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Importance of complete response for outcomes of pregnancy in patients with autoimmune hepatitis

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Abstract

Background and Aims: While some articles describe outcome of pregnancy in autoimmune hepatitis (AIH), there are less data evaluating influence of AIH control on maternal and perinatal outcomes. This study analysed outcomes of pregnancy and related possible risk factors in AIH.

Method: A retrospective multicentre cohort study on pregnancy in AIH was performed in 11 hospitals in the Netherlands. Maternal and neonatal outcomes were collected from records and completed by interview. Risk factors—including incomplete response, relapse and cirrhosis—for adverse outcomes were identified using logistic regression analysis.

Results: Ninety-seven pregnancies in 50 women resulted in 70 deliveries (72%) with a live birth rate of 98.5%. AIH relapse occurred in 6% during pregnancy, and in 27% of

Abbreviations: AASLD, American Association for Study of Liver Disease; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; APGAR, Appearance-Pulse-Grimace-Activity-Respiration; AST, aspartate aminotransferase; CI, confidence interval; EASL, European Association for the Study of the Liver; IBD, inflammatory bowel disease; ICP, intrahepatic cholestasis of pregnancy; ICSI, intracytoplasmic sperm injection; IgG, immunoglobulin G; IQR, interquartile range; HELLP, haemolysis elevated liver enzyme and low platelets; INR, International Normalized Ratio; IVF, in vitro fertilization; IUI, intrauterine insemination; LBW, low birth weight; MMF, mycophenolate mofetil; NICU, neonatal intensive care unit; OR, odds ratio; PBC, primary biliary cirrhosis; PE, pre-eclampsia; PIH, pregnancy-induced hypertension; PSC, primary sclerosing cholangitis; SLE, systemic lupus erythematosus; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; VLBW, very low birth weight.

post-partum episodes. Absence of complete biochemical response at conception was identified as risk factor for the occurrence of gestational and post-partum relapses. Relapse of AIH in the year before conception was a risk factor for the occurrence of both gestational relapses and post-partum relapses. No complete biochemical response increased the risk for hypertensive disorders during pregnancy and intrahepatic cholestasis of pregnancy (ICP). Cirrhosis was found to be a risk factor for miscarriages, but not for other outcomes.

Conclusion: Pregnancy in AIH is related to an increased incidence of maternal and fetal/neonatal complications; in most cases, outcome is good. Incomplete biochemical response at conception or relapse in the year before conception are risk factors for gestational and post-partum relapses, for hypertensive disorders and for ICP. Cirrhosis was a risk factor for miscarriages.

KEYWORDS
autoimmune hepatitis, outcome, pregnancy, remission

1 | INTRODUCTION

Autoimmune hepatitis (AIH) is diagnosed at all ages.[1,2] Prevalence is 18.3 per 100000 in the Netherlands.[3] One third of the patients already has cirrhosis at the time of diagnosis, and these patients seem more likely to develop severe complications.[4,5] First-line therapy is with azathioprine and glucocorticoids, but patients often require alternative treatments.[6] Most patients require life-long treatment.[7] With treatment, the prognosis without cirrhosis is comparable to the general population, while it is improved but below normal in patients with cirrhosis.[8] The level of aminotransferases during treatment is an important prognosticator for long-term survival.[5] In acute and acute severe AIH, short-term prognosis is related to improvement in liver function.[9] AIH also affects young women in their childbearing years.[10] The available evidence shows that overall the outcome of pregnancy in AIH is good, but it has been associated with an increased incidence of complications.[11–17] There are less data evaluating the influence of AIH control on maternal and perinatal outcomes. Therefore, the aim of this study was to investigate maternal and neonatal outcomes of pregnancy in patients with AIH, and to assess potential risk factors for adverse outcomes.

Key Points

- Outcome of pregnancy in autoimmune hepatitis (AIH) in general is good for mother and child in most of the cases, but with more complications than in healthy women.
- Women with AIH who become pregnant have more miscarriages than healthy women, especially if they have cirrhosis.
- Relapse of hepatitis is frequent after pregnancy; gestational relapses also can occur.
- Maintaining complete biochemical response in the year before conception is associated with less complications of pregnancy in AIH.

2 | METHODS

2.1 | Data collection

This retrospective multicentre cohort study was performed by the Leiden University Medical Center (LUMC) in collaboration with 10 other participating hospitals from the Dutch AIH Study Group (total five university and six general hospitals). Data on women with pregnancy and AIH were extracted from electronic patient medical records from the last two decades. If data regarding miscarriage were missing from the medical record, the patient was called for a phone interview to obtain additional information in order to minimize the number of missing data.

