AL-Qadisiah medical Journal Volume 1 number 1

THE ROLE OF TRANSPLACENTAL PASSAGE OF IMMUNOGLOBULIN IN THE INITIATION OF LABOUR

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Abstract

- **Objectives**

To establish the role of transplacental passage of Immunoglobulin G in the initiation of labor.

- **Design**

A study of Maternal and cord Immunoglobulin G levels after normal labor and elective caesarian section .

- **Setting**

Department of obstetric and gynecology in Kufa Medical College and Najaf maternity and Paediatric teaching hospital.

- Subjects

60 women's with spontaneous normal labor
60 women's with elective Caesarean Section.

- Main outcome measures:

Material and cord immunoglobulin levels measured by Immunodiffuse method and its relation to the mode of delivery and gestational age and difference between level of maternal immunoglobulin G and cord immunoglobulin in both modes of delivery.

Results:

1. Levels of cord IgG was significantly higher in cases delivered spontaneously by N. V. D. ($P<0.001$) compared with cases delivered electively by C. S.
2. It has been found that cord IgG levels increases with advancing gestational age.
3. The cord IgG levels were higher than maternal IgG levels in both modes of delivery.

Conclusions:

1. The cord IgG level increases with advancing gestational age reaching its maximum at 40 weeks and at the onset of spontaneous labour.
2. The transplacental passage of maternal IgG could play a role in the initiation of labour.

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Introduction

Although the exact metabolic and endocrine pathways that play a role in the initiation of labor are not yet known, many theories have been claimed to be involved in the parturition process.

Some of these theories are

1. The progesterone withdrawal theory

Despite the fascinating aspects of this theory, it still faces many criticisms such as: first, there is no substantive evidence for alteration in progesterone metabolism or sequestration. Second, there is no alteration in progesterone-binding protein or receptor numbers. As a result of these observations, it has been suggested that progesterone withdrawal is not a fundamental component of the initiation of labor. [1]

2. The oxytocin theory of parturition

Oxytocin is a nanopeptide synthesized in the supraoptic and paraventricular neurons to be stored in, and released by, the posterior pituitary gland. Most recently, it was discovered that oxytocin may be synthesized in uterine tissues or in the placenta. [2] Administration of this potent uterotonic agent may act synergistically with other uterotonins produced within the uterus will bring about orderly labor in near term pregnant women, i. e. to facilitate the success of parturition. So there is no evidence that oxytocin is involved in the initiation of human parturition. [3]

3. Prostaglandins and parturition

There is no convincing for an increase in the rate of PG formation in intrauterine tissues before the onset of human parturition, yet several facts have been attribute to the role of PG in the initiation of labor. Some of these include first, increase concentration of PG in amniotic fluid and of its metabolites in plasma and urine [4]. Second, it has been found that PG of 2-alpha is the effective PG in spontaneous labor and its stable metabolite increases during spontaneous and induced labor. [5]

4. Amnion contribution to parturition

Clinically, rupture or infection of the membranes, exposure of the membrane to hypertonic solution and tripping of the membrane away from the uterine walls may initiate labor or abortion. The explanation of these phenomena is that, PGs are present in the decidua and membranes of late pregnancy which will increase and stimulate labor following rupture of the membranes or ascending infection. [6]

Immunological Aspect of Parturition

Parturition is a process of giving birth that has many similarities to immune rejection, i. e. termination of immunologic tolerance between fetus and mothers. [7]

Immunoregulation of maternal recognition of fetal allograft

The question often raised: why the developing fetus, which posses paternal transplantation antigens foreign to its mother and is therefore similar to an allograft, is able to implant and grow in the uterus? [8] Various mechanisms have been proposed to explain the survival of the fetus in a potentially hostile immunology environment.

First: The anatomical barrier (the trophoblast) surrounds the fetus and prevents passage of maternal lymphoid cells.

