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Antenatal anti-D prophylaxis and D antigen negativity in pregnant women of the UAE: a cross-sectional analysis from the Mutaba'ah Study

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ABSTRACT

Objective This study aimed to determine the prevalence of the negative D antigen phenotype, adherence to routine antenatal anti-D immunoglobulin prophylaxis (RAADP) administration and D antigen sensitisation among pregnant women in the UAE.

Design Data was collected from pregnant women enrolled in the Mutaba'ah Study. The Mutaba'ah Study is an ongoing prospective mother and child cohort study in the UAE. Data were extracted from the medical records and baseline questionnaire administered to the participants between May 2017 and January 2021.

Setting The study was conducted in Al Ain city of the UAE.

Participants A total of 5080 pregnant women residing in Al Ain participated in the study.

Outcome measures The study estimated the prevalence of negative D antigen phenotype and the provision of RAADP in this population.

Results Of the 5080 pregnant women analysed, 4651 (91.6%) had D antigen positive status, while 429 (8.4%) were D-negative. D antigen sensitisation was low at 0.5%, and there was a high uptake of RAADP in the population at 88.8%.

Conclusions The adherence to RAADP is consistent with published data from other healthcare settings. Knowledge of the prevalence of D antigen negative mothers is crucial to the financial and resource consideration for implementing antenatal foetal cell-free DNA screening to determine foetal D antigen status.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study presents the first report of D antigen immune prophylaxis percentage coverage and alloimmunisation rate in the UAE.
⇒ The study included a large representative sample of pregnant women (5080) from the Emirati population.
⇒ The study provides insight for improving the provision of anti-D prophylaxis, which is crucial for financial and resource considerations for implementing antenatal foetal cell-free DNA screening to determine foetal D antigen status.
⇒ There was limited availability of laboratory data on antigens/variants/genotypes, which restricted further investigation of D antigen distribution.

INTRODUCTION

Rhesus (Rh) factor is a protein inherited on red blood cell (RBC) surfaces discovered by Landsteiner and Wiene in 1940.[1 2] The Rh blood group comprises over 50 antigens, with the D-antigen being the most clinically important. This blood group is second only to the ABO system in importance.[3] D antigen immunisation occurs when a D-negative mother is exposed to D-positive foetal blood, producing antibodies against foetal RBCs. The maternal immune response initially produces IgM antibodies, followed by IgG antibodies that cross the placenta.[4] In subsequent D-positive pregnancies, these antibodies may cause foetal and neonatal haemolysis, known as the haemolytic disease of the foetus and newborn (HDFN). Untreated HDFN can result in foetal heart failure, hydrops fetalis or even death and remains the leading cause of anaemia in newborns.[5] D antigen alloimmunisation leading to haemolytic disease of the foetus and newborn remained a major cause of perinatal mortality, morbidity and long-term disability. The prophylaxis for the prevention of D antigen alloimmunisation was developed in the 1960s.[6]

In 1971, the WHO technical report recommended routine postpartum administration of anti-D IgG. As a result, the rate of alloimmunisation dropped to approximately 2%.[5 7 8] The introduction of routine antenatal anti-D immunoglobulin prophylaxis (RAADP) was in the early 1980s, which involved the administration of antenatal prophylaxis during the third trimester of pregnancy. This policy reduced the sensitisation rate in the range of 0.17 to 0.28%.[9–11]

However, challenges exist in the use of anti-D Ig, including limited supply and the risk of transmission of blood-borne infectious diseases such as hepatitis C virus.[12] Moreover, it is noteworthy that there is racial variation in the prevalence of D antigen negativity worldwide. Evidence from various populations has already demonstrated how the incidence of maternal D antigen alloimmunisation has been significantly reduced in high-income countries due to the implementation of antenatal and postnatal prophylaxis guidelines.[9–11] Determination of the D antigen status of pregnant women allows healthcare providers to give the necessary precautions to reduce the foetus's risk.[13] On the other hand, the Department of Health in the Abu Dhabi Emirate of UAE plans to implement an antenatal cell-free DNA screening programme to determine foetal D antigen status for selective administration of anti-D prophylaxis. Knowledge of the prevalence of D antigen negative mothers and the current sensitisation rate is crucial to the financial and resource considerations before implementing this programme. To our knowledge, no published data exist on the prevalence of D antigen negativity among pregnant women in the UAE. The objective of the present study was to ascertain the prevalence of D antigen negativity and D antigen sensitisation among pregnant women in the UAE.