2.2 | Study design

Primary endpoints were adverse maternal outcomes. Secondary were fetal/neonatal outcomes. All women had to meet the criteria of definite AIH according to the International AIH Group's simplified diagnostic criteria.[18] Patients younger than 18 years or after liver transplantation before conception were excluded.

Adverse maternal outcomes were pregnancy-induced hypertension (PIH), pre-eclampsia (PE), eclampsia, haemolysis elevated liver enzymes and low platelets (HELLP) syndrome, intrahepatic cholestasis of pregnancy (ICP), gestational and/or post-partum relapses of AIH, gestational diabetes, preterm delivery, loss of remission (LOR)/complete biochemical response, decompensation of cirrhosis or

other complications during delivery. Miscarriage and termination of pregnancy were also reported.

Child related data collected were: gestational age at birth, birth weight, Appearance-Pulse-Grimace-Activity-Respiration (APGAR) scores at 1, 5 and 10 min after birth,[19] congenital malformations and infections and hospital admission after birth.

Changes in immunosuppression before conception, presence of cirrhosis, presence or absence of complete biochemical response at conception and/or a relapse in the year before conception were registered. Elevated serum aminotransferase concentrations before conception and the presence of cirrhosis were included as potential risk factors in the analysis.

2.3 | Outcome definitions

These are according to the current European Association for the Study of the Liver and American Association for Study of Liver Disease (AASLD) and the recent Delphi consensus on response criteria and endpoints in AIH.[20–22] A relapse of AIH was marked as laboratory results of elevated transaminase levels three times above the upper limit of normal (ULN); LOR was defined as elevated aminotransferases above the ULN, but less than three times ULN if these were normal previously or the presence of elevated immunoglobulin concentrations if these were normal previously. Complete biochemical response was defined as normal aminotransferase and immunoglobulin G levels. Partial biochemical response was defined as elevated aminotransferases above the ULN but less than three times ULN—in this article at time of conception. Of the child, data were collected regarding gestational age at birth, birth weight, APGAR scores at 1, 5 and 10 min, live birth rate, congenital malformations, congenital infections and hospital admission after birth, including neonatal intensive care unit (NICU) admission.

All research was conducted in accordance with both the Declarations of Helsinki and Istanbul; the study was approved by the ethics and/or institutional review committee of the LUMC as 'non-WMO study' with no need for written consent. Data will be provided upon any reasonable request.

2.4 | Statistical analyses

Statistical analyses were performed with IBM SPSS Statistics (Statistical Package for the Social Sciences, version 27.0, Chicago, IL, USA). Maternal characteristics at baseline and data on disease history and activity were reported as mean and standard deviation (SD) for normally distributed and continuous variables. Not normally distributed variables were presented as median and interquartile ranges (IQRs). Most of the outcomes were converted into categorical or binary variables.

Differences in nominal data were detected by using Fishers exact test or the Chi-squared test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using univariable logistic regression models adjusted for potential risk factors, excluding patients diagnosed with AIH during pregnancy. Potential risk factors for maternal and fetal/neonatal outcomes were calculated for continued pregnancies. Regarding miscarriages, all pregnancies were included in analysis. A p-value $< .05$ was considered statistically significant.

3 | RESULTS

Baseline characteristics are shown in Table 1. Fifty women with AIH were included, resulting in 97 pregnancies. Eight women (16%) were called for additional information in order to minimize missing data. Out of the 97 pregnancies, spontaneous conception occurred in 87 pregnancies. Ten pregnancies (10%) occurred by assisted conception methods as ovulation induction, intrauterine insemination (IUI) or in vitro fertilization or intracytoplasmic sperm injection (IVF/ICSI).

