Pregnancy course and neonatal outcome after exposure to leflunomide – 2 cases report and review of literature

Introduction
Leflunomide (LMF) is an immune-modulatory drug used in the therapy of Rheumatoid Arthritis (RA). After oral administration in the mucosa of digestive tract LMF is quickly converted to an active metabolite A77126 which is a competitive inhibitor of dihydroorotate dehydrogenase - enzyme required in pyrimidine synthesis resulting in decreased proliferation of T and B lymphocytes. As animal studies showed A77126 embryo- and fetotoxicity and no relevant epidemiological research in humans were available, LMF received category X pregnancy destination. This is a detailed presentation of two pregnancy cases during LMF therapy in Poland. The first patient was a multiparous woman suffering from RA for 17 years and treated with LMF during the last 16 months. The second woman was a primigravida with RA diagnosed 4 years ago and treated with LMF for the last 20 months. LMF wash-out procedures were started immediately as the patients referred with diagnosed early pregnancies with oral administration of 8g of cholestyramine tid for 11 days. After completing the procedure the patients were referred to the Gynecology and Obstetrics Department. The first pregnancy successfully finished with a vaginal delivery of a completely healthy, female newborn of 2540g at the 41st gestational week and the second patient also delivered vaginally a healthy female newborn of 3200g at 39th week of pregnancy.

Leflunomide (LMF) is an immune-modulatory drug used in the therapy of Rheumatoid Arthritis (RA) treatment [7,10]. As animal studies showed its embryo- and fetotoxicity and no relevant epidemiological research in humans were available, LMF received category X pregnancy destination. This is a detailed presentation of two pregnancy cases during LMF therapy in Poland. The first patient was a multiparous woman suffering from RA for 17 years and treated with LMF during the last 16 months. The second woman was a primigravida with RA diagnosed 4 years ago and treated with LMF for the last 20 months. LMF wash-out procedures were started immediately as the patients referred with diagnosed early pregnancies with oral administration of 8g of cholestyramine tid for 11 days. After completing the procedure the patients were referred to the Gynecology and Obstetrics Department. The first pregnancy successfully finished with a vaginal delivery of a completely healthy, female newborn of 2540g at the 41st gestational week and the second patient also delivered vaginally a healthy female newborn of 3200g at 39th week of pregnancy.
humans were available, LMF received category X pregnancy destination [7]. Therefore pregnancy must be excluded before LMF introduction and during the treatment plus 2 years after the therapy is completed. Women in reproductive age should use a reliable contraception [5]. When unexpected pregnancy occurs or patient wants to conceive earlier a wash-out procedure should be started immediately using oral administration of 8g cholestyramine tid, alternatively 50g of activated charcoal four times a day, both for 11 days, to obtain the leflunomide A771726 metabolite plasma level less than 0.02mg/L that is considered to have minimal risk for fetal development [1]. No detectable A771726 plasma levels of <0.02mg/L should be than confirmed by two separate tests 14 days apart [1] and it is advised to wait at least three menstrual cycles before conceiving [1].

The aim of this report is to present clinical management and outcomes of LMF-exposed pregnancies based on very detailed case presentations of such pregnancies reported in Poland for the first time.

1 Case Report
A thirty-eight-year old woman had been suffering from RA for 17 years. During the first 15 years she was treated with Methotrexat (17.5mg per week) and with low doses of steroids (Methylpredeton 4mg a day). In March 2005 because of an active RA LMF was introduced after pregnancy exclusion. The patient was informed that LMF could be potentially harmful to embryo and she must have avoided pregnancy during the therapy and two years after it was completed. The patient was introduced with a load-dose of 100mg LMF on the first three days and continued the dose of 20mg per day. During the first year of LMF therapy Disease Activity Score (DAS) was reduced from 7.36 points to 4.51 that according to European League Against Rheumatism (EULAR) response criteria meant a good therapeutic effect. Health Assessment Questionnaire (HAQ) was used to assess the patient’s physical function and improvement was noticed with a significant decrease from 3.75 to 1.5 points. In the 16th month of the LMF therapy the patients informed that she was pregnant and her last menstrual period (LMP) was 6 weeks and 2 days before. The LMF wash-out procedure was started immediately with an oral administration of 8g of cholestyramine tid for 11 days. After completing the procedure the patient refused to have the blood level of the A771726 metabolite checked. She was then referred to the Gynecology and Obstetrics Department of the Jagiellonian University as IV-gravida; IV-para in early pregnancy. During the first obstetrical consultation her past medical history was collected: LMP 12 weeks before; painless, irregular periods every 28–38 days lasting for 5 days. Vaginal deliveries as follows: 1991 alive female of 3350g of weight, born in the 41st week of gestation; 1993 alive female of 2850g, born in the 39th week of gestation; 1993 alive female of 3350g, born in the 39th week of gestation; 1992 alive female of 3200g, born in the 37th week of gestation.

