Associations between spontaneous preterm birth and maternal-newborn ABO blood phenotype pairs

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ABSTRACT

الأهـــداف: دراسة علاقة الولادة المبكرة التلقائية مع ازدواج فصائل الدم الأم –الجينيه ABO.

الطريقة: أُجريت هذه الدراسة الاسترجاعية في قسم الأطفال، جامعة الملك عبدالعزيز، الأحساء، المملكة العربية السعودية. شملت مجموعة الدراسة 631 ولادة مبكرة حية بحمل وحيد وبعمر حملي أقل من 37 أسبوع وفي الفترة الزمنية مابين أغسطس 2005م إلى مايو 2011م، أما مجموعة الشاهد فقد ضمت 2204 مولود حي بحمل وحيد تام الحمل مابين مايو 2008م إلى أبريل 2009م. لقد تم أخذ البيانات الخاصة بالأم والمواليد من قاعدة البيانات الخاصة بحديثي الولادة في وحدتنا ومن السجلات الخاصة بغرفة الولادة. ثم أُخذت معلومات حول فصائل الدم باستخدام برنامج معلومات المختبر المركزي، واستخدمنا اختبار كاي مربع لدراسة العلاقة بين الولادة المبكرة التلقائية وازدواج فصائل الدم ABO بين الأم والجنين.وقد استخدمنا مجموعة ازدواج A–A, B–B, O–O, AB–AB كمجموعة المرجع، واستخدمنا تحليل الانحدار اللوجستي للبيانات الثنائية لضبط عوامل الخطر الأربعة المثبتة والمتعلقة بالولادة المبكرة.

النتائج: أشارت نتائج الدراسة إلى أن الولادة المبكرة العفوية قد ترافقت مع ازدواج B–A (Odds ratio: 2.67, 95% confidence interval: 1.35–5.24, p=0.003) ومع ازدواج AB–B (Odds ratio: 1.97, 95% confidence interval: 1.04–3.74, p=0.04). وعندما قمنا بإجراء التحليل اللوجستي فقد بقيت هاتين العلاقتين هامتين.

خاتمة: أظهرت هذه الدراسة ترافق الولادة المبكرة العفوية مع ازدواج B–A وAB–B بين الأم والجنين. وتتطلب مثل هذه النتيجة دراسة تأكيدية وتوضيحيه إضافية حيث أنها يمكن أن تقلل الولادة المبكرة التلقائية.

Objectives: To study whether spontaneous preterm birth (SPB) is associated with maternal-newborn ABO blood phenotype pairs.

Methods: We conducted a retrospective case-control study in the Department of Pediatrics, King Abdulaziz Hospital, Al-Ahsa, Kingdom of Saudi Arabia. A total of 631 live singleton SPBs (<37 weeks) between August 2005 and May 2011 formed the case group. A total of 2,204 live singleton term births (≥37 weeks) between May 2008 and April 2009 formed the control group. We extracted data on the mothers and their newborns from our neonatal electronic database and delivery room log book. We extracted ABO blood phenotypes using Cerner's Lab Information Software. We used a Chi square test to study the association between SPB and maternal-newborn ABO pairs. We used a combination of maternal-newborn A-A, B-B, AB-AB, and O-O pairs as the reference group. We used a binary logistic regression analysis to adjust for 6 established risk factors for SPB.

Results: Spontaneous preterm birth was associated with only maternal-newborn pairs B-A (odds ratio: 2.67, 95% confidence interval: 1.35-5.24, p=0.003) and AB-B (odds ratio: 1.97, 95% confidence interval: 1.04-3.74, p=0.04). Both associations remained significant in the regression analysis.

Conclusion: Spontaneous preterm birth is associated with maternal-newborn B-A and AB-B pairs. This finding requires further confirmatory and exploratory study as it could reduce SPBs.

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Blood phenotype A and B antigens are present on fetal red blood cells, endothelial cells, and body fluids as early as the fifth week of pregnancy.[1] Maternal-fetal ABO interactions have been well documented such as maternal-fetal ABO incompatibility pairs being associated with spontaneous abortion.[2-8] However, for unknown reasons there are some inconsistencies on which maternal-fetal ABO pairs are most at risk. For instance, one study has cited the B-A pair, the mother's blood phenotype being B and the fetal blood phenotype being A, as being most at risk,[5] another study has cited the O-AB pair as being most at risk,[6] and a third study has cited A-B as being most at risk.[7] Spontaneous abortion puts subsequent pregnancies at risk of spontaneous preterm birth (SPB), and the risk is directly proportionate to number of previous abortions.[9,10] The association between SPB and maternal-newborn ABO pair has not been previously studied. We hypothesized that SPBs may be associated with specific maternal-newborn ABO pairs. Therefore, the aim of the current study was to study whether SPB is associated with maternal-newborn ABO blood phenotype pairs.