TABLE 1 Baseline characteristics

Baseline characteristics	*N* (%)
Number of included patients	50
Total of pregnancies	97
Median age at diagnosis · IQR ($n = 50$)	24 [10–38]
Median age at conception · IQR ($n = 97$)	32 [18–42]
Type AIH ($n = 50$)	
AIH type 1	48 (96%)
AIH type 2	2 (4%)
Presence of overlap ($n = 50$)	
AIH-PBC	4 (8%)
AIH-PSC	7 (14%)
No overlap	39 (78%)
Comorbidities ($n = 50$)	
Thyroid diseases	6 (12%)
SLE	2 (4%)
IBD	4 (8%)
Coagulative diseases[a]	4 (8%)
Celiac disease	1 (2%)
Sjogren's syndrome	1 (2%)
Presence of cirrhosis ($n = 50$)	9 (18%)
Conception method ($n = 97$)	
Spontaneous	87 (89.7%)
IVF/ICSI	6 (6.2%)
IUI	4 (4.1%)

Abbreviations: AIH, autoimmune hepatitis; AIH-PBC, autoimmune hepatitis-primary biliary cholangitis; AIH-PSC, autoimmune hepatitis-primary sclerosing cholangitis; IBD, inflammatory bowel disease; ICSI, intracytoplasmic sperm injection; IQR, interquartile range; IUI, intrauterine insemination; IVF, in vitro fertilization; SLE, systemic lupus erythematosus.

[a]Coagulative diseases: von Willebrand's disease, Factor V Leiden mutation, partially Alpha-1 Antitrypsin Deficiency, Anti Phospholipid Syndrome.

Seventeen of 97 pregnancies occurred in nine (of 50) women with cirrhosis (18%).

3.1 | Characteristics of disease activity and treatment

Characteristics regarding disease history and AIH activity and treatment are presented in Table 2. Almost all patients received pharmacological treatment before and during gestation (88% and 86% respectively). Thirty five percent of the pregnancies occurred while patients were receiving monotherapy prior to conception and in 36% of the pregnancies there was treatment with monotherapy during gestation. Fifty three percent of the conceptions occurred on combined immunosuppressive therapy including glucocorticoids before gestation and 50% were reported with such combined therapy during gestation. In the group treated with monotherapy, thiopurines (azathioprine, thioguanine and mercaptopurine) were prescribed most frequently (69% of the group treated with monotherapy before gestation and 71% during gestation). Twelve of the 97 pregnancies (12%) occurred without treatment for AIH before gestation and in 14 pregnancies (14%), there was no treatment for AIH during gestation. Three patients were diagnosed with AIH during the first trimester and therefore these patients did not receive any form of immunosuppressive medication before conception, and one patient did not use any medication before and during gestation for unknown reason. In one pregnancy the medication was stopped for unknown reasons before conception and one patient refused treatment during both pregnancies out of concern for side effects to the fetus/child. One patient had been in remission for years and was no longer on immunosuppressives at the time of her four pregnancies and one patient had discontinued her medication for AIH as part of a clinical trial 1 month before conception. In 22% of conceptions (21/97), a change in medication prior to or during gestation was made. Importantly, five women were treated with mycophenolate mofetil (MMF) before gestation, of which three women received MMF monotherapy prior to four planned conceptions and two patients were treated with MMF in combination with prednisone or budesonide in the pre-conception period. Because of expected teratogenicity, MMF was switched to budesonide in advance of two pregnancies and in the combined therapy MMF was replaced by azathioprine and 6-mercaptopurine prior to conception. One patient inadvertently continued MMF during the first 2 months of pregnancy as she was not yet aware of her pregnancy. In this patient, MMF was stopped directly after detection of the pregnancy and no immunosuppressive replacement was required during the rest of her pregnancy.

Regarding disease activity, the year before pregnancy was closely examined. In total, of 97 conceptions, 24% of the conceptions occurred without (aminotransferase >3× ULN) or during partial (>1× but <3× ULN) biochemical response. Ten relapses (10%) were reported in the year before conception and concerning these 10 relapses, six conceptions (60%) occurred in the absence of complete biochemical response.

TABLE 2 Characteristics of disease history and activity

Characteristics of disease activity	*N* (%)
Immunosuppressive regimen before conception (*n* = 97)	
Monotherapy	
Prednisolone	3 (3.1%)
Thiopurines[a]	28 (28.9%)
MMF	3 (3.1%)
Combination therapy	
Prednisolone+Thiopurine	39 (40.2%)
Budesonide+Thiopurine	7 (7.2%)
Prednisolone+MMF	1 (1.0%)
Budesonide+MMF	1 (1.0%)
Prednisolone+Budesonide	2 (2.1%)
Tacrolimus	1 (1.0%)
None	12 (12.4%)
Immunosuppressive regimen during gestation (*n* = 97)	
Monotherapy	
Prednisone	5 (5.2%)
Thiopurine	28 (28.9%)
Budesonide	2 (2.1%)
Combination therapy	
Prednisolone+Thiopurine	39 (40.2%)
Budesonide+Thiopurine	6 (6.2%)
Prednisolone+Budesonide	2 (2.1%)
Tacrolimus	1 (1.0%)
None[b]	14 (14.4%)
Change in pharmacological regimen prior to conception (*n* = 97)	21 (21.6%)
Relapse of AIH up to 12 months before conception (*n* = 97)	
Yes	10 (10.3%)
No	87 (89.7%)
Biochemical response at conception (*n* = 97)	
Yes	74 (76.3%)
Partially	8 (8.2%)
No	15 (15.5%)

Abbreviation: MMF, mycophenolate mofetil.

