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Fetal T-Lymphocyte Subpopulations in Normal Pregnancies

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Abstract
Peripheral blood T lymphocyte subpopulations were measured, using a fluorescence-activated cell sorter, in fetal blood samples obtained either by cordocentesis (n = 118) or at elective caesarean section (n = 14). Both the numbers and percentages of the total T lymphocytes (CD3+) and T-helper lymphocytes (CD4+) increased exponentially with gestation from respective means of 46% (1.15 × 10^9/l) and 29% (0.70 × 10^9/l) at 16 weeks to a plateau of 75% (3.11 × 10^9/l) and 54% (2.10 × 10^9/l) at 34 weeks. Similarly, the number of suppressor/cytotoxic T lymphocytes (CD8+) increased linearly with gestation from a mean of 22% (0.55 × 10^9/l) at 16 weeks to 24% (0.96 × 10^9/l) at 40 weeks; there were no natural cytotoxic T lymphocytes (CD3+CD56+) in any of the fetal blood samples. The helper-to-suppressor T lymphocyte ratio (CD4/CD8) increased exponentially with gestation from a mean of 1.22 at 16 weeks to 2.57 at 28 weeks. The alterations in T lymphocyte subpopulations were accompanied by changes in the expression of CD45RA, *L*-selectin, CD25 and HLA-DR. These alterations in T lymphocyte subpopulations with gestation reflect the pattern of maturation and development of the fetal cell-mediated immune system.

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Introduction

In intra-uterine life, the fetal lymphocyte count increases linearly with gestation, such that at 17 weeks, the lymphocyte count is 50% of the value at term [1]. In contrast, the fetal neutrophil count is very low until 32 weeks gestation, but increases exponentially thereafter to become the commonest leucocyte at term [1]. This pattern of fetal leucopoiesis may reflect alterations in fetal physiological priorities with gestation. Thus, the relatively high number of lymphocytes from an early stage of gestation may be necessary in host defence against viruses, which can be transmitted transplacentally. Furthermore, lymphocytes are essential for the early acquisition of immunological tolerance and antigen recognition [2, 3]. Neutrophils, which are primarily involved in host defence mechanisms against bacterial infection, are needed only during the late third trimester of pregnancy in preparation for postnatal survival; in intra-uterine life the placenta acts as an effective barrier to most bacteria [4].

The aim of the present study is to determine if the increase in fetal lymphocyte count with gestation is paralleled by maturation in T lymphocytes, as determined by alterations in lymphocyte subpopulations. Flow cytometry, which provides accurate and reproducible data on lymphocyte subpopulations, was used to measure helper, suppressor and cytotoxic T cells, and the expression of antigens which reflect T-lymphocyte function [5, 6].

Patients and Methods

Fetal blood samples were obtained by cordocentesis from 124 pregnancies undergoing prenatal diagnosis at 16–40 weeks gestation. The indications for fetal blood sampling included: (i) fetal karyotyping for women of advanced age that booked late and for low maternal serum alpha fetoprotein (n = 29); (ii) fetal blood grouping in red blood cell iso-immunized pregnancies and where the fetus was subsequently found to be Coombs'-negative (n = 11), and (iii) karyotyping for minor fetal malformations, such as choroid plexus cysts or hydronephrosis (n = 84). In all cases, the fetal abdominal circumference, blood gas values and haemoglobin concentration were within the appropriate

Table 1. List of the monoclonal antibody panel used to enumerate fetal T lymphocyte subpopulations, showing cluster designations or name (CD No./name), alternative nomenclature and reactivity/specificity

CD No./name	Alternative nomenclature	Reactivity/specificity
CD3	Leu 4, UCHT1, OKT3	T cell receptor, Pan T cell marker
CD4	Leu 3a	T helper/inducer lymphocytes
CD8	Leu 2a	T suppressor/cytotoxic lymphocytes
CD16/56	Leu 11/19 (NKH-1)	NK (CD3–) and natural cytotoxic T (CD3+) lymphocytes
CD45RA	Leu 18	naive T lymphocytes
CD25	IL2-R	activated lymphocytes
L-Selectin	Leu 8, LECAM-1	adhesion molecule on neutrophils and lymphocytes
HLA-DR		monocytes, B and activated T lymphocytes

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reference range for gestation and the fetal karyotype was normal.

