Annals of Neonatology Journal

OPEN ACCESS
ISSN: 2636-3596

Original Article

Protective Effect of Trans-placental Transferred Immunoglobulins against Neonatal Morbidities in A Tertiary Level Intensive Care Unit

Wafaa O. Ahmed[*1]; Walaa M. Kabiel[2]; Dalia A. Mohamed[3]

DOI: 10.21608/ANJ.2021.83662.1033

[*]**Correspondence**: Lecturer, Department of Pediatrics, Faculty of Medicine, Ain Shams, University, Egypt.
Email: wafaaosman83@med.asu.edu.eg
Full list of author information is available at the end of the article.

Abstract

Background: The levels of transplacental transferred immunoglobulins (Ig) carry protective effect to the neonate and varies by many factors as gestational age, maturity, body weight, hemodynamics and maternal diseases. **Aim:** This study aimed to measure the serum levels of Ig A and Ig G in neonates in different settings and to correlate their levels with neonatal morbidities. **Methods**: The study conducted during the period from June 2020 to January 2021 in a tertiary level NICU and included a total number of fifty one neonates. The measurement of serum Ig G and Ig A levels were measured by mininef method. **Results**: The mean value of Ig G and Ig A were 898 mg g/l and 16.3 g/l respectively. Ig G was directly correlated with the maturity, weight, early starting of feeding (p-value 0.001) while they correlated inversely with respiratory and inotropic support and CRP levels (p=value 0.001). Ig G was correlated inversely with the respiratory support whether CPAP or mechanical ventilation; being higher in neonates who didn't receive assisted ventilation. A cut off level of 512 g/l of Ig G was needed to detect increased risk of neonates to sepsis. Preterm babies had lower values than full term ones (p-value 0.001). **Conclusion**: Transplacental transferred immunoglobulins had a protective effect for neonates and their levels were inversely correlated with neonatal morbidities either in preterm or fullterm neonates

Key words: Neonates; Ig G, Ig A, Trans-placental; morbidities.

Introduction

Neonatal antibody production is inadequate due to B-cell immaturity and reduced B-cell Ag receptor (BCR) signaling. Also, neonatal B-cells express low levels of src family kinases; p55fgr and p59Fyn as compared to older children. The neonatal immune system is dependent on 3 axes, including; Pattern recognition is less developed in neonates than in older children, T-cell response marked by a deficient T-helper 2 (TH2) response and consequent interleukin deficits and inadequately differentiated B-cell response, making the infant prone to infection, especially preterm neonates. [1] IgG is actively transferred across the placenta starting after the first trimester and increases dramatically from 36 weeks till delivery. [2] Approximately 400 mg/dl of immunoglobulin G (IgG) is detected in 32-week preterm infants, so extreme preterm infants nevertheless have insufficient titers of protective antibodies, because most of them are transported after the 34th week of pregnancy.[3]

IgG is transported to the baby across both the placenta and breastfeeding and offers protection from infections in the first few months after delivery. These antibodies rapidly fade after the first 2 months of life, increasing the incidence of infection. The Fc neonatal receptor (FcRn) plays a main role in mediating trans-placental IgG transfer. [4] The transfer of IgG in preterm infants is lower as compared with term infants, especially those who are less than 36 weeks.[5]

Low birth weight may affect IgG transfer, as low antibodies levels were found in term neonates with intrauterine growth retardation (IUGR) [6]. Specific low levels of both IgG1 and IgG2 in premature and low birth weight neonates may explain their higher vulnerability to infections caused by polysaccharide-encapsulated pathogens that predominantly stimulate IgG2 production, such as group B streptococci (GBS). [7]

Methods

This is a prospective observational study recruited 51 neonates admitted to the NICU by simple random sampling. They were recruited from the Neonatal Intensive Care Unit (NICU) of El-Demerdash Hospital to participate in this study from June 2020 to January 2021.

Aim: We aimed to determine the evolution of the maternal-fetal transport of immunoglobulins during human pregnancy and their possible effect on neonatal morbidities during NICU admission.

