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## In utero exposure to Azathioprine in autoimmune disease. Where do we stand?

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**Abbreviations:**

AZA	Azathioprine
AI	Autoimmune Disease
IUGR	intrauterine growth restriction
SLE	Systemic lupus erythematoses
6 MP	6-mercaptopurine
6 TGN	6-thioguaninenucleotide
IBD	Inflammatory Bowel Disease
NI	Neurocognitive impairment
aPL	anti phospholipid antibody

## **Abstract**

Azathioprine (AZA), an oral immunosuppressant, is safe during pregnancy. Some reports suggested different impairments in the offspring of mothers with autoimmune diseases (AI) exposed in utero to AZA. These observations are available from retrospective studies or case reports. However, data with respect to the long-term safety in the antenatally exposed child are still lacking. The aim of this study is to summarize the current knowledge in this field and to focus on the need for a prospective study on this population. We performed a PubMed search using several search terms.

The actual data show that although the risk of congenital anomalies in offspring, as well as the infertility risk, are similar to those found in general population, there is a higher incidence of prematurity, of lower weight at birth and an intra-uterine delay of development. There is also an increased risk of materno- fetal infections, especially cytomegalovirus infection. Some authors raise the interrogations about neurocognitive impairment. Even though the adverse outcomes might well be a consequence of maternal illness and disease activity, interest has been raised about a contribution of this drug. However, the interferences between the external agent (in utero exposure to AZA), with the host (child genetic susceptibility, immune system anomalies, emotional status), environment (public health, social context, availability of health care), economic, social, and behavioral conditions, cultural patterns, are complex and represent confounding factors.

In conclusion, it is necessary to perform studies on the medium and long-term outcome of children born by mothers with autoimmune diseases, treated with AZA, in order to show the safety of AZA exposure. Only large-scale population studies with long-term follow-up will allow to formally conclude in this field.

## **Take home messages**

- There is no study on a significant number of subjects concerning the medium and long-term outcome of children born by mothers with autoimmune disease treated with AZA
- As AZA use is related to underlying disease and disease activity and many confounders interfere with AZA treatment, there is a major difficulty to distinguish between the influence of the disease itself on the risk of adverse birth outcome and potential AZA effects in offspring at medium and long term.
- Data need to be implemented with large, multicenter studies.

## 1. Introduction

Although autoimmune diseases (AI) are rare, their prevalence as whole group of diseases is estimated to be around 9.4% in the general population (1).

Beside a large variety of immunosuppressive drugs and biotherapies currently used, several new therapies emerge at now (2-4).

Nevertheless, several unmet need still remain in rheumatology and autoimmune disease (5).

The activity of disease in pregnant women with autoimmune diseases requires sometimes the use of immunosuppressive drugs, among which Azathioprine (AZA) is one of the best studied and widely prescribed. Although AZA is considered safe during pregnancy (6-8), some reports suggested different impairments in the offspring of mothers with AI exposed to AZA. The complications reported in these children mainly consisted in congenital malformations, preterm birth and low birth weight, neurocognitive problems, temporary immunological disturbances. These observations are mostly derived from retrospective studies (cohorts with no control groups) or case reports, therefore the quality of evidence of the relationship with antenatal exposure to AZA is low. Data with respect to the long-term safety in the antenatally exposed child are still lacking.

Prematurity and intrauterine growth restriction (IUGR) and some reversible hematological anomalies have been reported in children exposed to AZA, but maternal disease activity during pregnancy could be a confounder. In addition, some authors reported a lower birth weight and a higher rate of prematurity (9), impaired neonatal hematopoiesis (10), atrial or ventricular septal defects (11) after AZA in utero exposure. A maternal-fetal infectious risk (particularly to CMV) could be possibly related to the immunosuppression induced by AZA.

There are limited and controversial data on the long-term neurodevelopment of children exposed *in utero* to AZA (12-13). Most of the data regarding the use of AZA during pregnancy derive from non-systemic lupus erythematosus (SLE), non-systemic autoimmune diseases cohorts, but rather from renal transplantation. Some data are available from inflammatory bowel diseases (IBD) patients. There are also reports on neurocognitive impairment (autism, learning disabilities and special educational services) as related to AZA antenatal exposure in autoimmune diseases (14-15).

This review summarizes the current knowledge in the field of health of children exposed to AZA born to mothers with various AI and particularly with SLE and strengthens the need for a prospective study on this population.

We performed a PubMed search using the search terms *azathioprine AND in utero exposure, azathioprine AND birth outcome, azathioprine AND Intrauterine exposure, immunosuppressive therapy AND pregnancy, antirheumatic drugs AND pregnancy, azathioprine AND fetus, azathioprine AND paternal exposure, offspring and azathioprine, azathioprine AND infertility, fetal toxicity AND immunosuppressive drugs in pregnancy, azathioprine AND expectant fathers, azathioprine AND breast feeding, mercaptopurine AND birth outcome, thiopurine AND pregnancy, azathioprine AND inflammatory bowel disease, azathioprine AND Systemic lupus erythematosus, azathioprine AND Transplant, azathioprine AND Crohn's disease, azathioprine AND ulcerative colitis, azathioprine AND autoimmune disease, mercaptopurine AND inflammatory bowel disease, mercaptopurine AND Systemic*

*lupus erythematosus, mercaptopurine AND Transplant, mercaptopurine AND Crohn's disease, mercaptopurine AND ulcerative colitis, mercaptopurine AND autoimmune disease.*

References from selected papers were reviewed and used if relevant.

