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Systematic review with meta-analysis: outcomes of pregnancy in patients with autoimmune hepatitis

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Abstract

Background: Autoimmune hepatitis (AIH) is common in females of childbearing age. Although some studies have provided information about the outcomes of pregnancy, there remains uncertainty regarding conclusions.

Aim: To comprehensively explore the interactions between pregnancy and AIH.

Methods: Databases including PubMed, Embase, Cochrane Library and Science Citation Index Expanded were searched to collect available studies in relation to pregnancy in AIH patients (from inception to 28 August 2021). Pooled data were calculated using a random effects model with standardised mean difference (SMD), or risk ratio (RR), and 95% confidence intervals (CI).

Results: Twelve studies were considered eligible for meta-analysis. Data from 26 case reports/series were extracted for systematic review. AST level in AIH patients was significantly lower during pregnancy (SMD = −0.41, 95% CI = [−0.70, −0.12]; SMD = −1.60, 95% CI = [−2.76, −0.44]) and loss of biochemical remission occurred more frequently in post-partum (RR = 0.31, 95% CI = [0.19, 0.52]). Patients with portal hypertension or without established remission before conception presented as high-risk subgroups and the incidence of pre-term delivery was higher in these groups compared to other AIH patients (RR = 9, 95% CI = [1.22, 51.1]; RR = 0.05, 95% CI = [0.004, 0.38]). In population-based comparison, pre-term birth (RR = 2.45, 95% CI = [1.66, 3.62]) also occurred more often in AIH patients compared with the general population.

Conclusions: Successful pregnancy is a reasonable expectation in AIH. However, hepatic biochemistry should be monitored closely in both the puerperium and the post-partum period. Though some patients may present higher risk, with carefully selected therapeutic manipulation and multi-disciplinary care, the majority of mothers and infants should achieve uneventful outcomes.

As part of AP&T's peer preview process, a technical check of this meta-analysis was performed by Dr. Y. Yuan. The Handling Editor for this article was Dr Rohit Loomba, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic, progressive liver inflammatory disease that is characterised by female pre-ponderance, elevated serum transaminases and hypergammaglobulinemia. Serological evaluation often demonstrates detectable anti-nuclear antibodies (ANAs), anti-smooth muscle antibodies (anti-SMAs) and anti-liver kidney microsomal type 1 (anti-LKM-1) antibodies.[1,2] It can rapidly progress to cirrhosis or even liver failure.[3] To date, the incidence and prevalence of AIH have been increasing globally, especially in Europe and North America.[4] It is estimated that AIH is diagnosed in 2.08 (95% CI: 1.94–2.22)/100,000 per year in the UK and the ratio of male to female patients is almost 1:4.[5]

Many women with AIH are of childbearing age and express a strong desire to become pregnant. Questions such as "Will pregnancy increase the risk of AIH relapse?" or "What effect does AIH have on my newborn?" and "What do I do with the medication during pregnancy?" are commonly asked by both patients and healthcare staff alike. The maternal circulation represents a hyper-dynamic state during pregnancy and increases the metabolic burden of the liver to a certain extent.[6] Moreover, changes in hormone levels may also affect hepatic physiological function. The combined effect of these factors can lead to liver disease worsening during and after pregnancy[7] and adverse events such as prematurity, miscarriage and stillbirth may greatly increase.

Thus far, the largest single-centre study of highly focused patient outcomes of pregnancy in AIH patients was conducted at King's College Hospital including 53 women with 81 pregnancies.[8] Although there are retrospective studies reported by other centres,[9-12] no randomised controlled trial (RCT) has been conducted or is likely to be undertaken on this topic. Recently, Jamaly et al.[13] performed a meta-analysis to compare the pregnancy outcomes between AIH patients and the general population, however, there remain no answers to the following key questions: (1) Whether liver function and disease activity change during different time points (before pregnancy, gestation, post-partum)? (2) Whether the influence of AIH disease activity (with/without remission prior to pregnancy) or medication exposure (corticosteroids vs corticosteroids plus azathioprine) impacts both maternal and foetal outcomes? (3) Whether factors such as pre-/early conception counselling or portal hypertension impacts pregnancy outcomes? Therefore, we performed this systematic review with a meta-analysis aiming to comprehensively explore the interactions between pregnancy and AIH. Results from this study may also help provide guidance for the management of pregnancy in AIH.

2 | METHODS

2.1 | Registration

The protocol of this systematic review and meta-analysis is available in PROSPERO: CRD42020191597(https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020191597).

2.2 | Search strategy

Databases including PubMed, Embase, Cochrane Library and Science Citation Index Expanded were searched to collect available studies in relation to pregnancy in AIH patients. The primary search strategy was based on medical subject headings terms (MeSH), combined with free text words. The following keywords were used as MeSH: "pregnant," "pregnancy," "gravidity," "gestation," "autoimmune," "hepatitis," "AIH" and "AILD." The searching cut-off date was 28 August 2021. The detailed searching strategy was shown in Table S1.