The study group included neonates admitted to NICU with respiratory distress, jaundice, hypoglycemia, sepsis, and/or grower premature neonates. Exclusion criteria: neonates with an absolute lymphocytic count lower than 500/ul to exclude associated B cell immune deficiency. Detailed antenatal and natal history were taken, A detailed antenatal history was taken with emphasis on maternal vaccination status, drugs and diseases including hypertension, diabetes, urinary tract infection, fever, autoimmune collagen diseases, ex. Systemic lupus erythematosus (SLE), rheumatoid arthritis. General and local examinations for all neonates included in the study. Two milliliters of blood were withdrawn from all neonates and the following investigations were conducted: A Complete blood count was done by KX-21; Sysmex, Kobe (Japan), semi-quantitative CRP measurement by latex agglutination, using kits from Omega Diagnostic Ltd, Alva, (UK) and blood culture. For blood culture: 1 mL of blood was injected into the Bact/Alert culture bottle under complete aseptic conditions. The inoculated culture bottles were placed in the Bact/Alert instrument (bio-Mérieux, Marcy l'Etoile, France) for incubation and monitoring. Positive samples were Gram stained and subcultured on blood agar, MacConkey agar, and sabouraud dextrose agar supplemented with chloramphenicol

(Oxoid, England) and incubated at an appropriate temperature (37C). Identification of organisms was done with Vitek 2 compact (bio-Mérieux). Measurment of serum levels of Ig G and Ig A: we used MININEPH TM human Ig G and Ig A kits for in vitro diagnostic use Product Code: ZK012.R. The Binding Site Group Ltd, 8 Calthorpe Road, Edgbaston, Birmingham, B15 1QT, UK www.bindingsite.co.uk. The detection mean was 4860 mg/l (range=2930-8060) for Ig G and 130 mg/l (range=30-570) for Ig A.

Ethical considerations

All parents signed an informed consent form and the research was approved by the local Research Ethics Committee.

Statistical analysis

Data was collected, revised, coded and entered into the Statistical Package for Social Science (IBM SPSS) version 20. Qualitative data was presented as numbers and percentages, while quantitative data with parametric distribution was presented as mean, standard deviations, and ranges, while non-parametric data was presented as median and interquartile range (IQR). The comparison between two groups with qualitative data was done by using the Chi-square test and/or Fisher exact test was used instead of the Chi-square test when the expected count in any cell was found to be less than 5. The comparison between two independent groups regarding quantitative data with parametric distribution was done by using an Independent t-test, while the comparison between two independent groups with non-parametric data was done by using the Mann-Whitney test. Also, the comparison between more than two groups with quantitative data and non-parametric distribution was done by using the Kruskall-Wallis test.

Results

The fifty-one studied neonates were recruited and divided into full-term and preterm neonates, where the study group had 11 preterm and 40 full-term neonates. 52% of the studied group was

delivered by cesarean section. Out of the forty full-term neonates, 37.5% were males and out of the eleven preterm neonates, 54.5% were males. The mean weight of the recruited neonates was 2170±320 gm for full term and 1680±190 gm for preterm neonates. Out of fifty-one neonates, twenty-nine were appropriate for gestational age (AGA) and twenty-two were small for gestational age (SGA). Our study neonates were admitted due to the following diagnoses; respiratory distress, congenital heart disease, asphyxia, surgery, rule out of sepsis and jaundice. So, amongst them, twenty-eight neonates needed respiratory support during their NICU stay. Laboratory data are illustrated in (Table1). Correlation between Ig G and IgA with the clinical and laboratory data are shown in (Tables 2&3) as well as (Figures 1-4)

Discussion

We aimed to determine the evolution of the maternal-fetal transport of immunoglobulins during human pregnancy and their possible effect on neonatal morbidities during NICU admission. Our study group had a range Ig A level of 10-37mg/l, while the mean Ig G level was 1027± 477mg/l. This was reinforced by Chanjuan et al. [8] who found that newborn sera contained very little total IgA (average 0.10 mg/mL; range from 0.03 to 0.15 mg/mL) In contrast, there were high levels of serum IgG (average 10.3 mg/mL; range 7.3 to 16.1) in newborn sera. There was a significant statistical difference between full term and preterm neonates regarding IgG level (p-value = 0.00), while there was no difference regarding Ig A level.

