

PATERNAL EXPOSURE TO AZATHIOPRINE/6-MERCAPTOPYRINE – Experience of Berlin TIS

Introduction

Azathioprine (AZA) and its active metabolite 6-mercaptopurine (6-MP) are cytotoxic purine analogues used for treatment of inflammatory bowel disease or after organ transplantation. There are 3 recent reports with conflicting results on pregnancy outcome after paternal exposure to AZA/6-MP. (Rajapakse et al. 2000, Francella et al. 2003, Norgard et al. 2004). In addition, case reports were suggestive of a risk for chromosomal aberrations.

Methods

About 2% of consultations of the Berlin TIS are for paternal exposure. From 1988-4/2010 we had 449 inquiries concerning paternal exposure to AZA or 6-MP (Fig. 1). In 115 prospectively ascertained pregnancies follow-up (FUP) could be completed (Fig. 2). The control group were 341 non-exposed pregnancies matched for year of counseling.

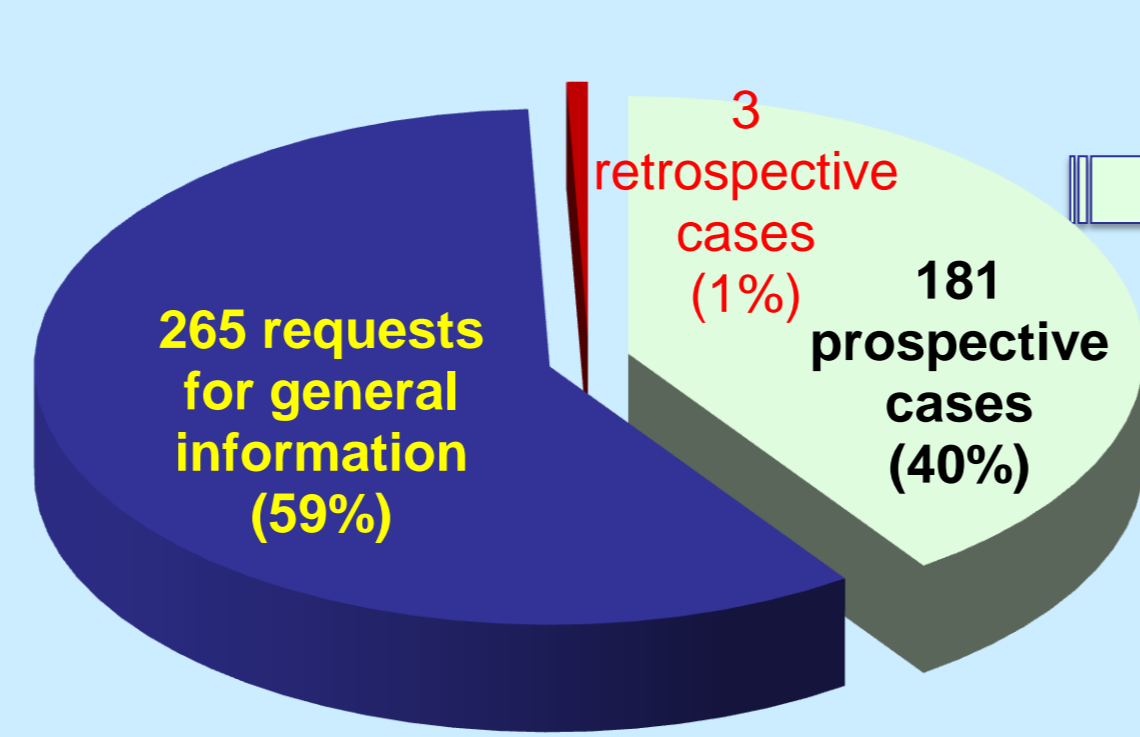


Fig. 1: 449 consultations on paternal exposure to AZA/6-MP.