Additionally, cord blood samples were collected from normal pregnancies undergoing elective caesarean section at 38–40 weeks gestation (n = 14), which was performed either because of previous caesarean section and suspected cephalopelvic disproportion or for breech presentation. In all cases the infants were normal and their birth weight was above the 5th centile for gestational age.

The study was cross-sectional and in each case gestation was determined from the maternal menstrual history and confirmed by an ultrasound scan in early pregnancy. Cordocentesis was performed without maternal sedation or fetal paralysis and in all cases umbilical venous blood was obtained. Kleihaur-Betke testing confirmed that all blood samples contained only fetal blood.

Fetal blood samples (180 μl) were collected into 20 μl of isotonic edetic acid solution (0.5 mmol/l in 0.15 mmol/l sodium chloride) and the full blood count was determined using a Coulter S-Plus counter (Coulter Electronics, Luton, England). Blood films were stained by the May-Grünwald-Giemsa method for the differential cell count. Blood samples (250 μl) were collected into heparinized syringes for measurement of oxygen tension and pH (Radiometer ABL 330, Copenhagen, Denmark). Blood samples (0.5 ml) were also collected into heparinized syringes for enumeration of fetal lymphocyte subsets, which was performed on the day of sampling.

Flow Cytometry

Fluorescein-isothiocyanate (FITC) or phyco-erythrin (PE) conjugated monoclonal anti-human antibodies (Becton Dickinson UK Ltd., Oxford, England) were used for simultaneous two-colour determination of T lymphocyte subpopulations using CD3, CD4, CD8, CD16/CD56, CD45RA, CD25, *L*-selectin and HLA-DR (table 1).

The whole-blood method was used for staining the cells with monoclonal antibody [7]. Cytometric analysis was carried out using fluorescence-activated cell sorter and Consort 32 software (Becton Dickinson). Samples were gated using forward angle and 90° light-scattering properties to exclude granulocytes, monocytes and platelets. Gated cells were analyzed with CD14/CD45 (monocyte/leucocyte marker), to ascertain that cells were lymphoid in origin. Control staining of fetal cells with anti-mouse monoclonal IgG2α-PE/IgG1-FITC was performed on each sample, and background readings of < 1% were obtained. A minimum of 5,000 cells were acquired in the lymphocyte fraction and analyzed to calculate the percentages of each subpopulation. The absolute counts were calculated as products of the absolute lymphocyte count and the percentages of each lymphocyte subpopulation.

Statistical Analysis

Regression analysis was used to determine the significance of any association between numbers and percentages of fetal lymphocyte subsets and gestational age. Normality of the distribution of residuals was examined; if this was skewed, logarithmic transformation was used to make the data Gaussian. The regression data were used to calculate the adjusted means and residual standard deviations. To determine the reference range with gestation in the original units (mean and individual 95% confidence intervals), the limits of the calculated reference range in logarithms were subjected to antilogarithmic transformation.

Results

With advancing gestation there was an exponential increase in the number and percentage of fetal CD3+ and CD4+ lymphocytes and the CD4/CD8 ratio (fig. 1, 2, table 2). The number of CD8+ lymphocytes increased linearly with gestation (fig. 2, table 2), while the percentage of CD8+ cells fell to a trough at 28 weeks and increased gradually afterwards (table 2). There were no CD3+CD56+ lymphocytes detected in any of the samples. The number of CD4+CD45RA+, CD4+*L*-selectin– and CD3+CD25– cells increased exponentially, while the number of CD8+ CD45RA+ cells increased linearly with gestation (fig. 3, 4, table 3).