2.3 | Study selection

Inclusion criteria were (1) patients: pregnant women with AIH, including both natural and assisted pregnancy; (2) type of studies: Clinical trials (randomised or non-randomised trials), comparative observational studies (eg cohort or case–control studies), single-arm cohort studies, case series and case reports. Both prospective and retrospective were eligible; (3) outcomes: reported primary outcomes contain at least one of the following items: laboratory test of liver function, flare/loss of biochemical remission of AIH, pregnancy outcome such as the need for caesarean section, pre-term delivery, congenital malformation, stillbirth, mortality of mothers and infants as well as post-operative complications and (4) the language of the published literature was limited to English only.

Exclusion criteria were (1) patients with no clear diagnosis of AIH; (2) patients with AIH and primary biliary cholangitis (PBC) overlapping syndrome; (3) for single-centre series with repeated publication or overlapping cases, we kept the research manuscript which had more comprehensive data and (4) letters, editorials, expert opinions and reviews were excluded to ensure only original data were used.

2.4 | Data extraction and risk of bias (quality) assessment

Data extraction from each study was conducted by two authors independently. Patient basic characteristics, changes in liver function during pregnancy, results of laboratory tests after delivery, post-operative complications and outcomes of both mothers and newborns have been extracted using a pre-designed data extraction form. For missing information, we attempted to contact the authors of all original articles.

The study quality assessment/risk of bias analysis was conducted by two reviewers independently. The Newcastle-Ottawa Scale (NOS) was applied to evaluate the quality of observational studies.[14] Regarding the NOS assessment, a maximum of one star could be assigned for each numbered item within the Selection and Exposure categories, whereas a maximum of two stars will be given for Comparability. Each study was awarded from 0 to 9 stars, and 0–3, 4–6 and 7–9 are considered low, moderate and high qualities, respectively, for the NOS scale. The assessment of publication bias was not conducted due to the small number of studies included (<10) for

all effect estimates. The quality of included case series and reports were assessed through Joanna Briggs Institute (JBI) critical appraisal tools to identify sources of possible bias.[15,16] During the process of data extraction and quality assessment, any disagreement was resolved by discussion or with review by a third reviewer if necessary.

2.5 | Statistical analysis

Quantitative analysis was performed by using a Review Manager (version 5.3.5 for Windows) recommended by the Cochrane Collaboration.[17] Dichotomous variables were calculated by risk ratio (RR) with a 95% confidence interval (CI), and continuous variables such as AST level with different units among studies were tested by the standardised mean difference (SMD) with a 95% CI.[18] A p value of <0.05 was considered statistically significant. Heterogeneity between studies was tested by χ^2 and I^2 tests and comparisons with a p value of <0.1 were defined as heterogeneous. A brief guide to the interpretation of the I^2 statistics is as follows: 50–90% may represent substantial heterogeneity and 75–100% as considerable heterogeneity. The related data were calculated with a random effects model.[19] For those results with statistical heterogeneity, a subgroup or sensitivity analysis was carried out to identify the source of heterogeneity based on (a) study design (case–control/cohort study), (b) country and (c) race and so on when appropriate. For a systematic review, individual patient data (IPD) were extracted from case reports and case series only. Fisher's exact test and chi-squared test were used for the statistical analysis of IPD using GraphPad Prism 8.0 (GraphPad Software, Inc.).[20]

3 | RESULTS

The flow chart of study screening and detailed selection is presented in Figure 1. Two reviewers (TF and ZL) reached an agreement on the finally included studies. A total of nine retrospective studies and three prospective cohort studies (including total 1538 pregnancies in AIH, 191,717,14 pregnancies in non-AIH) were considered eligible for quantitative synthesis.[8–12,21–27] Seven studies addressed the disease activity change during pregnancy and mortality information, four addressed the comparison of pregnancy outcomes between different drug therapies, three population-based cohort studies addressed the comparison of complications after delivery between AIH and matched non-AIH populations. IPD from 26 case reports/series was extracted for systematic review[28–53] while no RCT was found. Five national cohort studies[25–27,54,55] were screened during literature searching and all of them were population-based (AIH vs non-AIH) among which, three were from Sweden.[26,54,55] As some data were overlapping among these three studies, we only included the study containing the most comprehensive database published by Stokkeland et al.[26] to ensure the accuracy of analysis. Patients were predominantly within the third decade of life, while the youngest patients were 15 years and the oldest was 45 years. The diagnosis of definite AIH was established in most patients with the criteria defined by the revised International Autoimmune Hepatitis Group.[56] As to the patients from Steven et al.[9] clinical symptoms combined with liver histological changes, immune testing (29/34 ANA positive, 29/34 SMA positive, 23/28 HLA-8B positive) and HBV negativity lead to the diagnosis of AIH.

Common complications such as pre-term delivery (birth ≤37 weeks gestation), foetal loss (miscarriage or medical abortion/induction of labour before 20 weeks gestation due to the consideration of patient's health status), disease flare/loss of biochemical remission (serum aspartate aminotransferase [AST] activity increased twofold above the normal upper limit or increased AST and serum globulin concentration accompanied with re-emergence of symptoms) were recorded. The details are shown in Tables 1 and 2.