Methods. We conducted this retrospective case-control study, with a case:control ratio of 1:3, at the Neonatal Intensive Care Unit, Department of Pediatrics, King Abdulaziz Hospital (KAH), Al-Ahsa, Kingdom of Saudi Arabia. The standard of care at KAH is to determine the ABO phenotypes of all pregnant women, including those who are in labor or delivering. Since August 2005, we have determined the blood phenotype and direct antiglobulin test status of all live newborns using cord blood. The blood bank at KAH uses a standard gel technique (DiaMed-ID Micro Typing System, Cressier sur Morat, Switzerland) for blood phenotyping, and permanently stores the results using Cerner's Lab Information Software (LIS) (Cerner Corporation, Kansas City, MO, USA).

We selected live singleton SPBs (<37 weeks of gestation) at KAH between August 2005 and May 2011 as the case group, and live singleton term births (≥37 weeks of gestation) for one year (May 2008-April 2009) as the control group. We selected this control group because we had previously extracted and stored demographic data on some of them for another study.[11] We defined live births as fetuses of at least 23 weeks' gestation, or 500 g birth weight with any signs of life at delivery. We defined SPB as birth that followed spontaneous preterm labor or preterm premature rupture of membranes (PPROM).[12] Therefore, induced preterm births for maternal or fetal indications (n=395) were excluded. Maternal indications included gestational diabetes mellitus (GDM), preeclampsia/eclampsia, placental abnormalities, and various maternal diseases including sickle cell disease, epilepsy, systemic lupus erythematosus, and antiphospholipid antibody syndrome. Fetal indications included major congenital anomalies, small for gestational age (SGA), and nonreassuring fetal surveillance. We excluded 2 births because the cord blood was not sent for ABO phenotyping, and both infants were from the control group.

We extracted data on the 2,835 mothers and their newborns from our neonatal electronic database and delivery room log book. We included the earliest delivery if the mothers delivered more than once during the study period. We extracted data on established risk factors for SPB, which were available in our database. These were history of spontaneous abortion, primigravida, extreme reproductive age, assisted reproductive technology (ART), PPROM, and chorioamnionitis.[9,10,12-15] We extracted ABO blood phenotypes from LIS. We double-checked the data extraction and entries for completeness and accuracy. The characteristics of our community, obstetric service, neonatal service, and electronic neonatal database were previously reported.[16] We considered the gestational age to be the best obstetric estimate, which was based on first or second trimester obstetric ultrasound and last menstrual period. We used the Ballard score when the best obstetric estimate was uncertain.[17] We defined premature rupture of membranes as the spontaneous rupture of the amniotic membranes at least one hour before the onset of labor. Our database provides no data as to whether the chorioamnionitis were histological or clinical. However, our obstetricians are defining clinical chorioamnionitis as a maternal temperature greater than 38°C, in addition to 2 of the following signs: uterine tenderness, maternal or fetal tachycardia, and foul/purulent amniotic fluid. We defined GDM according to the guidelines of the American College of Obstetricians and Gynecologists.[18] We defined preeclampsia/eclampsia according to the Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy.[19] We defined ART as any drug or medical procedure that manipulates eggs or sperm to establish pregnancy. Placental abnormalities in our database included placenta previa, marginalis, accreta, and placental abruption. Major congenital anomalies

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Table 1 - Characteristics of pregnancies among spontaneous preterm and term births.

Characteristics	Spontaneous preterm births (n=631)		Term births (n=2,204)		*P*-value
Saudi mothers	629	(99.7)	2,201	(99.9)	0.62
Maternal age (years), mean (SD)	29	(7)	29	(6)	0.50
Extreme maternal reproductive age	157	(24.9)	429	(19.5)	0.003
Gravida, median (interquartile range)	3	(1-6)	4	(2-6)	0.06
Primigravida mother	158	(25.0)	389	(17.6)	<0.001
History of more than one spontaneous abortion	106	(16.8)	282	(12.8)	0.01
Assisted reproductive technique	9	(1.4)	8	(0.4)	0.01
Premature rupture of membranes	177	(28.1)	113	(5.1)	<0.001
Chorioamnionitis (histological/clinical)	33	(5.2)	1	(1)	<0.001

Values are expressed as number (percentage) unless otherwise indicated

in our electronic database included all structural, chromosomal, and genetic anomalies that have serious medical and/or surgical consequences. For the purpose of the study, we defined maternal age of less than 19 or more than 35 years of age as extreme reproductive age.[20] As birth weight charts for Saudi preterm newborns is not available, a newborn with a birth weight of less than the fifth percentile of the Kuwaiti birth weight chart was defined as SGA.[21] The Institutional Review Board at the National Guard Health Affairs approved the study without requiring informed consent.

