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Brief communication: A case of cyclophosphamide exposure in the first trimester of pregnancy

Dear Editor,

It is known that women with autoimmune diseases are mostly of childbearing age, therefore exposure to drugs used in treatment, such as cyclophosphamide, may be encountered at the beginning of the pregnancy. Studies have shown that cyclophosphamide may cross the placenta and cause fetal harm [1]. Here, we report a case of a 36-year-old pregnant woman who was inadvertently exposed to cyclophosphamide for multiple sclerosis (MS) in the first trimester of pregnancy.

A 36-year-old patient consulted the Teratology Information Service of Clinical Pharmacology, Marmara University School of Medicine Pendik Research and Training Hospital, Istanbul, for assessment of the teratogenic risk profile of cyclophosphamide exposure during her pregnancy. She had a diagnosis of MS for fifteen years, and at the time of the appointment, she was pregnant for 31 weeks. The patient had three previous pregnancies, which resulted in one full-term delivery, one miscarriage in week 8, and one elective abortion. According to the acquired information, exposure to cyclophosphamide (single dose of 1000 mg) comprised the first trimester and the beginning of the fourth month of pregnancy due to an MS attack. The patient had stopped taking cyclophosphamide because of side effects such as hair loss and menometrorrhagia a month before she became aware of her pregnancy. She was prescribed iron, vitamin B and C supplements during pregnancy. Also, it was learned that during the first trimester of the pregnancy, the patient used ciprofloxacin and ibuprofen for a mild urinary tract infection. After the delivery, she was prescribed ocrelizumab once every six months for MS.

Table 1
Outcomes of cyclophosphamide use in pregnant women.

Author and article	Number of women exposed	Number of fetuses	Trimester	Indication	Outcome	Clinical Features
Zemlickis et al. Teratogenicity and carcinogenicity in a twin exposed in utero to cyclophosphamide (1993)	1	2	All trimesters	Acute lymphocytic leukemia	Preterm	Malformation
Enns et al. Apparent cyclophosphamide (cytoxan) embryopathy: a distinct phenotype (1999)	1	1	1st	Systemic lupus erythematosus	Unknown	Malformation
Köseoglu et al. Cyclophosphamide therapy in a serious case of lupus nephritis during pregnancy. (2001)	1	1	2nd and 3rd	Lupus nephritis	Term	Healthy
Ertenli et al. Cyclophosphamide exposure during pregnancy: Two cases. (2001)	2	2	1st and 2nd	Systemic lupus erythematosus	Unknown	Healthy
Paladini et al. Prenatal detection of multiple fetal anomalies following inadvertent exposure to cyclophosphamide in the first trimester of pregnancy (2004)	1	1	1st	Lupus nephritis	Abortus	Malformation
Clowse et al. Cyclophosphamide for lupus during pregnancy. (2005)	2	2	1st	Lupus nephritis	Miscarriages	–
Lannes et al. Successful pregnancy after cyclophosphamide therapy for lupus nephritis (2011) (3)	5	5	1st	Lupus nephritis	3 term, 2 miscarriages	3 healthy children
Lazalde et al. Klippel-Feil syndrome in a boy exposed inadvertently to cyclophosphamide during pregnancy: a case report (2012)	1	1	1st	Lupus nephritis	Term	Malformation
Harward et al. The impact of cyclophosphamide on menstruation and pregnancy in women with rheumatologic disease (2013)	6	6	Unknown	Rheumatologic disease	3 preterm, 2 abortion, 1 miscarriage	Not defined
Nelson-Piercy et al Lesson of the month: selective use of cyclophosphamide in pregnancy for severe autoimmune respiratory disease. (2016) (4)	1	1	2nd and 3rd	Good pasture's syndrome	Delivery at 37th week	Healthy
	1	1	2nd and 3rd	Idiopathic pulmonary fibrosis	Preterm delivery at 31th week	Healthy
Sanseverino et al. Fetal cyclophosphamide syndrome case report. Bergamo Poster presentations (2020)	1	1	All trimesters	Systemic lupus erythematosus	Unknown	Malformation

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The patient had a caesarian section on the 38th week of gestation to deliver the baby. The baby's birth weight was 2970 g, and there were no congenital anomalies and no health issues during and after the delivery. The child is three years old now; she has routine pediatric health controls at Marmara University School of Medicine Pendik Research and Training Hospital, and no health abnormalities have been detected until this day.

It is well-known that the use of cyclophosphamide during pregnancy increases the incidence of certain malformations in the fetus and exposure to cyclophosphamide in the first trimester has been associated with malformations, especially in the palate and limbs [2]. Also, growth restriction, ear and eye anomalies were reported in exposed infants to cyclophosphamide. On the other hand, there have been reports of healthy pregnancy outcomes in first trimester exposure to cyclophosphamide, as seen in our case [3,4]. The rare reports about the outcomes of cyclophosphamide treatment in pregnant women and effects on infants in the literature also include cyclophosphamide use in combinations with other cytotoxic drugs (Table 1).

Exposure to cyclophosphamide in the second and third trimesters of pregnancy is less likely to cause fetal malformations. However, an association between preterm birth and fetal growth anomalies was detected. In some studies, fetal demise was seen with the exposure of cyclophosphamide in the third trimester [5]. On the other hand, these patients had severe chronic diseases and it has been considered that these fetal deaths may not be associated with cyclophosphamide exposure.

We reported a healthy outcome despite being exposed to cyclophosphamide during the first trimester of pregnancy. However, there is strong evidence that the use of cyclophosphamide during pregnancy increases the risk of fetal malformations. Therefore, the use of cyclophosphamide should be avoided during pregnancy. Also, strict birth control measures should be recommended to women of childbearing potential using cyclophosphamide to prevent fetal loss and malformations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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