Second: Lack of a full complement of immunogenic paternally derived histocompatibility antigen on the intervening layers of trophoblastic cells, thereby incapable of eliciting maternal effect or mechanisms. [9]

Third: Suppressor activity by fetal lymphoid cells, placental cells and hormones. [8]

Fourth: A suppressive agent is found within the placenta, appears to be a trophoblastic associated IgG [10]. More important, there is evidence that purified placentally derived IgG suppresses mixed lymphocyte reactions between individuals unrelated to either parent. [11]

It has also been suggested that the mother is simulated by antigens in the trophoblast to produce blocking antibodies, which inhibit the cell mediated rejection process. If a couple share more HLA antigens than usual the trophoblast may fail to stimulate the production of maternal blocking antibodies and the pregnancy is rejected, i. e. aborted. [6] On the other hand, an alteration of immune system results in increased recognition of trophoblastic tissue, perhaps it may expose an excessive number of antigens to the maternal circulation. So the protective factors can no longer maintain a privileged association. The result will be immunorejection similar to that seen in allograft transplantation. [12]

The transport of IgG from mother to the fetus

It is well established that all maternal IgG subclasses and allotypes cross the human placental barrier during pregnancy. But, there is a little, if any, transfer of IgM or IgA. [13] The active transport of IgG from mother to fetus commences at about 12 weeks gestation. [14] Although Fc receptors can be demostrated on trophoblastic tissue early in gestation, little maternal antibodies can be demostrated within the placenta until the second half of pregnancy. [15] There is a sudden increase in antibody transported across the placenta beyond 22 weeks of gestation. [16] This is, most probably, due to a rapid increase in syncytiotrophoblastic activity. Actually the maternal IgG levels within the placenta increase significantly throughout the third trimester. Precisely, there is an abrupt and significant increase in placental IgG at 32 weeks gestation [17]. A second significant rise in placental antibody occurs at approximately 40 weeks gestation.This could simply reflect a later phase of increased IgG transmission to the fetus. More important it might indicate an enhanced recognition of placental antigen by the maternal immune system. [12] Receptors expressed by human trophoblast have been reported to bind both monometric and aggregated IgG [25]

Functions of trnasplacental passage of IgG

a. Donation of maternal passive immunity:

It has been emphasized that the human fetus is donated maternal passive immunity through the human placenta prenatally. [26]

b. Blocking antibodies: (suppression of maternal immune system)

A real fact that IgG bound to polymorphic antigen is present on all term placentae. Such antigens are completely coated with antibodies in the intact unacidified vesicles [30]. Similar antigenic determinants appear to be present on peripheral blood lymphocytes, so that the system could be described as trophoblastic-lymphocytic cross-reactive (TLX). [31]

Subjects and methods

A prospective study was conducted on two groups of pregnant women attending Najaf Maternity and Pediatrics hospital in the period between 2nd of January 2000 and the middle of August 2001. The individual groups were divided as follows:

Group I: 60 healthy pregnant women who started spontaneous labor and delivered by normal vaginal delivery.

Group II: 60 pregnant women who were scheduled to be delivered by elective caesarean section indicated for mechanical problems as:

- Primigravid with breech presentation.
- Contracted pelvis.

The criteria, which were used for inclusion in this study, were:

1. Normal singleton pregnancy.
2. Gestational age of not less than 37 completed weeks confirmed by early ultrasound in the antenatal record (if present) and by history and examination.
3. No history of diabetes mellitus, hypertensive disorders of pregnancy.
4. Not Rh. Negative mothers.
5. No history of recent maternal infections
6. No history of recent vaccination

From both groups, history was taken including age, LMP, medical and obstetrical history concentrating on the current pregnancy antenatal record. Ultrasound examination in the early pregnancy, infection diseases during the last trimester and anti tetanus toxoid vaccination program, general examination of the mother including her pulse rate, temperature, blood pressure. Obstetrical examination to evaluate the gestational age the presenting part uterine contraction, pelvic examination .Immediately after delivery cc blood was taken from the mother and from the cord and kept in test tube, the newborn baby was examined by a pediatrician, recording its sex, birth weight. The blood samples were centrifugated and the serum kept in refrigerator (frozen), the method used to measure the level of IgG by radial immunodiffusion technique (R. I. D.).

Principles of procedure

Equal volumes of reference sera and test samples are added to wells in an agars gel containing a mono specific antiserum. The sample diffuses radially through this gel and the substance being assayed (antigen) forms a precipitin ring with the mono

specific antiserum. Ring diameters are measured and a reference curve is constructed on graph paper, unknown concentrations are determined from the reference curve.