3.1 | Meta-analysis

3.1.1 | Study assessment

All studies included were retrospective in nature. According to the NOS criteria, studies were awarded with stars from 2 to 9. More than half (8/12) of the studies were rated with five stars or more. These details are shown in Table S2.

3.1.2 | Disease activity

AST value during pregnancy was reported by three studies,[8,11,21] whereas ALT was reported in one.[21] Pooling of SMDs showed that AST levels in AIH patients were much lower during the gestation compared with pre-pregnancy (SMD = −0.41, 95% CI = [−0.70, −0.12], p = 0.006) or post-partum period (SMD = −1.60, 95% CI = [−2.76, −0.44], p = 0.007) (Figure 2a) and the overall RR showed a lower risk of biochemical flare during pregnancy compared with the post-partum (RR = 0.31, 95% CI = [0.19, 0.52], p < 0.00001) (Figure 2b).

3.1.3 | Pregnancy outcome

A comparison was made between patients who received corticosteroid monotherapy (Prednisolone) and patients who received corticosteroids with azathioprine. Four studies[8,10,22,23] were included in the analysis of foetal loss and three studies[8,22,23] provided data on pre-term delivery. No heterogeneity existed in the comparisons (χ^2 = 1.42, p = 0.70, I^2 = 0%; χ^2 = 1.52, p = 0.47, I^2 = 0%) (Figure 3a). Overall results revealed that there was no difference between the two groups in terms of the rates of foetal loss (RR = 0.98, 95% CI = [0.53, 1.78], p = 0.94) or pre-term delivery (RR = 0.63, 95% CI = [0.24, 1.65], p = 0.35) (Figure 3a).

Based on population comparison, there is no difference between the AIH group and non-AIH in the rate of caesarean section