The number of CD4+CD45RA–, CD8+ CD45RA–, CD4+*L*-selectin– and CD3+ CD25+ lymphocytes did not change significantly with gestation (fig. 3, 4). A small percentage of CD3+ lymphocytes expressed HLA-DR (mean = 1.11%, range = 0.00–3.77%, and this did not change significantly with gestation (r = 0.035).

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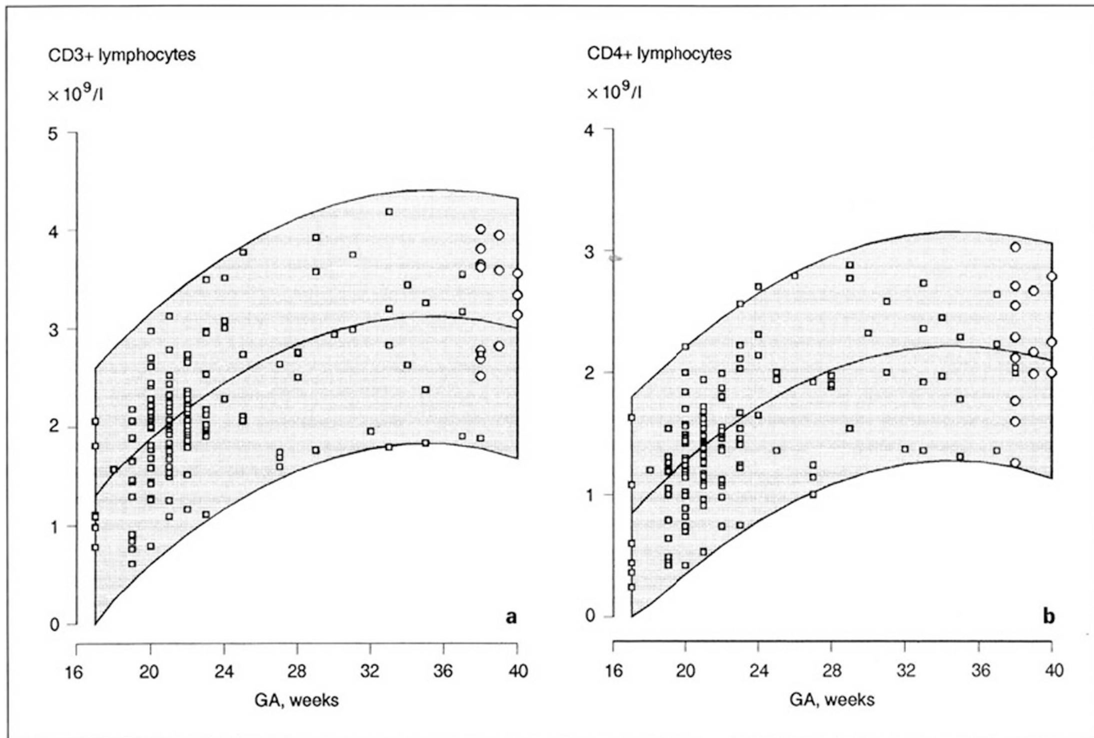

Fig. 1. Fetal CD3+ lymphocyte (**a**) and CD4+ lymphocyte (**b**) numbers plotted (□ = cordocentesis; ○ = caesarean section) as a function of length of gestation (CD3+ percentage: $r = 0.573$, $p < 0.0001$; CD3+ number: $r = 0.643$, $p < 0.001$; CD4+ percentage: $r = 0.587$, $p < 0.0001$; CD4+ number: $r = 0.664$, $p < 0.0001$). The sloping lines are the mean, 2.5th and 97.5th percentile values.

