Relationship between ABO blood group and pregnancy complications: a systematic literature analysis

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Abstract

Given the expression of ABO blood group antigens on the surface of a wide range of human cells and tissues, the putative interplay of the ABO system in human biology outside the area of transfusion and transplantation medicine constitutes an intriguing byway of research. Thanks to evidence accumulated over more than 50 years, the involvement of the ABO system in the pathogenesis of several human diseases, including cardiovascular, infectious and neoplastic disorders, is now acknowledged. However, there is controversial information on the potential association between ABO blood type and adverse pregnancy outcomes, including pre-eclampsia and related disorders (eclampsia, HELLP syndrome and intrauterine growth restriction), venous thromboembolism, post-partum haemorrhage and gestational diabetes. To elucidate the role of ABO antigens in pregnancy-related complications, we performed a systematic review of the literature published in the past 50 years. A meta-analytical approach was also applied to the existing literature on the association between ABO status and pre-eclampsia. The results of this systematic review are presented and critically discussed, along with the possible pathogenic implications.

Keywords: ABO blood group, pre-eclampsia, eclampsia, HELLP syndrome, venous thromboembolism.

Introduction

Along with their expression on red blood cells, ABO blood group antigens (namely, A, B, AB and O) are highly expressed by a large number of human cells and tissues including epithelia, platelets, vascular endothelia and neurons[1,2]. For this reason, a number of investigators have addressed whether this biological characteristic of the ABO system has clinical significance beyond that in transfusion and transplantation medicine. In fact, there is now a large body of evidence supporting the notion that ABO antigens are actively involved in the pathogenesis of various systemic diseases, including neoplastic, infectious, neurological and cardiovascular disorders[3-8]. While the non-O blood type-related increased circulating levels of von Willebrand factor (VWF), factor VIII (FVIII), cholesterol and several inflammatory cytokines (e.g., tumour necrosis factor-alpha, soluble intercellular adhesion molecule 1, E-selectin, P-selectin and interleukin-6) have been suggested as the most likely mechanisms for explaining the association between ABO blood group and arterial or venous thrombosis[9,10], the pathogenic mechanisms underlying the other ABO blood type-associated disorders are still largely unexplored. In addition, a number of studies have investigated the association between maternal ABO blood type and pregnancy complications, including pre-eclampsia and related disorders (e.g., eclampsia, the haemolysis, elevated liver enzyme, low platelets [HELLP] syndrome, intrauterine foetal growth restriction [IUGR]), venous thromboembolism (VTE), post-partum haemorrhage and gestational diabetes, although contradictory results have emerged. In order to elucidate the role of ABO blood types in these pregnancy-related disorders, we performed a systematic review of the existing literature.

Search methods

We systematically reviewed the scientific literature for published studies evaluating the interplay between maternal ABO blood types and pregnancy outcomes. We searched the MEDLINE and EMBASE electronic databases for the last 50 years (January 1965 - August 2015) with English language restriction. Only full-text articles were considered for this systematic review. The Medical Subject Heading and key words used were the following: "ABO blood group", "pregnancy", "preeclampsia", "eclampsia", "venous thromboembolism", "deep-vein thrombosis", "pulmonary embolism", "gestational diabetes", "post-partum hemorrhage", "pregnancy-induced hypertension" and "hemolysis, elevated liver enzymes, low platelets syndrome", "HELLP syndrome" "intrauterine fetal growth restriction" and "IUGR". We also hand-searched the reference lists of the most relevant items to identify any further eligible studies not captured in the initial literature search. All prospective and retrospective studies were included in the final analysis. Due to the paucity of published data, a meta-analysis of retrieved data (including more than three studies evaluable) was only possible for the association between ABO blood groups and pre-eclampsia.