MATERIALS AND METHODS

Study design and population

The study population consists of 5080 pregnant women who participated in the Mutaba'ah Study and gave birth between May 2017 and January 2021. The Mutaba'ah Study is an ongoing prospective mother and child cohort study in Al Ain city, UAE, which includes all pregnant women from the Emirati population aged 18 years and above, residents in Al Ain and able to provide informed consent for themselves as well as for their newborns.[14] Recruitment started in May 2017 and is ongoing in two major hospitals in the city, with follow-up of mothers and their offspring using questionnaires and medical record extractions until the child turns 18. Although mothers might participate in the Mutaba'ah Study with more than one pregnancy, no women were included more than once in this analysis. The study was approved by the United Arab Emirates University Human Research Ethics Committee (ERH-2017–5512) and the Abu Dhabi Health Research and Technology Ethics Committee (DOH/CVDC/2022/72), and informed written consent was obtained from all participants before the data collection.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of this study.

Primary and secondary outcomes

The medical records and baseline questionnaire from the first contact with pregnant women who gave birth between May 2017 and January 2021 were used to extract data for this analysis. The questionnaire provided self-reported information on consanguinity, education and employment status, which were coded as 'Yes' or 'No' for consanguinity and 'secondary school or less' or 'higher than secondary' for education and 'employed' or 'unemployed' for employment status. Maternal age, gravidity, parity, maternal and newborn ABO blood groups, D antigen statuses and related data, including the presence of D antibodies and administration of RAADP, were extracted from the medical records. The pregnant women are routinely tested for D antigen in the first trimester during the first antenatal visit. For D antigen negative women who are non-sensitised, the test is repeated before 28 weeks to select women who need RAADP. Furthermore, Kleihauer-Betke tests are also performed for women after delivery if it was clinically indicated (in case of massive antepartum haemorrhage).

ABO/D-antigen grouping and RBC antibody screening

All pregnant women attending the two antenatal care clinics were routinely tested for ABO and D antigen blood groups and screened for antibodies against RBC antigens. This screening is usually performed in the first trimester of pregnancy and before 28 weeks for select women who need RAADP. D antigen tests are also routinely done for some women after delivery if it is clinically indicated (in case of massive antepartum haemorrhage). Blood samples are analysed for ABO and D antigen blood groups in the two antenatal care clinics using the DiaClon ABO/D+Reverse Grouping ID-Card (Bio-Rad, Dreleich, Germany). Antibody screening is performed using ID DiaCell I-II-III (Bio-Rad, Dreleich, Germany). Further antibody identification is performed using indirect antiglobulin testing (IAT), ID-DiaPanel 11 cells panel (Bio-Rad, Dreleich, Germany). Determination of ABO and the RhD blood group in neonates is performed in cord blood samples using DiaClon ABO/Rh for newborn's DVI+Cards (Bio-Rad, Dreleich, Germany).

Statistical analyses

Descriptive statistics were performed to compare the distribution of ABO blood groups and D antigen status with data presented as counts and percentages for categorical variables and means and SD for continuous variables. Statistical analyses were performed using Stata 16 (Stata Corp, College Station, TX).

RESULTS

Sociodemographic characteristics of the study participants

The sociodemographic characteristics of the pregnant women in the study are provided in table 1. Of the 5080 pregnant women analysed, the mean age was 31 years (±6.1). The mean body mass index was 28.7 kg/m² (±5.9). About one-fifth (19.8%) of the participants were primigravida, while the majority (80.2%) were multigravida. Nulliparity was observed in 18.1% of the women, whereas 81.9% had multiparity. Regarding educational

Table 1 Participant's sociodemographic characteristics

Study participants	5080
Age*	31.0±6.1
Body mass index*	28.7±5.9
Gravida	
Primigravida	1005 (19.8)
Multigravida	4075 (80.2)
Parity	
Nulliparity	922 (18.1)
Multiparity	4158 (81.9)
Education	
Secondary school or less	2325 (45.8)
Higher than secondary	2350 (54.2)
Employment	
Unemployed	3199 (63)
Employed	1468 (37)

*Data presented as mean±SD. All other variables are presented as count (per cent).

attainment, 54.2% had higher than secondary education, while 45.8% had secondary school education or less. The majority of participants (63%) were unemployed, and 37% were employed (table 1).