Wartości referencyjne zakresu masy płodu w trakcie ciąży. 1. EFW - szacowana masa płodu na podstawie biometrii wykonanej w trakcie 3. badania ultrasonograficznego (USG); 2. EFW - szacowana masa płodu na podstawie biometrii wykonanej w trakcie 4. badania USG.

<table>
<thead>
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<th>Table I</th>
<th>Results of ultrasound fetuses’ biometry during gestation.</th>
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<td>Time of gestation according to LMP* [weeks-days]</td>
<td>Case 1</td>
<td>Case 2</td>
<td>Case 1</td>
<td>Case 2</td>
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<tr>
<td>Crown-rump length (CRL) [mm]</td>
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<td>9.2</td>
<td>18-6</td>
<td>25-4</td>
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<tr>
<td>Biparietal diameter (BPD) [mm]</td>
<td>30.5</td>
<td>24.4</td>
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<tr>
<td>Head circumference (HC) [mm]</td>
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<td>Abdominal circumference (AC) [mm]</td>
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<td>Femur length (FL) [mm]</td>
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<td>GASA** [weeks-days]</td>
<td>9.4-9.0</td>
<td>18-2</td>
<td>22.0</td>
<td>23.0</td>
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<tr>
<td>Expected fetal weight (EFW) [g] according to Headock formula C scale</td>
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<td>---</td>
<td>263</td>
<td>468</td>
</tr>
<tr>
<td>Newborn weight</td>
<td>Case 1</td>
<td>2540g</td>
<td>Case 2</td>
<td>3230g</td>
</tr>
</tbody>
</table>

**LMP - last menstrual period; ***GASA - growth adjusted sonographic age

*Log10(EFW) = 1.3596+0.00061xBPDxAC+0.424xAC+0.174xFL+0.0064xHC-0.00386xACxFL

In the 33rd week of gestation the patient was referred to the hospital due to threaten premature delivery. Standard therapy was introduced including intravenous application of magnesium sulfate and fenoterol additionally steroids (2 dosage of 12mg of Dexamethasone) were given for stimulating the fetal lungs maturity in case of preterm delivery. The patient was discharged after 5 days recovering completely from premature delivery symptoms.

In the 41st week of gestation according to LMP the patient was admitted to hospital in the first stage of labor. Physical examination at the delivery room revealed one live fetus in cranial presentation. In the 1st stage of labor delivery revealed one live fetus in cranial presentation. The cervix was soft and shortened with a 3cm dilatation. Because of weak uterus contractions a drip with oxytocin was introduced and a 2540g female newborn with 9 Ap-
2 Case Report

A thirty-year old women had been suffering from RA for 4 years. During the first 2 years she was treated with Methotrexat (17.5mg per week for two month), intramuscular gold injections (for one moth only), sulfaza-lazine (for 13 months 1g bid) and finally with Methotre-xat again. In September 2005 because of an active RA LMF was started after pregnancy exclusion. The patient was also informed that LMF therapy could be potential-ly embryo- and fetotoxic. LMF in a load-dose of 100mg on the first three days was introduced and continued in a dose of 20mg per day. During the first year of LMF therapy the patient’s general condition improved (de-crease in HAQ scale from 3.2 to 1.7 points) and also a reduction in DAS from 7.21 to 4.17 points was noticed. In the 28th month of the LMF therapy the patients infor-med that she was pregnant and LMF was 8 weeks and 1 day before. A LMF wash-out procedure was started immediately with an oral augmentation of 8g of chole-sytramine tid for 11 days and in subsequent two check-up tests the serum blood level of A71726 metabolite was undetectable. She was referred to the Gynecology and Obstetrics Department of the Jagiellonian Uni-versity. During first obstetrical consultation her medical hi-story was obtained: Primigravida with LMF 9 weeks be-fore; painful and heavy but regular periods every 28 days; lasting for 4 days. Pelvic examination revealed an enlar-ged uterus with the full and closed cervix. In ultrasound examination a single, viable fetus was visualized with heart rate 178 bits bpm, CRL=24,4mm was relevant for 9w0d. CBC, urinalysis and blood glucose level were normal also cervical cytology revealed benign cellular changes and cervical culture was negative for Neisseria gonorheae, Chlamydia trachomatis, Mycoplasma ho-minis and Group B Streptococci.