Operating procedure

R. I. D. plates used was manufactured by Medic company and the agar used in the plate contains 8 ml of a buffered agarose-antisum, mixture at PH 7.2 with (0.1%) sodium azide and (< 0.01%) thimecosal which contain (≤ 0.005%) mercury weight per volume and each plate contain 16 wells and the plates were stored between 4°C and 8°C and before dispensing the samples the plated left uncovered and turn them over 10 allow the condensed water present in the wells to flow out. Then the samples were thawed and 541 of the serum was recommended by using correctly calibrated micropipettes and the sampling were executed vertically and not obliquely over the well to avoid ovalisation phenomena of the reaction halo and avoiding overflow out of the well. The incubation at about 20C and in a covered humid incubator for 48 hours. Reading: The diameter of the precipitates was read and the relevant concentration was calculated corresponding to the precipitate diameter from the conversion table the diameter of the immunoprecipitate measured by optical reader. At the same time as the samples were prepared 3 caliberators with different known titers. (Medic Rid Standard) were used for standardization as quality central.

Results

1-Mode of delivery

In this a comparison was made between 60 pregnant women having spontaneous normal vaginal delivery (N.V.D.) and 60 pregnant women delivered electively by caesarean section (C.S.). There was a higher levels of IgG in both maternal and cord blood of women delivered spontaneously than IgG levels in maternal and cord of women delivered by elective C.S.at term .This results was highly significant (P< 0.001).

2-Gastational age

IgG levels in maternal and cord blood gradually increased with advancing age in both N.V.D. and elective C.S. and also IgG Levels higher in maternal and cord blood of women delivered spontaneously (P< 0.001) as shown in table (2A,B) and related groups.

3-Parity

There was no relationship between the parity of the mother and IgG levels in blood in both groups .A cmparison of both groups for the parity showed higher mean values of IgG levels in spontaneous N.V.D. than in elective C.S. for all parity distributions as shown in table (3A,B) and their related groups.

4-sex of the newborn baby

Male in spontaneous N.V.D. to female in elective C.S cases (P< 0.005) and female in spontenaous N.V.D. to female in elective C.S cases (P< 0.005) on the other hand no significant result was obtained neither neither in comparison of male to female in spontaneous N.V.D. group nor in male to female in elective C.S. group.(Table4A,B)

5-Age of mother

There was no relationship between the age of mother and IgG levels in blood in both groups. As shown in tables (5A and B) and their related graphs.

6- Birth weight

There was a significant relation between birth weight and IgG levels in maternal and cord blood in spontaneous N.V.D. and elective C.S. cases as shown in table (6A,B) and their related graphs.

Table (1) The relation between cases of spontaneous normal vaginal delivery and cases delivered electively by caesarean section according to levels of IgG in both maternal and cord blood.

IgG level (mg/dL)	Maternal blood				Cord blood			
	No.	%	C.S.no.	%	No.	%	C.S.no.	%
800-900	7	11.6	24	40	0	0	3	5
901-1000	8	13.3	18	30	6	10	21	35
1001-1100	10	16.6	9	15	9	15	24	40
1101-1200	10	25	6	10	18	30	9	15
1201&over	20	33.5	3	5	27	45	3	5
Total	60	100	60	100	60	100	60	100
	Pvalue <0.001				Pvalue<0.001			

Table (2A) The relation of IgG level in maternal blood and gestational age (weeks)in both N.V.D. and C.S. groups

Gestational age (weeks)	Maternal IgG in NVD			Maternal IgG in C.S.			P value
	No.	%	Mean±S.D.	No.	%	Mean±S.D.	
38	12	20	1086.53±160.8	3	5	954.34	<0.05
39	18	30	1128.71±167.2	27	45	957.19	<0.05
40	30	50	1241.55±208.8	30	50	979.42	<0.005
Total	60	100		60	100		

Table (2B) The relation of IgG level in cord blood and gestational age (weeks) in both N.V.D. and C.S. groups

Gestati-Onal age (weeks)	Vaginal delivery			Caesarian section			P value
	No.	%	Mean±S.D.	No.	%	Mean±CS	
38	12	20	1217.5±147.7	3	5	1075.63±0	<0.05
39	18	30	1267.3+195.2	27	45	145.8±187.6	<0.005
40	30	50	1306.04±202.5	30	50	1210.1±78.4	<0.005
Total	60	100		60	100		

Table (3A) The relation of IgG level in maternal blood and parity in both spontaneous N.V.D. and electietive C.S.