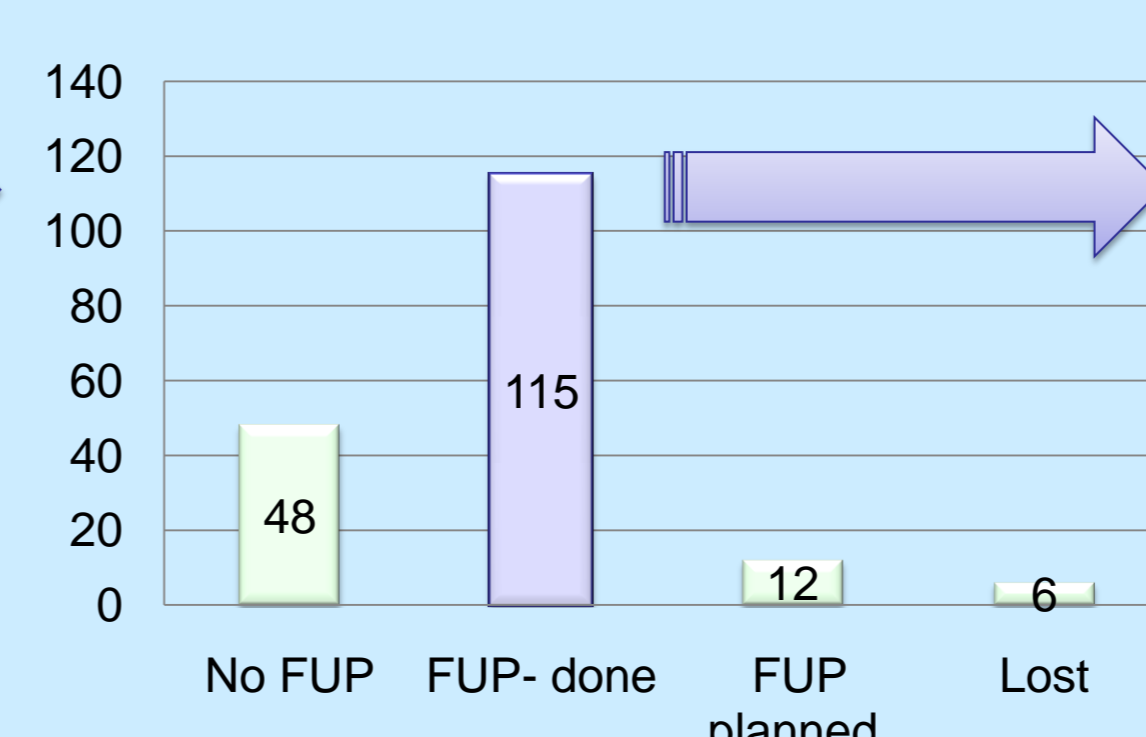


Fig. 2a: Follow-up rates of 181 prospectively ascertained pregnancies.