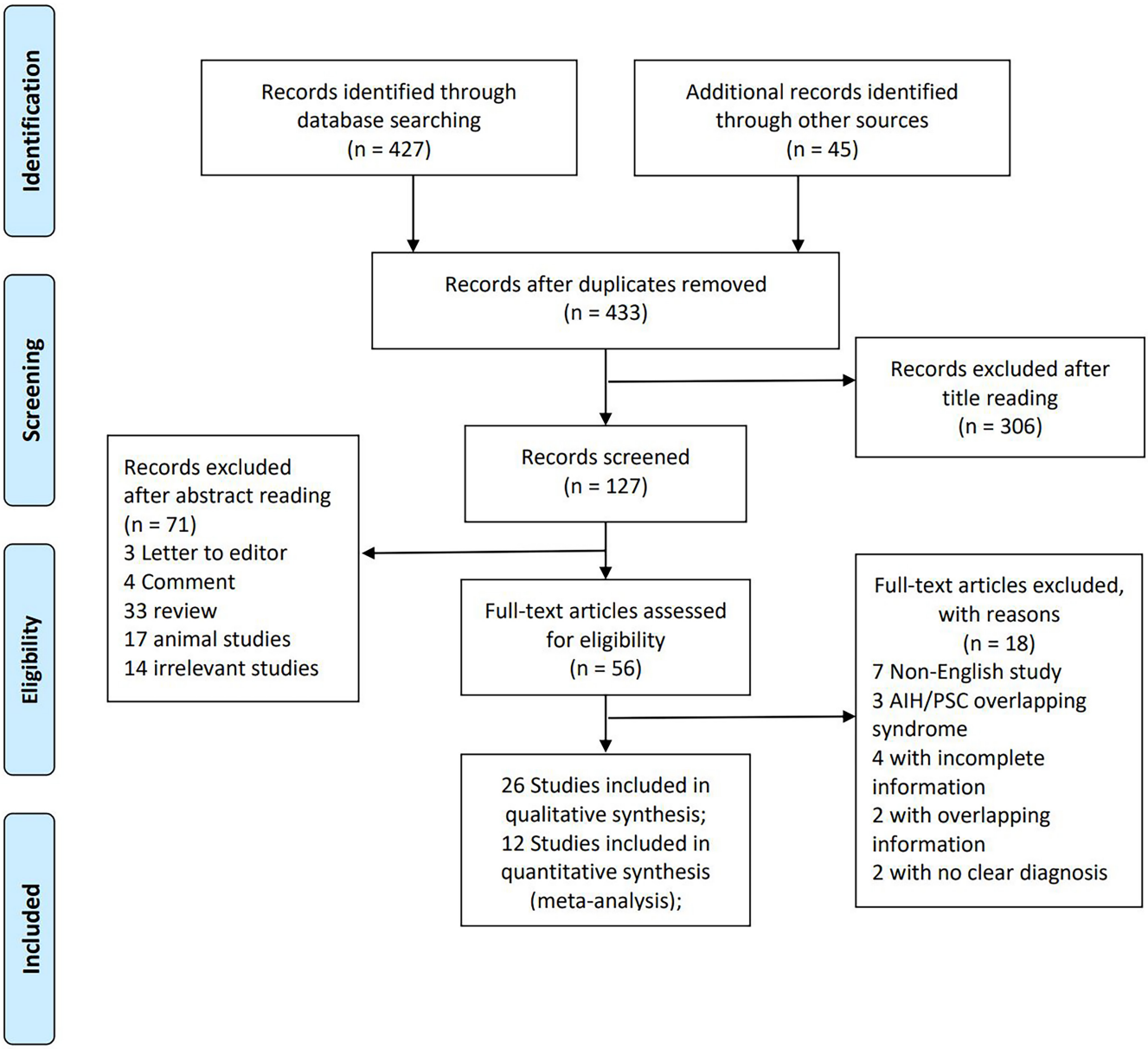


FIGURE 1 Flow chart of study screening and selection

(RR = 0.99, 95% CI = [0.89, 1.11], $p = 0.91$), congenital malformation(RR = 1.07, 95% CI = [0.59, 1.94], $p = 0.81$) or stillbirth (RR = 3.37, 95% CI = [0.95, 11.93], $p = 0.06$), but the rate of pre-term delivery (RR = 3.16, 95% CI = [2.36, 4.25], $I^2 = 0\%$, $p < 0.00001$) was higher in the AIH group (Figure 3b).

3.1.4 | Puerperium safety

Variceal bleeding during pregnancy was reported by three studies.[9–11] Pooling of RRs presented no statistical difference between gestation and post-partum period (RR = 0.61, 95% CI = [0.14, 2.57], $p = 0.50$) (Figure S1a). With regard to comparisons of population-based cohort studies, compared to the non-AIH population, although AIH patients had a higher risk of experiencing gestational diabetes mellitus (RR = 2.79, 95% CI = [1.54, 5.07], $p = 0.0008$), no difference was found in the incidence of maternal death (RR = 10.34, 95% CI = [0.65, 165.33], $p = 0.1$), pre-eclampsia (RR = 1.02, 95% CI = [0.51, 2.05], $p = 0.95$) and gestational hypertension (RR = 1.03, 95% CI = [0.26, 4.08], $p = 0.97$) (Figure S1b). Data from 236 mothers and 184 infants[8–11,21–23] revealed that the mortality rate was higher in newborns during the post-partum period compared to their AIH mothers (RR = 0.24, 95% CI = [0.06, 0.86], $p = 0.03$) (Figure S1c).

3.2 | Systematic review

For the systematic review, a total of 16 case reports, 10 case series (sample sizes ranging from 2 to 7) published between 1960 and 2018 were screened.[28–53] IPD from each study was collected using

TABLE 1 Summary of retrospective studies regarding pregnancy in patients with AIH

Author	Area	Size	Pregnancy	Age	Cirrhosis	Pre-term birth	Low birthweight	Foetal loss	Maternal death	Perinatal death	Congenital abnormality	Variceal bleeding		Flare	
												Gestation	Post-partum	Gestation	Post-partum
Steven et al. (1979)	Australia	16	30	21 (15–45)	16/16	7/23	8/23	7/30	0/30	4/23	1/23	1/30	3/30	2/30	NA
Izumi et al. (2003)	Japan	10	11	32 (26–37)	0/10	0/9	na	1/10	0/10	0/9	0/9	0/10	0/10	0/10	3/10
Schramm et al (2006)	Germany	22	42	29 (17–37)	4/22	17/35	NA	7/42	1/42	3/35	1/35	NA	NA	9/42	22/42
Debora et al. (2009)	Brazil	39	51	24 (17–34)	26/39	6/38	4/38	13/54	0/51	1/38	2/38	1/51	0	14/51	33/51
Roseli et al (2012)	Brazil	10	12	25 (16–33)	5/10	5/12	7/12	1/13	0/12	0/12	0/12	0/12	0/12	0/12	1/12
Westbrook et al (2012)	United Kingdom	53	81	26 (16–42)	21/53	12/61	NA	20/81	4/81	2/61	1/61	1/81	2/81	6/81	20/81
Braga et al (2016)	Portugal	7	9	31.3 (25–43)	2/7	2/6	1/6	3/9	0/9	0/6	0/6	0/9	0/9	2/9	0/9
Llovet et al. (2019)	Italy	36	46	33 (29–34)	7/36	1/44	NA	2/46	0/46	NA	0/44	NA	NA	0/46	10/46
Kathryn et al (2021)	United Kingdom	20	27	29 (24–35)	12/27[a]	8/27	NA	NA	NA	NA	NA	0	NA	NA	15

Abbreviation: NA, not available.

[a]At pregnancy level.