[a]Thiopurines: azathioprine, thioguanine or 6-mercaptopurine.

[b]One patient accidentally continued the use of MMF during the first 2 months of gestation because of an unknown pregnancy. MMF was stopped directly after detection of the pregnancy.

3.2 | Maternal outcomes

Maternal outcomes are shown in Table 3. Of 97 pregnancies, 22 cases of miscarriage (23%) and five terminations of pregnancy (5%) were reported.

In six pregnancies, pregnancy-induced hypertension (9%) was reported and seven cases (10%) of PE were diagnosed. There were

two cases of HELLP syndrome. Nine cases (9%) of gestational diabetes were reported. Eight participants (11%) developed symptoms of pruritus and elevated bile acid levels in the blood test, the diagnosis of ICP was made and these patients received treatment with ursodeoxycholic acid (UDCA). In one patient, diagnosis of ICP was an indication for delivery induction at 38 weeks with bile acid levels of 122 μmol/L. Regarding the patients with pre-existing cirrhosis, one case of hospital admission owing to acute decompensation of cirrhosis with hepatorenal syndrome and in addition HELLP syndrome was reported, resulting in termination of pregnancy at 22 weeks.

Three patients developed a first manifestation of AIH during the first trimester of her pregnancy. Relapses of AIH occurred in 23 of 70 completed pregnancies (33%). These were four gestational relapses and 19 relapses in the post-partum period. Specifically, 22% of the women (11/50) developed one or two post-partum relapses. No patients developed relapses of AIH both during and after gestation. Eight patients (11%) showed elevated aminotransferase levels (LOR) after delivery, although adjustment of immunosuppressants was not required. A significant association was found between the absence of complete biochemical response at conception or a relapse the year before conception and the occurrence of gestational relapses ($p = .02$ and $p = .01$) and post-partum relapses ($p = .01$ and $p = .03$). The existence of cirrhosis was not associated with adverse neonatal outcomes or hypertensive disorders and no association was found between the presence of cirrhosis and the manifestation of gestational or post-partum relapses.

3.3 | Fetal/neonatal outcomes

Fetal and neonatal outcomes are shown in Table 4. Of all reported pregnancies ($n = 97$), 71 children with a median gestational age of 38 weeks were born (IQR: 24–42 weeks). One pregnancy ended with the birth of twins and one stillbirth at 24 weeks was reported resulting in a live birth rate of 99% (70/71 children born alive).

Sixteen of 70 pregnancies were delivered preterm (23%), of which 12 cases of preterm birth (between 32 and 37 weeks), three cases of very preterm birth (birth between 28 and 32 weeks) and one case of extreme preterm birth at 24 weeks of gestation were reported. One preterm birth was because of placenta previa and therefore an emergency caesarean section was performed at 34 weeks of gestation. One other patient suffered from ICP and was initiated to preterm delivery due to excessive serum bile acid levels. Owing to fetal distress, an emergency caesarean section was performed on the twin pregnancy at 33 weeks. One premature birth took place as a result of solutio placentae and another as a result of placental insufficiency and growth retardation because of PE. In 11 pregnancies, the underlying cause of preterm birth was unknown.

One case of an unknown congenital malformation was reported, in this pregnancy, azathioprine monotherapy was used. The outcome