## **2. Pharmacological properties of AZA**

Azathioprine is an antimetabolite which is 80% metabolized to *6-mercaptopurine* (6-MP). 6-MP, in turn, is changed into the active metabolite 6-thioguaninenucleotide (6-TGN). Approximately 47% of orally given AZA is absorbed, whereas 6-MP is, on average, only 16% absorbed. A teratogenic potential in humans has not been identified. It may be prescribed during pregnancy. The placental transfer is limited (16); however, 6-TGN was found in similar concentrations in the erythrocytes of three mothers and their healthy newborns (17). Jharap et al. discussed whether the maternally derived metabolites, and not the maternal drug, crossed the placental barrier (18). They prospectively analyzed thiopurine metabolism before, during, and after pregnancy in 30 mother-child pairs (31 infants) and found that during pregnancy, maternal 6-TGN decreased, while 6-methylmercaptopurine (6-MMP) increased (18).

The enzyme inosinotriphosphorylase is lacking in the fetal liver, and, as it converts AZA to its active form, the fetus should therefore be theoretically protected from AZA crossing the placenta (19-20).

## **3. Use of AZA during pregnancy: data on teratogenicity**

AZA has been shown to induce teratogenic effects (limb, eye, digits, skeletal, CNS) in various animals (rat, mouse, rabbit, and hamster) (21).

There are no conclusive cases of human malformations attributed to maternal treatment with AZA.

U.S. Food and Drug Administration's (FDA) pregnancy category places AZA in category D (for all Trimesters): there is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Also, the Australian TGA Drug Evaluation Committee's category places AZA in category D drugs which have caused, are suspected to have caused, or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

CRAT (French Teratogenic Agents Reference Center) advises to not discontinue treatment if AZA is necessary for the mothers' health during the preconception period and pregnancy, as data with respect to potential malformations are reassuring.

According to CRAT, on few small-sized clinical series in which children exposed in utero to AZA were followed-up until 18th years old showed reassuring data; only one case of hepatoblastoma was reported.

Most of the reports with respect to AZA come from the National Transplantation Pregnancy Registry (NTPR) in the United States related to immunosuppressive medication and

pregnancy, although the authors estimate that all of the registry data combined only represents one-third of the available information (22-24).

Some authors analyzed the pregnancy outcomes in female renal transplant recipients with SLE versus those with other diagnoses (25). Overall, children's health was reported to be good, prematurity and low birthweight were found in both groups and there were no apparent malformations (25). They found that outcomes were comparable to renal recipients with other diagnoses.

There are also some reports in AI, but consistent data are mostly available in IBD. Anecdotal experience has associated prenatal exposure to AZA with different congenital anomalies, but none of them were clearly linked to the drug. Other reported events after antenatal exposure to AZA were transient chromosomal anomalies in clinically normal infants (26).

Rajapakse et al reported a higher incidence of spontaneous abortions and congenital malformations in children with fathers treated with 6-MP for IBD at conception or in the previous 3 months as compared with a control group (27). Nevertheless, the overall rate of congenital malformations was similar with the rate observed in the general populations of newborns.

Subsequently, these data were not confirmed by other groups (28).

All these data are summarized in table 1.

#### **4. In utero exposure to AZA: are there any consequences on birth weight and gestational age at delivery?**

Consistent data with respect to birth weight and term birth originate mostly from registries of renal transplant patients (22-25, 30-33).

In most of the series of children from one of parents with renal transplants, which were prenatally exposed to AZA, premature birth and lower weight at birth were reported (22-25, 30-33).

There are further information available in AI, particularly in IBD and SLE.

The observations on offspring of parents with IBD are controversial, as some authors reported higher rates of prematurity and lower birth weight (9, 35-36, 42), data not confirmed by others (28, 38, 43, 45, 46) (table 2).

#### **5. Use of AZA during lactation**

Azathioprine and its metabolites were found in breast milk, exposing the child to 0.1% of the maternal dose (47).

World Health Organization Rating advises to avoid breastfeeding during the intake of AZA.

Breastfeeding while treated with AZA is not recommended by the manufacturer (48). Therefore, related to the tumorigenic potential of azathioprine, the manufacturer advice to discontinue nursing or discontinue the drug.



Low concentrations of AZA and its metabolites are found in breast milk (49). In a prospective observational study low 6-mercaptopurine (MP-6 levels) were detected in 2 of 31 breast milk samples (n=10), and the absence of detectable infant serum MP-6 or 6 thioguanine nucleotide (6-TGN) levels led the authors to suggest that AZA-treated women with normal thiopurine methyltransferase activity may breastfeed (50). Another prospective study in 8 children extrapolated a maximum infant exposure of less than 0.008 mg 6-MP/kg/body weight/day (less than 1% of the maternal dose) (51).

Two other cases were reported by Moretti ME et al who suggested a negligible infant exposure, with no adverse events in infant's breastfed by mothers receiving AZA (52).

Recently, it has been reported that breastfeeding does not expose the newborn to an increased risk of infections (53). Nevertheless, lack of evidence and/or expert consensus lead to the recommendation for determining infant risk when used during breastfeeding. A balance between potential benefits of drug treatment against potential risks should be addressed before prescribing this drug during breastfeeding.

## **6. Fertility**

Overall reports converge to the conclusion that AZA does not influence the fertility of women. In men treated with AZA, Dejaco et al reported normal semen quality and quantity despite long-term treatment exposure (54).