TABLE 2 Summary of population-based cohort studies about pregnancy outcomes in AIH and non-AIH patients

Author/nation	Gronbaek et al./Denmark		Stokkeland et al./Sweden		Wang et al./USA	
Group	AIH	Non-AIH	AIH	Non-AIH	AIH	Non-AIH
Size	70	662	171	576,642	935	18,594,410
Age (years)	29 (25–32)	29 (26–32)	≥30, *n* = 77; <30, n = 94	≥30, *n* = 292,330; <30, *n* = 284,312	29.6 (0.41)	28.5 (0.003)
Diabetes (*n*, %)	4 (5.71)	5 (0.76)	5 (2.92)	3373 (0.58)	20 (2.14)	204, 515 (1.10)
Systemic lupus (*n*, %)	1 (1.43)	1 (0.15)	4 (2.34)	269 (0.05)	NA	NA
Ulcerative colitis (*n*, %)	6 (8.67)	3 (0.45)	11 (6.43)	1434 (0.25)	NA	NA
Rheumatoid arthritis (*n*, %)	0	1 (0.15)	4 (2.34)	483 (0.08)	NA	NA
Crohn's disease (*n*, %)	2 (2.86)	5 (0.76)	6 (3.51)	1377 (0.24)	NA	NA
Caesarean section (*n*, %)	22 (31.43)	167 (25.23)	31 (18.13)	96,622 (16.76)	295 (31.55)	6,120,243 (32.91)
Pre-term delivery (*n*, %)	12 (17.14)	40 (6.04)	28 (16.37)	28,822 (4.99)	80 (8.56)	854,895 (4.60)
Gestational diabetes (*n*, %)	NA	NA	8 (4.68)	6475 (1.12)	80 (8.56)	718,165 (3.86)
Gestational hypertension (*n*, %)	NA	NA	4 (2.34)	6112 (1.06)	20 (2.14)	722,000 (3.88)
Pre-eclampsia (*n*, %)	3 (4.29)	30 (4.53)	5 (2.92)	15,744 (2.73)	NA	NA

Abbreviation: NA, not available.

a pre-designed form. The median age of patients in these reports was 28 years (range 19–36 years). Data on patient status before conception, medical management during pregnancy and outcomes for mothers and infants are summarised in Table S3. In order to minimise the potential heterogeneity and to explore the outcome difference among subpopulations of AIH patients, all patients were stratified according to several confounding factors such as pre-pregnancy portal hypertension, presence of remission before conception and previous pregnancy history.

Results showed that no statistical difference in post-partum flare rates (RR = 1.78, 95% CI = [0.58, 5.2], $p = 0.39$) existed between patients with and without portal hypertension, whereas patients with portal hypertension had a higher risk of experiencing a gestational flare (RR = 3.15, 95% CI = [1.27, 8.26], $p = 0.02$) and pre-term delivery (RR = 2.6, 95% CI = [1.17, 6.54], $p = 0.036$). Patients in remission before conception experienced fewer disease flares during the post-partum period (RR = 0.14, 95% CI = [0.02, 0.65], $p = 0.01$), and experienced lower pre-term delivery rates (RR = 0.13, 95% CI = [0.02, 0.58], $p = 0.003$) (Table 3).

4 | DISCUSSION

Extensive research over decades has improved our understanding of the pathogenesis of AIH. However, there is still an urgent need to explore the specific risks and potential complications of pregnancy in AIH patients in order to improve maternal and foetal outcomes. In this meta-analysis, we have demonstrated that (1) AIH disease activity subsides during pregnancy, whereas post-partum flare increased in frequency; (2) utilisation of azathioprine was not associated with increased rates of adverse pregnancy events such as premature birth or foetal loss; (3) pre-existing portal hypertension or loss of biochemical remission before conception present as high-risk factors in pregnant AIH women for eventful pregnancy and (4) compared to the general population, although pre-term delivery occurred more often in AIH patients, adverse pregnancy events including gestation hypertension, pre-eclampsia, variceal bleeding, stillbirth or congenital malformation did not significantly increase.

It has been reported that high oestrogen levels during pregnancy could change the hepatic microenvironment through cytokine profile shift and increment in anti-inflammatory cells.[57,58] Disease activity subsides when it transits from a state that is conducive to the proliferation and differentiation of cytotoxic T cells to the profile of anti-inflammatory characteristics.[49] This meta-analysis supported these observations: average AST levels in AIH patients was significantly lower during gestation ($p < 0.01$). Most AIH patients can maintain relatively stable liver function or even achieve remission during pregnancy, whereas post-partum flares/loss of biochemical remission happen more frequently. However, some subgroups of AIH patients still present with a high risk when getting pregnant. Although the risk of variceal bleeding did not significantly increase, patients with pre-existing portal hypertension were at increased risk of developing fluctuation in disease activity. These patients represent a challenging population who need to be closely monitored during pregnancy.

From the perspective of health economics, it is important to ensure that AIH patients with high-risk characteristics have informed pre-conception counselling as the cost of treating late adverse pregnant events is high. Recent clinical practice guidelines recommend that pre-conception counselling should be added into management paradigms for AIH patients.[59] This could help patients to understand the merits of multi-disciplinary treatment and to ensure that they have a rapid referral to specialised centres where experienced