The next USG was made in the 18th week of ges-tation based on the LMF. Fetal biometry corresponded with gestational age (table 1). Doppler flow velocity in UA MCA were normal with CPr=1.8, FM were observed and FHR was regular, 145 bpm; placenta present on the back wall of the uterus type I according to Gran-num scale with no signs of detachment and AFI was 102mm.

The third USG was made in the 23rd week of ges-tation. The fetal anatomy was accurately checked re-vealing no abnormalities or malformations. Fetal bio-metry was assessed for 22 w0d of gestation (Table 1). FM were present, FHR was regular, 145 bpm; placenta present on the back wall of the uterus type I in Grannum scale without any symptoms of detachment, AFI was 98mm.

The OGTT result was within limits and also no ab-normal results of routine laboratory tests were presents. In the 32nd week of gestation USG revealed nor-mal fetal development without any symptoms of growth restriction (Table 1) with CPR=3.2. All the additional la-boratory tests as well as physical examination were nor-mal.

In the 38th week of gestation according to LMF the patient was admitted to the delivery room in the first stage of labor with regular contractions. Physical examination at admission showed a single life fetus in longitudinal cranial presentation with regular heart rate of 135 bpm. The cervix was soft and shortened with a 2cm dilatation. Because of weak uterus contractions an intravenous application of a solution of 5U of oxytocin in 500ml of 0,9%NaCl was started. After 3 hours and 30 minutes of the first stage and 10 minutes of the second stage a 3200g female newborn with 10 Apgar points in the first minute (and 10 Apgar points in the 5th minute) was de-livered vaginally. After parturition of a complete placenta the episiotomy that was performed during the second stage of delivery was managed with absorbable sutures. The third stage of delivery was managed subsequent-ly 10 minutes and 2 hours. Pediatric examination of the newborn revealed no abnormalities.

Comment

Because of scarce clinical data LMF is con-tradicted for pregnant women and nurs-ing mothers. Chakravarty et al. reported 10 pregnancies during LMF treatment from which two full-term healthy newborns, one preterm newborn with no malformations were delivered and two pregnancies had been being continued at the time of report-ing [2]. Additionally one miscarriage and two legal abortion took place in this presented group of patients and two cases were lost at follow-up [2]. In the 2004 Chambers et al. reported 43 LMF-exposed pregnancies com-pared to 78 pregnant RA controls and 47 non-diseased pregnant controls [3]. The prevalence of newborn malformations was similar between the three groups however LMF-exposed women and RA controls more often delivered preterm compared to non-disease controls, also mean birth weight of full term infants in both RA groups was lower compared to non-disease controls. The larg-est group of 310 LMF-exposed pregnancies (of these 164 with known outcome: 36 miscarriages; 43 terminations; 85 term pregnancies with malformations in seven cases) reported Ostensen based on the manufac-ture’s data collected up to 2003 year, however no further details were published [8]. Recently De Santis et al. have presented 5 well-documented cases of maternal LMF exposure in pregnancy from which four un-derwent voluntary abortion and only one healthy male newborn of 2600g was deliv-ered by Caesarean section at 39th week of ges-tation [4]. No wash-out procedure was applied in any case [4].

Also one case of a twin pregnancy was reported with a normal neonatal outcome [10]. In the first presented case a three-week difference was noticed in the pregnancy duration based on LMF compared to fetal USG biometry. However this difference was observed from the point when the first USG was performed and was steady during the whole pregnancy (table I, figure 1) also the newborn weight was at 10th percentile rel-evant for 38th week of gestation. After ex-clusion of pregnancy pathology irregularity of periods was considered to be the cause of this difference.

Because of this presented pregnancy was uneventful and resulted in delivery of the completely healthy newborn.

The wash-out procedure was started in both cases immediately after the patients referred with diagnosed pregnancy, neverthe-less the fetuses were exposed to A71726 during early organogenesis, however no congenital malformations occurred.

As collecting data of outcomes of LMF-exposed gestations is essential in adverse events risk estimation [9] we do hope that others Author will find this report useful in their research.

References