Statistical analyses. We present descriptive results for all quantitative variables as means (standard deviation, [SD]) for normally distributed data or medians (interquartile range) for data that were not normally distributed. We used t-tests for parametric data, and the Mann-Whitney test for non-parametric data. We present the results for all qualitative variables as numbers (percentage). We used a Chi-squared test and Fisher exact test when appropriate to analyze qualitative variables and the association between SPB and maternal-newborn ABO pairs. We calculated odds ratio (OR) and 95% confidence interval (CI) to assess the association between maternal-newborn ABO pairs and SPB. We used a combination of A-A, B-B, AB-AB, and O-O pairs as the reference group for these calculations. A multivariable binary logistic regression analysis was used to adjust for 6 established significant risk factors for SPB. These were history of more than one spontaneous abortion, primigravida, extreme reproductive age, ART, PPROM, and chorioamnionitis. We used a likelihood ratio test to assess the significance of the regression models, and the Hosmer-Lemeshow test to assess their goodness-of-fit. A 2-sided *p*-value <0.05 was considered statistically significant for all tests. We did not adjust the significance level for multiple comparisons.[22] The Statistical Package for Social Sciences version 19 (SPSS Inc., Chicago, IL, USA) was used for all data analyses.

Results. A total of 631 out of 1,089 preterm births during the study period met the inclusion criteria. One hundred and seventy of the SBPs were less than 34 weeks of gestation (early SPB) and 461 were between $34^{0/7}$-$36^{6/7}$ weeks of gestation (late SPB). **Table 1** summarizes the characteristics of pregnancies among spontaneous preterm and term births. The distribution of maternal-newborn rhesus (Rh) pairs was comparable in both the spontaneous preterm and term births (data not shown). **Table 2** summarizes the distribution of maternal-newborn pairs among spontaneous preterm and term births. As **Table 3** indicates, the SPB was only associated with maternal-newborn B-A pair (OR: 2.67, 95% CI: 1.35-5.24, *p*=0.003) and AB-B pair (OR: 1.97, 95% CI: 1.04-3.74, *p*=0.04). Both associations remained independently significant after adjusting for another 6 risk factors for SPB (**Table 3**). Both early SPB and late

Table 2 - Distribution of maternal-newborn ABO pairs among spontaneous preterm and term births.

Maternal-newborn ABO phenotype	Spontaneous preterm births (n = 631)		Term births (n = 2,204)	
A-A	91	(14.4)	361	(16.4)
A-B	10	(1.6)	26	(1.2)
A-AB	14	(2.2)	31	(1.4)
A-O	48	(7.6)	188	(8.5)
B-A	15	(2.4)*	20	(0.9)
B-B	67	(10.6)	230	(10.4)
B-AB	11	(1.7)	38	(1.7)
B-O	36	(5.7)	144	(6.5)
AB-A	10	(1.6)	42	(1.9)
AB-B	15	(2.4)†	27	(1.2)
AB-AB	7	(1.1)	9	(0.4)
O-A	36	(5.7)	148	(6.7)
O-B	35	(5.5)	118	(5.4)
O-O	236	(37.4)	822	(37.3)

Values are expressed as number (percentage). *Less than 34 weeks of gestation (n=5), †less than 34 weeks of gestation (n=3)

Table 3 - Maternal-newborn ABO pairs and risk for spontaneous preterm birth.