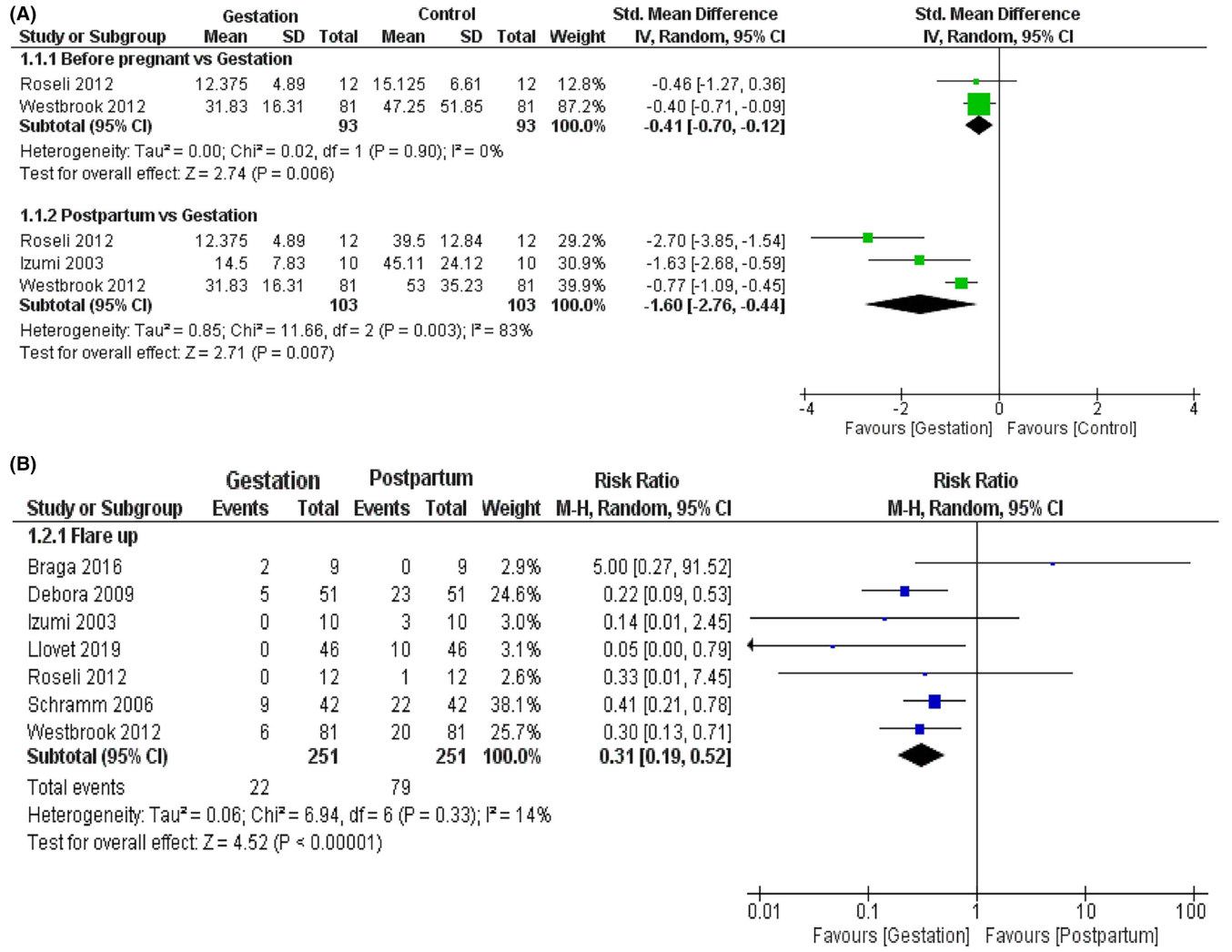
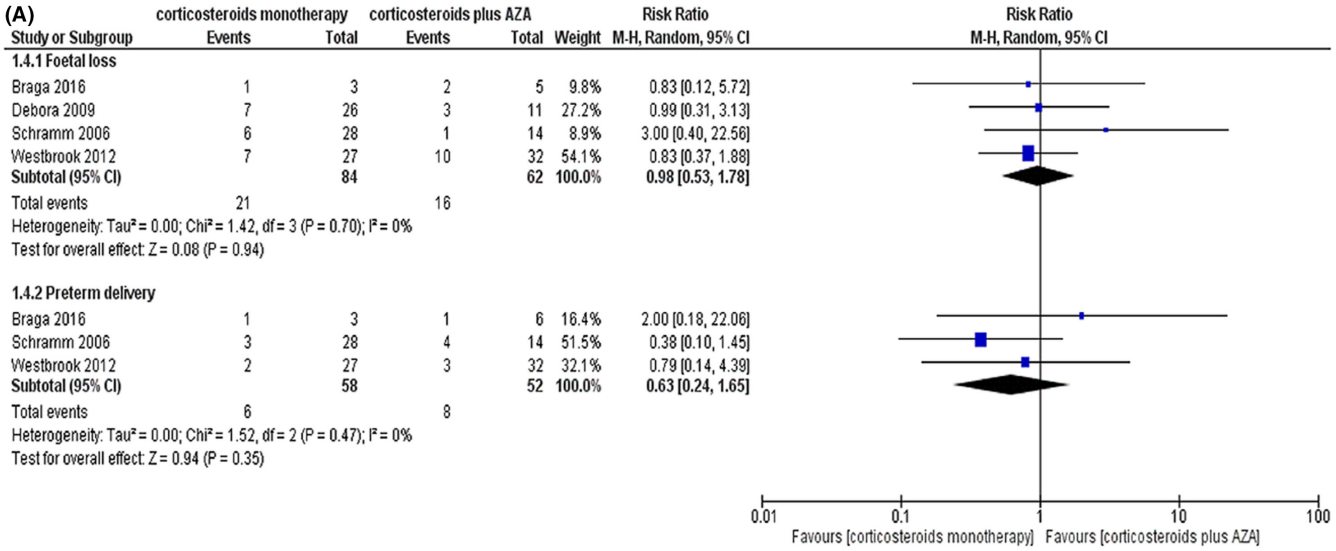


