IgG Subclasses and Antibodies to Group B Streptococci, Pneumococci, and Tetanus Toxoid in Preterm Neonates after Intravenous Infusion of Immunoglobulin to the Mothers

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ABSTRACT. High doses of intravenous immunoglobulin were given to seven pregnant women between the 27th and 36th wk of gestation who were at risk for preterm delivery. Determinations of IgG subclasses and of antibodies against group B streptococcal serotypes, pneumococcal polysaccharides, and tetanus toxoid were done in maternal serum before and after intravenous IgG infusion and after delivery in cord serum. Substantial transplacental passage of the infused material could be observed in five cases where delivery occurred at the 34th wk or later. After the 36th wk of gestation, IgG subclass and antibody concentrations in cord serum were increased up to the levels in the maternal serum. (*Pediatr Res* 20:933-936, 1986)

Abbreviation

IGIV, intravenous immunoglobulin

Preterm neonates are known to be highly susceptible to systemic bacterial infections (1). This increased risk is due in part to the immaturity of the immune system and to an incomplete transplacental transfer of protective IgG antibodies from the mother (2-7). Sidiropoulos *et al.* (8) have shown that the administration of IGIV in combination with antibiotics was effective in the treatment of neonatal sepsis, particularly in premature babies. As a consequence of this previous work, the question was asked whether perinatal or prenatal infection could be prevented by giving IGIV to pregnant women who were at risk for preterm delivery. As a first step, we studied the possibility of a transplacental passage of IGIV administered in the last trimester of pregnancy. This report provides evidence that all four IgG subclasses and various specific antibodies present in the IGIV preparation are transferred from the mothers to the babies.

PATIENTS

The study included seven women between the 27th and the 36th wk of pregnancy who were at risk for preterm delivery with preterm labor, rupture of the membranes, or signs of chorioam-

nionitis. The gestational age was assessed by serial ultrasonography and examination of the newborns. Informed consent was obtained from all women. Immunoglobulin applications consisted of intravenous infusions of 24 g IgG (Sandoglobulin) at each of 5 consecutive days (6% solution in 0.9% saline, 10 drops/min). In addition, the patients received the antibiotics amoxicillin (4 g/day) and clindamycin (1.8 g/day). Monitoring of pulse and blood pressure, cardiotocography, and clinical observation did not show any side effects attributable to IGIV in mothers and infants. Serum samples were obtained immediately before the first and after the last infusion. In three women in whom delivery was delayed for 8-25 days after the last infusion, additional samples were taken at the time of birth. Cord blood samples were collected at delivery. The serum was kept at -20° C until assayed.

METHODS

IgG subclasses. IgG subclass specific reagents were prepared by immunizing sheep with isolated myeloma proteins and quantitative determinations were done with a solid phase radioimmunoassay as described (9, 10). Binding inhibition curves were established using the WHO reference plasma 67/69, the IgG subclass concentrations of which are known (9).

Determination of antibodies. Determinations of antibodies to surface antigens of group B streptococci (types Ia, Ib, II, and III), to pneumococcal polysaccharides (types 6A, 19F, and 23F), and to tetanus toxoid were performed using radioimmunoassay and ELISA procedures are described in detail elsewhere (11, 12). Values were expressed in arbitrary units or in IU/ml.

RESULTS

Table 1 summarizes the results of IgG subclass determinations in maternal and cord blood samples of six pregnancies. In the patients Ag and Th who were delivered after 28 wk of pregnancy, the IGIV infusions resulted in a pronounced increase of all four IgG subclass serum concentrations. In Ag, cord blood subclass concentrations were lower than those observed in the maternal preinfusion sample and corresponded to values reported in the literature for that gestational age (2, 4, 5). In Th, cord blood subclass levels were comparable to those observed in the maternal preinfusion sample and thus exceeded the expected values. In Ry and Le who were delivered at the 34th and 35th wk of gestation, the situation was complicated by long intervals between infusions and birth (11 and 25 days). Again, in the

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Table 1. *Effect of high-dose immunoglobulin infusions on IgG subclass concentrations in maternal and cord serum*