Table 2. Reference ranges for percentage (%) and number ($\times 10^9$/l) of fetal T (CD3+), T-helper (CD4+) and T-suppressor (CD8+) lymphocytes (mean and 95% confidence interval) with gestation (GA) in weeks

Ga	Total T, %		Total T, n		T-helper, %		T-helper, n	
	mean	95% CI	mean	95% CI	mean	95% CI	mean	95% CI
16	46	26–67	1.14	0.00–2.46	29	11–46	0.70	0.00–1.66
18	53	33–74	1.54	0.24–2.82	35	18–52	1.00	0.07–1.94
20	59	39–80	1.88	0.61–3.16	40	23–57	1.28	0.35–2.20
22	64	44–85	2.18	0.91–3.46	45	28–61	1.51	0.58–2.44
24	69	48–89	2.44	1.17–3.72	48	31–65	1.71	0.78–2.65
26	72	52–92	2.66	1.38–3.94	51	34–68	1.89	0.95–2.82
28	74	54–94	2.83	1.55–4.12	53	36–70	2.02	1.08–2.96
30	75	55–95	2.97	1.68–4.25	54	37–71	2.12	1.18–3.06
32	75	55–96	3.06	1.77–4.34	54	37–71	2.18	1.25–3.12
34	75	55–95	3.11	1.82–4.39	53	36–70	2.21	1.28–3.15
36	73	53–93	3.11	1.83–4.40	52	35–69	2.21	1.27–3.15
38	71	50–91	3.07	1.78–4.37	50	32–66	2.17	1.23–3.12
40	68	47–89	3.00	1,67–4.31	47	29–63	2.10	1.14–3.06

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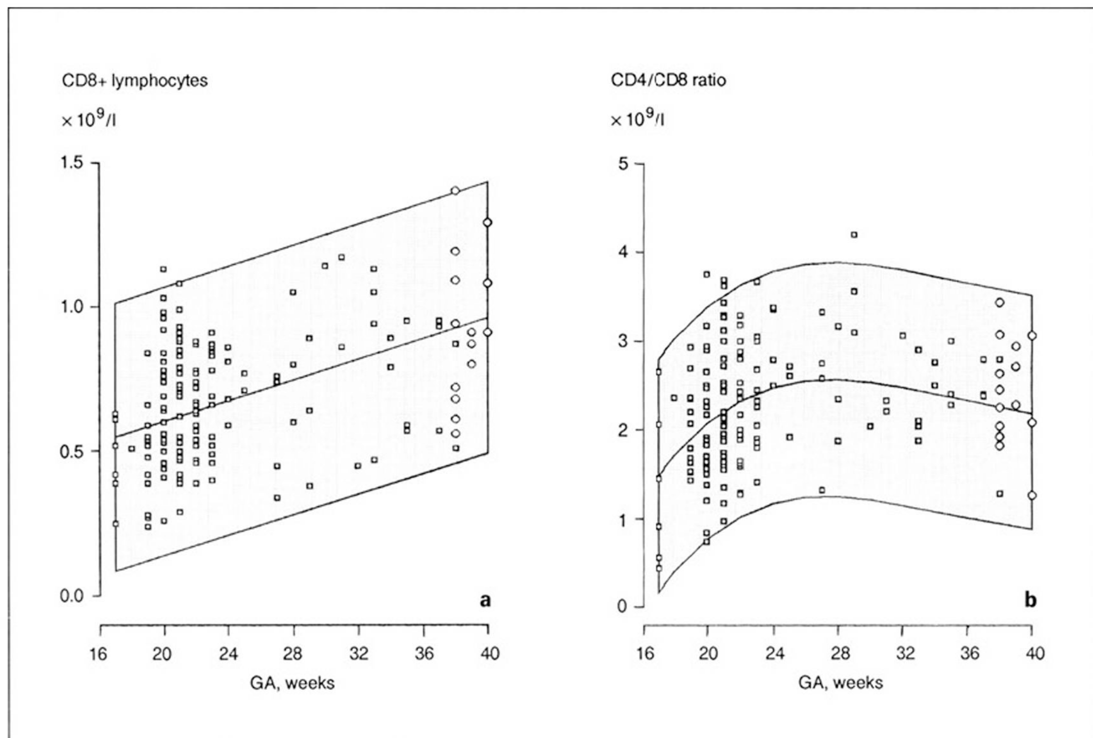