FIGURE 2 Forest plots of disease activity. (A) Comparison of AST level between different time points and (B) comparison of the rates of flare between pregnancy and post-partum

hepatologists can provide immediate management for hepatic dysfunction in pregnancy. This systematic review reveals that the proportion of patients having pre-/early conception counselling was not high. Importantly, pre-conception counselling should reinforce physicians and patients to achieve remission before pregnancy. Our study showed that AIH patients without remission before conception tend to have a higher incidence rate of post-partum flare and pre-term delivery.

Common immunosuppressive drugs for AIH include steroids, azathioprine, mycophenolate tacrolimus and cyclosporine. Many centres suggest that azathioprine should not be continued in pregnant AIH patients to avoid the theoretical risk of drug-induced foetal injury.[60–62] Despite the previous listing as a Class D drug by the U.S. Food and Drug Administration, no solid evidence to date suggests that exposure to azathioprine is associated with adverse foetal outcomes.[63] Moreover, clinical experience from our centre and others indicates that its use alone or in combination therapy with prednisolone/prednisone is safe and well tolerated.[8,64] Results from this study also revealed that there is no significant difference in the rate of pre-term delivery or foetal loss between corticosteroid monotherapy and combination therapy. In the AASLD Practice Guidelines (2019), it suggests that azathioprine can be continued throughout pregnancy.[59] Treatment strategies should be adjusted according to individual patient need to accommodate the existence of high risk.

In recent years, improved guidelines and better treatment options have improved both maternal and foetal outcomes in AIH patients, but the incidence of some obstetric complications is still higher in AIH pregnancies. Our analysis showed that pre-term delivery and gestational diabetes occurred more often in AIH. For some high-risk subgroups, the incidence of post-partum flare and pre-term delivery is even higher. After integrating the data from population-based studies, a supplementary finding from our study was that although AIH women were more often accompanied by concomitant immune diseases (Figure S2), serious pregnancy-related complications such as gestation hypertension, pre-eclampsia variceal bleeding, stillbirth or congenital malformation did not significantly increase. There was also no difference in maternal death compared to that in the general