ABO blood group and pre-eclampsia

Pre-eclampsia, defined as hypertension (≥90 mmHg) accompanied by proteinuria (≥300 mg/24 hours) after 20 weeks of gestational age[11], is one of the leading causes of maternal and foetal morbidity and mortality, since it can progress to eclampsia (characterised by the occurrence of convulsions), HELLP syndrome, and may be associated with fibrin deposition in the placental microcirculation and consequent IUGR (defined as neonatal birth weight below the 10th percentile)[12,13]. Although various studies have investigated a possible relationship between maternal ABO antigens and pre-eclampsia[14-24], there is no consensus on whether a true association does exist. In a study conducted by May, British women with A blood type had a 2.7-fold higher risk of pre-eclampsia compared with O type individuals[16]. Similarly, Spinillo and Colleagues[19] and Hiltunen and Colleagues[22] found that the risk of pre-eclampsia was increased by 2.1- to 3.1-fold in Italian and Finnish gravidas with AB blood type compared to that in women with O blood type. In a study conducted in pregnant Thai women, the risk of pre-eclampsia was 1.7-fold higher in women with A and AB blood types compared to the risk in O type individuals[24]. However, an impact of ABO blood types on pregnancy complications was not observed by Scott and Colleagues in a study conducted in the USA[17] and, more recently, by Witsenburg and Colleagues[20] and Clark and Colleagues[21], in two studies of Dutch and Scottish women, respectively.

Systematic review and meta-analysis

A systematic review of the literature initially identified 117 potentially relevant citations in the last 50 years. Following the exclusion process (87 references were excluded as not relevant, 8 after language restriction and 13 because they did include relevant information, such as definitions of diseases or ABO blood group distribution in both patients and controls), a total of nine studies (7 case-control studies, 2 cohort studies) were identified and considered eligible for this systematic review[16-24]. A meta-analysis was then performed including these nine eligible studies. Table I summarises the main characteristics of the studies.

Methods

The main outcome was the incidence of pre-eclampsia or eclampsia. The case-control studies were evaluated by study odds ratio (OR) meta-analytical pooling, whereas the cohort studies were evaluated by pooling the study relative risk. The Mantel-Haenszel method of weighting was used. The heterogeneity was quantified by the I^2 statistic[25]. When heterogeneity was large (I^2>50%), the DerSimonian-Laird random effects procedure was followed[26]. The influence of each individual study on the overall meta-analysis summary estimate was assessed by sensitivity analysis. This was based on single study omission, extended to all studies, in turn; this procedure was limited to case-control studies. The difference of prevalence of the group O in cases and in controls was also evaluated by meta-analytical pooling.

Results and discussion

The nine case-control studies were analysed to evaluate the association between group O exposure and outcome by OR pooling (Figure 1). The effect size was 0.77 (95% confidence interval [CI]: 0.67-0.88), which is significantly lower than one, implying a lower prevalence of this blood group in patients with pre-eclampsia (p=0.000) in comparison to non-O group women. The heterogeneity was low (I^2=28.2%). These findings suggest that group O was associated with lower odds of the outcome. The pooled difference of prevalence of group O in cases and in controls was –6.6% (95% CI: −10.9 to −2.3%). No single study was essential for the overall significance after sensitivity analysis (Figure 2). Of these case-control studies, two were evaluable for a differential prevalence of group A, and three for a differential prevalence of group AB (Figures 3 and 4). For group A the effect size was 1.78 (95% CI: 1.04-3.07), significantly higher than one, thus implying a higher prevalence of this blood group among the patients with pre-eclampsia (p=0.037). The heterogeneity was substantial (I^2=63.7%). For group AB the effect size was 1.94 (95% CI: 1.20-3.13), also higher than one (p=0.007). The heterogeneity was also substantial (I^2=64.2%). These data indicate that having blood group A or AB was associated with higher odds of the adverse outcome. The two cohort studies were submitted to evaluation of probability of pre-eclampsia due to group O by RR pooling (Figure 5). The effect size was 0.95 (95% CI: 0.93-0.97). Again, the resulting estimation was significantly lower than one, implying a lower probability of pre-eclampsia in this group than in non-O group women (p=0.000). The heterogeneity was low (I^2=0%).