## **7. In utero exposure to AZA and fetal morbidity and mortality**

IUGR has been reported in fetuses of renal graft mothers treated with corticosteroids and AZA (52% vs. 17%,  $P = 0.001$ ) (33, 55).

A higher rate of hospitalization in neonatal intensive care unit (35% vs. 6%,  $P = 0.01$ ) (33), perinatal mortality (OR 20, 95%CI 2.5-161.4) (32), and stillbirth (32) have been also observed in offspring of renal transplant patients exposed to AZA.

Cytomegalovirus infection (29-31, 56), and observations of jaundice, respiratory distress syndrome (29), diabetes mellitus, asthma (32) were anecdotally reported.

These data are summarized in table 3.

**8. Immunological impairment** was also observed; in most of the cases such as transient lymphopenia and depressed haematopoiesis (10, 26, 29-31, 44, 56-58).

Two cases of severe immune deficiency (56, 58) in children from renal transplant recipients and another case of autoimmunity in a child from SLE mother (59) were also reported.

Postnatal enhancement of T cell maturation, but otherwise normal immunological development was reported in one case (60).

In the offspring of parents with various AI the response to vaccination with C. Tetani toxoid was tested and 17% of the children did not achieve a protective titer of anti C. Tetani toxoid IgG (61).

Nevertheless, no immunological impairment has been reported in this population (61-63).

The findings on immunological impairment of children are summarized in Table 4.

### **9. Outcome of children born to mothers with systemic lupus erythematosus. Is there any evidence of long-term effect of AZA exposure during intrauterine life?**

There is consensus in international groups on the use of AZA during pregnancy. In 2007, the European League Against Rheumatism (EULAR) released recommendations for the treatment of SLE (65).

International groups have been working on the use of anti-rheumatic drugs during pregnancy (6, 8, 66-69).

The 2017 EULAR actualized these recommendations on pregnancy, in which it is clearly stated that AZA is a drug to be considered for the maintenance of SLE remission during pregnancy (6).

Several factors possibly interfering with the intrauterine life were suggested to possess a major role in the global development of the children:

- 1) Maternal disease activity (70-74).
- 2) SLE autoantibodies such as anti-Ro/SSA antibodies (70): antiphospholipid antibodies (aPL) (75-78).
- 3) Anti-rheumatic drugs (73-74, 14-15).

These factors could have some potential consequences on children, such as intrauterine growth retardation (IUGR) and prematurity (70-71). In the postnatal life, three patterns of outcomes have been particularly studied in children born to mothers with SLE:

- a) Infectious diseases
- b) Neurocognitive impairment
- c) Immunological abnormalities

These different potential factors responsible for the occurrence of a developmental impairment, as well as the potential consequences of these factors are summarized in the figure 1.

Several studies highlighted gestational complications and impaired developmental outcome related to the activity of disease during pregnancy (70-74). The studies of Neri et al (71) and of Ross et al (70) showed not only a risk of prematurity, a low weight at birth and the intra-uterine delay of development, but also learning difficulties, to be directly correlated with disease activity of the pregnant women.

Neurocognitive impairment (NI) has been described in preschool-age children of SLE mothers and it has been suggested that it would be related to different factors. However, the

pathogenic mechanisms are unknown. Ross et al reported that SLE in pregnant women is associated with an increased risk for learning impairment in children, particularly in male offspring, and suggested as being related to maternal antibodies (ab) anti-Ro (70). NI in children has been considered as potentially related to maternal disease or prematurity (72-74), and/or aPL (75-78), and/or treatment of mothers (73-74).

Although immunosuppressants such as AZA are considered safe during pregnancy (6 -8), some data report immune anomalies and NI (autism, learning disabilities and special educational services) as related to AZA antenatal exposure (14, 15) in SLE. Maternal SLE is significantly associated with attention disorders after multivariate analysis including treatment during pregnancy in some studies (79, 80).

The consequences of AZA utilization in the respective fathers is also a matter a debate, but nowadays data are available only from non-SLE cohorts (27, 81).

*In utero* AZA exposure was found to be associated with increased utilization of special educational services (14), but breast-feeding does not expose the newborn to infectious risks (53). However, series are very small, retrospective, not homogenous and no formal conclusion could be drawn. The larger retrospective series (15) showed a risk of autism

disorders in SLE offspring but missed to explore all the different items of the children outcome (neuro-cognitive development, height and weight development, immunity, infectious risk). Also, in this retrospective study only in 7 children AZA exposure could be identified.

These data are summarized in table 5.

However, these data remain controversial.

## **10. Discussion**

Although Azathioprine is an “old” immunosuppressive therapy, recent data are available.

Therefore, new mechanisms and effects have been reported (83, 84). Recently, it has been shown that azathioprine increases BAFF levels in systemic lupus erythematosus (83). Moreover, although an increased risk of cervical HPV infection in women with SLE compared to healthy controls was found, AZA treatment is not associated with the risk of cervical infection in SLE women (84).

This drug still raises interrogations.

Nowadays, it is not known if the reported impairments described in offspring from parents treated with AZA are exclusively related to the exposure to AZA, or if several complementary factors act as confounding factors such as the contribution of the maternal/paternal disease, the immune anomalies, the socio-economic and environmental exposure; and also if a particular category of children are particularly predisposed to develop these disabilities.