TABLE 3 Maternal outcomes

Maternal outcomes	*N* (%)
Pregnancy outcomes ($n = 97$)	
Completed pregnancies	70 (72.1%)
Miscarriage	22 (22.7%)
Termination of pregnancy	5 (5.2%)
Mode of delivery ($n = 70$)	
Vaginal	50 (71.4%)
Assisted vaginal	4 (5.7%)
Caesarean section (planned)	8 (11.4%)
Caesarean section (emergency)	8 (11.4%)
Delivery ($n = 70$)	
>37 weeks	54 (77.2%)
Delivery between 32 and 37 weeks	12 (17.1%)
Delivery between 28 and 32 weeks	3 (4.3%)
Delivery between 24 and 28 weeks	1 (1.4%)
Hypertensive disorders ($n = 70$)	
Pregnancy-induced hypertension	6 (8.6%)
Pre-eclampsia	7 (10%)
HELLP	2 (2.9%)
None	55 (78.5%)
Gestational diabetes ($n = 70$)	
Yes	9 (12.9%)
No	61 (88.6%)
ICP ($n = 70$)	
Yes	8 (11.4%)
No	62 (94.3%)
Adverse maternal outcomes	
Acute decompensation of cirrhosis ($n = 17$)	1 (2%)
Post-partum haemorrhage ($n = 70$)	10 (14.3%)
Gestational relapse ($n = 70$)	
Yes	4 (5.7%)
No	66 (94.3%)
Post-partum relapse ($n = 70$)	
Yes	19 (27.1%)
No	51 (72.9%)
Loss of disease remission after delivery ($n = 70$)	
Yes	8 (11.4%)
No	62 (88.6%)
Complete biochemical response 1 year after delivery ($n = 70$)	
No	9 (12.9%)
Partially	4 (5.7%)
Yes	54 (77.1%)
Missing data[a]	3 (4.3%)

Abbreviation: ICP, intrahepatic cholestasis of pregnancy.

[a]Three patients had recently given birth and therefore no data were available for the complete year post-partum.

TABLE 4 Fetal/neonatal outcomes

Fetal/neonatal outcomes	*N* (%)
Delivery outcomes (*n* = 71[a])	
Live birth	70 (98.5%)
Stillbirth	1 (1.5%)
Median gestational age · IQR (*n* = 70)	38 weeks [24–42]
Preterm	12 (17.1%)
Very preterm	3 (4.3%)
Extreme preterm	1 (1.4%)
Median birth weight · IQR (*n* = 71)	3125 [645–4290]
Low birth weight	10 (14.1%)
Very low birth weight	3 (4.2%)
Median APGAR scores (*n* = 71)	
1 min · IQR	9 [0–10]
5 min · IQR	10 [0–10]
10 min · IQR	10 [0–10]
Missing data	4 (5.6%)
Congenital malformations (*n* = 74)	1 (1.4%)
Congenital infections (*n* = 71)	5 (7.0%)
Missing data	3 (4.2%)
Hospital admission after birth (*n* = 71)	25 (35.2%)
NICU admission after birth (*n* = 71)	9 (12.7%)
Missing data	3 (4.2%)

Abbreviations: APGAR, Appearance-Pulse-Grimace-Activity-Respiration; IQR, interquartile range; NICU, neonatal intensive care unit.

[a]One delivery of twins was reported.

of the fetus exposed to MMF for the first 2 months of gestation was excellent. The median APGAR scores were 9, 10 and 10, respectively, at 1, 5 and 10 min after birth in (IQR: 0–10). Twenty five children were admitted to the hospital after birth (35%), of which nine were admitted to the NICU. Low birth weight (LBW) (dysmaturity) and preterm delivery were significantly associated with hospital admission ($p < .001$). Median birth weight was 3125 grams (IQR: 645–4290). Ten infants were born with dysmaturity (14%), of which three children had a very LBW (4%).

3.4 | Risk factors for adverse outcomes

Table 5 shows that in univariate logistic regression, a relapse of AIH in the year before conception increased the risk for gestational and post-partum relapses (OR: 10 and 5.714, 95% CI: 1.19–84.32 and 1.21–26.931). Additionally, absence of complete biochemical response at conception significantly increased the risk for relapse during gestation and in the post-partum period with an OR of 19.125 and 6.523 (95% CI: 1.77–207.21 and 1.61–26.38) respectively. The use of mono- or combination therapy, change in immunosuppressive regimen at conception and the existence of cirrhosis did not affect the occurrence of relapses of AIH.

No statistically significant associations were found between loss of disease remission after delivery and respectively: relapse in the year before conception, absence or presence of complete biochemical response of AIH at conception, usage of monotherapy versus combination therapy, change in immunosuppressive regimen before conception and the presence of cirrhosis.

As shown in Table 6, absence of complete biochemical response at the time of conception was a risk factor regarding the occurrence of ICP and hypertensive disorders during pregnancy (OR: 6.857, CI: 1.39–33.85 and OR: 9.000, CI: 1.47–55.07 respectively). No risk factors were found for the occurrence of gestational diabetes.