Taken together, the results of the pooled analysis of the data indicate that O blood type may exert some protective effects against the development of pre-eclampsia compared with non-O blood type. However, a note of caution is necessary. The prevalence of group O was highly variable, ranging from 21 to 48% in the cases and from 32 to 48% in the controls, which may suggest the presence of heterogeneity in the ethnic background of the study participants. The very low number of studies supporting the investigations on group A and AB is another important aspect. This holds true also for the causal effect of group O in the cohort

Table I - Association between ABO blood type and pre-eclampsia: a systematic literature review.

First author, year[ref.]	Study design	Cases N (%)	Controls N (%)	Main results
May, 1973[16]	Case-control	47 10 O (21.3), 37 non-O (78.7), A 31	400 182 O (45.5), 218 non-O (54.5) A 172	A blood group was associated with a 2.7-fold increased OR of pre-eclampsia compared with O blood type
Scott, 1976[17]	Case-control	46 22 O (47.8), 24 non-O (52.2) 15 A, 7 B, 2 AB	4,494 2,139 O (47.6), 2,355 non-O (52.4) 1,705 A, 511 A, 139 AB	No association between ABO blood group and the risk of pre-eclampsia
Amin, 1989[18]	Case-control	368 106 O (28.8), 262 non-O (71.2) 112 A, 112 B, 38 AB	342 123 O (36.0), 219 non-O (64.0) 98 A, 93 B, 28 AB	Significant reduction ($p<0.05$) in group O in cases compared with healthy controls
Spinillo, 1995[19]	Case-control	204 74 O (36.3), 130 non-O (63.7) 84 A, 30 B, 16 AB	744 288 O (38.7), 456 non-O (61.3) 356 A, 80 B, 20 AB	Maternal AB blood group (8% in cases *vs* 3% in controls) was associated with an increased risk (adjusted OR 3.07, 95% CI: 1.48-6.36) of severe pre-eclampsia
Witsenburg, 2005[20]	Case-control	36* 11 O (30.6), 25 non-O (69.4)	272 111 O (40.8), 161 non-O (59.2)	No effect of ABO blood group was observed on the risk of pregnancy complications (pre-eclampsia, HELLP syndrome and PIH)
Clark, 2008[21]	Prospective cohort	66 32 O (48.5), 32 non-O (51.5)	3,919 2,055 O (52.4), 1,864 non-O (47.6)	No effect of ABO blood type on the risk of pre-eclampsia
Hiltunen, 2008[22]	Case-control	248 72 O (29.0), 176 non-O (71.0) 104 A, 40 B, 32 AB	679 217 O (32.0), 462 non-O (68.0) 294 A, 124 B, 44 AB	AB blood group was associated with an increased risk of pre-eclampsia (OR 2.1, 95% CI: 1.3-3.5) compared with non-AB blood group
Lee, 2012[23]	Cohort	37,814 13,881 O (36.7), 23,933 non-O (63.3) 17,408 A, 4,430 B, 2,095 AB	641,926 243,041 O (37.9), 398,885 non-O (62.1) 291,453 A, 74,147 B, 33,285 AB	Women with AB blood group had the highest risk of developing pre-eclampsia (OR 1.10, 95% CI: 1.04-1.16) and severe pre-eclampsia (OR 1.18, 95% CI: 1.07-1.30)
Phaloprakarn, 2013[24]	Case-control	350 105 O (30.0), 245 non-O (70.0) 100 A, 113 B, 32 AB	5,320 1,956 O (36.8), 3,364 non-O (63.2) 1,153 A, 1,832 B, 379 AB	Blood types A (28.6% in cases and 21.7% in controls) and AB (9.1% in cases and 7.1% in controls) were associated with an increased risk of pre-eclampsia compared with blood type O (RR for A blood type: 1.7, 95% CI: 1.3-2.3, p=0.001; RR for AB blood type: 1.6, 95% CI: 1.1-2.6, p=0.01)

*Combined group with pre-eclampsia, HELLP syndrome and PIH.
RR: relative risk; OR: odds ratio; CI: confidence interval; HELLP: haemolysis, elevated liver enzymes, low platelets; PIH: pregnancy-induced hypertension.

