Asian Journal of Medicine and Health
1(2): 1-8, 2016, Article no.AJMAH.29065

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Effect of Previous Stillbirth on the Formation of Alloantibody among Women in Sokoto Tertiary Hospital

I. Z. Isaac[1*], R. T. John[2], M. Imoru[3], F. P. Udomah[1], O. Erhabor[1], I. G. Ango[2] and S. Nasir[2]

[1]Department of Haematology and Blood Transfusion Science, Faculty of Medical Laboratory Science, Usmanu Danfodiyo University, Sokoto, Nigeria.
[2]Department of Obstetrics and Gynaecology, Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria.
[3]Department of Haematology and Blood Transfusion Science, Aminu Kano University Teaching Hospital, Kano, Nigeria.

Authors' contributions

This work was carried out in collaboration between all authors. Authors IZI and OE designed the study, wrote the protocol and interpreted the data. Authors MI and FPU anchored the field study, gathered the initial data and performed preliminary data analysis. While authors RTJ, IGA and SN managed the literature searches and produced the initial draft. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJMAH/2016/29065
Editor(s):
(1) William CS Cho, Queen Elizabeth Hospital, Hong Kong.
Reviewers:
(1) Alaa Mosbah, Mansoura University, Egypt.
(2) Georgios Androutsopoulos, University of Patras, Rio, Greece.
(3) Yaşam Kemal Akpak, Ankara Mevki Military Hospital, Turkey.
Complete Peer review History: http://www.sciencedomain.org/review-history/16467

Original Research Article

Received 20th August 2016
Accepted 21st September 2016
Published 6th October 2016

ABSTRACT

Aim: Stillbirth is one of the most common adverse pregnancy outcomes with numerous causes and effects. We intend to investigate the effect of previous stillbirth on the formation of alloantibodies among women requiring blood transfusion.
Study Design: One hundred and fifty three women with mean age of 29.97±9.724 years were recruited for the study which was conducted from August to October 2015.

**Corresponding author: E-mail: isaaczama@yahoo.co.uk;*

Materials and Methods: The patients' plasma samples were screened for the presence of clinically significant alloantibodies by Ortho Biovue system cassettes (AHG/Coombs) technique using the Lorne Laboratories of UK antibody screen cells and panel cells.
Results: The prevalence of previous stillbirth was found to be 25.5%, and was highest among reproductive age group (21 – 40 years). There was a statistically significant relationship between age groups and stillbirth (P = 0.011). The study revealed that the prevalence of alloantibodies was 16.3% among the women. We observed that 10 out of 25 (40%) of alloantibodies positive women were women with previous stillbirth and 10 out of 39 women with previous stillbirth formed alloantibodies. Although, 96.4% of the women were Rh D positive and 4(2.6%) were Rh D negative, only 1(0.7%) with Rh D negative had alloantibodies. The effect of the number of previous stillbirth on the formation of alloantibodies was found to have a statistical significant relationship (P = 0.021). The Odds Ratio of 1.949 was obtained for cohort alloantibodies positive of previous stillbirth.
Conclusion: We concluded from this study that the prevalence of alloantibodies among these women was high, and the number of stillbirths has a significant effect on the formation of alloantibodies. We therefore recommend for alloantibodies screening in women who had a history of stillbirth.

Keywords: Stillbirth; alloantibodies formation; Sokoto; Nigeria.

1. INTRODUCTION

Stillbirth as defined by the WHO is a baby born with no sign of life at or after the 28 weeks' of gestation [1]. In 2015 there were 2.6 million stillbirths globally with more than 7, 178 deaths per day and the majority of the deaths occurring in developing countries. Ninety – eight percent occurred in low and middle income countries [2]. The stillbirth rate in sub-Saharan Africa was reported to be approximately 10 times that of developed countries (29 vs. 3 per 1000 births). [2] Nigeria for example is said to record 313,700 stillbirths in 2015, ranking second after Indian.

