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Short communication

Methotrexate embryopathy after exposure to low weekly doses in early pregnancy

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ABSTRACT

Objective: Methotrexate (MTX) is a potent teratogen when used in high doses for cáncer or termination of tubal pregnancy. In contrast, it has been perceived as safe when used once weekly at low dose for rheumatological conditions.

Methods: A prospective observational controlled study of women exposed to low dose MTX. The control group were women exposed to MTX only before conception.

Results: Among the 8 MTX-exposed pregnancies, there was a case of typical MTX embryopathy, the first to be described to date at this lower once weekly dose Schedule.

Conclusions: This case has important implications for rheumatologists treating women of reproductive age, as the assumption of fetal safety of MTX, implied from small cohorts, is premature.

Methotrexate (MTX) is commonly prescribed to women of reproductive age treated for numerous autoimmune conditions such as rheumatoid arthritis, systemic lupus erythematosus, as well as after organ transplant [1]. This anticancer drug has been shown to be a potent teratogen in animal studies [2,3], as well as among women receiving high doses for cancer, or for termination of tubal pregnancies [4,5]. However, the fetal safety of the lower weekly dose used in autoimmune diseases has been only sparsely studied. In general, these studies failed to show increased teratogenic risk, and none of them reported on typical cases of MTX (Aminopterin) embryopathy with doses lower than or equal to 10 mg given once weekly [4].

The objectives of the present study were to describe pregnancy outcomes among women who consulted the Argentine Teratogenic Agents Information Service "Fetal Health" following exposure to MTX during pregnancy or during the 6 months prior to conception, before pregnancy outcome was known.

1. Patients and methods

We analyzed the medical records of pregnant women who consulted "Fetal Health" to obtain information about the potential risks of drug use during pregnancy between 2005 and 2012. We identified 18 pregnant women who were exposed to MTX during pregnancy or during the 6 months prior to conception; 14 patients participated in a follow-up telephone interview, while 4 patients were lost for follow-up. All women contacted "Fetal Health" before the outcome of their pregnancy was known.

We collected information regarding the outcome of the pregnancy (newborns without birth defects detected in the neonatal period, newborns with birth defects, fetal death or miscarriage). The babies with birth defects were evaluated by medical geneticists and underwent additional studies.

Patients were divided into two groups: **group 1** included women who were exposed to MTX during the first trimester of pregnancy ($n = 8$), and **group 2** included patients who were exposed to the drug only during the 6 months prior to conception ($n = 6$).

2. Results

In **group 1**, upon physical examination and additional tests we detected 6 healthy newborns, 1 case of Down syndrome, and 1 case consistent with MTX (Aminopterin) embryopathy (Table 1).

The baby with MTX embryopathy was the second daughter of a 29 years old mother with rheumatoid arthritis. She was exposed to MTX 7.5 mg orally weekly until week 10 of gestation. The mother also used fluconazole (150 mg orally weekly) and rofecoxib (25 mg a day) during the first trimester of pregnancy, and meprednisone (8 mg a day), ranitidine (300 mg daily) and isoniazid

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Table 1
Group 1: Women exposed to low dose weekly MTX during the first trimester of pregnancy.

Case	Maternal information			Methotrexate exposure			Other exposures during the first trimester of pregnancy				Outcome of pregnancy			
	Age (years)	Gravity	Parity	Weekly dose (mg)	Route of administration	Gestational age (calculated either from the first day of the last menstrual period or by ultrasound measurements) (weeks and days of gestation)	Drugs	Chronic maternal diseases	Acute maternal diseases	Tobacco use	Gestational age (calculated by ultrasound measurements or by physical examination) (weeks)	Sex	Weight (g)	Health status
1	29	2	1	7.5	Oral	0–10w	Meprednisone, rofecoxib, ranitidine, isoniazid, fluconazole	Rheumatoid arthritis	Mycosis	No	31	Female	900	Newborn with methotrexate embryopathy
2	19	1	0	10	Oral	2w3d–4w2d	Hydroxy-chloroquine, folic acid	Scleroderma, dermatomyosi-tis	No	No	40	Female	3200	Healthy newborn
3	17	1	0	15	Oral	0–6w3d	Meprednisone, folic acid	Polyarticular arthritis	No	No	40	Female	3100	Healthy newborn
4	34	3	2	15	Oral	0–3w4d	Diclofenac, omeprazole, folic acid	Rheumatoid arthritis	No	Yes	38	Male	2800	Healthy newborn
5	32	2	1	10	Oral	0–4w4d	No	Rheumatoid arthritis	Flu-like syndrome	No	35	Female	2500	Healthy newborn
6	23	2	1	5	Oral	0–9w	Meprednisone, buflomedil, folic acid	Systemic lupus erythematosus	No	No	38	Male	2400	Healthy newborn
7	33	2	0	10	Oral	0–5w	Prednisone, hydroxychloro-quine	Rheumatoid arthritis	No	No	38	Male	2800	Healthy newborn
8	35	1	0	10	Oral	0–5w	No	Rheumatoid arthritis	No	No	39	Male	2600	Newborn with Down syndrome and complete atrioventricular canal defect