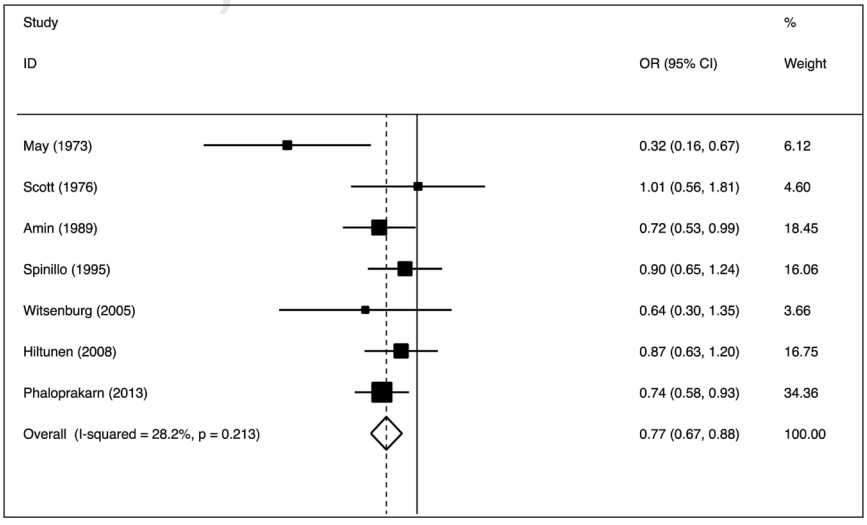

Figure 1 - Association of the group O with pre-eclampsia (OR meta-analytical pooling, fixed effect).
OR: odds ratio; CI: confidence interval.

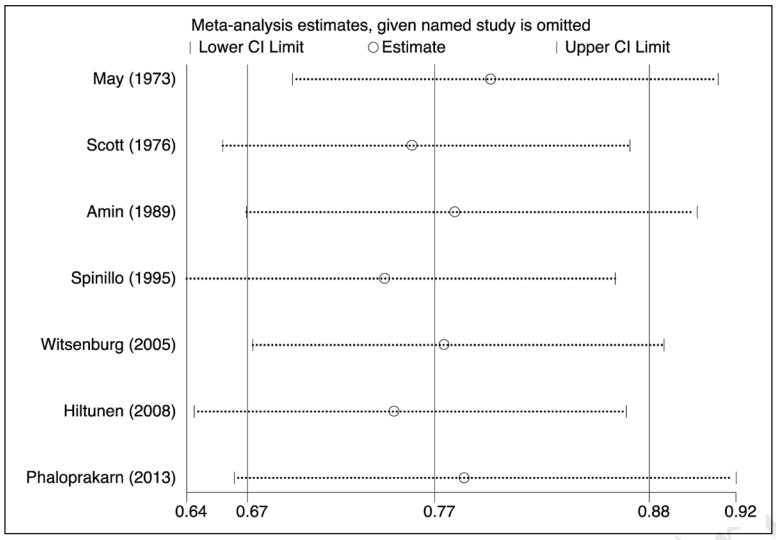

Figure 2 - Sensitivity analysis of the association of group O with pre-eclampsia (OR meta-analytical pooling, fixed effect).
No study, if omitted, changed the overall effect to non-significance. Indeed, the 95% CI never overlaps the null value of one.
OR: odds ratio; CI: confidence interval.

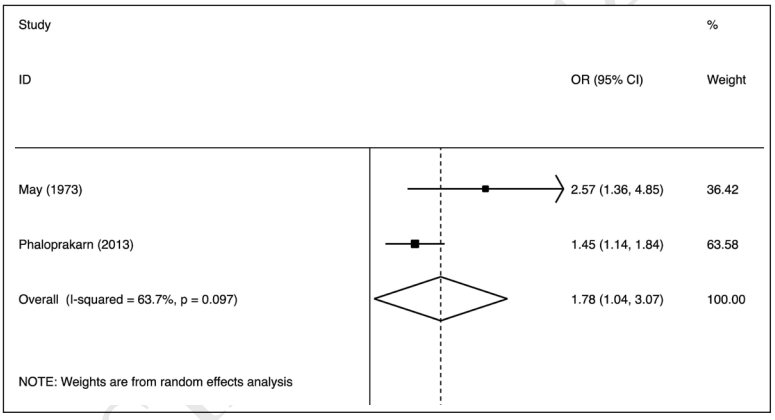

Figure 3 - Association of group A with pre-eclampsia (OR meta-analytical pooling, random effects).
OR: odds ratio; CI: confidence interval.