Usually, the arrival of a healthy, newborn baby is often eagerly anticipated by parents and families, but sadly, for some families the loss of a baby through stillbirth can turn a joyous occasion and time for celebration into the cause of lasting and devastating psychological and emotional distress. Stillbirth is a relatively common phenomenon, with one in Parents who experience stillbirth being at risk of suffering from a number of detrimental psychosocial effects including grief, [3,4] depression, [5] anxiety, [6] post-traumatic stress disorder, [7] and guilt and self-blame [8,9,10]. While these effects may ease with time, for some parents and other family members, recovery can take many years, [11,12] One recent study showed that in comparison to parents who gave birth to a healthy baby, parents who had lost their baby through perinatal loss scored significantly higher on the depression, anxiety, dissociation, sleep disturbances, somatization, interpersonal sensitivity and aggression subscales of the Trauma Symptom Checklist [13]. Stillbirth has also been identified as a potential risk factor for subsequent marital conflict and the breakdown of relationships [14,15]. The aim of this present studies was to determine the effect of previous stillbirth on the formation of alloantibodies.

Stillbirth is an alloimmunization event and it has been reported that a previous stillbirth increases the risk of future stillbirth, coupled with the fact that Nigerian women are not fortunate enough as their counterpart in the developed world where routine antenatal alloantibodies screening is carried out and routine anti-D prophylaxis given to women who are Rh D negative at 28 weeks of gestation, we anticipated a high prevalence of alloantibodies in this study population.

1.1 Study Design and Site

The study was a cross-sectional descriptive study to find the effect of previous stillbirth on the formation of alloantibodies among women requiring a red cell transfusion.

We recruited 153 women in whom a red cell transfusion was indicated by convenience in this present study from a tertiary hospital in Sokoto Nigeria. Sokoto is the capital city of Sokoto state.

1.2 Sample Size Determination

The sample size was determined using G*power 3.0.10 software.

1.3 Inclusion Criteria

All consenting women in whom a red cell transfusion was indicated were eligible for recruitment into the study.

1.4 Exclusion Criteria

All non- consenting women and women in whom red cell transfusion was not indicated.

1.5 Ethical Clearance

Ethical clearance was obtained from the ethical committee of the Specialist hospitals, Sokoto. While informed consent was sought from all participants in this study.

2. METHODS

2.1 Ortho Biovue Typing Technique for RhD Red Cell Antigens

i. A 0.8% suspension of washed cells in 0.8%) Ortho red cell diluent was prepared.
ii. A 50 ul of suspension of washed test cells and 40 ul of the Lorne reagent was dispensed into the appropriate Ortho Biovue system cassettes (AHG/Coombs) reaction cambers.
iii. The cassette was incubated for 15 minutes at 37℃.
iv. The cassette was centrifuged for 5 minutes in an Ortho Biovue system centrifuge.
v. The result was read macroscopically for agglutination which indicated the presence of the appropriate red cell antigen.

2.2 Ortho Biovue Technique for Alloantibodies Screening in the Serum

i. Each 50 ul of suspension of ALBAcyte CAT reagent red cells (1, 2 and 3) for antibody screening and 40 ul of the patient's serum was dispensed into the appropriate Ortho Biovue system cassettes (AHG/Coombs) reaction cambers.
i. The cassette was incubated for 15 minutes at 37℃.
ii. The cassette was centrifuged for 5 minutes in an Ortho Biovue system centrifuge.
iii. The result was read macroscopically for agglutination in any of the three (3) reaction cambers which contains the patient's serum, which indicate the presence of an alloantibodiy.

The data obtained were presented in cross tabulation and hypothesis was tested with statistical software (SPSS version 20) at 0.05 significant levels and 95% confidence using the Person Chi-square test.