Patients (gestational age at delivery)	Interval between 5th infusion and delivery	Serum samples	Concentrations of IgG subclasses (g/liter)			
			IgG1	IgG2	IgG3	IgG4
Ag (28th wk)	1 day	Maternal				
		preinfusion	6.6	3.3	0.6	0.3
		postinfusion	19.3	10.1	1.3	0.6
		Cord blood	4.5	0.9	0.2	0.1
Th (28th wk)	1 day	Maternal				
		preinfusion	9.4	2.0	0.4	0.1
		postinfusion	14.7	5.1	0.9	0.2
		Cord blood	9.7	1.3	0.3	0.1
Ry (34th wk)	11 days	Maternal				
		preinfusion	8.0	0.8	0.5	<0.01
		at delivery	11.9	4.6	0.7	0.7
Le (35th wk)	25 days	Cord blood	10.6	1.2	0.4	0.1
		Maternal				
		preinfusion	6.0	2.9	0.4	0.1
		postinfusion	15.9	8.4	1.0	0.4
		at delivery	7.5	5.1	0.4	0.2
Cr (36th wk)	8 days	Cord blood	6.9	4.5	0.4	0.1
		Maternal				
		preinfusion	7.4	2.6	0.3	0.1
Sc (37th wk)	1 day	at delivery	17.1	8.4	1.0	0.3
		Cord blood	13.0	6.1	0.5	0.4
		Maternal				
		preinfusion	6.1	1.4	0.7	0.2
		postinfusion	16.0	7.4	1.1	0.5
		Cord blood	15.0	6.5	1.2	0.5

maternal sera a marked increase of all subclass levels was achieved by the infusions of IGIV. In cord serum of Ry, the IgG1 level was higher than in the maternal preinfusion sample. In addition IgG4 could be demonstrated in the cord serum, whereas in maternal preinfusion serum of Ry, this subclass was lacking. Similarly in samples from Le the IgG2 level was higher in cord than in preinfusion maternal serum. Patients Cr and Sc were delivered at the 36th and 37th wk of gestation. The IgG subclass concentrations in both cord sera were markedly higher than in the maternal preinfusion samples and approximated maternal values at the time of birth.

Antibody levels determined in maternal and cord serum samples are shown in Table 2. Immunoglobulin infusions were followed by an increase of all antibody concentrations in the maternal sera. In cord blood of the babies born after 28 wk of pregnancy, antibody concentrations were lower than or similar to those in the maternal preinfusion samples. A different situation was noticed at the 34th and 35th wk of gestation, where cord serum antibody levels were generally higher than in corresponding maternal preinfusion samples but still below maternal values at the time of delivery. These data were corroborated by the findings in another pregnancy (Fig. 1): patient Sb had received three infusions of 24 g IGIV each at 3 consecutive days when spontaneous delivery took place in the 35th wk of pregnancy. Even at this short interval between infusions and birth, cord serum levels of antibodies to group B streptococcal antigens exceeded preinfusion levels and approached values of the maternal sample at delivery. Finally, Table 2 shows the antibody concentrations observed in serum samples from Cr and Sc who were delivered after 36 and 37 wk of gestation. In both cord sera, antibody levels were close or identical to those in maternal serum at the time of birth and thus markedly higher than in the preinfusion maternal sera. Thus, the IgG subclass concentrations and the data from antibody determinations in maternal and cord sera are in agreement. Taken all together, the results provide evidence for significant transplacental passage of IGIV.