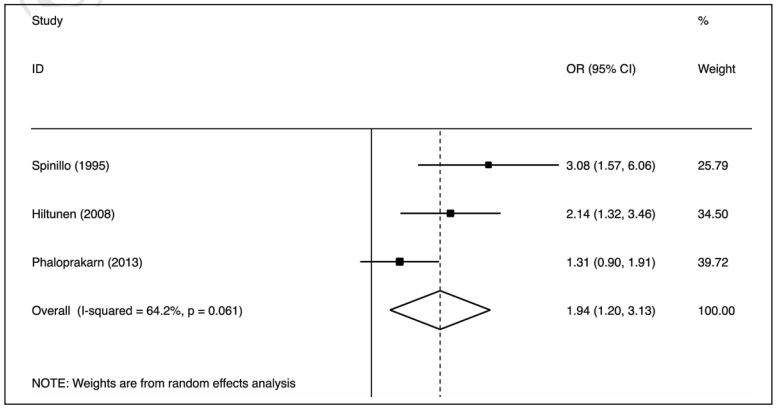

Figure 4 - Association of group AB with pre-eclampsia (OR meta-analytical pooling, random effects).
OR: odds ratio; CI: confidence interval.

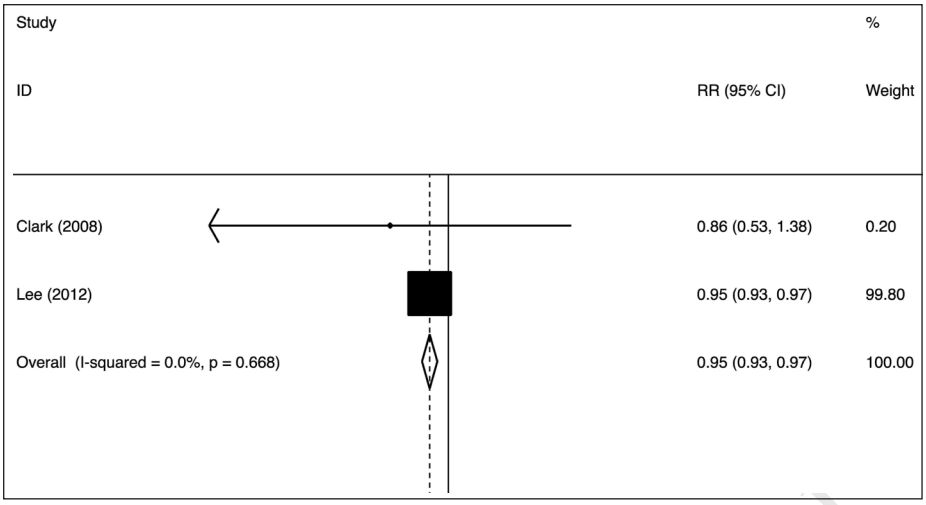

Figure 5 - Putative causal effect of group O *vs* non-O on pre-eclampsia (relative risk meta-analytical pooling, fixed effect).
RR: risk ratio; CI: confidence interval.

studies, which were dominated by the overwhelming weight (99.8%) of the study by Lee and Colleagues[23]. Taken together, the results of our systematic review and meta-analysis are seemingly divergent from those published by Clark and Wu in 2008[14], in which a consistent positive influence of ABO blood group on pre-eclampsia could not be found in the 17 eligible studies (O *vs* non-O blood group: pooled OR of 1.01, 95% CI: 0.91-1.12). A possible explanation for this difference probably lies in the inclusion criteria used in our meta-analysis (inclusion of studies published in the last 50 years), thus including more recent studies with a better design and a more accurate definition of the patient populations.