3. RESULTS

The result indicated that the prevalence of stillbirth was 25.5%, the prevalence of stillbirth based on age group showed that stillbirth rate was highest between ages 21 – 30 years with prevalence of 9.8%, followed by ages 31 to 40 years. There was a statistical significant different between age groups and stillbirth (P = 0.011), however there was no significant correlation (r = -0.153 and P = 0.063). Table 1 showed that the prevalence of alloantibodies among women requiring red cell transfusion was 16.3%. It also indicated that 15 out of 114 (13.2%) of the women who had no previous stillbirth developed alloantibodies; 7 out of 34 (20.6%) of the women who had one previous stillbirth, developed alloantibodies; 2 out of 4 (50.0%) of the women who had two previous stillbirth, developed alloantibodies and 1 out of 1 (100%) of the women who had three previous stillbirth, developed alloantibodies. There was a statistical significant different between alloantibodies formation and number of previous stillbirth (P = 0.021) and this also correlates significantly (r = -0.2 and P = 0.008). Table 2 showed the prevalence of alloantibodies formation against previous stillbirth status, it indicates that 10 out of 25 (40%) of alloantibodies positive women were women with previous stillbirth and 10 out of 39 women with previous stillbirth forms alloantibodies. There was however, an insignificant statistical difference between alloantibodies formation and stillbirth status (P = 0.07). Table 3, indicated that 96.4% of the women were Rh D positive and 4(2.6%) were Rh D negative of which only 1(0.7%) showed alloimmunization. Table 4 showed the prevalence of alloantibodies according to age groups, it indicated an insignificant effect of age groups on the formation of alloantibodies. P = 0.114. However, the highest prevalence of alloantibodies formation was found in 21 – 30 age group followed by 31 – 40 age group with respective prevalence of 12(7.8%) and 8(5.2%).

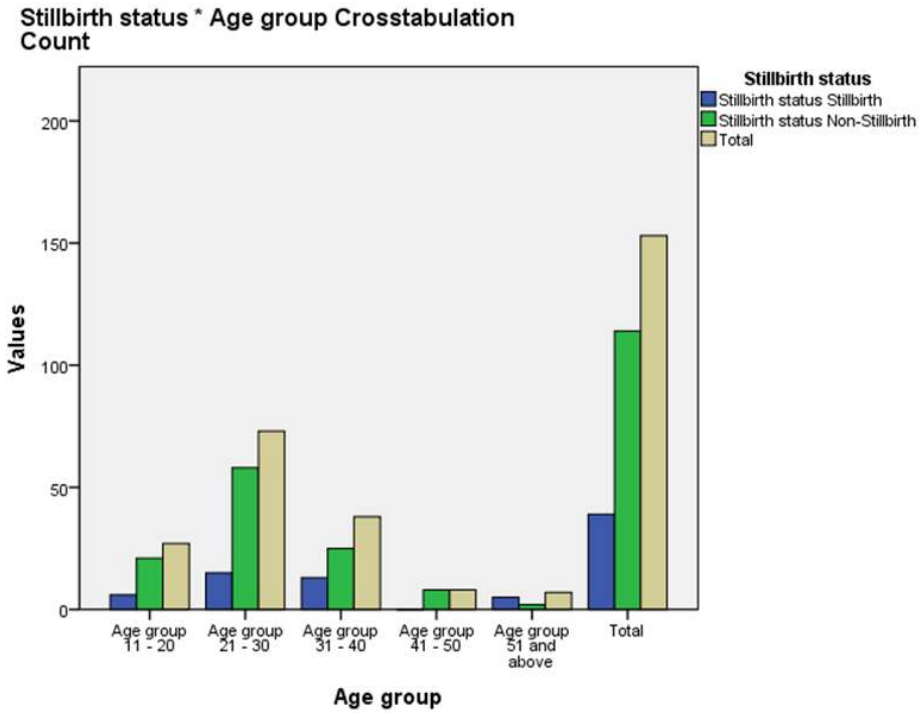

Fig. 1. Bar chat of number of stillbirth against age groups

The above figure showed the prevalence of still birth based on age group, there was a statistical significant different between age groups and stillbirth (P = 0.011)

Table 1. Prevalence of alloantibodies formation against previous history of number of stillbirths

No. of stillbirth	Alloantibody			X^2	df	*P* - value
	Positive	Negative	Total			
0	15(9.8%)	99(64.7%)	114(74.5%)	9.729	3	0.021
1	7(4.6%)	27(17.6%)	34(22.2%)			
2	2(1.3%)	2(1.3%)	4(2.6%)			
3	1(0.7%)	0(0.0%)	1(0.7%)			
Total	25(16.3%)	128(83.7%)	153(100.0%)			

The above table showed the prevalence of alloantibodies formation against the number of previous stillbirth. There was a significant statistical different between alloantibodies formation and history of previous stillbirth (P = 0.021) and this also correlates significantly (r = -0.2 and P = 0.008). X^2 = critical value of chi square, df = degree of freedom

