Early Human Development, 32 (1993) 81–85

EHD 01369

Fetal C-reactive protein

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(Received 14 August 1992; revision received 27 October 1992; accepted 28 October 1992)

Summary

C-reactive protein (CRP) was measured in fetal blood obtained by cordocentesis from 17 patients with preterm prelabour rupture of the membranes (PPROM). CRP was detected in the blood of eight of the 17 fetuses. Six fetuses, five of whom may have been infected had CRP $\geq$ 0.8 mg dl^{-1}. The remaining 11 fetuses as well as 25 healthy term infants who had cord blood taken immediately post delivery had CRP $<$ 0.6 mg dl^{-1}. These results suggest that elevation of fetal CRP levels may be a useful indicator of fetal infection in pregnancies complicated by PPROM.

Key words: C-reactive protein; fetus; infection

Introduction

C-reactive protein (CRP) is an acute phase protein, the levels of which rise in response to tissue injury and this can indicate the presence of infection. Indeed, measurement of CRP in maternal blood has been used in the prediction of chorioamnionitis in pregnancies complicated by preterm prelabour rupture of the membranes (PPROM) [3,4]. There are, however, no data available regarding fetal C-reactive protein levels and whether these might alter in response to infection. We now report fetal CRP levels obtained before labour in pregnancies complicated by PPROM and their relationship to the presence of infection.

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Patients and Methods

Seventeen patients with PPROM were recruited into the study at a median of 2 days (range 1–38) after membrane rupture. Their median gestational age at membrane rupture was 27 weeks (range 18–33). At recruitment, observations were made of uterine tenderness, temperature and fetal heart rate (FHR) patterns. In addition maternal urine and blood were cultured and maternal white blood cell count measured. Cordocentesis was performed and fetal blood (2 ml) was taken for culture, full blood count, blood gases, karyotype and measurement of CRP. For the latter blood was collected in EDTA, plasma separated by centrifugation and stored at −70°C. All samples were defrosted and analyzed in a single batch using a nephelometer and specific antiserum for CRP coated onto latex spheres. The lower limit of sensitivity of this assay was 0.23 mg dl^{-1}, in adults a CRP level of 0.5 mg dl^{-1} differentiating between pathological and healthy sera [1]. The CRP levels were not available to the clinical staff and thus did not influence the patients' management. Control samples for CRP estimation were obtained from cord blood at the delivery of 25 term infants. All had had uncomplicated pregnancies and none were asphyxiated. Eighteen underwent vaginal delivery and seven were delivered by caesarean section.

The mothers were randomised to receive antibiotics (amoxycillin) or placebo (Table I) as part of a large clinical trial to assess if antenatal administration of antibiotics altered the outcome of pregnancies complicated by PPROM. They were monitored throughout the rest of their pregnancy and immediately prior to delivery, for changes in their vital signs indicative of infection. Only one mother's clinical condition subsequently deteriorated and she was thought to be infected; as a consequence the cordocentesis was repeated. This was performed 34 days after the original fetal sampling.

After delivery, the placentae were examined histologically for chorioamnionitis and peripheral swabs and blood taken from the neonates were cultured. The patients were subdivided into three groups: (i) proven infection, if the blood cultures from the fetuses or neonates were positive, (ii) suspected infection, if either at cordocentesis or after delivery, maternal blood and/or urine cultures were positive, or there was histological evidence of chorioamnionitis, or the cultures from the peripheral swabs from the neonates were positive, (iii) no evidence of infection.

Approval for this study was granted by our Hospital Ethics Committee.

Results

Details of gestational age at PPROM, cordocentesis and delivery, as well as findings from the maternal and fetal investigations are shown in Table I. There were no procedure-related complications of the cordocenteses. In eight of the 17 fetuses CRP was detected, that is the CRP level was greater than the lower limit of the assay.

One fetus (case 1) had a positive blood culture (*Viridans streptococci*). This infant delivered within 24 h of the cordocentesis and died in the neonatal period. In a further four fetuses infection was suspected: positive maternal blood culture (*Viridans streptococci*), chorioamnionitis and neonatal colonisation (*Viridans streptococci*),

TABLE I

Patient characteristics and fetal CRP levels.