Although the definitive pathogenic mechanism is still unknown, the existence of a pro-thrombotic state may be regarded as the most plausible factor linking pre-eclampsia with ABO blood types. Indeed, while non-O blood groups are well recognised risk factors for thrombosis due to the higher levels of VWF and FVIII compared to those in subjects with O blood type, a number of studies identified a causative role of hypercoagulability in the risk and severity of pre-eclampsia[27]. Indeed, several investigators have consistently reported that VWF and/or FVIII levels are increased in pre-eclamptic women compared to those in women with healthy pregnancies[28-31]. This finding is in keeping with the epidemiological observation of an association between the risk of developing pre-eclampsia and AB blood type[19,22-24], which is characterised by the highest VWF and FVIII levels among the different antigens of the ABO system[32]. Notably, reduced levels of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13), an enzyme responsible for cleavage and clearance of ultralarge VWF (ULVWF, the most haemostatically active form of VWF) from the circulation, have also been reported in patients with pre-eclampsia or HELLP syndrome in some studies[33-35], but not in others[36,37]. The resulting increased levels of ULVWF may trigger platelet aggregation, thus causing diffuse occlusion of placental arterioles, a key event in the pathogenesis of pre-eclampsia and related disorders[38]. The endothelial injury and dysfunction then activates endothelial cells, which in turn release active VWF that can perpetuate and even worsen placental insufficiency through a vicious circle[34,39]. However, besides the imbalance between ADAMTS13 activity and VWF levels, other mechanisms may come into play. The metabolism of placental protein 13 (PP13), a placenta-specific galectin exerting important immune biological functions at the maternal-foetal interface and now considered an early biomarker of severe pre-eclampsia, is regulated by ABO blood groups. PP13 binds to the beta-galactosides (N-acetyl-galactosamine, galactose and fucose) located at terminal positions on ABO antigens and this sequestration process may reduce PP13 levels in the first trimester, thus predisposing to pregnancy complications, including pre-eclampsia. The effect seems to be more pronounced in pregnant women with the AB blood group, because the concomitant presence of A and B antigenic determinants results in more efficient binding to PP13, thus lowering PP13 serum levels[40]. Finally, another putative mechanism could involve up-regulation, by polymorphisms in the *ABO* locus, of circulating levels of the aforementioned inflammatory cytokines, which are also strongly associated with pre-eclampsia[41-43]. All these mechanisms are biologically plausible and, as one does not exclude the other, it is possible that they be concomitantly present[44].

ABO blood group and disorders related to pre-eclampsia

Fewer studies have specifically addressed the relationship between ABO blood types, HELLP syndrome and IUGR, two conditions sharing the same pathogenesis as pre-eclampsia (i.e., uteroplacental insufficiency). As regards HELLP syndrome, a retrospective study conducted on 547 Turkish women with pre-eclampsia found that the incidence of HELLP syndrome was two times higher in O Rh-negative patients than in the overall study population (48% *vs* 24%, OR 3.1, 95% CI: 1.28-7.43)[45]. By contrast, no association between any ABO blood type and HELLP syndrome was observed in the study by Witsenburg and Colleagues[20], although a separate analysis with pre-eclampsia and pregnancy-induced hypertension was not performed. As regards IUGR, a prospective case-control study conducted by Clark and Greer showed no association between this condition and ABO genotype or phenotype, although a significant relationship was observed between maternal secretor/Lewis status and occurrence of foetal growth restriction (secretor *vs* non-secretor: OR 1.70, 95% CI: 1.08-2.69; Lewis(b) *vs* Lewis(a): OR 1.80, 95% CI: 1.15-2.83)[46]. Non-significant effects on foetal growth were observed in the Glasgow Outcome APC resistance and Lipid (GOAL) study when non-O group subjects were compared with O group subjects[21]. Similar conclusions were drawn in the study by Witsenburg and Colleagues[20], despite the fact that FVIII levels were higher in the IUGR group and thus associated with a nearly 3-fold higher risk of IUGR. Interestingly, a recent study found a negative combined influence of smoking and A blood type on birth weight[47], although no significant relationship between ABO blood type and low birth weight was observed in another investigation[24].