Maternal-newborn ABO phenotype	Odds ratio (95% confidence interval)*	Adjusted odds ratio (95% confidence interval)*
A-B	1.36 (0.65-2.85)	1.25 (0.58-2.74)
A-AB	1.60 (0.84-3.04)	1.52 (0.77-3.00)
A-O	0.91 (0.65-1.27)	0.90 (0.63-1.29)
B-A	2.67 (1.35-5.24)†	2.66 (1.30-5.47)§
B-AB	1.03 (0.52-2.03)	1.04 (0.50-2.19)
B-O	0.89 (0.61-1.30)	0.95 (0.64-1.42)
AB-A	0.84 (0.42-1.70)	0.81 (0.39-1.69)
AB-B	1.97 (1.04-3.74)‡	2.20 (1.14-4.28)**
O-A	0.86 (0.59-1.26)	0.75 (0.49-1.13)
O-B	1.05 (0.71-1.56)	0.98 (0.64-1.49)

*Combination of maternal-newborn A-A, B-B, AB-AB, and O-O pairs is the reference group for all other ABO pairs,
†p=0.003, ‡p=0.04, §p-0.008, **p=0.02

SBP were associated with B-A pair (OR: 3.56, 95% CI: 1.31-9.67, p=0.008 and OR: 2.36, 95% CI: 1.10-5.10, p=0.02,). Late SBP was associated with AB-B pair (OR: 2.10, 95% CI: 1.05-4.19, p=0.03), but early SPB was not (OR: 1.58, 95% CI: 0.47-5.30, p=0.46).

Discussion. Our study showed that SPB is associated with 2 maternal-newborn ABO pairs, B-A and AB-B. These associations remained independently significant after adjusting for 6 established risk factors for SPB. Our novel findings identified 2 new risk factors for SPB that require further confirmatory and explanatory study, as it could reduce SPBs in some cases.

Our findings are partially consistent with abortion literature. While 3 studies have found maternal-fetal B-A and AB-B pairs are deleterious,[7,8,10] one study did not conclude the same.[9] The abortion literature, although inconsistent, has found more maternal-fetal pairs that are deleterious, including A-B, A-AB, B-O, and O-AB.[5-8] Around one third of all pregnancies are aborted unrecognizably.[23] This may be more recurrent or more frequent among B-A and AB-B pregnancies as these pairs are associated with spontaneous abortion. As stated in the introduction that spontaneous abortion puts subsequent pregnancies at risk of SPB, unrecognized spontaneous abortion may account partly for our findings, which require exploration in a prospective study. Certainly, immune factors cannot account for our results. While the presence of anti-A, or the absence of anti-B could account for the B-A pair, no increase in SPBs was seen for the B-AB pair. No immune mechanism could be called to account for the increased risk in the AB-B pair. The B-A and AB-B pairs share the absence of the maternal immunoglobulin anti-B with 5 other pairs, but only B-A and AB-B were significantly associated with SPB. This suggests that there may be an unusual maternal-fetal interaction among B-A and AB-B pairs. However, the peculiar design of a retrospective case-control study and the small number of births among B-A and AB-B pairs preclude identifying the exact causal relationship between SPB and both B-A and AB-B pairs. Identification of causal association requires a different study design.

Our findings may reduce or prevent SPBs in some cases as B-A, and AB-B pairs could be anticipated before pregnancy by using the Punnett Square based on parental ABO phenotypes. Consequently, this could be utilized in premarital/preconception screening and counseling programs, which have been found to be very effective in reducing the rate of high risk matings.[24] Maternal-fetal B-A and AB-B pairs could be identified during early pregnancy by noninvasive fetal ABO genotyping on maternal blood, which has been found to be precise and clinically feasible.[25] Consequently, a medical intervention could be applied when the causal relationship between these 2 pairs and preterm birth is identified. However, our findings require further larger confirmatory cohort studies before making a firm recommendation.

In addition to the inherent limitations of this type of study, we would need more participants among AB-B pairs to be powered to detect the small percentage difference with 80% power and 5% level of significance. The small number of AB-B pairs among early SPB (n=3) may account for our finding that early SPB was not associated with the AB-B pair. We did not have data on other risk factors for SPB, including maternal nutritional status, maternal psychological characteristics, and cervical length. Indeed, these risk factors are not necessary to be plausible confounders.[26] For instance, they may not be confounders based on epidemiological criteria for confounder as their association with maternal-newborn ABO pairs is unlikely.[26] However, a strength of our study is its homogeneous population in terms of ethnicity (Arab Muslims), singleton pregnancies, and the absence or scarcity of several known maternal risk factors for SPB, including smoking, alcohol consumption, single mothers, induced abortion, long work hours, and hard physical work.[12]

We conclude that SPB is associated with maternal-newborn B-A and AB-B pairs. As our findings have not been reported before, and because association does not imply causation, further larger confirmatory cohort and exploratory studies are required before firm conclusions can be drawn.

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