Pariety	Maternal IgG level in N.V.D.			Maternal IgG level in C.S.			Pvalue
	No.	%	Mean +S.C.	No.	%	Mean±C.S	
1	17	28	1182+89.4	23	39	916.82+87.2	<0.005
2-4	28	47	1090.98+180.7	22	37	1006.74+138.4	<0.05
5&over	15	25	1168.1+289.4	15	25	944.87+62.3	<0.005
Total	60	100		60	100		

Table (3B) The relation of IgG level in cord blood and parity in both spontaneous N.V.D. and elective C.S.

Pariety	Cord IgG level in N.V.D.			Cord IgG level in C.S.			Pvalue
	No.	%	Mean±S.D.	No.	%	Mean±CS	
1	17	28	1281.3+171.3	23	39	1043+26.8	<0.0005
2-4	28	47	1201.91+210.5	22	37	980+453.4	<0.05
5&over	15	25	1251.84+235	15	25	1000.2+54.3	<0.005
Total	60	100		60	100		

Table(4A) The relation of IgG level in maternal blood and parity in both spontaneous N.V.D. and elective C.S.

Pariety	Maternal IgG level in N.V.D.			Maternal IgG levl in C.S			Pvalue
	No.	%	Mean±S.D	No.	%	Mean±CS	
1	17	28	1182+89.4	23	39	916.82+87.2	<0.005
2-4	28	47	1090.98+180.7	22	37	1006.74+138.4	<0.05
5&over	15	25	1168.1+289.4	15	25	944.87+62.3	<0.005
Total	60	100		60	100		

Table (4B) The relation of IgG level in cord blood and sex of baby in both N.V.D. and elective C.S.

Sex	Cord IgG level in N.V.D.			Cord IgG level in C.S			Pvalue
	No.	%	Mean±S.D.	No.	%	Mean±CS	
Male	30	50	1202.82+211.4	26	44	993.9+74.3	<0.005
Female	30	50	1295.22+203.1	34	56	1062.7+101.5	<0.005
Total	60	100		60	100		

Table(5B) The relation of IgG level in cord blood and maternal age in both spontaneous N.V.D. and elective C.S.

Maternal age	Maternal IgG level in N. V.D.			Maternal IgG level in C.S.			Pvalue
	No.	%	Mean±S.D.	No.	%	Mean±CS	
<20	6	10	1351.09+166.1	0	0		
20-24	12	20	1082.1+70.5	9	15	1049.7+34.3	<0.05
25-29	12	20	1183.6+266.8	21	35	977.29+64.3	<0.05
30-34	18	30	1091.35+167.3	12	20	1038.34+64.3	<0.005
35-39	12	20	1193.04+286.8	12	20	897.83+41.4	<0.005
≥40	0	0		6	10	929.29+99.6	
Total	60	100		60	100		

Table (5B) The relation of IgG level in cord blood and maternal age in both N.V.D. and elective C.S. groups

Sex	CordIgG level in N.V.D.			Cord IgG level in C.S.			Pvalue
	No.	%	Mean±S.D.	No.	%	Mean±CS	
<20	6	10	1430.28+164.5	0	0		
20-24	12	20	1140.25+46.6	9	15	1114.74+79.1	<0.05
25-29	12	20	1309.10+284.8	21	35	1034.05+84.6	<0.005
30-34	18	30	1168.29+168.4	12	20	1055.76+76.4	<0.05
35-39	12	20	1337.98+211.6	12	20	1007.3+67.9	<0.005
≥40	0	0		6	10	966.1789.9	
Total	60	100		60	100		

Table (6A) The relation of IgG level in maternal blood and weight of baby in both N.V.D. and elective C.S. groups

Weight of baby	Maternal IgG level in. N.V.D			Maternal IgG level in C.S.			Pvalue
	No.	%	Mean±S.D.	No.	%	Mean±CS	
2500-2999	6	10	1195.07+128.7	6	10	984.6+78.3	<0.005
3000-3499	30	50	1199.22+203.2	30	50	1019.8+123.7	<0.0005
3500-3999	15	25	1034.88+158.5	21	35	912.58+54.16	<0.005
4000&over	9	15	1122.13+228.3	3	5	876.43+0	<0.005
Total	60	100		60	100		