115 completed follow-ups

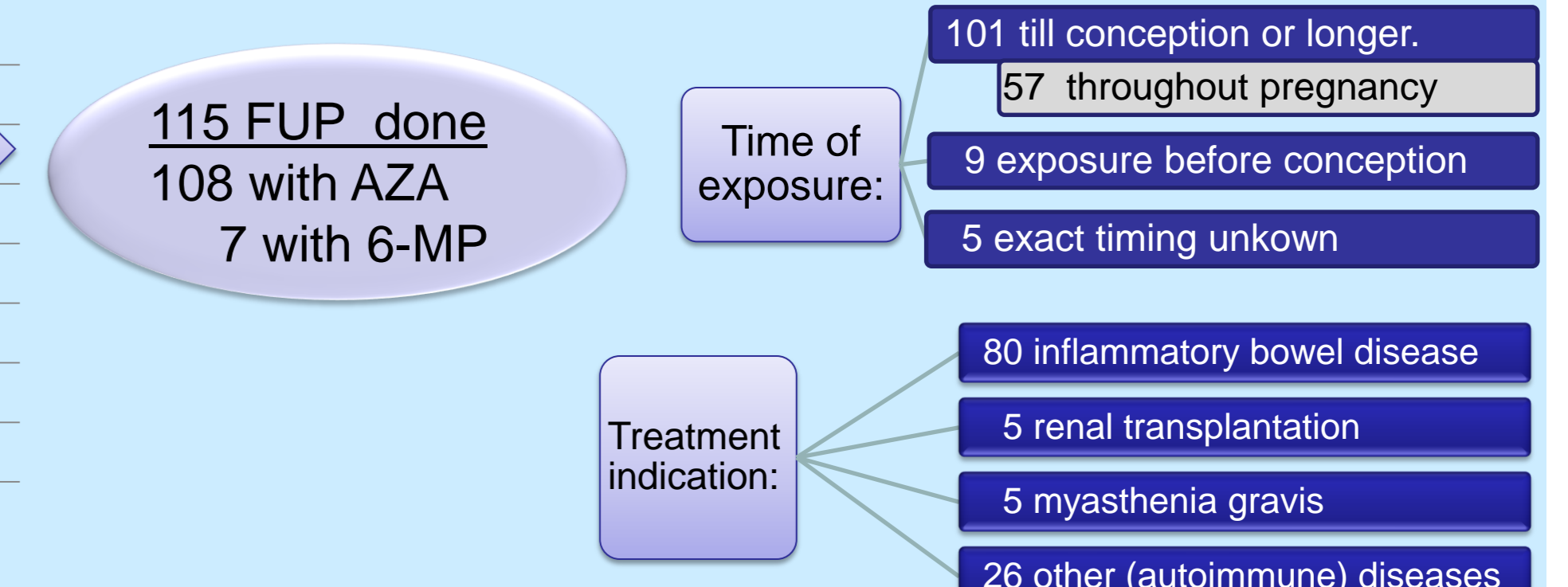


Fig. 2b: Time of exposure and treatment indication for 115 pregnancies with completed FUP.

Results

Maternal characteristics (A), pregnancy outcome (B), neonatal characteristics (C) and birth defects (D) were compared between exposed and controls.

