Fetal plasma interferon gamma concentration in normal pregnancy

A. Abbas, MD, B. Thilaganathan, MD, A.G.S. Buggins, BSc, D.M. Layton, MD, and K.H. Nicolaides, MD
London, England

OBJECTIVE: Our purpose was to investigate changes with gestation in fetal plasma interferon gamma concentration.
STUDY DESIGN: A cross-sectional study at the Harris Birthright Research Centre for Fetal Medicine, London, was performed. Enzyme-linked immunoassay was used to measure plasma concentration in 54 fetal blood samples obtained by cordocentesis or cardiocentesis at 12 to 37 weeks' gestation.
RESULTS: The concentration of interferon gamma in fetal plasma decreased exponentially from a mean of 1.2 U/ml at 12 weeks' gestation to a mean of 0.5 U/ml at 37 weeks ($r = 0.460$, $p < 0.001$).
CONCLUSIONS: The presence of high levels of fetal interferon gamma in the first trimester suggests that it may play an important role in early fetal immunologic development. Furthermore, this study has established reference ranges for interferon gamma that may be of value in the prenatal diagnosis of congenital infection. (Am J Obstet Gynecol 1993;168:1414-6.)

Key words: Cordocentesis, fetal blood, interferon gamma, fetal immunology

Analysis of lymphocyte subpopulations in fetal blood by means of flow cytometry has shown that natural killer cells are the major circulating leukocyte in the first trimester of pregnancy.[1-4] It was proposed that the function of the natural killer cells is to confer innate immunity on the fetus at a stage of development when cell-mediated and humoral immune responses are immature.[1, 5] Interferon gamma (IFN-γ), a lymphokine with proved antiviral activity, has been shown in both in vitro and in vivo studies to substantially increase the cytolytic and secretory activity of natural killer cells.[6] The aim of this study was to determine whether plasma IFN-γ is present in the fetal circulation and, if so, whether its concentration is elevated in early pregnancy.

Patients and methods

In a cross-sectional study of 54 pregnancies fetal blood samples were obtained either by fetal cardiocentesis from women undergoing elective termination of pregnancy for social indications at 12 to 17 weeks ($n = 14$) or by cordocentesis for prenatal diagnosis at 18 to 37 weeks ($n = 40$).[7] The indications for cordocentesis were fetal karyotyping because of advanced maternal age ($n = 11$), for minor fetal malformations, such as choroid plexus cysts or hydronephrosis ($n = 26$), and for fetal blood grouping in red blood cell–isoimmunized pregnancies where the fetus was subsequently found to be Coomb's-negative ($n = 3$). In all cases the fetal karyotype was normal and the abdominal circumference, blood gas values, and hemoglobin concentration were within the appropriate reference range for gestation.[8, 9]

In each case gestation was determined from the menstrual history and confirmed by an ultrasonographic scan in early pregnancy. Cordocentesis was performed without maternal sedation or fetal paralysis, and in all cases umbilical venous blood was obtained. Fetal cardiocentesis was performed under general anesthesia and immediately before termination of pregnancy. Kleihauer-Betke testing confirmed that all blood samples contained only fetal blood. Fetal blood samples (400 μl) were collected into 20 μl of isotonic edetic acid solution (0.5 mmol/L in 0.15 mmol/L sodium chloride) and centrifuged immediately and the plasma separated and stored at −20° C. An enzyme-linked immunoassay technique was used for measurement of plasma IFN-γ (MEDGENIX, Brussels). The intraassay and interassay coefficients of variation were 3.2% and 7.7%, respectively, and the minimal detectable concentration was 0.03 IU/ml.

Regression analysis was used to determine the significance of any association between the concentration of IFN-γ and gestational age. Logarithmic transformation was used to make the data Gaussian. The transformed data were used to calculate the adjusted means and residual SDs.

From the Harris Birthright Research Centre for Fetal Medicine and the Department of Haematological Medicine, King's College Hospital School of Medicine and Dentistry.
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Reprint requests: Kypros H. Nicolaides, MD, Department of Obstetrics and Gynaecology, King's College of Medicine, Harris Birthright Research Centre, Denmark Hill, London, England SE5 8RX.

