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Long-term follow-up of children exposed intrauterine to maternal thiopurine therapy during pregnancy in females with inflammatory bowel disease

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SUMMARY

Background
Inflammatory bowel disease (IBD) affects a substantial number of female patients in their reproductive years. Therefore, many physicians face the dilemma whether thiopurines, prescribed to maintain remission, can be taken safely during pregnancy. Data on long-term development outcome of children exposed to maternal thiopurine therapy are very limited.

Aim
To assess the long-term effects of *in utero* exposure to thiopurines during pregnancy on infant health status.

Methods
A prospective multicentre follow-up study was performed in children exposed intrauterine to maternal thiopurine therapy. Physical, cognitive and social aspects of infant health status were assessed with the 43-item TNO-AZL Preschool Children Quality of Life Questionnaire (TAPQOL). Furthermore, information on visits to general practitioner and medical specialists, and physician's advice regarding lactation was evaluated. Data were compared with normative data from a control group consisting of 340 children.

Results
Thirty children were included in this study [median 3.8 years (IQR 2.9–4.7)]. No differences on global medical and psychosocial health status were found between children exposed to intrauterine thiopurines and the reference group. Exposure to intrauterine thiopurines was not associated with increased susceptibility to infection or immunodeficiency in childhood. Twenty-one of 30 children were exclusively formula-fed based on a negative advice of medical specialists directed at thiopurine use during lactation.

Conclusions
Thiopurine use during pregnancy did not affect long-term development or immune function of children up to 6 years of age. Our results underscore the present notion that mothers, even those using thiopurines, should be encouraged to breastfeed their infants.

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INTRODUCTION

The conventional immune modulating thiopurines mercaptopurine (MP) and its pro-drug azathioprine (AZA) are widely prescribed in inflammatory bowel disease (IBD) mainly to maintain clinical remission.[1, 2] As IBD affects significant numbers of female patients in their reproductive years,[3, 4] the dilemma whether thiopurines can be taken safely during pregnancy and lactation affects many patients and their treating physicians.[5] The US Food and Drug Administration (FDA) has classified MP and AZA as category D medications, indicating that thiopurine use in pregnancy may be acceptable, although foetal risk may exist.[6] Therapeutic benefit is clearly demonstrated, as active colitis or flare-up of disease during pregnancy is associated with low birthweight and prematurity.[7, 8] On the other hand, teratogenicity shown in animal studies and potentially serious neonatal complications reported in several case studies have raised concern about the detrimental effects of thiopurine (metabolites) on neonatal outcome.[9–13] In recent (prospective) studies analysing the pharmacological aspects of thiopurine use during pregnancy and effects on birth outcome, it has been shown that thiopurine exposure is not associated with congenital abnormalities, but may increase the risk of preterm birth and neonatal anaemia.[6, 14] Studies concerning the safety of maternal thiopurine use in lactation have described that thiopurine use during breastfeeding is safe, despite the detectable (low) concentration of thiopurine metabolites in breast milk. Breastfeeding should therefore be recommended, considering its beneficial therapeutic effects for the nursing IBD mother.[15–17] However, data on long-term effects of maternal thiopurine use during pregnancy on health status of children are limited to one (retrospective) small study, which showed no differences in infection rate in children breastfed by mothers receiving thiopurines for IBD as compared with children breastfed by mothers without immunosuppressive therapy.[18] Knowledge about long-term outcome is essential. Potential negative effects may have significant implications for the therapeutic strategy of pregnant IBD patients. Proof of the absence of negative effects may result in better compliance by decreasing fear of harm to the foetus and infant.[19–21] The aims of this study were to assess the long-term effects of *in utero* exposure during pregnancy and by lactation to thiopurines on infant health status. This follow-up study was based on a cohort from a prospective multicentre study on pharmacological aspects and neonatal outcome of *in utero* exposure to conventional thiopurine therapy, as described by Jharap *et al.*[14]

MATERIAL AND METHODS

In this study, we prospectively followed a cohort of neonates who participated in a multicentre study on pharmacological aspects and neonatal outcome of *in utero* exposure to conventional thiopurine therapy.[14] In this study, 31 neonates of 30 IBD patients on steady state AZA or MP treatment during the entire pregnancy were included between January 2006 and January 2011. Characteristics of the IBD patients are given in Table 1. Criteria for inclusion in this prospective study were as follows: age between 1 and 6 years, *in utero* exposure to thiopurines, and parental ability to understand and complete a Dutch questionnaire. Questionnaires were mailed between June 2012 and August 2012 to all 30 participants. Mailing was preceded by telephone contact to enhance participation.