Therefore, a recent meta-analysis of 24 cohort and 4 case-control studies identified learning disorders (LD) in 21.4–26% of SLE offspring, exceeding the prevalence in the general population (85). In lupus offspring compared to controls a twofold increased rate of autism spectrum disorders (ASD) in one study and a two- to threefold increased risk for speech disorders in 3 studies were reported (85). In four studies of this meta-analysis dyslexia and reading problems have been reported in 14.3–21.6% of lupus offspring with a clear male predominance (81). Some divergent results were found for attention deficit and behavior

disorders; and notably IQ and motor skills were not affected in respectively 7 and 5 studies (85).

Data with respect to the occurrence of immune abnormalities in SLE offspring are controversial (61-63). Temporary immunological and NI in children from SLE mothers were reported at birth (42, 57). Therefore, it is important to search for a potential impairment of the immune system in children from SLE parents with or without AZA treatment after the age of 24 months; age when their immune system is developed. The role of immune abnormalities related to parental immune background with further consequences of the NI of the child could be also suggested.

In the recent meta-analysis of 28 studies by Yousef Yengej et al. the positivity of maternal anti-Ro/SSA antibodies was associated with learning disorders in the offspring in one study (85). No formal conclusions could be drawn with respect to the other SLE-related antibodies and neurocognitive outcome of children as they were only very rarely studied (85).

As literature objectified correlations between the nervous and immune systems development, and as immune anomalies were described in neurocognitive disease (86, 87), it is essential to identify the potential impairment of the immune system in children from SLE mothers in whom mental health impairment will be detected.

Nowadays, all these data are controversial, as well as the responsibility of the SLE activity itself, the concomitant presence of different antibodies such as aPL, other antibodies in mothers (anti-Ro/SSA, anti-La/SSB), and/or the direct deleterious effects of drugs.

Besides these risk factors, prematurity, genetics, environmental and socioeconomic factors, as well as sex determinants (70); societal, cultural, lifestyle, epidemiological, economic and environmental factors could be responsible for the global developmental outcome and particularly neurocognitive and immunological outcome of these children.

Moreover, children are a part of families, of the society, so there is a need to assure their wellbeing and to be understood holistically. The interferences between the external agent (in utero exposure to AZA), with the host (child genetic susceptibility, immune system anomalies, emotional status), environment (public health, social context, availability of health care), economic, social, and behavioral conditions, cultural patterns, are complex and the need to conclude on their potential participation to the well-being of this population is mandatory. As related to maternal background, several genetic, geoepidemiologic, but also socio-economic and cultural factors, could display an impact on the results of such studies, we consider that it is essential to state on the safety of AZA in offspring from AID mothers, both at birth, but also at medium term, *i.e.* at least three years of age, representing the minimal period required to evaluate the neurocognitive potential and the social integration in the preschool life.

## **11. Conclusion**

AZA, an immunospressive used in patients with a large diversity of autoimmune disease and transplantation (3, 4, 25, 26, 28, 31, 34-36, 38, 39, 45, 88-93), is generally the immunosuppressive of choice in high-risk pregnancy because of the safety profile and its steroid-sparing property (6-8).

As AZA use is related to underlying disease and disease activity, there is a major difficulty to distinguish between the influence of the disease itself on the risk of adverse birth outcome and potential AZA effects. Another major problem complicating the interpretation of data is the confusion by different indications.

Many confounders interfere with AZA treatment like indication for treatment and concomitant medication. Patients with autoimmune disease and especially transplant recipients usually do not receive monotherapy, and therefore adverse outcomes in this group could relate to the underlying disease as well as concomitant medications, several of them powerful immunomodulators.

The adverse pregnancy outcomes described in older studies were an increased rate of spontaneous miscarriage, preterm delivery and low birthweight, which could have been caused by the underlying disease rather than by the use of thiopurines. More recent controlled studies, such as for instance, in IBD, reported no increased risk for adverse pregnancy outcome in IBD patients treated during pregnancy with thiopurines, compared with pregnancy outcomes of IBD patients without this treatment (94, 95).

Nevertheless, nowadays, there is no study on a significant number of subjects concerning the medium and long-term outcome of children born by autoimmune disease mothers, and particularly SLE mothers, treated with AZA and, consecutively, the necessity of such a study to show the safety of AZA exposure is mandatory. Even though the adverse outcomes might well be a consequence of maternal illness and disease activity, interest has been raised about this drug and data need to be implemented with large, multicenter studies.

Only large-scale population with long-term follow-up, and taking into account several variables such as maternal background, immune system anomalies, genetic, geoeconomic, socio-economic and cultural factors would allow formal conclusions in this field.

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Number	References	Study design	Sample size	Maternal/paternal disease requiring AZA intake during pregnancy/prior to conception	Main findings of the study
	<b>Data on teratogenicity</b>				
1.	22 -24, 29-31	Register National Transplantation Pregnancy Registry (NTPR) in the United States related to immunosuppressive medication and pregnancy	135 post-kidney transplant received AZA	Renal transplant mother  Renal transplant father (received long-term azathioprine)	1/135 polydactyly  1/135 lumbar-area myelomeningocele bilateral dislocated hips, and bilateral equinovarus
2.	32	Retrospective case-control studies Toronto Renal Transplant Program	32 live-born children delivered by 26 mothers  44 pregnancies (39 received AZA)	Renal transplant	1/32 multiple congenital anomalies
3.	33	Case-control studies	48 live offspring of 73 pregnancies  38 women	Renal transplant	2/48 major anomalies (4.2%), subcoronal hypospadias and rudimentary thumb,  10/48 mild errors of morphogenesis (20.8%)  BUT not differ significantly from those in the control group (4.2% and 16.6%, respectively).
4.	26	Case report	2	Renal transplant	Chromosomal aberrations which disappeared by 32 and 20 months, respectively.