It was postulated that the largest amount of immunoglobulins are transferred in the third trimester. [2] Vertical transfer of IgG begins in the 13th week of pregnancy and progresses in a linear fashion until maturity. Preterm neonates had lower levels of Ig G than full-term neonates in our study, which is consistent with the findings of Antoine and colleagues [9], who found a rise in IgG levels in the

fetus between 17 and 41 weeks of pregnancy due to increased expression of the FcRn receptor late in the third trimester of pregnancy. According to other studies, fetal IgG levels were approximately 5%–10% of maternal levels during weeks 17–22 and approximated 50% of maternal levels between weeks 28–32. [6, 12]

Transplacental IgG transfer during pregnancy provides passive immunity for the neonate and is crucial for protection against infection in early life. The endocytosis of IgG occurs via pH-dependent binding with FcRn through the placental syncytiotrophoblast cell layer. [3] So it is protected from proteolytic degradation, and then released from FcRn to return to normal pH. This study confirmed that IgG levels were lower in babies suffering from sepsis whose mothers had a history of antenatal infections ex. urinary tract infection during pregnancy ($p<0.05$)[4].The current study confirmed that both high CRP and early starting of breast feeding are the most independent predictors of positive sepsis (F-ratio = 20.4, $p<0.001$), using multi regression analysis. The Diagnostic validity test for diagnosing susceptibility to sepsis showed an IgG level of 1045mg/l had specificity of 52%, sensitivity of 96.2%, positive predictive value of 67.6%, and negative predictive value of 92.9%.

Maternal morbidity like diabetes mellitus may affect antibody transfer while the mechanism of maternal hyperglycemia on FcRn and IgG transfer is still unclear. [10] In the current study, Ig G levels were lower in babies of diabetic mothers than in non-diabetic mothers ($p=0.03$). In agreement with our results were the studies done by Eduardo et al. and Enock et al. who investigated the transfer of IgG in normo-and hyperglycemic mothers and confirmed that antibody levels in hyperglycemic mothers were significantly lower than in normoglycemic mothers [10, 15]. This could be explained by the fact that hyperglycemia may alter antibody

production in women during pregnancy and, subsequently, it may decrease immunoglobulin production. [10]

Our finding was opposed by the study done by Stach et al. [13] who demonstrated an increased level of IgG transferred from hyperglycemic mothers to their babies. This could be explained that maternal hyperglycemia may enhance IgG transfer and they also found increased number of glucose transporters in the placenta of diabetic women [12,13,15]. Additionally, normoglycemic mothers tends to give birth earlier than hyperglycemic mothers and their newborns tend to be smaller. [15,16]

Malnutrition, maternal hypertension and vaccination in pregnancy may influence the transplacental transfer of antibodies and therefore the protection of the infant. Malnutrition decreases antibody transfer while early vaccination and, surprisingly, maternal hypertension may increase antibody transfer. It was found that hypertension can increase through placental vascular affection that renders antibody transport easier. [9]

Another gestational morbidity is maternal hypertension, which affects 2–3% of pregnancies. It is either gestational or chronic hypertension. [17] Chronic hypertension carries great maternal and perinatal morbidity and mortality, mostly due to complications of preeclampsia. There is an increased risk of premature birth, small for gestational age, intrauterine growth retardation, death, placental hemorrage, abruption and cesarean delivery. [18] The current study observed that hypertensive mothers gave birth to very low birth weight neonates (VLBW).