For the assessment of quality of life of the children, we used the 43-item TNO-AZL Preschool Children Quality of Life Questionnaire (TAPQOL).[22] TAPQOL is a validated tool to assess physical, cognitive and social aspects of health status in preschool children (1–6 years), and enables detection of differences between healthy and less healthy children.[23, 24] The child's functioning is assessed on 12 domains; gastrointestinal, dermatological, pulmonary, sleep, appetite, problem behaviour, mood, anxiety, energy level, communication (cognitive functioning), social functioning and motor functioning. TAPQOL is based on parental reporting, reflecting the child's health state in the last 3 months; the items on behaviour and functioning are based on comparison to healthy,

Table 1 | Characteristics of maternal IBD patients on steady state AZA or MP treatment during the entire pregnancy

Total (*n*)	30
Age (years) (median (IQR))	30 (27–33)
Disease (*n*) (CD/UC)	24/6
Type of thiopurine (*n*)	
AZA	28
MP	2
Dosage of AZA (mg/kg) (median (IQR))	1.93 (1.46–2.23)
Dosage of MP (mg/kg)	0.94–1.32
Co-medication at inclusion (*n*)	
Mesalazine	6
Prednisone enema	2
Infliximab	2
Adalimumab	1
Laxatives	2

AZA, azathioprine; CD, Crohn's disease; MP, mercaptopurine; IBD, inflammatory bowel disease; IQR, interquartile range; UC, ulcerative colitis.

age-matched children. Most questions consist of two sub-questions: the first one measuring the presence of health status problems or functional limitations, the second one assessing the impact of these health status problems or limitations on well-being. A syntax file provided by the authors of the TAPQOL is used to convert the raw TAPQOL scores to a 0–100 scale. Higher scores indicate better functioning in the relevant scale. Data were compared with normative data from a control group consisting of 340 Dutch children, provided by the authors of the TAPQOL.[22]

In addition to the TAPQOL questionnaire, parents were asked to provide information on the child's growth parameters, medication, visits to general practitioners (GP) in the 6 months prior to inclusion, frequency and reason for visits to medical specialists, laboratory investigations, physicians advice regarding lactation and potential side effects from vaccination (defined as fever >39.5°C, partial or complete loss of consciousness or seizures within a week after vaccination). Finally, parents were asked how they considered the general development of their child, compared with age-matched children.

Ethical considerations

The study was approved by the Medical Ethics Committee of all participating hospitals. All parents signed the informed consent.

Statistics

Data analysis was performed with the statistical Package for Social Sciences (SPSS, Chicago, IL, USA), Windows version 15.0. Descriptive statistics were used to describe the characteristics of the participating children in this study. TAPQOL scale scores were constructed with a syntax file provided by the authors of the TAPQOL before statistical analysis was done. Missing scores were handled according to the guidelines of the questionnaire. One-sample-sign and binomial tests were performed to assess whether the median of the TAPQOL scales scores of the children exposed to thiopurines differed from the reference group. Differences between study group and normative group were quantified by calculating the effect sizes. This was done by dividing differences in mean TAPQOL scale scores between the two study groups by the standard deviation of the scores in the normative group. According to the guidelines of Cohen, effect sizes of circa 0.1 were considered to be small, effect sizes of circa 0.5 moderate and effect sizes of approximately 0.8 large.[24] To compensate for multiple testing, a P value of <0.005 was considered significant.

RESULTS

Thirty-one TAPQOL questionnaires were sent to 30 families. Twenty-seven families (90%) completed and returned the questionnaires. In three cases, the addressed family returned two questionnaires, one from the twins from the previous study and two from siblings in the age category of 1–6 years and also exposed *in utero* to thiopurines. A total of 30 children were eligible for evaluation. The median age was 3.8 years (IQR 2.9–4.7), the proportion of boys was slightly higher (57%, $n = 17$) than girls. All children showed length-for-age and weight-for-length within the normal range (±2 s.d.). Infants exposed to thiopurines during intrauterine life did not differ from the control group in 11 of the 12 examined domains [gastrointestinal, dermatological, pulmonary, sleep, problem behaviour, mood, anxiety, energy level, communication (cognitive functioning), social functioning and motor functioning], but they had a significantly higher score with regard to appetite compared with controls (Table 2). Although the normative cohort used to generate the TAPQOL instrument differed significantly in age from our study population (median 2.5 years; IQR 1.8–3.2; $P = 0.000$), analysis of an age-matched cohort constructed out of the reference group did not influence the results.