Table 2. Prevalence of alloantibodies formation against previous history of stillbirth status

Stillbirth status	Alloantibody			X^2	df	*P* - value
	Positive	Negative	Total			
Stillbirth	10(6.5%)	29(19.0%)	39(25.5%)	3.313	1	0.07
Non-Stillbirth	15(9.8%)	99(64.7%)	114(74.5%)			
Total	25(16.3%)	128(83.7%)	153(100.0%)			

The above table showed the prevalence of alloantibodies formation against history of stillbirth status, there was an insignificant statistical difference between alloantibodies formation and stillbirth (P = 0.07). X^2 = critical value of chi square, df = degree of freedom

Table 3. Prevalence of alloantibodies formation against Rh D blood group

Rh D	Alloantibody				df	*P* - value
	Positive	Negative	Total	X^2		
Positive	24(15.7%)	125(81.7%)	149(97.4%)	0.225	1	0.635
Negative	1(0.7%)	3(2.0%)	4(2.6%)			
Total	25(16.3%)	128(83.7%)	153(100.0%)			

The above table indicated that 96.4% of the women re Rh D positive and 4(2.6%) are Rh D negative of which 1(0.7%) showed Rh D alloimmunization

Table 4. Prevalence of alloantibodies among women requiring red cell transfusion according to age groups

Age group	Alloantibody			X^2	df	*p*
	Positive	Negative	Total			
≤ 20	1(0.7%)	26(17.0%)	27(17.6%)	7.459	4	0.114
21 - 30	12(7.8%)	61(39.9%)	73(47.7%)			
31 - 40	8(5.2%)	30(19.6%)	38(24.8%)			
41 - 50	1(0.7%)	7(4.6%)	8(5.2%)			
≥51	3(2.0%)	4(2.6%)	7(4.6%)			
Total	25(16.3%)	128(83.7%)	153(100.0%)			

The above table showed the prevalence of alloantibodies according to age groups, it indicated an insignificant effect of age groups on the formation of alloantibodies. P = 0.114. However, the highest prevalence of alloantibodies formation was found in 21 – 30 age group followed by 31 – 40 age group with respective prevalence of 12(7.8%) and 8(5.2%). X^2 = critical value of chi square, df = degree of freedom

4. DISCUSSION

We observed in this present study the prevalence of previous stillbirth as 25.5%. This value is much higher than that reported in the US and also higher than the value quoted for developed countries. It was reported that stillbirths constitute half of all perinatal mortality in the United State with prevalence rate of 6.2%, [1] and the value quoted for developed countries was 5.3 per 1000 [16]. However, our finding was similarly higher to what was reported in Abuja, Nigeria of 34.1%, [17] and 32.2 per 1000 deliveries estimated for SSA and the rate of 25.5 per 1000 deliveries, quoted for developing countries [16]. It was reported that stillbirths and neonatal death occurred as a result of poor maternal health, inadequate care during pregnancy, inappropriate management of complications during pregnancy and delivery, poor hygiene at delivery and the first critical hours after birth and lack of appropriate newborn care [18]. This could be some of the reasons for higher stillbirth rate in the developing countries and in our study in particular as all these factors are found in most developing countries like Nigeria. Low budgetary allocation for health sector, lack of qualified health workers and brain drain in the health sector may also have contributed to the observed high stillbirth rate in Nigeria.

We also observed that the prevalence of previous stillbirth was highest among ages 21 – 30 years with prevalence of 9.8%, followed by ages 31 to 40 years. There was a statistical significant difference between age groups and stillbirth (P = 0.011), however there was no significant correlation (r = -0.153 and P = 0.063). This findings is at variance with previous reported work carried out in Abuja Nigeria in which none of the socio-demographic variables was found to be significantly associated with perinatal mortality. But our findings agrees with several previous studies where maternal age, weight and height were shown to have variable degrees of association with stillbirth and early neonatal deaths [19,20-25]. Trends in the risk of late fetal mortality, prematurity and low birth weight associated with advanced maternal age was also reported in Spain [26].