Stach et al examined the effect of pregnancy-induced hypertension on IgG transfer and found that hypertension led to increased transfer of IgG against Klebsiella spp. [13], considering that Klebsiella is one of the most common organisms found in the cultures of sick neonates. The current study divided neonates born to hypertensive mothers

into neonates born to mothers either with preeclampsia or with transient gestational hypertension and found that among neonates born to preeclamptic mothers had lower levels of Ig G (p-value 0.05)

Twenty three mothers had received tetanus toxoid vaccine while eleven mothers received inactivated influenza virus vaccine. There were no significant differences between both groups as regards the level of immunoglobulin G transfer and the incidence of sepsis. (P-value 0.06& 0.072 respectively)

The current study found that SGA neonates had a lower level of Ig G. This comes in agreement with studies by Schur et al., 1988 [19]. and Okoko et al., 2001[7] that demonstrated a reduced transfer of antibodies in term low birthweight infants The current study concluded that maternal and type of delivery didn’t influence placental antibody transfer and this was also confirmed by Doroudchi et al., [20].

Neonatal sepsis is one of the main causes of mortality and morbidity among VLBW infants, where mortality is up to 50%. Many studies have reinforced the role of immunoglobulins in the treatment of neonatal sepsis.[21- 23] Other studies showed that intravenous immunoglobulin (IVIG) had no effect on morbidity and mortality.[24] In the current study, two neonates received IVIG at a dose of one gram per kilogram but didn't show clinical or laboratory improvement.

There are conditions in which placental transmission of antibodies is injurious to the fetus. One of them is neonatal lupus erythematosus (NLE) which is a passively acquired autoimmune disease with serious clinical complications, which is congenital heart block, which occurs in about 2% of mothers with autoantibodies. [26]

The current study had three mothers had a diagnosis of SLE and two mothers with rheumatoid arthritis respectively. It was observed that there was a significant difference in the level of transferred IgG being higher among neonates of SLE mothers (P-value 0.04) compared to

neonates born to mothers with rheumatoid arthritis.

The current study showed that Ig A was not correlated with the maturity, birth weight, feeding intolerance and sepsis. Its protective role against different neonatal morbidities during NICU admission needs further studies with larger sample size.

Many limitations and confounding factors remain in modern laboratory diagnostic methods. As a result, the difficulty of a vast battery of sepsis biomarkers has been resolved in order to establish the perfect diagnostic and prognostic parameter that may overcome these traditional diagnostic roadblocks. [7] Various indicators, such as leukocyte cell surface antigens su, have recently been researched.

Conclusions

Trans placental transferred immunoglobulins had a protective effect for neonates and their levels were inversely correlated with neonatal morbidities either in preterm or full-term neonates

Lists of abbreviations:

AGA: Appropriate for gestational age

BCR: B cell Ag receptor,

CPAP: Continuous positive airway pressure

GBS: Group B streptococci,

IgA: Immunoglobulin A

IgG: Immunoglobulin G

IVIG : Intravenous immunoglobulin

NLE: Neonatal lupus erythematous

SLE: Systemic lupus erythematosus

SGA: Small for gestational age

VLBW: Very low birth weight

Author's contributions

WOA, WK, DAM equally contributed in the study concept, design, supervision, methodology, data collection and statistical analysis. WOA collected the data. WK performed the investigations and laboratory workup and DAM wrote the first draft of the manuscript. All authors reviewed and approved the final manuscript for publication.

Conflict of interest

The authors have no conflict of interests to declare.

Funding

This study received no special funding and was totally funded by the authors.

Author's details

[1]Department of Pediatrics, Faculty of Medicine, Ain Shams University, Egypt

[2]Department of Clinical pathology, Faculty of Medicine, Ain Shams University, Egypt

[3] Department of medical biochemistry and molecular biology, Faculty of Medicine, Ain Shams University, Egypt.