Regarding the outcomes of preterm birth and LBW, no risk factors were identified (Table 7). Lastly, cirrhosis was found to be a risk factor for miscarriages (OR: 3.617, CI: 1.13–11.54). No other correlations between the presence of cirrhosis and adverse outcomes for both mother and child were observed.

4 | DISCUSSION

In the first place, this study confirmed that in general the maternal and neonatal outcomes of pregnancy in AIH are good, but that there is an increased rate of complications compared to the general population. Secondly, risk factors for adverse outcomes were identified, including disease activity before pregnancy. Importantly, complete biochemical remission at conception and absence of relapses in the year before pregnancy were associated with less maternal complications, especially gestational and post-partum relapses, hypertensive disorders and ICP. Thirdly, cirrhosis was a risk factor for fetal loss, which had an increased incidence in women with AIH.

Pregnancy in AIH resulted in a childbirth rate of 72% and 98.5% of the sustained pregnancies. About one fourth of the pregnancies ended in miscarriage and one stillbirth was reported. This is slightly higher than the 20% miscarriage rate in the general population reported in guidelines and previous studies[23] and in line with 24% and 29% reported by some in AIH,[14,24] while others reported miscarriage rates of 9%, 17% and 10% in AIH.[13,16,25] Underreporting may have been present in some studies, while data in this study were completed by telephone interview.

Subfertility is common among women with chronic liver disease.[26,27] Six pregnancies in five women were induced by IVF, with live birth rate of 50%. Aminotransferases were stable in 83% of these pregnancies; in one non-cirrhotic pregnancy there was incomplete biochemical response at conception, and this pregnancy resulted in miscarriage. This is in line with the study of Rahim et al., were AIH was stable in 72% of the reported pregnancies.[26]

In this study, 17.1% and 4.3% of the continued pregnancies ended in preterm delivery (between 32 and 37 weeks) and very preterm birth (between 28 and 32 weeks), respectively, which is higher compared to the Dutch population (6.7% and 1.1% respectively).[28] However, regarding extreme preterm birth, our study reported one case (1.4%), which was comparable to the 0.5% reported in the general population.

TABLE 5 Univariable logistic regression analysis of pre-pregnancy factors and relapse or loss of remission

Independent variables	OR (95% CI)		OR (95% CI)		OR (95% CI)	
	Outcome variable		*Outcome variable*		*Outcome variable*	
Risk factors present before gestation	Post-partum relapse	*p*-value	Gestational relapse	*p*-value	Loss of disease remission after delivery	*p*-value
Relapse in the year before conception						
No	Reference		Reference		Reference	
Yes	**5.714 (01.21–26.93)**	**.03**	**10.000 (1.19–84.32)**	**.03**	3.111 (0.51–18.98)	.22
Biochemical response at conception						
No	**6.523 (1.61–26.38)**	**.01**	**19.125 (1.77–207.21)**	**.02**	2.667 (0.42–16.90)	.30
Partially	0.621 (0.07–5.72)	.67	0.000 (0.000)	1.00	4.800 (0.70–33.11)	.11
Yes	Reference		Reference		Reference	
Use of immunosuppressive medication						
None	0.893 (0.15–5.20)	.90	0.000 (0.00)	1.00	0.00 (0.00)	1.00
Monotherapy	1.480 (0.48–4.55)	.49	0.370 (0.04–3.78)	.40	4.227 (0.78–22.93)	.10
Combination therapy	Reference		Reference		Reference	
Change in immunosuppressive regimen before conception						
No	Reference		Reference		Reference	
Yes	1.896 (0.61–5.90)	.27	2.882 (0.38–22.08)	.31	1.725 (0.37–8.05)	.49
Presence of cirrhosis						
No	Reference		Reference		Reference	
Yes	0.409 (0.04–3.05)	.34	2.810 (0.26–30.81)	.40	1.122 (0.12–10.52)	.92

Abbreviations: CI, confidence interval; OR, odds ratio.

The bold value indicates the significant associations.

LBW and very low birth weight (VLBW) were noted in 14.1% and 4.2% in this study versus 4.8% and 0.9% in the general population.[28] The incidence of preterm birth was similar compared to 12%–22% reported in AIH,[14–17,24] with exception of 7% in a small study.[29] No risk factors were found for preterm birth and no association was found between the use of azathioprine and preterm birth.