A) Maternal characteristics

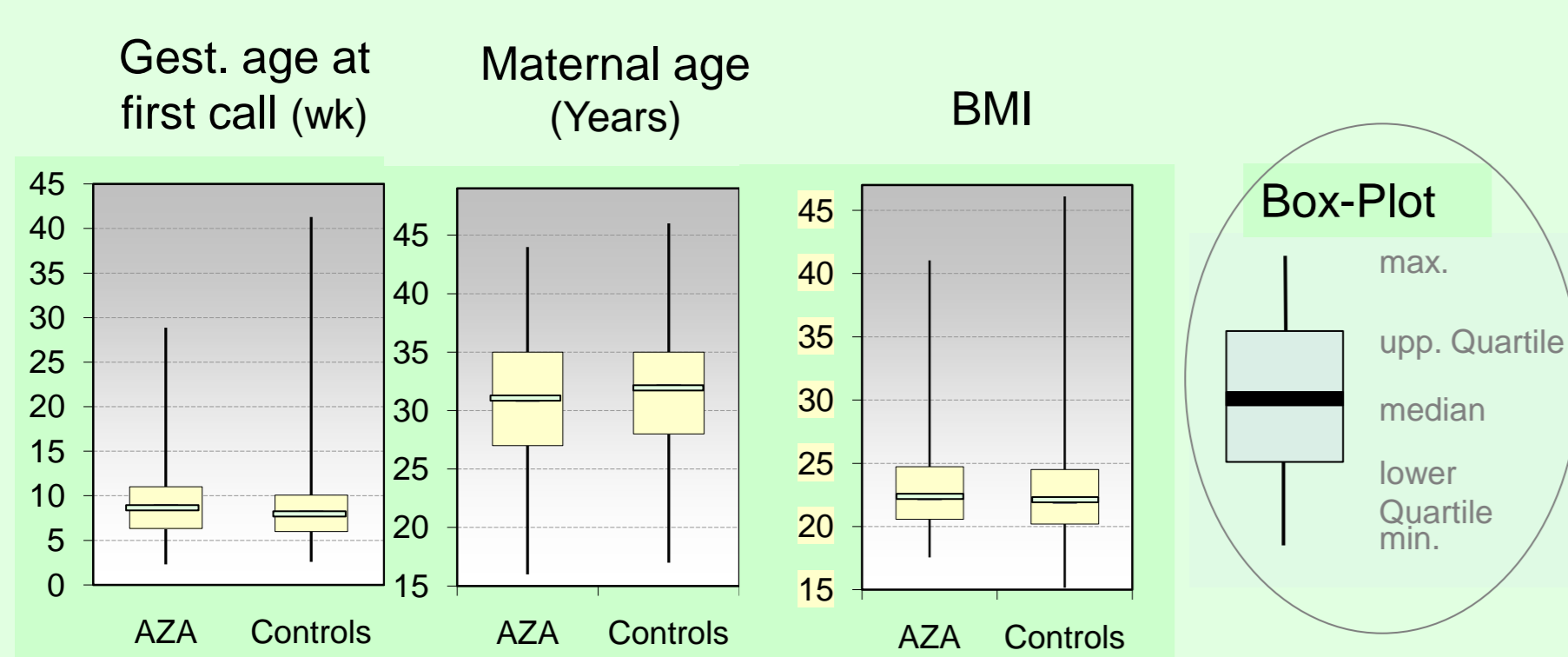


Fig. 3: a) Gestational age (GA at first call, maternal age and BMI in cases and controls b) explanation of box-plot.

- There were no differences for gestational age at call, maternal age and BMI as demonstrated by the box plot.
- But more mothers from the control-group planned their pregnancies, were better educated and smoked less (data not shown).

B) Pregnancy outcome

	AZA n=115*	Control n=341**
Spont. abortion	9	24
ETOP	7	3 [#]
Stillbirth	0	1
Live born	100	320

* 1 twin pregnancy
** 5 twin pregnancies and 1 triplet
[#] 2 ETOPs because of genetic disorders.

Tab 1: Summary of pregnancy outcome: spontaneous abortion and ETOP.