Table 2 | TNO-AZL Preschool Children Quality of Life Questionnaire (TAPQOL) scores of study group (children exposed to intrauterine thiopurines) compared with reference scores

Domain	Study group ($n = 30$) Mean (s.d.)	Reference group ($n = 340$) Mean (s.d.)	Effects size (d)	P value
Stomach	87.2 (15.6)	91.8 (13.8)	0.3	0.08
Skin	87.2 (13.3)	91.7 (10.8)	0.4	0.03
Lung	97.0 (9.7)	93.6 (16.2)	0.2	0.3
Sleep	90.1 (14.5)	82.3 (17.3)	0.4	0.02
Appetite	92.8 (10.4)	84.6 (13.2)	0.6	0.001
Liveliness	97.2 (10.8)	98.0 (8.0)	0.1	0.6
Positive mood	97.8 (7.2)	98.7 (6.5)	0.2	0.5
Problem behaviour	73.6 (19.0)	67.7 (15.3)	0.4	0.05
Anxiety	78.9 (18.0)	77.8 (17.9)	0.03	0.9
Social	96.1 (9.5)	91.3 (15.3)	0.3	0.1
Motor	98.5 (4.8)	98.5 (4.4)	0.01	0.9
Communication	96.2 (6.7)	91.7 (9.9)	0.5	0.01

To compensate for multiple testing, P values of <0.005 are considered significant.

Regarding visits to the general practitioner in the 6 months prior to inclusion, no statistically significant differences were seen between those who were exposed to thiopurines vs. those who were not (study group 47%, reference group 53%, $P = 0.53$). Reasons to visit the general practitioner in the study group reflected minor medical disorders, such as eczema, feeding problems, constipation and upper respiratory tract infections. At the time of completing the questionnaire, nine children used medication for these problems (proton pump inhibitor,[2] oral laxatives,[3] topical corticosteroids[2] and salbutamol inhalator[2]). No severe infections, defined as infections requiring intravenous treatment or that led to hospitalisation, nor malignancies were reported.

Since birth, 50% of the children (15/30) were referred to a paediatrician, four for regular follow-up related to prematurity and one each for suspicion of neurofibromatosis I (not confirmed by DNA analysis), respiratory syncytial virus infection, acute gastroenteritis, upper respiratory tract infection with dyspnoea, gastro-oesophageal reflux disease, food allergy, developmental dysplasia of the hip, constipation, lipoma, suspicion of urinary tract abnormality (not confirmed) and recurrent upper respiratory tract infections. Information on frequency of referrals to medical specialists of children of the reference group was not available. Laboratory investigation was performed in nine children; no signs of myelosuppression or liver test abnormalities were reported. All children but one complied to the Dutch vaccination schedule (including vaccination against diphtheria, tetanus, pertussis, polio, Haemophilus influenzae type b, pneumococcal disease, measles, mumps, rubella, from which the last three mentioned are live attenuated vaccines), none of the vaccinated children experienced serious side effects.

The majority of this study group, 21 of 30 children, was exclusively formula-fed following a negative advice of a medical specialist directed at thiopurine use during lactation. Two children were already weaned within 3 months after birth for the same reason. Mean duration of breastfeeding in the nine breastfed children was 7 months (range, 3–13 months). No statistically significant differences were found in any of the 12 TAPQOL domains between breastfed and formula-fed children.

All parents except one considered the general development of their child as nondeviant compared with age-matched children. One child was considered excessively active, according to the parents in line with a suspected attention deficit disorder, but medical consultation had not been taken place to evaluate this problem.

DISCUSSION

To our knowledge, this is the first prospective study evaluating the long-term development of children exposed intrauterine to thiopurine (metabolites) during pregnancy. Physical, social and psychological aspects of the development were assessed by TAPQOL, a validated 43-item questionnaire covering 12 domains, extended with questions directed at consumption of medical care, lactation and potential serious adverse reactions to vaccinations. Our results suggest that *in utero* exposure to thiopurines is not associated with negative effects on long-term childhood development or susceptibility for infectious disease.