The prevalence of alloantibodies among women requiring red cell transfusion in this study was found to be 16.3%. Although, 96.4% of the women were Rh D positive and 4(2.6%) were Rh D negative, only 1(0.7%) showed alloimmunization. This prevalence is as high as that found among sickle cell disease patients. In Saudi Arabia, Bashawari [27] in his study, reported that 48 out of 350 sickle cell anaemic patients (13.7%) formed clinically significant alloantibodies. This is also within the range of the

rate of alloimmunization of sickle cell patient reported in literature [28]. Our observed frequency is however, at variance with previous reports of Jeremiah et al. [29] who identified alloantibodies in the serum of 3.4% of pregnant women studied. Natukunda et al. [30] also reported a lower prevalence, in their work involving a total of 214 transfused Ugandans 6.1% of subjects possessed red cell alloantibodies. Antenatal screening of 3,000 patients who were grouped and screened in Zimbabwe indicated an overall antibody incidence of 1.7%. A reviewed work in India on isoimmunisation of transfused patients, found that the prevalence in those patients who had had at least one transfusion is in the range of 3 – 10% [31].

The prevalence of alloantibodies formation among women with previous of stillbirth was 40%. This meant that for every 10 women who devaloped alloantibodies in their serum, 4 would be those with previous stillbirth. There was however, an insignificant statistical difference between alloantibodies formation and stillbirth status (P = 0.07) and also correlates insignificantly at r = 0.2 and P = 0.07. We carried out risk estimate at 95% confidence level and obtained Odds Ratio of 1.949 with lower and upper limits of respectively 0.955 and 3.975. Interestingly, when we did the analysis of prevalence of alloantibodies against number of previous stillbirths using the Pearson's chi square test, we found a significant relationship at P = 0.021 which correlates significantly with r value of -0.2 and P = 0.008 as shown in Tables 1 and 2. What this meant in essence was that the presence or not of the occurrence of stillbirth has no effect in the development of alloantibodies, but subsequent stillbirth in a woman has a strong effect in the development of alloantibodies. This can be attributed to the fact that the immune response at first stimulation, either as a result of trans-placental or foeto-maternal haemorrhage (FMH) which do occur during pregnancy or at delivery, [26,32] can lead to immunization to any clinically significant antigen if the mother is exposed to foetal red cells containing an antigen which she lacks. This first stimulation produces few IgM antibodies that last for a short period of time, but exposure to the same antigen for the second time result in a concerted production of antibodies of the immune (IgG) type that can cross the placental membrane and cause HDFN or foetal death. This may also be a contributing factor where prior stillbirth is associated with increased risk of future stillbirth in a woman. Report has indicated that foetal-maternal hemorrhage was a common cause of stillbirth and screening for the fetal-maternal hemorrhage using the Kleihauer-Betke test (KBT) was advised [33].

Various reports has associated prior stillbirth with increased risk of stillbirth in future pregnancies and the risk was reported to depend on the etiology of the prior stillbirth, presence of foetal growth restriction, gestational age of the prior stillbirth, and race [34,35,36,37]. Various reports has also indicated that categorization of the cause of the initial stillbirth will allow better estimates of individual recurrence risk and guide management, [38,39] and that the recurrence risk for stillbirth was twofold to tenfold increase in the next pregnancy [40,41]. We therefore advocate that all women who had a stillbirth should be screened for the present of alloantibodies as a guide in the management of the future pregnancy.

We also found out that the prevalence of alloantibodies among this study population was highest among ages 21 – 40, this corresponded to the age group in which the stillbirth rate was high as indicated in Fig. 1 and Table 3 above. This age group is the sexually active age and may probably account for high stillbirth rate and high prevalence of alloantibodies. It was reported that the probability of alloimmunization is a quadratic function of age and the formation of red cell antibodies may be influenced by the patients' age at which the transfusions occur [42].

5. CONCLUSION

We concluded from this study that the prevalence of the history of previous stillbirth was high and that stillbirth status has no significant effect in the formation of alloantibodies, however, subsequent stillbirth has a significant effect on the formation of alloantibodies and correlates significantly. We therefore advocate that all women who had a stillbirth should be screened for the present of alloantibodies as a guide in the management of the future pregnancy and to aid in the global effort to reduce stillbirth to about 12 or less per 1000 births by 2030.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/16467