Table (6B) The relation of IgG level in cord blood and weight of baby in both N.V.D. and elective C.S.groups

Weight of baby	Cord IgGlevel in N.V.D.			Cord IgG level in C.S.			Pvalue
	No.	%	Mean±S.D.	No.	%	Mean± CS	
2500-2999	6	10	1268.8+160.9	6	10	1053.9+66.3	<0.05
3000-3499	30	50	1299.5+107.8	30	50	1064.1+111.5	<0.0005
3500-3999	15	25	1177.38+133	21	35	984.3+63.3	<0.0005
4000&OVER	9	15	1199.11+204.8	3	5	1034.61+0	<0.05
Total	60	100		60	100		

RID PLATES-CONVERSION TABEL

NAME OF THE TEST : IgG SAMPLE DISPENSING: 5ul

SAMPLE DILUTION : SERUM NOT DILUTED

NORMAL VALUES: 800 mg/dl

Diameter (mm)	Concentration mg/dl (CRM470)
4.0	101.81
4.1	125.70
4.2	150.19
4.3	175.28
4.4	200.95
4.5	27.21
4.6	254.07
4.7	281.51
4.8	309.55
4.9	338.17
5.0	367.39
5.1	397.19
5.2	427.59
5.3	458.57
5.4	490.15
5.5	522.31
5.6	555.07
5.7	588.42
5.8	622.35
5.9	656.88
6.0	692.00
6.1	727.70
6.2	764.00
6.3	800.89
6.4	838.36
6.5	876.43
6.6	915.09
6.7	954.34
6.8	994.18
6.9	1034.61
7.0	1075.63
7.1	1117.23
7.2	1159.43
7.3	1202.22
7.4	1245.60
7.5	1289.57
7.6	1334.13
7.7	1379.28
7.8	1425.02
7.9	1471.35
8.0	1518.27
8.1	1565.79

Diameter (mm)	Concentration mg/dl (CRM470)
8.2	1613.89
8.3	1662.58
8.4	1711.86
8.5	1761.73
8.6	1812.20
8.7	1863.25
8.8	1914.89
8.9	1967.12
9.0	2019.95
9.1	2073.36
9.2	2127.36
9.3	2181.96
9.4	2237.14
9.5	2292.91
9.6	2349.28
9.7	2406.23
9.8	2463.78
9.9	2521.91
10.0	2580.64
10.1	2639.95
10.2	2699.86
10.3	2760.36
10.4	2821.44
10.5	2883.12
10.6	2945.38
10.7	3008.24
10.8	3071.69
10.9	3135.72
11.0	3200.35
11.1	3265.57
11.2	3331.38
11.3	3397.77
11.4	3464.76
11.5	3532.34
11.6	3600.51
11.7	3669.27
11.8	3738.62
11.9	3808.56
12.0	3879.08
12.1	3950.20
12.2	4021.91
12.3	4094.21

Discussion

In this study it is of great interest that a conciderable level of IgG was found in cord blood of term infants by immuno diffusion test, this in agreement with other study who measure the I gG level by direct immuno flouresent assay(31,32) The cord IgG was found to be of maternal origin crossing the placental barrier through Fc recptor on syncytiotrophoblast (20,23,24,25,29) The worker attributed that Feto – maternal immunological relationship through out prehnancy was maintend by the shielding role of blocking antbodies binding to the trophoblastic tissue . These antibodies were found to be Of IgG type directed mainly against product of fetal tissue .any alteration of this suppressor activity near term might well result in increase recognition of trophoblastic tissue by maternal immune system . Another group of worker shed a light on placental aging process near term. An excessive number of antigens probably exposs to maternal circulation so that various protective factors can no longer maintain privileged association .(12,22,32) It has been found that neonatal IgG concentration are higher following vaginal delivery than after elective C/S. This suggest that uterine contractions provide a final boost of maternal IgG to the fetus .An interesting finding was observed in this study that IgG level increase with advancing gestational age. This increment could be due to rapid increase in the syncytiotrophoblasticactivity after the third trimester (12,16,17)

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