Distribution of D antigen status by ABO

Table 2 presents the distribution of ABO groups and D antigen status among 5076 women with valid ABO status. The overall distribution of ABO groups in the cohort of pregnant women was as follows: 52.2% for blood group O, 29.0% for blood group A, 15.2% for blood group B and 3.6% for blood group AB. The intergroup distribution of D-negative status was 8.3%, 9.6%, 6.2% and 9.9% for blood groups O, A, B and AB, respectively.

Neonatal D antigen status

Of the 429 pregnant women with D-negative status, there were 3 cases of stillbirths among non-sensitised women. In addition, there were two sets of twin pregnancies, with D antigen status for the twins being O negative/O positive and A positive/A negative. We considered them both as positive singletons. Of the 426 neonates born to D-negative women, 144 (34%) had a D-negative phenotype, while 282 (66%) had a D-positive phenotype.

Table 2 Distribution of ABO groups and D antigen status

ABO blood groups	Total (N=5076)	Negative (N=428)	Positive (N=4648)
A	1473 (29.0)*	141 (9.6)	1332 (90.4)
B	772 (15.2)*	48 (6.2)	724 (93.8)
AB	182 (3.6)*	18 (9.9)	164 (90.1)
O	2649 (52.2)*	221 (8.4)	2428 (91.7)

Data presented as N (%).
*Proportion of the total 5076 study population.

Antenatal D antigen prophylaxis

In figure 1, the flow chart displays the total number of participants with D-negative status, 429. Out of these, two women were anti-D sensitised (0.5%). The number of non-sensitised D-negative women was 427. Among these, 19 women did not receive anti-D based on their husband's D status, while the antenatal records were unavailable for seven women. Thus, the total number of women eligible for anti-D prophylaxis was 401. Of these eligible women, 356, representing 88.8%, received anti-D prophylaxis, as documented. However, 45 women had no documented antenatal administration of anti-D prophylaxis.

DISCUSSION

Our study provides the first report on the prevalence of D antigen negativity and D antigen alloimmunisation among pregnant women in the UAE. The prevalence of D-negativity among the Emirati population stood at 8.4%, and D antigen sensitisation in this population was 0.5%. Of the 429 women who were D-antigen negative, 85 were primigravida. We did not exclude these women from calculation of sensitisation rate due to the possibility that they can have miscarriages that are not clinically recognised. Moreover, there is a small risk of sensitisation from previous blood transfusion. The provision of RAADP was documented in 88.8% of this population. The distribution of D antigen negativity varies among ethnicities globally and regionally within countries. In the USA, the frequency of D-negative individuals is highest in white non-Hispanics, reaching up to 17.3% and 7% in blacks and Hispanics.[15] Regionally, D antigen negativity was reported as 10% in neighbouring Oman[16] and the Kingdom of Saudi Arabia.[17] D-negative frequency is lowest in the Mongolian ethnicity of China (0.3%).[18] Regional variations from 16.3% to 9.2% have been reported in Turkey.[19] In our study cohort, 8.4% of pregnant women were D-negative. There were two earlier studies from the UAE, one from the Al Ain region[20] and another from the Kalba region,[21] which reported a prevalence of 9.6% and 8.9%, respectively. A recent study from the Abu Dhabi Emirate of UAE[22] reported a D-negative frequency of 6.8% among Emirati blood donors. All results reported from UAE are below 10%, making them comparable with our findings.