Fig. 2. Fetal CD8+ lymphocyte number (**a**) and helper to suppressor ratio (**b**) plotted (□ = cordocentesis; ○ = caesarean section) as a function of length of gestation (CD8+ percentage: $r = 0.268$, $p < 0.001$; CD8+ number: $r = 0.446$, $p < 0.0001$; CD4/CD8: $r = 0.456$, $p < 0.0001$). The sloping lines are the mean, 2.5th and 97.5th percentile values.

T-suppressor, %		T-suppressor, n	
mean	95% CI	mean	95% CI
24	13–35	0.55	0.09–1.01
22	12–33	0.58	0.12–1.05
21	11–31	0.62	0.16–1.08
20	10–30	0.65	0.19–1.11
19	9–30	0.69	0.23–1.15
19	8–29	0.72	0.26–1.18
19	8–29	0.76	0.30–1.22
19	8–29	0.79	0.33–1.25
19	9–30	0.82	0.36–1.29
22	10–30	0.86	0.40–1.32
21	11–31	0.89	0.43–1.36
22	12–33	0.93	0.46–1.39
24	13–35	0.96	0.49–1.43

Discussion

The findings of this study, of an increase in the total number of T (CD3+), T helper (CD4+), T suppressor/cytotoxic (CD8+) lymphocytes and the consequent increase in the CD4/CD8 ratio with gestation, reflect the maturation of the fetal immune system. In contrast to our findings, previous studies of CD3+, CD4+ and CD8+ lymphocyte subpopulations in fetal blood have either demonstrated no significant changes in these subsets with gestation (table 4) [8–14], or a non-significant fall in the ratio of CD4+ to CD8+

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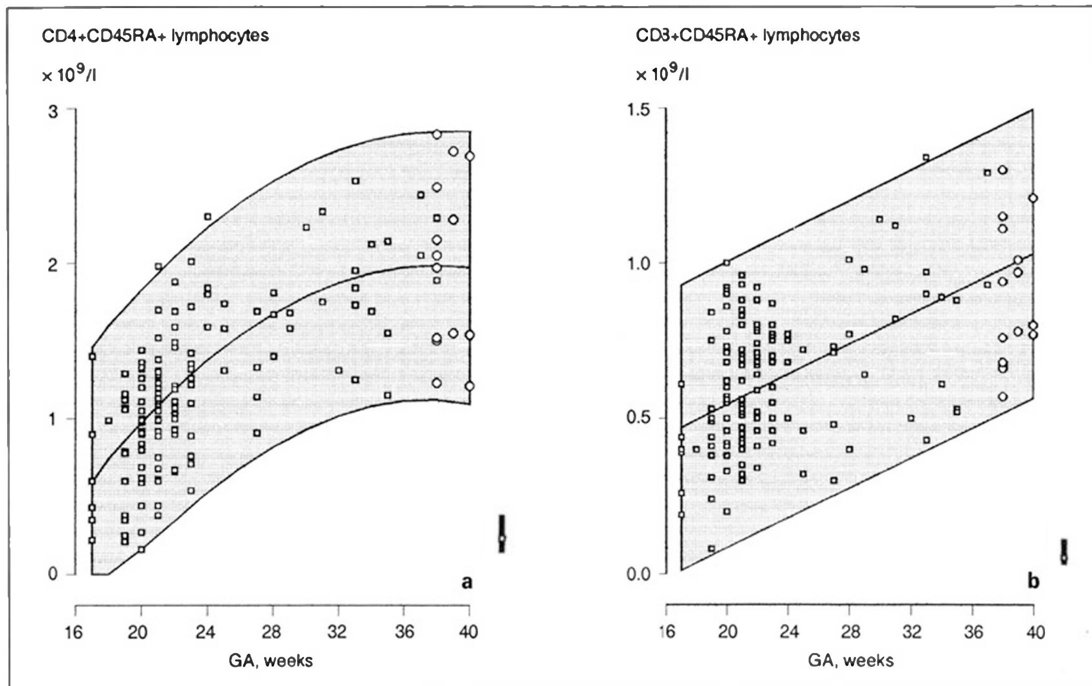