Date received: 18th June 2021, accepted 29th July 2021

References

1. Jack C, Hesam K, Aneeq M, Brea Davidson1, Évila d, Silva L, etal. Innate Immunity of Neonates and Infants. Front. Immunol 2018; 30: 9-1759.
2. Genevieve G, David R, Geeta K and Sallie R. The Impact of IgG transplacental transfer on early life immunity. Immunohorizons 2018; 2(1):14-25.
3. Patricia P, Camila Q, Ana L, Cláudia A, Magda C. Placental Transfer in Healthy and Pathological Pregnancies. Immunological Aspects of Human Reproduction. Volume 2012: 1-13.
4. Christopher R. Beth H and Christine E. Factors Affecting the FcRn-Mediated Transplacental Transfer of Antibodies and Implications for Vaccination in Pregnancy. Front Immunol 2017; 8: 1294.
5. Malek A, Sager R, Kuhn P, Nicolaides KH, Schneider H. Evolution of maternofetal transport of immunoglobulins during human pregnancy. Am J Reprod Immunol 1996; 36:248–55.
6. Kim J, Mohanty S, Ganesan LP, Hua K, Jarjoura D, Hayton WL, et al. FcRn in the yolk sac endoderm of mouse is required for IgG transport to fetus. J Immunol 2009; 182: 2583–9.
7. Okoko JB, Wesumperuma HL, Hart CA. The influence of prematurity and low birthweight on transplacental antibody transfer in a rural West African population. Trop Med Int Health 2001; 6:529–34.
8. Chanjuan S, Huanbin X, David L, Ronald S and Xiaolei W: Development of serum antibodies

during early infancy in rhesus macaques: implications for humoral immune responses to vaccination at birth. Vaccine. 2014; 32(41): 5337–5342.

9. Antoine M, Ruth S. Peter k, Kypros H. Nicolaides, Andhenning S: Evolution of Maternofetal Transport of Immunoglobulins During Human Pregnancy. American lournal of Reproductlve Imrnunolog. 1996; 36:248-255.
10. França EL, Calderon Ide M, Vieira EL, Morceli G, Honorio-França AC. Transfer of maternal immunity to newborns of diabetic mothers. Clin Dev Immunol 2012: 928187.
11. Mammaro A, Carrara S, Cavaliere A, Ermito S, Dinatale A, Pappalardo EM, et al. Hypertensive disorders of pregnancy. J Prenat Med 2009; 3:1–5.
12. Saji F, Koyama M, Matsuzaki N. Current topic: human placental Fc receptors. Placenta. 1994; 15(5):453–466.
13. Stach SC, Brizot ML, Liao AW, Palmeira P, Francisco RP, Carneiro-Sampaio MM, et al. Placental transfer of IgG antibodies specific to Klebsiella and pseudomonas LPS and to group B streptococcus in twin pregnancies. Scand J Immunol 2015; 81:135–41.
14. Morceli G, França E L, Magalhães V B, Damasceno D C, Calderon I M P, and Honorio-França A C . Diabetes induced immunological and biochemical changes in human colostrum.Acta Paediatrica, International Journal of Paediatrics 2011; 100 (4): 550–556
15. de Souza EG, Hara CC, Fagundes DL, de Queiroz AA, Morceli G, Calderon IM, et al. Maternal-foetal diabetes modifies neonatal Fc receptor expression on human leucocytes. Scand J Immunol 2016; 84 :237–44.
16. Gaither K, Quraishi A N, and Illsley N P, “Diabetes alters the expression and activity of the human placental GLUT1 glucose transporter,” Journal