The two clinical sites of this study follow the recommendations of the National Institute for Health and Care Excellence for RAADP.[23] The adherence to RAADP guidelines in the study cohort was 88.8%. This adherence rate is suboptimal and comparable to that reported in Canada, which stood at 85.7%.[24] The UK's adherence rate ranged between 80% and 90%.[25] There is certainly a need to improve compliance with RAADP to optimise the quality of care for pregnant women with D-negative phenotypes. The alloimmunisation rate in the study

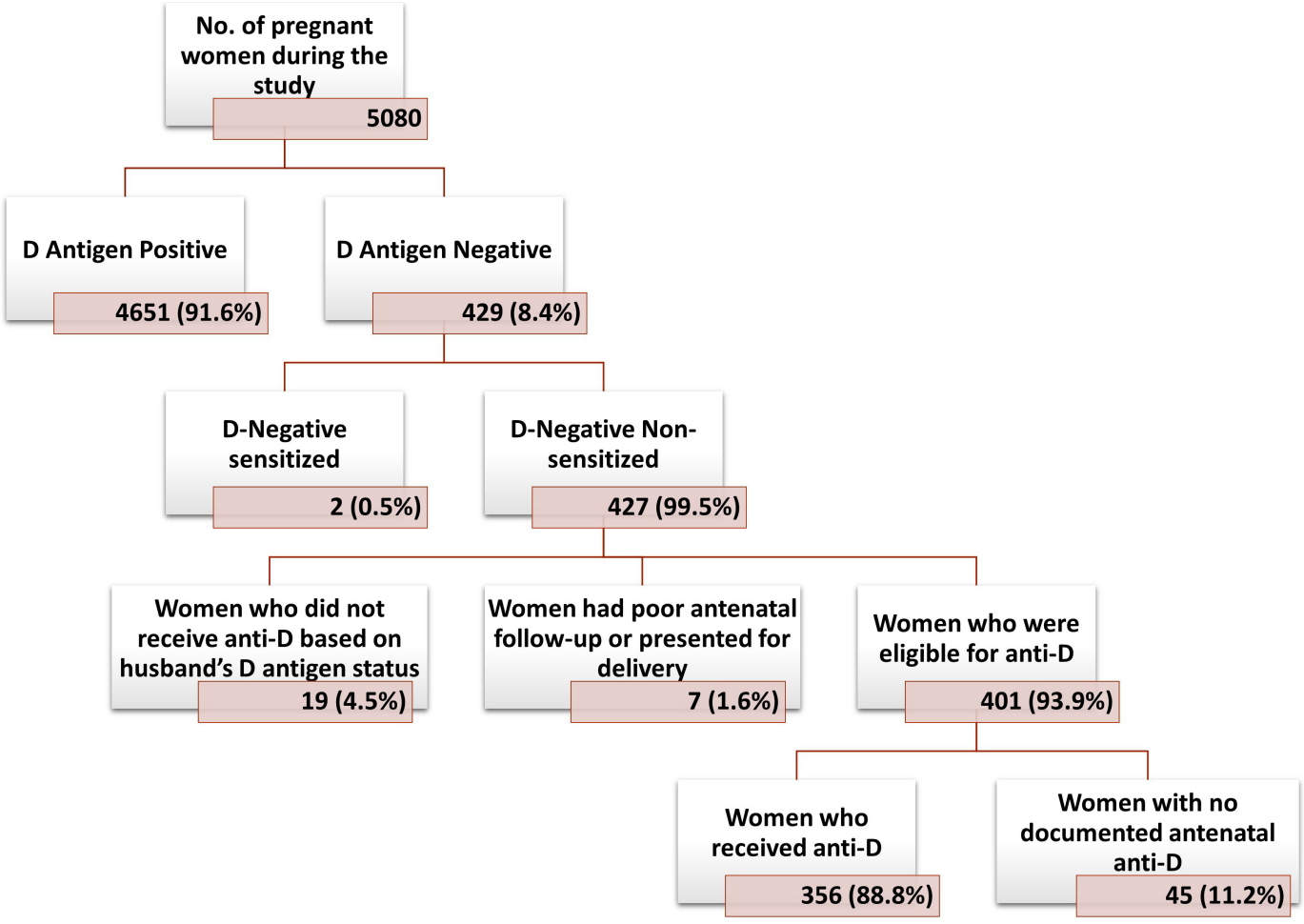

Figure 1 Flow chart of antenatal D antigen prophylaxis.