DISCUSSION

Maternal IgG is known to be transferred across the placenta, probably by an active transport mechanism involving Fc receptors for IgG molecules on the syncytiotrophoblast membrane (13, 14). Fetal serum levels of the four IgG subclasses increase proportionally with the gestational age (2-5). At the normal term of delivery cord serum levels of IgG and IgG subclasses are often found to be approximately 10% greater than the maternal levels (2-5, 15). A similar correlation to gestational age has been observed for levels of antibodies to group B streptococci (6, 7). Their presence in cord serum was shown to reduce the susceptibility to neonatal group B streptococcal infections (16). To our knowledge, passage of other specific antibodies in relation to gestational age has not been reported. The pregnant women in the present study were at risk for preterm delivery and placental dysfunction could not be excluded. Nevertheless, the transport mechanism was still operative. Our results indicate that the placental Fc receptors and the subsequent steps involved in the transport across this biological barrier recognized and handled molecules of the infused immunoglobulin preparation such as endogenous IgG. This was demonstrated by the passage of all four IgG subclasses and of a number of antibodies specific for group B streptococcal and pneumococcal serotypes and for tetanus toxoid. As in physiological conditions, the extent of this transport depended on the gestational age. According to a limited passage at 28 wk, cord serum IgG subclass and antibody concentrations were lower than or similar to those in the maternal preinfusion samples. At 34 wk and particularly at 36 wk of gestation, the transport mechanism was working more effectively producing increments of IgG subclass and antibody concentrations in cord serum which were already visible 3 days after the start of the infusions. In view of the small number of patients studied, the data have to be interpreted with caution. However, there is evidence from this pilot study that high doses of IGIV given to mothers after approximately 34 wk of gestation could

Table 2. *Effect of high-dose immunoglobulin infusions on antibody levels in maternal and cord serum*

Patients (gestational age at delivery)	Serum samples	Group B streptococcal antigens				Pneumococcal antigens				Tetanus toxoid (IU/ml)
		Ia	Ib	II	III	3	6A	19F	23F	
Ag (28th wk)	Maternal preinfusion	910*	1170	660	760		180*	290	140	1.3
	postinfusion	2170	2150	1140	1820		330	440	310	6.8
	Cord blood	800	430	460	580		160	210	70	<0.8
Th (28th wk)	Maternal preinfusion	1300	1790	610	1060	10	90	280	120	1.4
	postinfusion	2210	2560	1170	1570	70	190	440	270	5.5
	Cord blood	1200	1360	720	1130	10	120	300	110	1.2
Ry (34th wk)	Maternal preinfusion	540	1230	410	550	30	50	70	20	2.7
	at delivery	1770	2220	880	1280	150	210	390	220	6.7
	Cord blood	1170	1540	820	840	80	150	210	120	6.8
Le (35th wk)	Maternal preinfusion	530	1410	540	500		80	100	50	<0.8
	postinfusion	2300	2110	1190	1740		250	330	230	7.8
	at delivery	1310	1900	820	1200		200	270	150	2.9
	Cord blood	1150	1840	680	920		140	200	130	2.0
Cr (36th wk)	Maternal preinfusion	930	1190	580	660	10	150	400	150	<0.8
	at delivery	2230	2080	900	1500	140	230	520	290	7.0
	Cord blood	2000	1790	870	1400	110	230	450	330	4.8
Sc (37th wk)	Maternal preinfusion	1010	1020	530	1050	30	120	240	80	<0.8
	postinfusion	2490	2080	1070	1760	140	240	550	100	7.3
	Cord blood	2240	2460	1210	1660	300	250	430	270	5.9

* Values are expressed in arbitrary units.

Fig. 1. Concentrations of antibodies to group B streptococci of types Ia, Ib, II, and III (arbitrary units in cpm) in serum samples from patient Sb. Delivery was in the 35th wk of gestation after three infusions of a total of 72 g Sandoglobulin. The infusions resulted in an increase of all four antibody levels in maternal serum. Note that anti-Ia, anti-II, and anti-III concentrations in cord serum were markedly higher than in the maternal preinfusion sample taken 3 days before delivery.

compensate for the physiological antibody deficiency in fetuses of that age. The possible clinical significance of this observation remains to be tested.

Polyspecific immunoglobulin preparations for intravenous use differ in their biological properties according to the manufacturing procedures which sometimes include enzymatic and chemical modifications of the Fc portion of the IgG molecules (17). One

would assume that these procedures had an influence on trans-placental passage. Recently, a modified IgG preparation used for replacement therapy in two- antibody-deficient mothers was shown to cross the placental barrier (18). Apparently, treatment of IgG molecules of this preparation with reducing and alkylating agents did not abolish this biological property. The existence of quantitative differences between IGIV preparations in this respect will have to be demonstrated in future studies.

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