Fig. 3. Number of fetal CD4+CD45RA+ (**a**) and CD8+CD45RA+ (**b**) lymphocytes plotted (□ = cordocentesis; ○ = caesarean section) as a function of length of gestation (CD4+CD45RA+ number: r = 0.705, $p < 0.001$; CD8+CD45RA+ number: r = 0.547, $p < 0.0001$). The sloping lines are the mean, 2.5th and 97.5th percentile values. The vertical bar on the right represents the median and interquartile range for the CD45RA– cells (CD4+CD45RA– number: median = 0.23 × 10^9/l, range = 0.14–0.38 × 10^9/l; CD8+CD45RA– number: median = 0.05 × 10^9/l, range = 0.03–0.09 × 10^9/l).

Table 3. Reference ranges for the number (× 10^9/l) of fetal CD4+CD45RA+, CD8+CD45RA+, CD+*L*-selectin+ and CD3+CD25– lymphocytes (mean and 95% confidence interval) with gestation (GA) in weeks

Fa	CD4+CD45RA+		CD8+CD45RA+		CD4+*L*-selectin+		CD3+CD25–	
	mean	95% CI	mean	95% CI	mean	95% CI	mean	95% CI
16	0.48	0.00–1.35	0.47	0.01–0.93	0.63	0.00–1.50	1.06	0.00–2.24
18	0.74	0.00–1.60	0.52	0.06–0.98	0.89	0.04–1.75	1.36	0.21–2.50
20	0.98	0.13–1.83	0.56	0.11–1.02	1.13	0.28–1.98	1.63	0.50–2.76
22	1.19	0.34–2.04	0.61	0.15–1.07	1.34	0.49–2.19	1.88	0.75–3.01
24	1.38	0.53–2.23	0.66	0.20–1.11	1.52	0.67–2.37	2.10	0.97–3.23
26	1.54	0.68–2.39	0.70	0.25–1.16	1.68	0.83–2.53	2.29	1.15–3.43
28	1.68	0.82–2.53	0.75	0.29–1.21	1.82	0.96–2.67	2.46	1.31–3.60
30	1.79	0.93–2.64	0.80	0.34–1.26	1.92	1.07–2.78	2.59	1.45–3.74
32	1.87	1.02–2.73	0.84	0.38–1.30	2.01	1.15–2.86	2.70	1.56–3.85
34	1.94	1.08–2.79	0.89	0.43–1.35	2.07	1.21–2.92	2.78	1.64–3.93
36	1.97	1.11–2.83	0.94	0.48–1.40	2.10	1.24–2.96	2.84	1.69–3.98
38	1.99	1.12–2.85	0.98	0.52–1.45	2.11	1.25–2.97	2.86	1.71–4.02
40	1.97	1.10–2.85	1.03	0.56–1.50	2.10	1.22–2.97	2.86	1.68–4.04