cohort was 0.5%. This rate agrees with a report from a 14-year observation of an antenatal care programme in England.[25] Surprisingly, 4.5% of D-negative pregnant women in our population did not receive RAADP based on the father's D antigen status. This practice is not recommended by any guidelines;[23 26–28] moreover, there is a risk that the foetus might have a weak D antigen and a D-positive phenotype.[29] There is a minor risk that the father may have a serologically weak D phenotype, and the foetus might have inherited a weak D gene, hence an RhD-positive phenotype. This type of D antigen is weakly expressed in RBCs, and this antigen cannot be detected by routine methods. Although the weak D antigen frequency is low, its strong immunogenicity may result in alloimmunisation.[30]

No cases of weak D alleles have been reported in the UAE population. However, a recent case in Saudi Arabia within the Gulf Cooperation Council (GCC) countries documented two women with D antigen variants DAU2/DAU6 and Weak D type 4.1 associated with anti-D alloimmunisation.[31] There is a significant prevalence of weak D type 4.0 alleles in Tunisia, with 1 in 105 RH haplotypes.[32] An Egyptian study found that 4.5% of D-negative samples were classified as D variants, with molecular typing of these samples revealing that 32% were weak D type 4.2, 16% were weak D type 4.0/4.1 and 2% were weak D type 15.[33] The remaining 50% of samples likely comprised partial D or other rare weak D types.[33] There are challenges associated with the use of anti-D IgG, including limited supply and the risk of transmission of blood-borne infectious diseases such as hepatitis C virus.[12] Studies on recombinant anti-D Ig have revealed variable efficacies and no comparable activity to conventional anti-D Ig.[34]

Studies have demonstrated that cell-free foetal DNA could be detected in the plasma of pregnant women, paving the way for genotyping and determining the foetal D antigen phenotype in D-negative pregnant women with high sensitivity and specificity.[35 36] Yang *et al* concluded that high-throughput foetal cell-free DNA testing is sufficiently accurate to detect foetal D antigen status in D-negative women and would considerably reduce unnecessary treatment with RAADP.[37] Many countries, including the UK, the Netherlands, Norway, Finland, Sweden, France, Germany and Australia, have adopted nationwide foetal D antigen screening in early pregnancy for D-negative women and adopted targeted antenatal anti-D immunoglobin prophylaxis (TAADP).[23 38–40] The practice of TAADP based on foetal D antigen genotyping would avoid unnecessary treatment in approximately 34% of D-negative pregnant women in our study, in whom the

foetus was confirmed to be D-negative. TAADP avoids unnecessary anti-D prophylaxis for any sensitising event and the risk of exposure to pooled donor blood products. Furthermore, it reduces the need for frequent antenatal visits for surveillance of foetal anaemia when the foetal genotype is D-negative. The main challenge with using the foetal D antigen blood genotyping assay is its high cost. The evidence of the cost-effectiveness of foetal D antigen blood genotyping assay remains controversial. A recent systematic review found that potential savings to its use require further research.[41]

This study included a large representative sample of pregnant women from the Emirati population. It is also the first to report the UAE's D antigen immune prophylaxis percentage coverage and alloimmunisation rate. The results are consistent with published data from other healthcare settings. However, the limited availability of laboratory data on antigens/variants/genotypes restricted further investigation of its distribution and correlations. Besides, some participants in our study gave birth in the two participating maternity units, and their antenatal care was conducted by other centres whose medical records we could not access. This limited our ability to investigate the adherence to antenatal prophylaxis following sensitising events such as vaginal bleeding or following invasive perinatal testing. The study nonetheless provides important insight for improving the provision of appropriate anti-D prophylaxis. It is crucial for financial and resource considerations for implementing antenatal foetal cell-free DNA screening to determine foetal D antigen status.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by United Arab Emirates University Human Research Ethics Committee (ERH-2017-5512) and the Abu Dhabi Health Research and Technology Ethics Committee (DOH/CVDC/2022/72). Participants gave informed consent to participate in the study before taking part.

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