5.	25	Register National Transplantation Pregnancy Registry (NTPR) in the United States related to immunosuppressive medication and pregnancy	38 SLE patients (60 pregnancies) 274 non SLE (374 pregnancies)	Female renal transplants with systemic lupus erythematosus compared to female renal transplants with other diagnoses.	No apparent predominant structural malformations and good overall childhood health in both groups
6.	34	Prospective series	15 pregnancies (follow-up 10 years)	Autoimmune hepatitis	1/15 Perthes' disease of the hip at age 7
7.	35	Case-control studies based on Danish population registries	76 exposed pregnancies in 69 women	Inflammatory bowel disease (IBD), organ transplants and several autoimmune diseases	Congenital anomalies 6/64 (9.4%) 1.1 OR 95% CI (0.5–2.9) *** The study lacked knowledge of patient compliance, treatment dose/length, data on smoking/alcohol use, and data on miscarriages/induced abortions
8.	11	Swedish Medical Birth Register.	476 women used AZA in early pregnancy	Inflammatory bowel disease patients	Congenital malformations 6.2% in the AZA group and 4.7% among all infants born (adjusted OR: 1.41, 95% CI: 0.98-2.04).  Ventricular/atrial septal defects (adjusted OR: 3.18, 95% CI: 1.45-6.04).



9.	36	Case-control studies	<p>9 pregnancies exposed 30 days before conception or during the first trimester.</p> <p>10 pregnancies exposed during the entire pregnancy.</p> <p>11 different exposed women</p> <p>Compared with 19 418 pregnancies in which no drugs were prescribed to the mothers.</p>	IBD	2/9 Congenital (women exposed in early pregnancy (OR ¼ 6.7, 95% CI: 1.4–32.4),
10.	27	Case control	<p>1. group 1 50 pregnancies father exposed</p> <p>-1A 13 (exposed within 3 months of conception).</p> <p>-1B 37</p> <p>2. group 2. 90 pregnancies</p>	IBD	<p>4/ 13 (30%) pregnancies in group 1A associated with complications.</p> <p>2/13 (15%) spontaneous abortions,</p> <p>2/13 (15%) congenital anomalies</p> <p>-missing thumb</p> <p>-acrania with multiple digital and limb abnormalities.</p> <p>Risk of complications was significantly increased when compared with group 1B (p &lt; 0.013) and group 2 (p &lt; 0.002).</p> <p>***The incidence of pregnancy-related complications was significantly increased when the fathers used 6-MP within 3 months of conception.</p>

11.	36	Danish Medical birth registry and Danish National Hospital Discharge Registry	10 mother versus 19418	55% IBD 45% other disease	Increased Risk Congenital malformations OR 6.7 (95%CI 1.4-32.4)
12.	37	Case report	1	Chron's disease prior to conception in father	WAGR syndrome (Wilms tumor, aniridia, genital anomalies, and retardation)
13.	28	Retrospective case-control	462 (155 had conceived at least 1 pregnancy after developing IBD)	IBD (mother and/or father)	No statistical difference in conception failures such as spontaneous abortion secondary to birth defect,  major congenital malformation,  neoplasia,  increased infections among male or female patients taking 6-MP compared with controls (RR = 0.85 [0.47-1.55], P = 0.59).
14.	38	Retrospective case control study 10 years database of Australian birth records	93 births from 63 women  19 births in the exposed group during first trimester  74 births in the control group	IBD	<b>No congenital anomalies when compared with unexposed controls</b>
15.	9	Meta-analysis		IBD mothers and fathers	In mothers <ul style="list-style-type: none"> <li>no overall association with congenital anomalies</li> <li>OR 1.45 (95% confidence interval 0.99-2.13)</li> </ul> In fathers pooled

					OR for congenital anomalies 1.87 (95% CI 0.99-2.13)
16.	39	Retrospective 8 years case control study	178 pregnancies in 172 women  87 exposed to azathioprine (AZA-group)  91 not exposed (NO AZA-group).	SLE	No congenital anomalies when compared with unexposed controls
17.	40	Prospective comparative observational study using the French pregnancy database TERAPPEL	124 women exposed to azathioprine during the 1st trimester  124 pregnancies exposed to another drug used for the same indication.	ALL Disease	Not statistically associated with the risk of all birth defects ([7.3% vs. 5.4%]; [OR=1.36; 95%CI: 0.44-4.20]) nor with major birth defects (5.2% vs. 1.8% [OR=2.96; 95%CI: 0.56-15.64]).
18.	41	Measure in peripheral blood lymphocytes from control, healthy subjects and immunosuppressed recipients of cadaveric donor kidneys with and without skin cancer of the frequency of sister chromatid exchange (SCE)	43 control subjects  30 transplant recipients with no history or evidence of cancer  7 transplant recipients with skin cancer	Renal transplant	chromosomal damage