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Table I. Reference range for fetal plasma IFN-γ concentration

Gestation (wk)	IFN-γ concentration (U/ml)		
	5th Percentile	Mean	95th Percentile
12	0.41	1.17	3.11
13	0.39	1.13	3.00
14	0.38	1.09	2.90
15	0.36	1.06	2.79
16	0.35	1.02	2.70
17	0.34	0.98	2.60
18	0.32	0.95	2.51
19	0.31	0.92	2.43
20	0.30	0.88	2.34
21	0.29	0.85	2.26
22	0.27	0.82	2.19
23	0.26	0.79	2.11
24	0.25	0.77	2.04
25	0.24	0.74	1.97
26	0.23	0.71	1.91
27	0.22	0.69	1.84
28	0.21	0.66	1.78
29	0.20	0.64	1.73
30	0.19	0.61	1.67
31	0.18	0.59	1.62
32	0.17	0.57	1.56
33	0.16	0.55	1.51
34	0.15	0.53	1.47
35	0.14	0.51	1.42
36	0.13	0.49	1.37
37	0.13	0.47	1.33

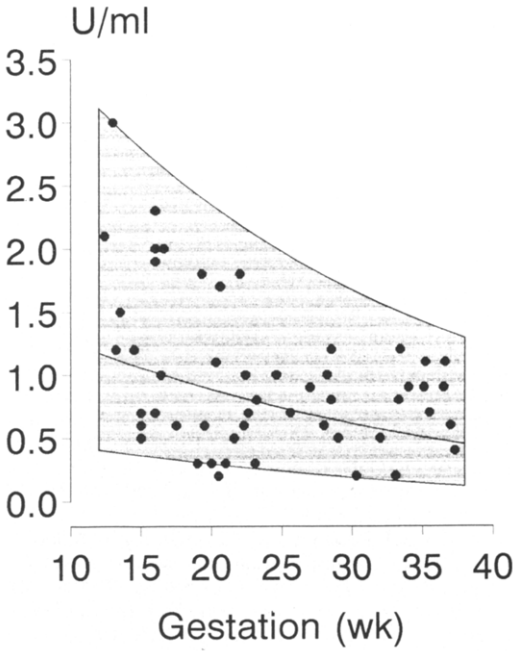

Fig. 1. Individual values and reference range (mean, 5th and 95th percentiles) for fetal plasma IFN-γ concentration with gestation.

Results

Fetal plasma IFN-γ concentration decreased with gestation, and the association was best described by a quadratic equation (Fig. 1, Table I).

Comment

This study has demonstrated that IFN-γ is present in the fetal circulation from as early as 12 weeks and that the plasma concentration decreases exponentially with advancing gestation. Because previous animal studies have shown that IFN-γ does not cross the placenta[10, 11] and none of our patients had history or clinical evidence of recent infection, the observed alterations with gestation in fetal plasma IFN-γ concentration are likely to reflect physiologic changes with fetal development.

Possible sources of IFN-γ in the fetal circulation are T lymphocytes, natural killer cells, monocytes, and tissue macrophages.[12] However, fetal macrophages are functionally immature, and production of IFN-γ is impaired.[13] Furthermore, in early pregnancy, when the fetal plasma IFN-γ is high, the fetal T lymphocyte and monocyte counts are low.[2, 4] Therefore the most likely source of fetal plasma IFN-γ is natural killer cells, which are also high in early pregnancy and decrease with advancing gestation.[1] An alternative source may be the placenta, because tissue culture studies have documented the presence of IFN-γ messenger ribonucleic acid in trophoblasts.

A possible role for IFN-γ is protection of the fetus from viral infection. Innate host defense against viral infection, which is the major function of IFN-γ in adults,[14] would be especially important in the fetus in early pregnancy, when there is a sparsity of circulating neutrophils, low levels of both T and B lymphocytes, and poor transplacental transfer of maternally derived immunoglobulins.[2-4, 15] IFN-γ has direct antiviral properties that are thought to be mediated by its effects on cellular metabolism and viral ribonucleic acid expression.[16] Additionally, IFN-γ may confer antiviral properties on the fetus by increasing natural killer cell production and cytotoxicity.[12] IFN-γ has also been shown to protect uninfected host cells from natural killer cell cytotoxicity while increasing the sensitivity to lysis of host cells expressing viral antigens.[17, 18]

This study has demonstrated that circulating IFN-γ is present in relatively high concentrations in early fetal life. This is compatible with the hypothesis that in early fetal development immunity is provided by innate rather than adaptive mechanisms. Furthermore, the data provide a reference range for the prenatal diagnosis of congenital infections.

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