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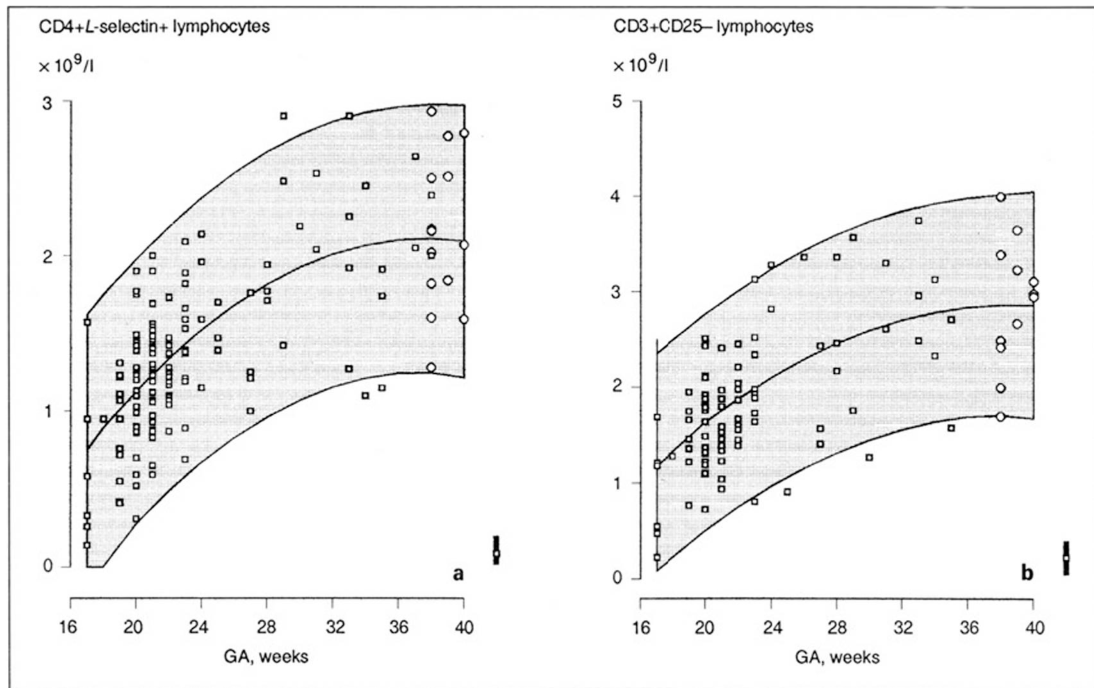

Fig. 4. Number of fetal CD4+*L*-selectin+ (**a**) and CD3+CD25– (**b**) lymphocytes plotted (□ = cordocentesis; ○ = caesarean section) as a function of length of gestation (CD4+*L*-selectin+ number: $r = 0.697$, $p < 0.001$; CD3+CD25– number: $r = 0.655$, $p < 0.05$). The sloping lines are the mean, 2.5th and 95.5th percentile values. The vertical bar on the right represents the median and interquartile range for the *L*-selectin– and CD25+ cells, respectively (CD4+*L*-selectin– number: median = 0.09×10^9/l, range = $0.00–1.08 \times 10^9$/l; CD3+CD25+ number: median = 0.23×10^9/l, range = $0.00–0.80 \times 10^9$/l).

Table 4. Data from previous studies on fetal peripheral blood lymphocyte subpopulations showing T-helper (CD4), T-suppressor (CD8) percentages and the ratio of CD4 to CD8 cells (CD4/CD8); the authors, year of publication, gestational age (GA), number of patients in the study (n) and mode of sampling are also shown (sample)

Authors	Sample	GA	n	CD4, %	CD8, %	CD4/CD8
Kotylo et al., 1990 [8]	CS/SVD	37–40	60	44	20	2.35
Bradstock et al., 1988 [9]	CS/SVD	37–40	25	53	15	3.53
Thomas and Linch, 1983 [10]	CS/SVD	26–36	38	25	11	2.27
		37–40	10	24	13	1.85
Moretta et al., 1991 [11]	CS/SVD	25–37	43	40	20	2.00
Rainaut et al., 1989 [12]	FBS	20–26	25	40	8	5.70
	CS/SVD	37–40	6	52	10	5.00
De Waele et al., 1988 [13]	FBS	16–20	7	48	18	2.95
		20–27	10	50	23	2.41
Lucivero et al., 1991 [14]	FBS	18–20	25	43	20	2.15

CS = Cesarean section; SVD = spontaneous vaginal delivery; FBS = cordocentesis.

