent exposure. So, can the authors clarify why the incidence of congenital malformations is significantly lower when compared with similar studies? Four fetuses were lost (two miscarriages and two stillborns) during the second trimester of pregnancy, could this have been caused by congenital malformations?

We agree that maternal prognosis is primordial. In certain cases, treatment needs to start promptly, and chemotherapy in the first trimester does not always lead to major fetal complications. Nevertheless, the first trimester of pregnancy remains the highest teratogenic risk period and the utmost amount of caution is warranted. Pros and cons need to be thoroughly discussed with the patient and her partner before commencing therapy. We look forward to the reaction of Dr. Avilés and his team, so that treatment of pregnant patients with cancer can continue to improve.

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Yours sincerely,
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Letter to the Editor