Case No.	Gestational age (weeks)			Antibiotic therapy	FHR	NST	Maternal temperature		White blood cell count			Fetal CRP	Maternal CRP
	SROM	FBS	Delivery				1	2	Fetal	Maternal 1	Maternal 2		
1	23 + 5	23 + 6	24 + 0	P	154	NR	37.0	38.0	6.4	13.5	—	6.22	8.72
2	30 + 0	30 + 1	30 + 3	A	144	NR	36.5	37.8	4.0	17.0	—	2.36	<0.23
3	25 + 6	26 + 0	28 + 4	A	150	R	37.0	37.8	12.1	11.5	16.6	1.89	<0.23
4	27 + 1	27 + 5	28 + 2	A	142	R	36.5	37.0	10.0	15.04	22.0	1.11	<0.23
5	27 + 5	28 + 1	31 + 2	A	144	R	36.5	37.8	4.6	10.1	18.0	<0.23	0.75
5	27 + 5	31 + 1	31 + 2	A	138	R	37.5	37.8	6.4	18.0	—	0.93	9.88
6	32 + 1	32 + 2	32 + 5	P	132	R	36.5	36.0	4.8	5.5	6.5	1.39	1.77
7	31 + 6	32 + 0	37 + 4	P	145	R	36.5	37.0	6.3	14.6	10.3	0.58	<0.23
8	33 + 1	33 + 5	36 + 0	P	139	R	36.7	37.0	5.6	7.1	7.1	0.28	<0.23
9	18 + 0	22 + 6	23 + 5	A	152	R	36.8	36.2	5.3	9.8	—	<0.23	1.43
10	32 + 4	32 + 5	33 + 5	A	138	R	37.2	36.0	6.2	10.2	14.4	<0.23	0.69
11	30 + 4	30 + 5	32 + 2	P	134	R	36.7	36.8	10.2	15.9	18.3	<0.23	0.54
12	31 + 2	31 + 5	35 + 2	A	138	R	36.7	36.5	4.5	6.0	10.4	<0.23	0.41
13	26 + 4	26 + 6	27 + 2	P	148	R	37.1	36.8	6.1	13.4	24.7	<0.23	0.38
14	23 + 6	24 + 1	24 + 4	P	162	NR	36.7	37.4	3.1	8.9	—	<0.23	<0.23
15	22 + 4	28 + 0	35 + 2	P	135	R	36.5	36.5	5.0	15.5	16.7	<0.23	<0.23
16	27 + 4	28 + 0	29 + 4	A	140	R	36.5	37.2	—	—	—	<0.23	<0.23
17	28 + 3	29 + 4	32 + 3	P	147	R	36.5	38.5	3.9	14.6	17.7	<0.23	<0.23

SROM, spontaneous rupture of membranes; NST, non-stress test at the time of FBS; FBS, fetal blood sample; R, reactive; A, amoxycillin; NR, non-reactive; P, placebo; FHR, fetal heart rate; 1, at the time of the FBS; 2 at delivery.

(case 2); maternal *Escherichia Coli* urinary tract infection and bacteraemia (case 3); maternal leukocytosis (white blood cell count $>20\,000$ mm^{-3} in the absence of steroid administration for at least 48 h) and neonatal colonisation (*Proteus* sp), (case 4); maternal pyrexia and chorioamnionitis (case 5). Case 5 was the patient whose clinical condition deteriorated and was resampled, she was pyrexial at the second procedure. Immediately prior to delivery all five mothers whose fetuses had proven or suspected infection had uterine tenderness and four were pyrexial (Table I). No other mother developed uterine tenderness. Only one fetus had a heart rate outside the normal range (case 14, fetal heart rate 162), this fetus was non-infected. Four FHR patterns were non reactive, but two non-reactive CTGs were documented in the non infected group. The fetal white blood cell count was raised in six patients, three in the non-infected group.

The five fetuses in whom infection was proven or suspected, had CRP levels >0.8 mg dl^{-1}, median CRP level 1.89 mg dl^{-1} (range 6.22–0.93) (Table I). Only one other fetus had a CRP > 0.8 mg dl^{-1}. The remaining 11 fetuses and all 25 term infants had CRP < 0.6 mg dl^{-1}. There was no significant correlation ($r = -0.045$, $P < 0.05$, Spearman's correlation coefficient) between the fetal CRP and the maternal CRP at the time of cordocentesis (Table I).

Discussion

We have detected CRP in certain fetuses, eight of 17 of our study group. Since there is no transplacental transfer of CRP [2], the observed fetal level must be fetal in origin. The low levels of CRP in blood samples we obtained after delivery from normal infants at term, further demonstrate the lack of placental transfer, as the infant levels did not reflect the rise in CRP that is seen in women during labour. The lack of a significant correlation between the fetal and maternal CRP levels at cordocentesis, further supports the postulate [2] of little transplacental transfer of CRP.

In six fetuses the CRP level was greater than 0.8 mg dl^{-1}. At cordocentesis no mother was in labour, none of the fetuses had congenital abnormalities, undergone intrauterine transfusion or subsequently died in utero [5]; thus we do not feel the CRP elevation was a non-specific indicator of tissue damage. In five of these six fetuses from pregnancies complicated by PPROM, elevation of the CRP level was associated with infection. Although fetal infection was suspected in four of these cases, the neonatal blood cultures were negative and only two of the four infants had bacterial colonisation [6]. All four mothers, however, had received antibiotics immediately following the cordocentesis. It is tempting to speculate that maternal antibiotic administration prevented neonatal septicaemia. The extent to which measurement of CRP in the fetal circulation will prove to be a more sensitive and specific indicator of chorioamnionitis than estimation of maternal CRP levels remains to be determined. Our results, however, do demonstrate that the fetus is capable of producing CRP and suggest that elevated fetal CRP levels is an indicator of fetal infection in pregnancies complicated by PPROM.

Acknowledgments

Dr P.J. Thompson is supported by the Medical Research Council. We are grateful to Ms Sue Williams for secretarial assistance.

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