of Clinical Endocrinology and Metabolism 1999 (84): 695–701

17. Levy O. Innate immunity of the newborn: basic mechanisms and clinical correlates. Nature Reviews Immunology. 2007; 7(5):379–390.
18. Chen H, Xu J, Lu Q, Ma T. Immunohistochemical analysis of globulin and complements in blood vessels of placental villi during pregnancy induced hypertension. J Tongji Med Univ 1996; 16:253–6.
19. Schur PH. IgG subclasses. A historical perspective. Monogr Allergy 1988.: Available from: https://www.ncbi.nlm.nih.gov/pubmed/3290655.
20. Doroudchi M, Samsami Dehaghani A, Emad K, Ghaderi A. Placental transfer of rubella-specific IgG in fullterm and preterm newborns. International Journal of Gynecology and Obstetrics. 2003; 81(2):157–162.
21. Haque KN, Remo C, Bahakim H. Comparison of two types of intravenous immunoglobulins in treatment of neonatal sepsis. Clin Exp Immunol 1995; 101: 328-333.
22. Yu Z and Lennon V A. Mechanism of intravenous immune globulin therapy in antibody-mediated autoimmune diseases. New England Journal of Medicine 1999; 340: 227–228
23. Samuelsson A, Towers T L, and Ravetch J V. Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. Science 2001; 291: 484–486
24. Ohlsson A, Lacy J. The Cochrane Library. Oxford: Update software; 2010. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. Cochrane Database of Systematic Reviews 2010 Mar 17; (3):CD001239.
25. Kobayashi R, Mii S, Nakano T, Harada H, and Eto H.Neonatal lupus erythematosus in Japan: a review of the literature. Autoimmunity Reviews 2009 ;8: 462–466

Table (1): Serum levels of immunoglobulin G , A and hematological parameters

Variable	**Mean ± SD**	**Minimum**	**Maximum**	**25%**	**75%**
Ig G mg/l	898.08 ± 503	154	2509	512	1102
IgA mg/l	16.36 ±4.94	10	37	12.25	17.75
Platelets (10^9/L)	342 ±140	24	917	245	464
TLC (10^9/L)	10.97±2.69	8.5	18.3	9.67	12.73
Hemoglobin (g/dL)	12.569±2.6	3.2	17.7	10	14

IgG: immunoglobulin G, IgA : immunoglobulin A, TLC: total leucocyte count,

Table (2): Correlation between serum level of immunoglobulin G and clinical data

Ig G/Variable		N(%)	Median	25%	75%	Mean	SD	P- value
Maturity	**Fullterm**	11(21.6%)	925.5	716	1190.75	1027	447	0.001**
	Preterm	40(78.4%)	432	191	504	381.9	145.99	
Birth weight	**AGA**	22(43.1%)	502	389.75	1228	504.3	179.64	0.001**
	SGA	29(56.9%)	1045	893.5	614.75	1183.2	468.2	
Sepsis	**Yes**	28(54.09%)	1048.5	773.25	1129	2005	605.75	0.001**
	No	23(45.1%)	512	432	740	855	295.94	
Respiratory support	**Yes**	22(43.1%)	1070	758.75	1342	2319	354	0.001**
	No	29(56.9%)	665	461.5	881	1267	254	
Antibiotics	**Yes**	25(49%)	1095	854.5	1228	2009	438.87	0.001**
	No	26(51%)	539.5	441.75	763.25	661.8	455.68	
Feeding intolerance	**Yes**	17(33.3%)	453	248.5	539.5	1997	175.3	0.001**
	No	34(66.6%)	997.5	765.5	1220	583	473.68	
Inotropic drugs	**Yes**	34(66.6%)	980	755	1202.25	1997	477.19	0.001**
	NO	17(33.3%)	453	248.5	539.5	1040	257.96	

*0.05; significant, **0.001; highly significant
AGA: appropriate for gestational age, SGA: small for gestational age

Table (3): Correlation between serum level of immunoglobulin A and clinical data

Ig A/Variable		N (%)	Median	25%	75%	Mean	SD	P value
Maturity	**Fullterm**	11(21.6%)	18	15.75	18.25	16.12	5.44	0.30
	Preterm	40(78.4%)	15.5	12.25	17.75	17.3	1.7	
Birth weight	**AGA**	22(43.1%)	15	10	31	16.429	5.67	0.06
	SGA	29(56.9%)	16	10	37	16.3	4.42	
Sepsis	**Yes**	28(54.0%)	16.59	13	31	15.59	3.75	0.04*
	No	23(45.1%)	15	10	37	16.17	5.76	
Respiratory support	**Yes**	22(43.1%)	10	8	13	18	3.9	0.11
	No	29(56.9%)	16.5	7	31	27	5.7	
Antibiotics	**Yes**	25(49%)	16	12	28	16	3.39	0.20
	No	26(51%)	18	10	37	17	6.03	
Feeding intolerance	**Yes**	17(33.3%)	15.5	10	31	21	6.2	0.07
	No	34(66.6%)	16	10	37	27	4.31	
Inotropic drugs	**Yes**	34(66.6%)	16	10	37	16.55	5.64	0.08
	NO	17(33.3%)	16	11	22	15.9	3.02	