Hypertensive disorders during pregnancy occurred in 14.3% of the study population, similar to the AIH study by Wang, and higher than the 4.2–7.9% in the general population.[30,11] Frequencies of gestational diabetes and ICP were higher in this study than in the general population: 12.9% and 11.4% versus 3.5% and 2%.[31,32]

Only two of nine women with AIH and gestational diabetes were treated with glucocorticoids, similar to previous literature.[11] The incidence of caesarean sections was slightly higher than in the general population (22.8% vs. 16%).

Gestational and post-partum AIH relapses were reported in 32.8% of the valid cases, a percentage comparable to previous literature.[13,14,24] The occurrence of relapses prior to conception or during gestation did not negatively affect neonatal outcomes in this study. However, a significant association was found between the absence of complete biochemical response at conception or a relapse in the year before conception and the occurrence of gestational and post-partum relapses. There is one report by Westbrook with similar findings.[13] During gestation, the equilibrium between Th1 and Th2 immune responses shifts, induced by a decrease in the release of type 1 cytokines and an increase in type 2 cytokines.[4,33] Sex hormones may additionally influence this process. The interaction of oestrogen and progesterone provides an increase in Th2 cells which may contribute to an improvement in AIH during pregnancy.[34] After delivery, the Th1/Th2 ratio moves back towards normal with an increase in Th1, leading to post-partum relapses in some cases.[4] The reason for the occurrence of gestational relapses despite a protective immunological state remains unclear.

In (pre)-eclampsia, next to placental insufficiency and endothelial dysfunction, a pro-inflammatory state, oxidative stress and maternal or environmental factors appear to play a role in pathogenesis.[35] This would be compatible with the increased incidence of hypertensive disorders of pregnancy if AIH is not in remission. In ICP, genetic defects in at least six canalicular transporters have been found, nuclear receptor-driven alterations in bile acid and lipid metabolic pathways during gestation are present, and association studies stress the variability of genotypes, different penetrance and influence of environmental factors.[36] It is known that induction of an aseptic and septic acute phase response leads to the down-regulation of basolateral and canalicular organic anion transporters via IL-6.[37] We therefore speculate that, if AIH is not in remission, hepatic inflammation may diminish the function of canalicular transporters and possibly also change nuclear receptor-driven pathways, facilitating development of ICP in susceptible mothers.

TABLE 6 Univariable logistic regression analysis of pre-pregnancy factors for other maternal outcomes

Independent variables	OR (95% CI)		OR (95% CI)		OR (95% CI)	
	Outcome variable		*Outcome variable*		*Outcome variable*	
Risk factors present before gestation	ICP	*p*-value	Gestational diabetes	*p*-value	Hypertensive disorders[a]	*p*-value
Disease activity before gestation						
Relapse in the year before conception						
No	Reference		Reference		Reference	
Yes	1.122 (0.12–10.52)	.92	0.00 (0.00)	1.00	0.879 (0.09–7.68)	.88
Biochemical response at conception						
No	**6.857 (1.39–33.85)**	**.02**	0.643 (0.07–5.83)	.69	4.500 (0.84–23.99)	.08
Partially	0.00 (000)	1.00	1.071 (0.11–10.29)	.95	**9.000 (1.47–55.07)**	**.02**
Yes	Reference		Reference		Reference	
Usage of immunosuppressive medication						
None	2.071 (0.31–13.68)	.45	2.857 (0.34–20.47)	.30	0.00 (0.00)	1.00
Monotherapy	0.558 (0.09–3.30)	.52	1.667 (0.34–8.18)	.53	1.217 (0.31–4.73)	.78
Combination therapy	Reference		Reference		Reference	
Change in immunosuppressive regimen before conception						
No	Reference		Reference		Reference	
Yes	1.725 (0.37–8.05)	.49	0.739 (1.14–3.92)	.72	1.179 (0.27–5.12)	.83
Presence of cirrhosis						
No	Reference		Reference		Reference	
Yes	3.111 (0.51–18.98)	.22	2.619 (0.44–15.58)	.29	0.000 (0.000)	1.00

Abbreviations: CI, confidence interval; OR, odds ratio; ICP, intrahepatic cholestasis of pregnancy.

[a]Hypertensive disorders: one or more of the following outcomes: Pregnancy-induced hypertension (PIH) or pre-eclampsia (PE).

The bold value indicates the significant associations.