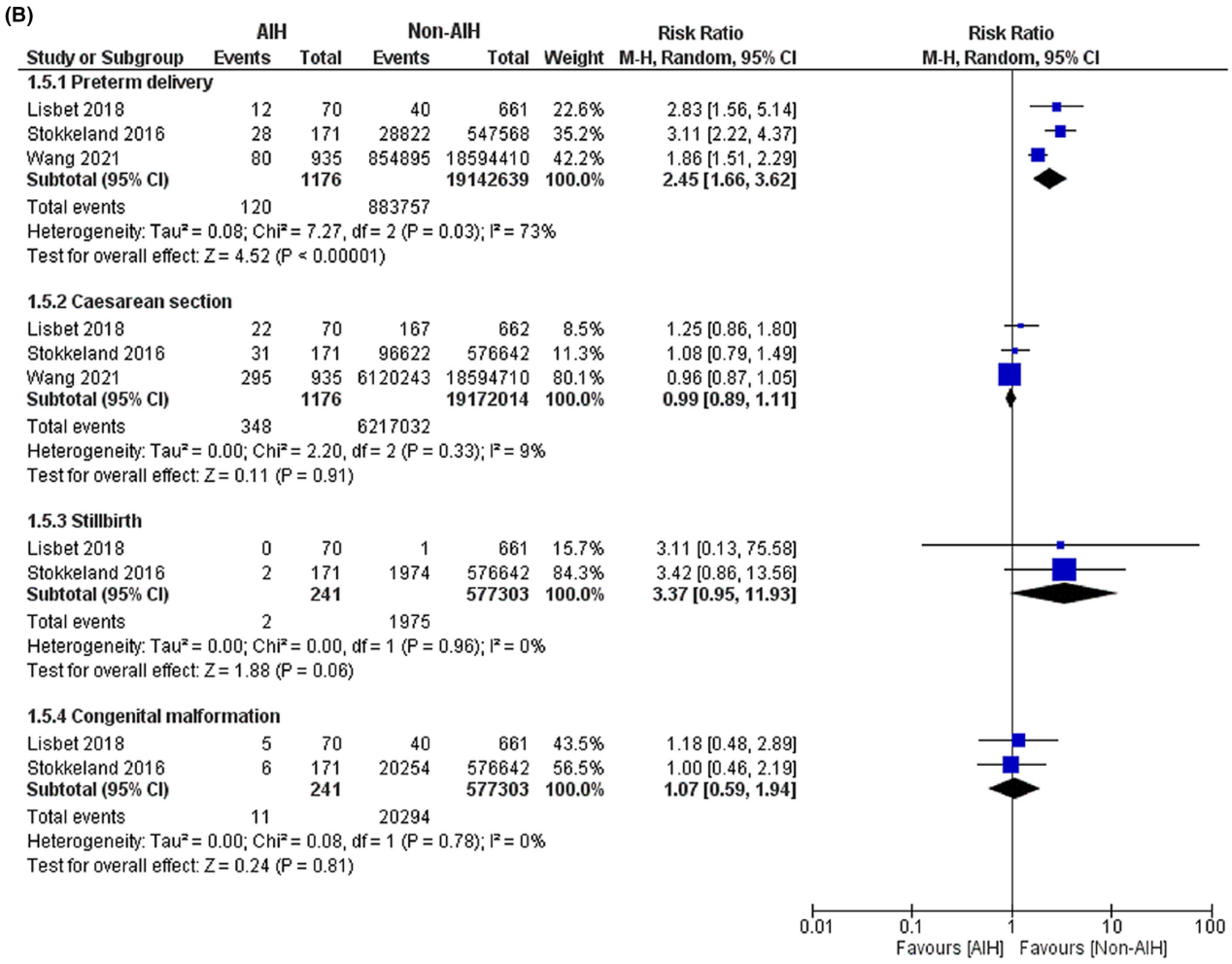


FIGURE 3 Forest plots of pregnancy outcomes. (A) Comparisons of foetal loss and pre-term delivery between corticosteroids monotherapy and corticosteroids plus azathioprine combination therapy and (B) comparisons of pre-term delivery, caesarean section, stillbirth and congenital malformation between AIH and non-AIH patients

population. However, this does not mean favourable maternal and foetal outcomes can be anticipated from every single pregnancy. The final pregnancy outcome for high-risk patients (cirrhosis, portal hypertension) is still difficult to predict. Moreover, compared to AIH mothers, the mortality rate was also higher in newborns during the post-partum period.

TABLE 3 Systematic review of pregnancy outcomes in different subsets of AIH patients

Outcomes	Condition	References	Risk ratio	95% CI	*p* value
Flare Aduring pregnancy	Portal hypertension	28,29,32–40,42,45,47,49,52,53	3.15	1.27–8.26	0.02
	Remission before conception	28,29,31–38,40,45,47,48,50,51,53	0.86	0.30–2.23	>0.99
	Previous pregnant history	28,29,31–40,42,45,47–53	0.21	0.04–0.96	0.07
Flare post-partum	Portal hypertension	28,29,31–40,42,45–47,49,52	1.78	0.58–5.21	0.39
	Remission before conception	28–38,40,45–48,50,51	0.14	0.02–0.65	0.01
	Previous pregnant history	28–40,42,45–52	1.24	0.47–2.74	0.71
Variceal bleeding during pregnancy	Portal hypertension	28–30,32–40,42–45,47,49,52,53	4.36	0.71–28.4	0.48
	Remission before conception	28–38,40,43–45,47,48,50,51,53	0.62	0.09–3.79	>0.99
	Previous pregnant history	28–40,42–45,47–53	0	0–2.54	0.56
Pre-term delivery	Portal hypertension	28–30,32–47,49,52,53	2.6	1.17–6.54	0.036
	Remission before conception	28–37,39,41–45,47,48,50,51,53	0.13	0.02–0.58	0.003
	Previous pregnant history	28–37,39,41–45,47–53	1.23	0.50–2.40	0.7
Low birthweight	Portal hypertension	28–29,32,34,36,37,39,41–44,47,49,52,53	1.33	0.60–3.07	0.65
	Remission before conception	28–32,34,36,37,41,43,44,47,50,51,53	0.18	0.03–1.14	0.16
	Previous pregnant history	28–32,34,36,37,39,41–44,47,49–53	0.67	0.12–1.89	>0.99
Perinatal death	Portal hypertension	28–30,32–39,41–47,49,52,53	2.08	0.46–9.39	0.63
	Remission before conception	28–38,40,41,43–48,50,51,53	0	0–1.91	0.28
	Previous pregnant history	28–39,41–53	1.02	0.16–5.78	>0.99

It is worth noting that limitations exist in relation to this study. Firstly, the studies included in the meta-analysis and systematic review were all retrospective, thus may introduce an inevitable risk of bias. Secondly, included studies are reported over a large time span (1963–2021) by virtue of event rarity, the improvements in the overall management and outcome of AIH have occurred during the study time period. Therefore, there is inevitable heterogeneity in the comparison of some outcomes.

In conclusion, although the risk of having some specific complications may increase in AIH patients, in general, pregnancy could be well tolerated by mothers with AIH and their foetuses. For some high-risk groups, closer monitoring must be applied to improve both maternal and foetal outcomes.

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AUTHORSHIP

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Author contributions: TFS, YM and MAH were involved in the conception and design of the study; TFS, ZLH and YM participated in the search strategy and evaluated the articles for eligibility. TFS and ZLH performed the statistical analysis. All authors were involved in the results discussion. TFS drafted the manuscript. ZLH, RH, YM and MAH performed proof reading and editing.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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