*0.05; significant, **0.001; highly significant
AGA: appropriate for gestational age, SGA: small for gestational age

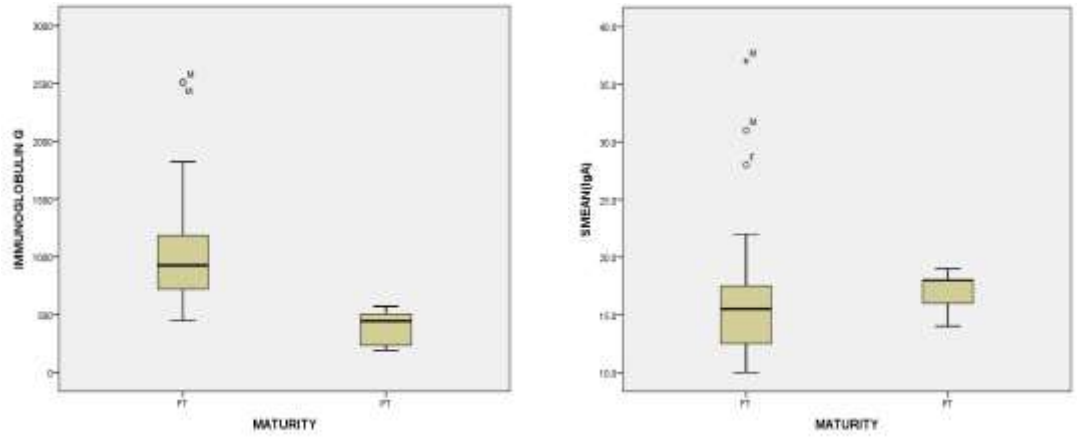

Figure (1): Comparison between Ig G and IgA levels among fullterm and preterm neonates