Cirrhosis may increase the risk of pregnancy.[38] In this study, patients with cirrhosis had a higher miscarriage rate, but otherwise similar maternal and neonatal outcomes. The latter is in accordance with some publications.[16,24] However, in the study of Westbrook, 40% (33/81) of the conceptions in AIH occurred in women with cirrhosis, of which 21% developed severe maternal or fetal complications.[13] Terrabuio reported a rate of cirrhosis in 68% and two (8%) developed adverse maternal outcomes.[14] Danielsson Borssén mentioned 41% cases with cirrhosis, and found a higher rate of miscarriage in women with cirrhosis like in this study.[24] Although the association between higher MELD scores at conception and the increased risk of adverse maternal outcomes was just not statistically significant (p = .07), Westbrook considered this association clinically significant.[13] It is possible that pregnancy in Child–Pugh A cirrhosis carries a risk similar to that of AIH patients without cirrhosis, but this cannot be firmly concluded since often MELD or Child–Pugh scores were not reported in the various studies. Differences in MELD scores may likely have contributed to the differences in adverse outcomes reported. The majority of maternal deaths occurred in women with cirrhosis. Therefore, it seems that especially women with cirrhosis and a higher MELD score should be informed on the increased risks of pregnancy.[39]

Past studies showed that women with AIH who discontinued immunosuppression during pregnancy more frequently experienced relapses.[21,24] No association between the use of azathioprine and an increased incidence of poor maternal and fetal outcomes was found, similar to studies on inflammatory bowel disease (IBD),[40,41] and a systematic review.[17] In contrast to two small studies,[14,29] and the guideline of the AASLD—which advises against the use of azathioprine during pregnancy—but in accordance with the European guideline, azathioprine can be prescribed and continued safely during pregnancy, while MMF is teratogenic and has to be stopped—and usually replaced by azathioprine—before conception.[2,20]

4.1 | Strengths and limitations

The relatively small sample size is a limitation, but the number of patients and pregnancies is comparable to most previously published studies. Data were collected both in university and general hospitals in different parts of the Netherlands, which makes this cohort comparable to AIH patients in the general population. A more detailed analysis of outcomes and risk factors than in other studies was possible, including a detailed analysis of AIH disease activity before pregnancy.

In conclusion, despite a high miscarriage rate, pregnancy has acceptable outcome in most of the patients with AIH. Absence of complete biochemical response at conception and a relapse of AIH

TABLE 7 Univariable logistic regression analysis of pre-pregnancy factors for neonatal outcomes

Independent variables	OR (95% CI)		OR (95% CI)		OR (95% CI)	
	Outcome variable		*Outcome variable*		*Outcome variable*	
Risk factors present before gestation	Miscarriage	*p*-value	Preterm birth	*p*	Low birth weight	*p*-value
Disease activity before gestation						
Relapse in the year before conception						
No	Reference		Reference		Reference	
Yes	0.775 (0.15–3.95)	.76	1.4143 (0.21–6.30)	.88	1.567 (0.28–8.87)	.61
Biochemical response at conception						
No	1.112 (0.31–3.96)	.87	0.667 (0.13–3.49)	.63	0.956 (0.18–5.13)	.96
Partially	0.437 (0.05–3.81)	.45	0.500 (0.06–64.55)	.54	0.717 (0.08–6.64)	.77
Yes	Reference		Reference		Reference	
Usage of immunosuppressive medication						
None	0.786 (0.28–3.35)	.74	0.391 (0.04–3.62)	.41	0.563 (0.06–5.39)	.62
Monotherapy	0.136 (1.14–1.31)	.14	1.042 (0.32–3.35)	.95	1.174 (0.33–4.14)	.80
Combination therapy	Reference		Reference		Reference	
Change in immunosuppressive regimen before conception						
No	Reference		Reference		Reference	
Yes	0.268 (0.06–1.26)	.10	0.867 (0.24–3.11)	.83	0.788 (0.19–3.24)	.74
Presence of cirrhosis						
No	Reference		Reference		Reference	
Yes	**3.617 (1.13–11.54)**	**.03**	0.00 (0.00)	1.00	0.00 (0.00)	1.00

Abbreviations: CI, confidence interval; OR, odds ratio.
The bold value indicates the significant associations.

in the year prior to conception are risk factors for relapses of AIH during and after pregnancy and for hypertensive disorders and ICP during pregnancy. Therefore, maintaining remission before, during and after pregnancy is a priority for maximizing the chance of a successful outcome.

CONFLICT OF INTEREST

All authors report no potential conflicts of interest relevant to the manuscript.

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