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cells [10, 12, 13]. The discrepancy may be a consequence of the narrow gestational ranges examined, or the small number of patients used in the previous studies. Furthermore, data derived from analysis of cord blood obtained at term or premature delivery may have been affected by the stress of delivery or the underlying reason for premature birth, such as infection or hypoxia [9–11]. Additionally, most previous studies have used techniques to enumerate lymphocytes that may result in inaccurate estimations or selective loss of cellular populations [9–13]. Two studies which used direct whole blood staining techniques to examine T lymphocyte subpopulations in large numbers of patients at 18–20 weeks and at term, respectively, demonstrated results consistent with the data of the present study [8, 14].

The finding that with advancing gestation there is an increase in the number of CD4+CD45RA+ and CD8+CD45RA+ lymphocytes presumably reflects the pattern of thymic development [17, 18]. In postnatal life, CD45RA+ cells are produced by the thymus, are functionally 'naive' and are referred to as 'resting' lymphocytes. These cells, with development of functional capacity and activation, acquire the CD45RO and lose the CD45RA isotype [15]. Two previous studies have shown that in fetal life, the expression of CD45RA and CD45RO isotypes is also reciprocal [8, 14]. The CD4+CD45RO+ 'memory' or 'activated' lymphocytes recognize soluble antigen, modulate immunoglobulin production by B lymphocytes and differ functionally from CD45RA+ cells in activation requirements and lymphokine secretion [16]. The constant number of CD4+CD45RA– lymphocytes shown in this study may represent a population of 'activated' lymphocytes that are directed against either foreign or endogenous antigens. Furthermore, the findings that the majority of T cells are of the 'naive' phenotype are in accordance with the results of functional tests, demonstrating the lack of in vitro helper activity for adult B lymphocytes [21, 22].

The finding that the number of CD3+CD25– lymphocytes also increases exponentially with gestation is further supportive evidence for this pattern of thymic maturation. The CD25 antigen (interleukin-2 receptor) is expressed by activated T lymphocytes, and it would be expected that the CD4+CD45RA+ and CD8+CD45RA+ cells produced by the thymus are inactive [19, 20]. In addition, the number of 'active' CD3+CD25+ and CD4+CD45RO+ lymphocytes reported in this study are similar. The findings of a very low percentage of HLA-DR expressing T lymphocytes (<2%) offers a further explanation for the decreased T-B lymphocyte co-operation demonstrated in cord blood at delivery [23, 24].

The finding that the number of CD4+ cells expressing *L*-selectin increases with gestation is compatible with maturation of the fetal cell-mediated immune system. The successful transmigration of lymphocytes from the luminal surface of the endothelium into the tissues is dependent upon *L*-selectin during the initial tethering event [25]. Activation leads to shedding of *L*-selectin from the lymphocyte, allowing de-adhseion from endothelial ligands. These activated *L*-selectin-negative T lymphocytes mediate the majority of in vitro helper functions for immunoglobulin production as demonstrated by their effect on B cell differentiation into plasma cells [26]. The expression of *L*-selectin would also be required for transmigration of mature lymphocytes out of the peripheral circulation.

This study has established reference ranges with gestation for various fetal T lymphocyte subpopulations and contributes to a better understanding of the ontogeny of the immune system during intra-uterine life. A clearer un-

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derstanding of the mechanisms mediating lymphocyte maturation in the fetus, which may include specific growth factors and cytokines, together with enumeration of lymphocyte subsets, could provide a basis for prenatal diagnosis of immunodeficiencies and congenital infection, therapeutic manipulation aimed at the prevention of infection in premature neonates and intra-uterine bone marrow transplantation.

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