Thiopurines and neonatal outcome

Jharap and colleagues recently demonstrated that the foetus of mothers using thiopurine therapy for inflammatory bowel disease is exposed *in utero* to pharmacologically active 6-thioguanine nucleotides (6-TGN), with a strong correlation between maternal and foetal 6-TGN levels.[14] It was therefore recommended to monitor maternal thiopurine metabolite concentration during pregnancy, to confirm compliance and to avoid potentially toxic foetal 6-TGN levels.[14] Potentially serious neonatal complications of thiopurine exposure have been reported in several case studies, including myelotoxicity, immunosuppression, neonatal infections, severe combined immune deficiency and hypogammaglobulinemia.[9–12] Furthermore, several studies have investigated whether maternal MP and AZA usage was associated with congenital malformations and preterm birth, but results are heterogeneous and contradictory.[25–27] In a recent systematic review and meta-analysis on the effects of thiopurine exposure on three birth outcomes (low birthweight, congenital abnormalities and preterm birth), it was concluded that thiopurine exposure was not associated with low birthweight or congenital abnormalities, but was associated with preterm birth.[6] The results of the recent study of Jharap *et al.*, showing no increased prevalence of low birthweight, major congenital abnormalities and preterm birth, were not included in this systematic review.[14]

Breastfeeding

Traditionally, breastfeeding by IBD patients on thiopurine therapy has been discouraged because of theoretical

risks of bone marrow suppression, vulnerability to infection and pancreatitis.[15] Recent studies, measuring drug levels in human milk and infant blood,[15–17] all conclude that concentrations in breast milk are low, that breastfeeding by thiopurine appears to be safe, and that breastfeeding should, even in this population, be recommended because of its beneficial effects.[28] Despite this consensus of the European Crohn's and Colitis Organization (ECCO), still relatively few IBD-suffering mothers breastfeed their infants, in particular when using thiopurine derivatives. This may reflect maternal fear for potential detrimental effects to the infant.[29] In this study, the majority of infants (77%) were withheld from breastfeeding following a negative advice from a medical specialist regarding thiopurine use and concurrent lactation. We found no statistically significant differences between the breastfed and formula-fed children with regard to TAPQOL scores in any of the 12 domains, but it has to be taken into account that the number of breastfed children is small to draw firm conclusions. However, in line with the current consensus, our findings underline the recommendation that mothers using thiopurines should (also) be encouraged to breastfeed their child.

Long-term follow-up

Information on the long-term developmental outcome of infants exposed to thiopurines during pregnancy is scarce. A recent study compared infection rates in 15 breastfed children by mothers receiving AZA (median dosage 150 mg/day) for IBD, with 15 children breastfed by mothers without immunosuppressive therapy. Assessment was performed by questionnaires at the mean ages of 3.3 and 4.7 years respectively. No differences were found in infection rates between the two groups, and all infections reported were childhood diseases as commonly seen in the general population.[18] In this study, only one of 30 children had been admitted to the hospital, because of dehydration complicating viral gastroenteritis. No differences were found between the two groups regarding visits to general practitioner during the last 6 months prior to inclusion. Since birth, 50% (15/30) of the children had visited a paediatrician because of a wide range of indications, none of them being linked to congenital abnormalities or suspected immune disorders. None of the children had suffered serious infections, adverse vaccination reactions or malignancies, although the number of infants in our study is limited and follow-up is obviously too short to draw definitive conclusions with regard to tumorgenicity. At birth, 60% of all children had mild anaemia, most likely caused by the maternal thiopurine use.[14] However, this was not related to clinically relevant haemodynamic symptoms, reflected by normal Apgar scores directly after birth in all cases. Follow-up of haemoglobin levels has not been performed routineously. In nine children, laboratory investigation was done for different indications; no signs of myelosuppression or liver test abnormalities were reported. Our results show that exposure to intrauterine thiopurines is not associated with increased susceptibility to infection or immunodeficiency in childhood. Furthermore, no relevant differences were found between children exposed to intrauterine thiopurines and the reference group on global medical and psychosocial health status. This is in line with the parents reported perception of their child's general development. Our results have to be confirmed in studies with larger number of infants.

In summary, thiopurine use during pregnancy and lactation did not affect long-term development or immune function of children up to 6 years of age. There is no direct medical reason to change thiopurine medication in IBD patients just because of pregnancy. The results of this study underscore the present, but usually denied, notion that mothers using thiopurines should be encouraged to breastfeed their infants, a notion that should be more acknowledged among medical specialists.

AUTHORSHIP

Guarantor of the article: T. G. J. de Meij.

Author contributions: T. G. J. de Meij, B. Jharap, A. A. van Bodegraven and N. K. H. de Boer performed the research. T. G. J. de Meij, B. Jharap, A. A. van Bodegraven and N. K. H. de Boer collected and analysed the data. T. G. J. de Meij, B. Jharap, C. M. F. Kneepkens, A. A. van Bodegraven and N. K. H. de Boer designed the research study and wrote the article. T. G. J. de Meij, B. Jharap, C. M. F. Kneepkens, A. A. van Bodegraven and N. K. H. de Boer contributed to the design of the study. All authors approved the final version of the manuscript.

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APPENDIX

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