**Table 1: Data on potential teratogenicity impact of AZA.**

Number	References	Study design	Sample size	Maternal/paternal disease requiring AZA intake during pregnancy/prior to conception	Main findings of the study
	<b>Lower birthweight, prematurity</b>				
1	22 -24, 29-31	Register National Transplantation Pregnancy Registry (NTPR) in the United States related to immunosuppressive medication and pregnancy	103 in utero exposure	Renal transplant	<b>Lower birthweight, prematurity</b> 7/103 (7%)
2	32	Retrospective case-control studies Toronto Renal Transplant Program	44 pregnancies (39 received AZA)  32 live-born children delivered by 26 mothers	Renal transplant	<b>-Increased prevalence of preterm birth,</b> -mean gestational age at delivery in the study group was 36.5 +/- 2.7 weeks compared to 40.2 +/- 1.6 weeks in the control group (P < 0.001).  <b>-Low birth weight</b> mean birthweight in the study group was 2.54 +/- 0.67 kg, compared to 3.59 +/- 0.53 kg in the control group (P < 0.0001).
5.	33	Case-control studies	38 patients  48 live offspring of 73 pregnancies  Compared with 48 offsprings of 41 women with renal disease	Renal transplant	<b>-Increased prevalence of preterm births</b> (60% vs. 21%, P = 0.001),  <b>-Growth restriction</b> 52% versus 17% P 0.001
6.	25	Register National Transplantation Pregnancy Registry (NTPR) in the United	38 SLE patients (60 pregnancies) versus 274 non SLE	Female renal transplants with systemic lupus erythematosus compared to female renal transplants with other	<b>Prematurity and low birthweight in both groups.</b>

		States related to immunosuppressive medication and pregnancy	(374 pregnancies)	diagnoses.	
7.	44	Review		Chronic renal disease	No overall association with poor pregnancy outcomes
8.	35	Case-control studies based on Danish population registries	76 exposed pregnancies in 69 women	Inflammatory bowel disease (IBD), organ transplants and several autoimmune diseases	<p><b>-Increased preterm birth</b>, 17/65 (26.2%) 1.9 OR 95% CI (1.1–3.3)</p> <p><b>-Low birth weight</b> at term 2/48 (4.2%) 1.7 OR 95% CI (0.3–8.7)</p>
9.	36	Case-control studies Danish Medical birth registry and Danish National Hospital Discharge Registry	10 mother versus 19418 11 women	55% IBD 45% other disease	<p><b>-Increased risk of preterm birth</b> 6.6 (95%CI 1.7-25.9) 3/10 preterm children OR 6.6 (95% CI: 1.7–25.9) (women exposed during the entire pregnancy)</p> <p><b>-3/10 Low birth weight</b> ratios Odds 3.8 (95% CI: 0.4–33.3) (women exposed during the entire pregnancy)</p>
10.	42	Danish Medical birth registry and Danish National Hospital Discharge Registry	900 children	Crohn's disease	<p><b>Preterm births</b> more prevalent among AZA/6-MP-exposed women i.e. 25%, compared with the reference group (6.5%).</p> <p>Risk of preterm birth 4.2 (95% CI 1.4-12.5)</p>

11.	9	Meta-analysis		IBD mothers and fathers	<b>In mothers</b> a higher rate of <b>prematurity</b> OR 1.67 (95% confidence interval 1.26-2.2)  <b>No overall association with lower birth weight</b> OR 1.01 (95% confidence interval 0.96-1.06)
12.	43	Case-control studies	101 women	IBD	<b>No overall association with poor pregnancy outcomes,</b>  *** ? for children outcome
13.	28	Case-control studies	155 male and female patients	IBD	<b>No overall association with poor pregnancy outcomes,</b>
14.	38	Retrospective case control study 10 years database of Australian birth records	93 births from 63 women  19 births in the exposed group during first trimester  74 births in the control group	IBD	<b>No higher risk of preterm birth, low birth weight</b>  <b>No neonatal adverse effects</b>
15.	39	Retrospective 8 years case control study	178 pregnancies in 172 women  87 exposed to azathioprine (AZA-group)  91 not exposed (NO AZA-group).	SLE	Similar rate of live births, spontaneous abortions, mean birth weight, weeks of gestation, rate of birth weight <2500 g, and low birth weight
16.	40	Prospective comparative observational study using the French pregnancy database TERAPPEL	124 women exposed to azathioprine during the 1st trimester  124 pregnancies exposed to another drug	All disease	The rate of preterm births (22.5% vs. 27.3%, P=0.579) was similar regardless of the exposure period to azathioprine

			used for the same indication.		
17.	45	Registry Italian study group of kidney in pregnancy  4 years	121 live-born after kidney transplant  610 live-born in Chronic kidney disease (CKD)  1418 low-risk controls	Renal transplant	Risk for preterm and early-preterm delivery in liveborn from patients compared to controls.  linked to CKD stage (2-5 vs 1: relative risk 3.42 and 3.78) and hypertension (RR 3.68 and 3.16)  The maternofetal outcomes in patients with kidney transplantation are comparable with those CKD patients
18.	46	Registry Italian study group of kidney in pregnancy  13 years	222 pregnancies with live-born babies after transplantation  1418 low-risk controls	Renal transplant	Higher risk of preterm delivery in later CKD stages, an increase in preterm delivery and a decrease in SGA across periods.