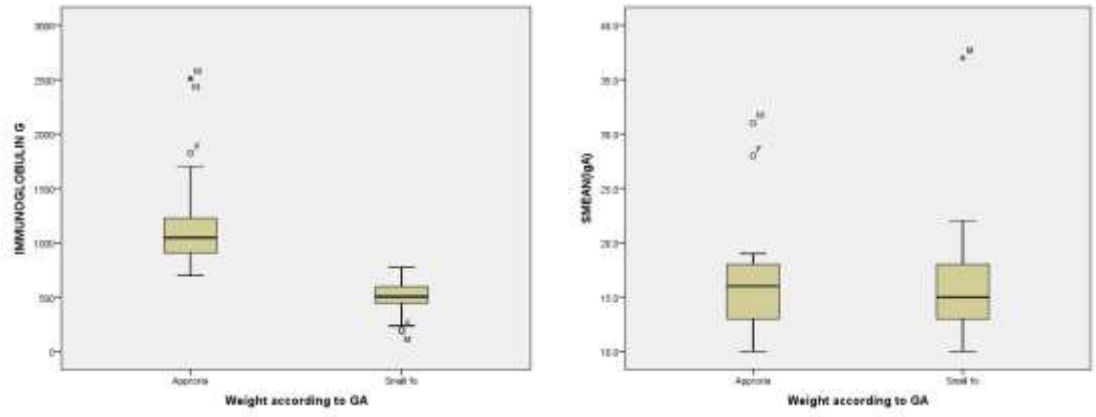

Figure (2): Comparison between Ig G and IgA levels among AGA and SGA neonates

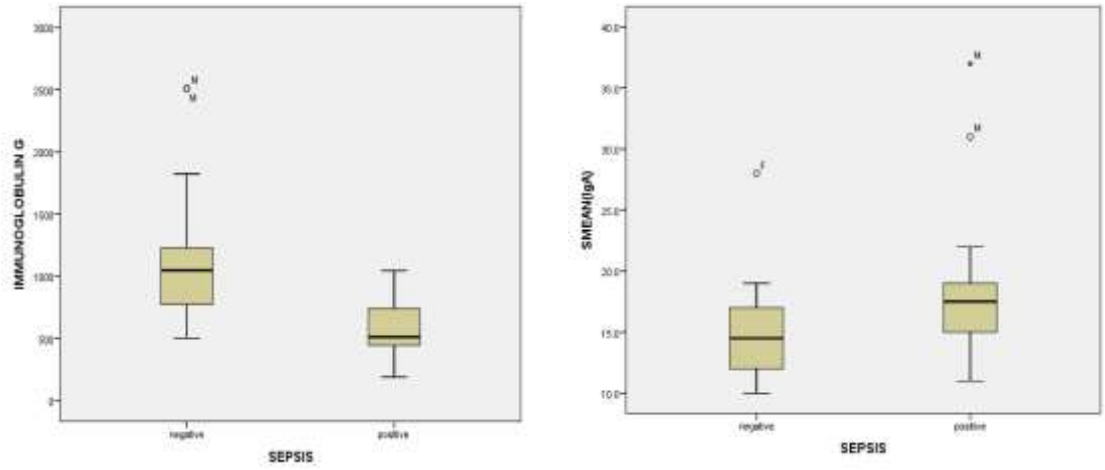

Figure (3): Comparison between Ig G and IgA levels among neonates with and without sepsis

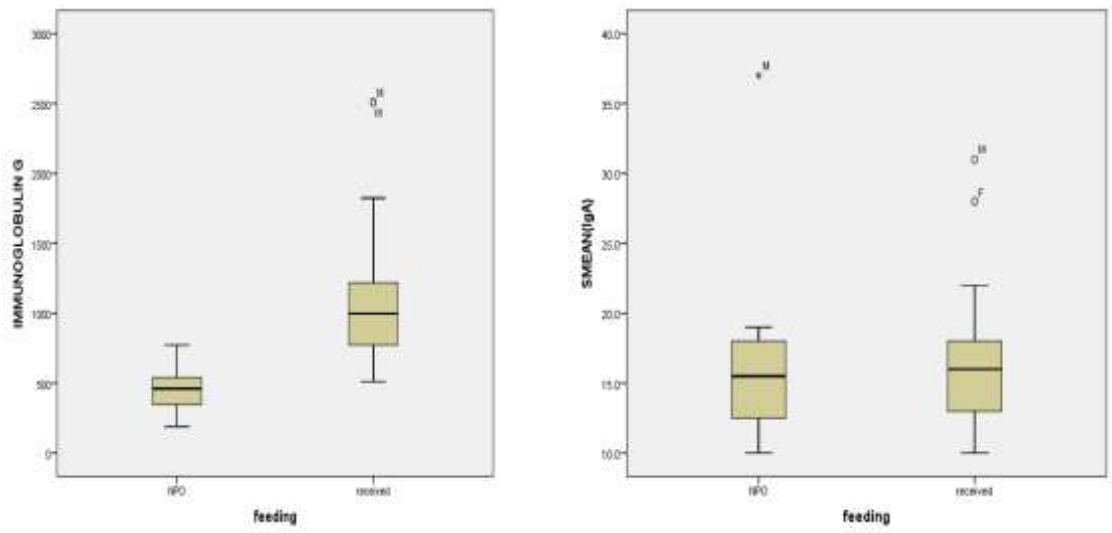

Figure (4): Comparison between Ig G and IgA levels among neonates with and without feeding intolerance

Citation: Wafaa O. Ahmed; Walaa M. Kabiel; Dalia A. Mohamed. "Protective Effect of Trans-placental Transferred Immunoglobulins against Neonatal Morbidities in A Tertiary Level Intensive Care Unit". *Annals of Neonatology Journal*, 2022(1):27-44. doi: 10.21608/anj.2021.83662.1033