ABO blood group, venous thromboembolism and haemorrhagic complications

It is now well acknowledged that non-O blood type individuals have an approximately 2-fold higher risk of developing VTE than have O type subjects[48-51]. In contrast, individuals with O blood type have VWF plasma levels 25-35% lower than those in non-O individuals, thus exhibiting a modestly increased risk of haemorrhage[52]. Only a few studies have analysed this issue in the context of pregnancy and the puerperium. The first observation dates back to 1969 and was made by Jick and Colleagues[53], who conducted a case-control study in women from the UK, Sweden and USA, and reported a 2.1 relative risk of VTE (95% CI: 1.5-3.1) among pregnant women with non-O blood group compared with those with blood group O. A similar study performed in 1970 by Talbot and Colleagues[54] found a relative risk of 1.7 (95% CI: 1.1- 2.6) in a subgroup of pregnant British women. In a subsequent study conducted in the same geographical area, compared with the incidence in subjects with O blood type, blood group A was found to increase the incidence of both antenatal VTE (adjusted OR: 1.9, 95% CI: 1.2-3.0) and post-natal VTE (adjusted OR: 1.6, 95% CI: 1.2-2.2)[55]. Increased risk estimates of VTE for women with blood groups A and AB were found in both pregnancy (adjusted OR: 3.9, 95% CI: 1.5-9.7 and 2.2, 95% CI: 0.4-12.5, respectively) and in the puerperium (adjusted OR: 2.4, 95% CI: 1.0-4.9 and 2.7, 95% CI: 0.8-9.3, respectively) in a nested case-control study conducted in Denmark by Larsen and Colleagues[56]. As far as regards the ABO-related risk of bleeding, a case-control study carried out by Chauleur and Colleagues in France found that O blood group was independently associated with a significant risk of severe post-partum haemorrhage (adjusted OR: 1.84, 95% CI: 1.32-2.57)[57]. Despite these results, no influence of ABO blood groups on the risk of VTE or post-partum haemorrhage was observed in the aforementioned prospective GOAL study[21].

ABO blood group and gestational diabetes

Due to the influence of ABO antigens on circulating levels of E-selectin, P-selectin, tumour necrosis factor-α, soluble intercellular adhesion molecule-1 and interleukin-6[41,42] combined with the observed association between these biomarkers and insulin resistance and the development of type 2 diabetes mellitus[58], several epidemiological studies have explored the relationship between ABO blood group and diabetes, but their findings were mostly inconsistent[59-66]. Nevertheless, only a few investigators have analysed this association in a subset of pregnant women. A recent study on 792 healthy Iranian women reported that those with AB blood type had higher fasting glucose levels in the second trimester than those with A blood type[67]. Another study identified a higher prevalence of O blood type in pregnant Turkish women with gestational diabetes mellitus than in non-diabetic pregnant women (52.2% *vs* 33.3%)[68]. By contrast, no significant association was found between ABO blood group and risk of developing gestational diabetes mellitus in a retrospective cohort study on 5320 pregnant women who attended a tertiary care centre in Thailand[24]. Finally, a more recent prospective study conducted in China reported that AB blood group was a protective factor against gestational diabetes mellitus (AB *vs* non-AB blood types: OR: 1.44, 95% CI: 1.13- 1.83)[69].

Conclusions

Several studies have convincingly proven that the ABO blood type not only plays a role in transfusion

and transplantation medicine, but is implicated in the pathogenesis of a kaleidoscope of human disorders. The results of this systematic review support for the first time the existence of a consistent influence of ABO status on the risk of developing pre-eclampsia. Specifically, women with a non-O blood type were found to have a moderately increased risk of this condition compared with the risk in those with O blood type. The systematic analysis of the literature data also suggests that non-O pregnant women have an increased incidence of VTE compared with that in pregnant women with O blood type. Less evidence is available for the association with other adverse pregnancy outcomes, reflecting the paucity of published clinical data. Thus, further prospective studies including large populations of patients are warranted to assess the role of ABO blood group in identifying women at risk of developing pre-eclampsia or other pregnancy-related complications. Experimental investigations are also needed to unravel the underlying pathogenic mechanisms of these interactions.

The Authors declare no conflicts of interest.

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