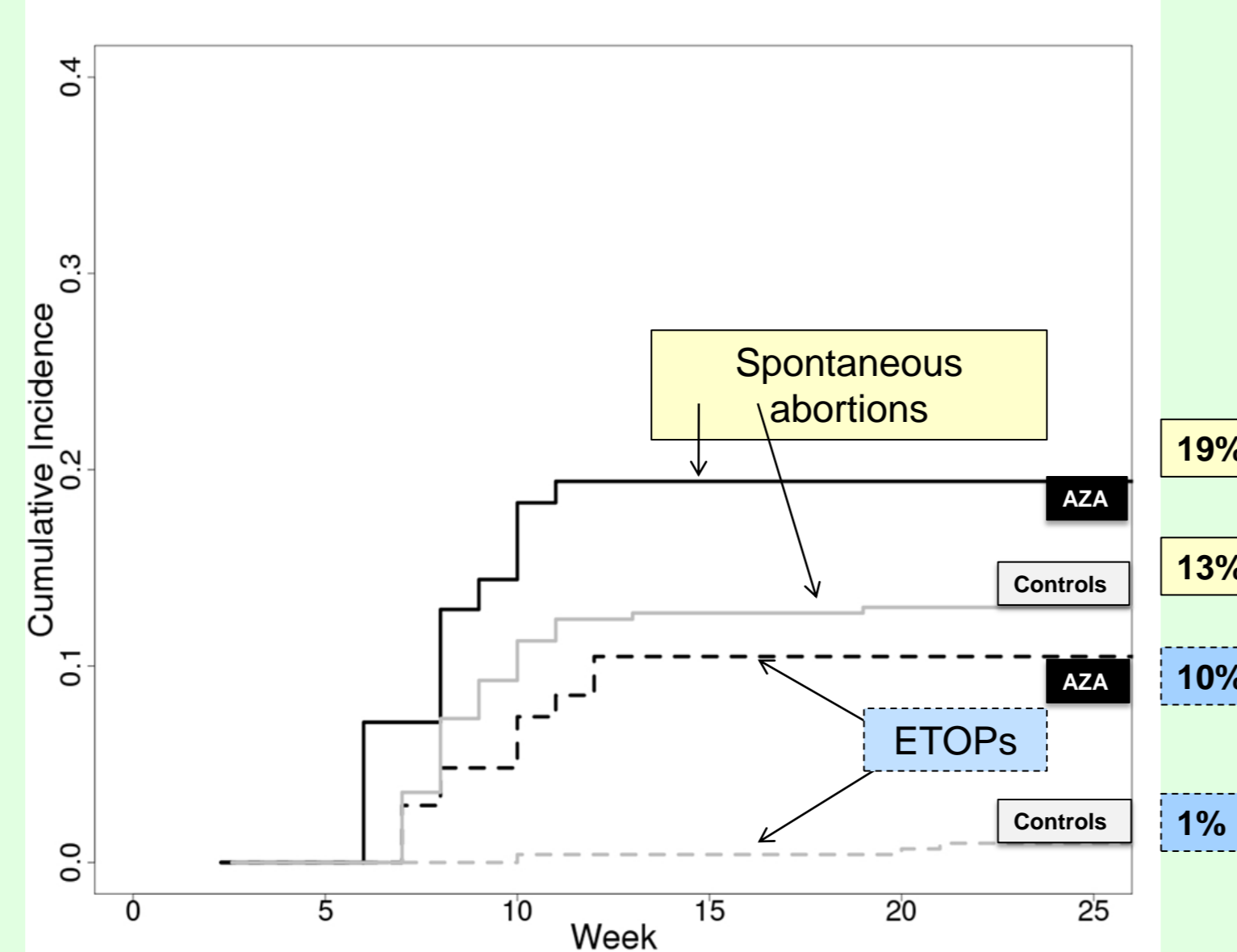


Fig. 4: Estimates of cumulative incidences for spontaneous abortions and ETOPs.

C) Neonatal characteristics

	AZA (n=100)	Controls (n=320)
Gestational age at birth (wk)*	40 (39-41) (29.6-42.3)	40 (38.1-40.3) (32-43)
Birth weight (g)*	3520 (3233-3718) (1320-4480)	3400 (3050-3730) (1320-5485)
Preterm birth	7% (7/100)	10% (32/320)

* Median (lower and upper quartile) (min. and max.)
Tab. 2: Median of gestational age at birth and birth weight and preterm birth. Data was available from at least 98 newborns of exposed and 318 control pregnancies.

- The rate of preterm birth was not increased in the exposed pregnancies. Birth weights of controls were slightly lower than of the exposed group.
- There was no difference in sex ratio distribution, length and head circumference (data not shown).

D) Birth defects

	AZA n = 115*	Controls n = 341**
Major birth defect	3	8
Minor birth defect	8	13
Genetic	0	5*

* 1 twin pregnancy
** 5 twin pregnancies and 1 triplet
[#] 2 ETOPs because of genetic disorders.

Tab. 3: Numbers of birth defects.

- The rate for major birth defects in the exposed group was not increased.
- The higher number of birth defects in the exposed group was not significant.

Birth defects in the exposed group:

(Time of exposure in brackets: i.e. L= long term)

3 major birth defects:

- small muscular VSD, spontaneous closure with 6 month, horseshoe kidney, hemangioma on the bottom (L)
- VSD, pulmonary stenosis* (1. Trim)
- PFO, motor retardation, dyspraxia** (L)

* gest. diabetes in the mother
**maternal diseases and co-medication

8 minor birth defects:

- 3 children with umbilical hernias (all L)
- 2 children with small hemangiomas (all L)
- Small PFO, no ASD (3 month preconceptional)
- Hip dysplasia IIc (wk 0-1)
- Xanthoma upper lip (L)

	AZA	Controls	OR 95% CI	p-value
All birth defects	11,0% 11/100	8,0% 26/324	1.42 0.61-3.11	0.42
Major birth defects	3,0% 3/100	2,5% 8/321	1.21 0.20-5.16	0.73

Tab. 4: Odds ratio, 95% confidence interval and results of Fishers exact test.

Discussion

- We did not observe an increased risk for birth defects after paternal exposure to azathioprine or 6-MP.
- There was a slightly higher rate of spontaneous abortions in the exposed (19%) vs. controls (13%). However, both rates lie within the normal range.
- The higher rate of ETOPs in the exposed group (10% vs. 1%) might be due to fear of medication and more unplanned and unwanted pregnancies in the exposed group.
- No chromosomal aberrations or genetic diseases were observed in the exposed group. However, the numbers are still too small to exclude a small genetic risk.

Conclusions

No specific adverse effects were observed after paternal treatment with azathioprine. Although data is still limited, we see no need to terminate a pregnancy or for invasive diagnostics only because of paternal treatment with azathioprine or 6-MP. Family planning does not need to be delayed in case of inevitable paternal therapy. High resolution ultrasound during pregnancy could be offered to those couples to confirm normal development of the fetus.