**Table 2: Data on birthweight and birth term impact of the in utero AZA exposure.**

Number	References	Study design	Sample size	Maternal/paternal disease requiring AZA intake during pregnancy/prior to conception	Main findings of the study
	<b>Infection</b>				
1	22-24, 29-31	Register National Transplantation Pregnancy Registry (NTPR) in the United States related to immunosuppressive medication and pregnancy	103 in utero exposure	Renal transplant	1/103 (1%) cytomegalovirus infection,
2	56	Case report	1		cytomegalovirus infection
	<b>Other disease and/or developmental impairment</b>				
1	33	Case-control studies	38 patients 48 live offspring of 73 pregnancies  Compared with 48 offsprings of 41 women with renal disease	Renal transplant	intrauterine growth restriction (IUGR), (52% vs. 17%, P = 0.001),  Hospitalisation in neonatal intensive care unit (35% vs. 6%, P = 0.01),
2	55	Case control	18 patients 20 pregnancies  And 5000 control	Renal transplant	5 times more frequent fetal growth retardation
3	32	Retrospective case-control studies Toronto Renal Transplant Program	44 pregnancies	Renal transplant	4 fetal death (10%) stillbirth 1/32 insulin-dependent diabetes mellitus, 2/32 asthma



4	36	Danish Medical birth registry and Danish National Hospital Discharge Registry	10 mother versus 19418	55% IBD 45% other disease	Increased Risk of Perinatal mortality OR 20 (95%CI 2.5-161.4),
5	22 -24, 29-31	Register National Transplantation Pregnancy Registry (NTPR) in the United States related to immunosuppressive medication and pregnancy	103 in utero exposure	Renal transplant	7/103 in utero exposure (7%) jaundice, respiratory distress syndrome

**Table 3 Data on infection, other disease and/or developmental impact related to AZA in utero exposure.**

Number	References	Study design	Sample size	Maternal/paternal disease requiring AZA intake during pregnancy/prior to conception	Main findings of the study
	<b>Immunological</b>				
	22 -24, 29-31	Register National Transplantation Pregnancy Registry (NTPR) in the United States related to immunosuppressive medication and pregnancy	103 in utero exposure	Renal transplant	1/103 (1%)  lymphopenia, reduced levels of immunoglobulin G and M, and reduced thymic shadow regressive in 10 weeks
2	10	Prospective cohort	10 pregnancies in 8 women	Renal transplant	6/10 (60%) leucopenia 3/10 (30%) thrombopenia  ***significant correlation between cord leucocyte count and maternal leucocyte count at delivery but no longer at 32 weeks gestation.
3	57	Medical birth registry of Norway and Norwegian Prescription database	1461 women 1198 fathers 101 received AZA=	Various disease	Temporary immunological impairment
4	42	Danish Medical birth registry and Danish National Hospital Discharge Registry	900 children	Crohn's disease	Temporary immunological impairment  congenital anomalies prevalent among AZA/6-MP-exposed compared with reference group (15.4%vvs 5.7%).  risk of CAs 2.9 (95% CI 0.9-8.9),
5	26	Case report	2	Renal transplant	Transient lymphopenia and cortisol levels
6	56	Case report	1	Renal transplant	Transient lymphopenia severe immune deficiency
7	58	Case report	1	Renal transplant Mother	Neonatal pancytopenia and severe combined immunodeficiency

8	59	Case report	1	SLE	Development of autoimmunity
9	60	Case report	1	Renal transplant	Postnatal enhancement of T cell maturation, but otherwise normal immunological development
10	61	Case control	22 babies versus 6 controls	Autoimmune diseases	Response to vaccination with C. Tetani toxoid. <ul style="list-style-type: none"> <li>• 5/ 28 (17%) did not achieve a protective titer of anti C. Tetani toxoid IgG.</li> <li>• No clear relationship was found between specific drug exposure and antibody response.</li> </ul>
11	64	Case control	9 babies versus 14 controls  Mean age 11 months (range, 1-17).  Only one exposed to AZA	Connective tissue diseases	No significantly different <ul style="list-style-type: none"> <li>• Complete blood count,</li> <li>• IgA, IgG, IgM, IgG subclasses</li> <li>• lymphocyte subpopulations</li> <li>• serum levels of anti-HBsAg</li> <li>• presence of autoantibodies (ANA, ENA)</li> </ul>
12	63	Case control	14 babies (mean age 11 months, range 1-24)	Mothers with autoimmune diseases	No statistically significant differences between exposed and not exposed babies: <ol style="list-style-type: none"> <li>complete blood count,</li> <li>immunoglobulin levels and IgG subclasses,</li> <li>antibody response to hepatitis B vaccine,</li> <li>leukocyte subpopulations and</li> <li>interleukin-2 and interferon gamma in vitro production by resting or activated peripheral blood mononuclear cells.</li> </ol> ***Different treatments including AZA so small subgroups

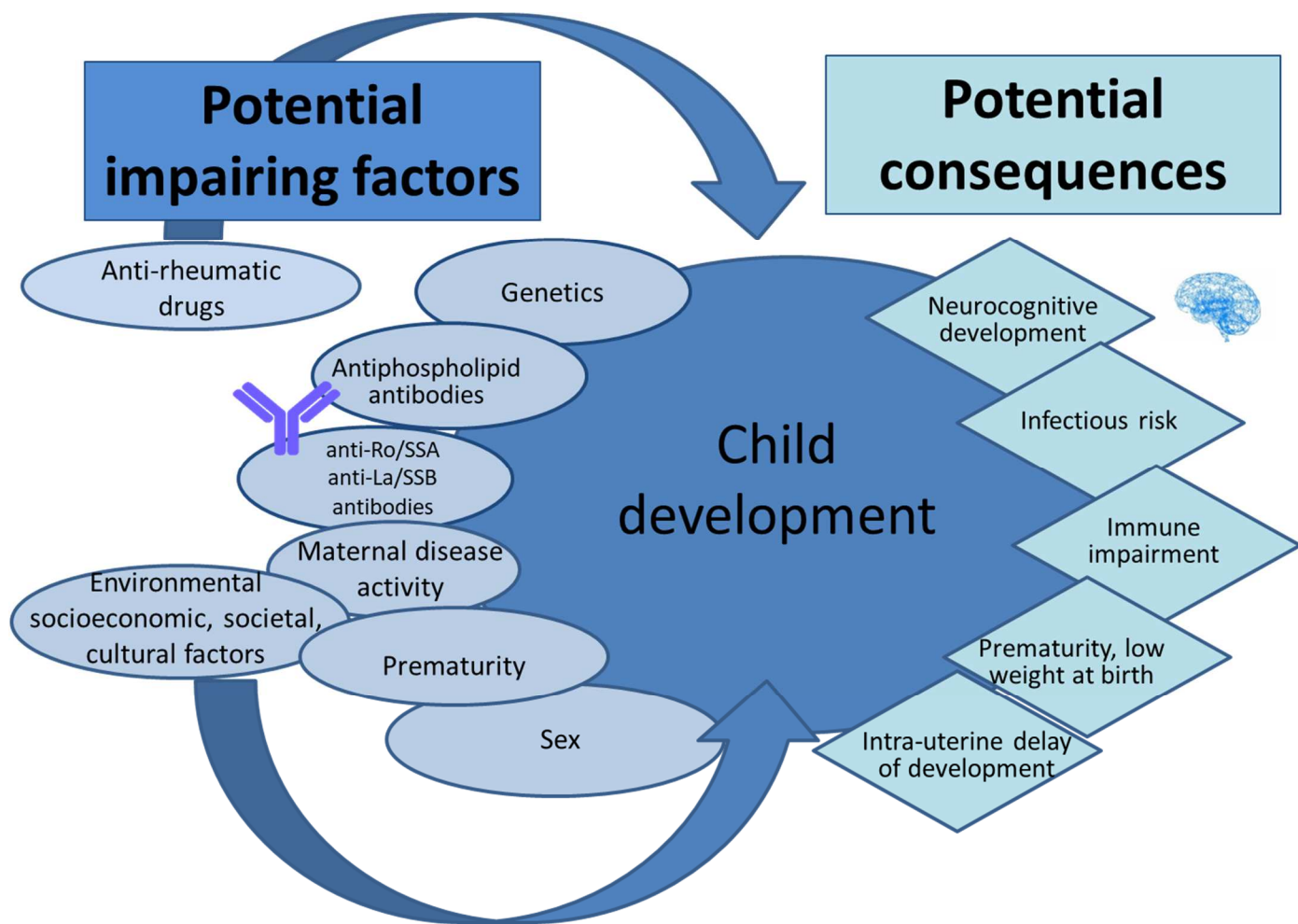
13	62	Case control	<p>19 infants exposed in utero to glucocorticoid alone or in combination with azathioprine, cyclosporine A, or hydroxychloroquine</p> <p>15 age-matched infants</p>	Mothers with autoimmune diseases	<ul style="list-style-type: none"> <li>• No differences in terms of</li> <li>• absolute lymphocyte count, percentage of B and T lymphocytes,</li> <li>• and immunoglobulin production</li> </ul> <p>No immune system dysfunction</p>
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**Table 4 : Data on immunological impact of AZA exposure**

Number	References	Study design	Sample size	Maternal/paternal disease requiring AZA intake during pregnancy/prior to conception	Main findings of the study
<b>Neurocognitive</b>					
1	32	Retrospective case-control studies Toronto Renal Transplant Program	44 pregnancies 32 children	Renal transplant	1/32 moderate to severe sensorineural hearing loss, 1/32 learning disability 1/32 pervasive developmental disorder
2	82	Canadian healthcare database, with a mean follow up of 9.1 years	719 SLE mothers and 8493 controls	SLE mothers	Attention disorders reported in 9.9 of cases and 6.1 of controls, HR 1.73, lowered to 0.97 when maternal drugs were included
3	5	Canadian healthcare database, with a mean follow up of 9.1 years	719 SLE mothers and 8493 controls	SLE mothers	Autism in 1.4% versus 0.6% of controls, OR =2.25 (1.13-4.45)  *** However information on in-utero drug exposure was available only for 22% of the SLE group and 21% of controls and had no influence on autism
4	76	Cohort of infants (median age 9 months)	12	SLE patients	No autistic disorders  ***However median age was 9 months
5	13	Case control	13 children with in utero AZA exposure  47 non exposed	SLE patients	7/13 (54%) versus 8 (17%) of 47 nonexposed children (P < 0.01) needed special educational services (SE).  AZA <ul style="list-style-type: none"> <li>significantly associated with SE utilization occurring from age 2 years onward (odds ratio 6.6, 95% confidence interval 1.0-43.3),</li> <li>bordered on significance for utilization at any age or age &lt;2 years.</li> </ul>

6	14	Prospective cohort	60 eligible offspring from 38 mothers  13 children with in utero AZA exposure  median follow-up of 5.7 years (OR 3.4-9.2).	SLE patients	25% of children were affected in global neurocognitive development  Speech disorders in 20% of children  These data were confounded by AZA exposure ( $p < 0.05$ ) and APS presence ( $p < 0.05$ )
7	79	Primary healthcare centres and school health services database		Mothers with Ro SSA antibodies	Maternal SLE is significantly associated with attention disorders after multivariate analysis including treatment during pregnancy
8	80	Case control	154 individuals ages 8-20 years  154 controls	women with SLE	more evidence of developmental difficulties, immune related disorders, and nonrighthandedness after multivariate analysis including treatment during pregnancy.

**Table 5: Data on AZA in utero exposure and neurocognitive impact**



**Figure 1: Potential impairing factors and their potential consequences in child development.**