

Serum prostate-specific antigen measured in children from birth to age 18 years

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We measured prostate-specific antigen (PSA) in serum from 94 cord-blood samples, from 44 newborns, and from 330 children up to age 18 years, using a highly sensitive "third-generation" PSA assay on the IMMULITE® (Diagnostic Products Corp.) analyzer. The serum was that remaining after cross-matching for blood transfusion. Most children were hospitalized for special care or surgery. We found detectable concentrations of PSA ($\geq 0.003 \mu\text{g/L}$) in many cord sera and in sera from both male and female neonates. PSA was more frequently detectable in cord and newborn sera from males than from females, but there was considerable overlap in values between the sexes, negating any possible usefulness of PSA for assigning male gender to newborns with ambiguous genitalia. PSA decreased to undetectable concentrations in most prepubertal males and females but became detectable around the age of puberty in males. We speculate that the presence of detectable PSA in cord and newborn sera results from androgenic stimulation of prostatic tissue in males or from stimulation of breast or other tissue by prolactin or progesterone in females.

INDEXING TERMS: pediatric chemistry • neonates • steroid hormones • sex-differentiation disorders

Prostate-specific antigen (PSA) is a 33-kDa single-chain glycoprotein produced in males by epithelial cells lining the ducts of the prostate gland. The highest concentrations of PSA are found in seminal fluid, where it is believed to act as a serine protease and liquifactor [1]. Because of this association with seminal fluid, PSA was first described as γ -seminoprotein [2]. Its presence in normal prostate tissue and prostatic tumors and in serum from

men seemed to confirm its prostate specificity [3, 4], although recent studies with highly sensitive PSA assays have detected PSA in the absence of functional prostatic tissue [5, 6]. We speculated that PSA might be a useful marker of androgen action in the presence of functional prostatic tissue in the neonate, because fetal and neonatal serum concentrations of testosterone are higher than those of other prepubertal children [7] and because PSA expression is androgen dependent [8]. Accordingly, we thought PSA might be useful in assigning sex in cases of ambiguous genitalia. We measured PSA in a small group of newborn sera with the Ciba Corning ACS 180 Analyzer, but many values were close to or below the detection limit on that instrument, $18 \mu\text{g/L}$ [9]. To study this further, we investigated the relationship between sex and PSA in the newborn period, using a highly sensitive Third Generation PSA assay (IMMULITE). We extended the study to childhood and puberty because of the paucity of information about serum PSA in children.

Materials and Methods

PSA ASSAY

We measured serum PSA with the IMMULITE automated chemiluminescence immunoassay Third Generation PSA assay (Diagnostic Products Corp., Los Angeles, CA). The analytical detection limit of the assay, defined as 2SD above the response at zero dose, was $0.003 \mu\text{g/L}$ and the assay range extended to $20 \mu\text{g/L}$.

SAMPLES

For ethical reasons, we used blood serum remaining after cross-matching children before surgery or other periods of care in a pediatric tertiary referral center. We reviewed the admission diagnosis or case records and confirmed that none had ambiguous genitalia or other endocrine disorders, none had urogenital trauma, and none was receiving steroid therapy. We eliminated samples from children whose records showed that they had received blood transfusions or infusions of blood products within the preceding 6 months. The procedures followed were in accordance with the policies of the Human Subjects Review Board at our institution.

There were 374 pediatric patients (196 males and 178 females), including 44 neonates (postnatal ages, 1 to 2 days). The

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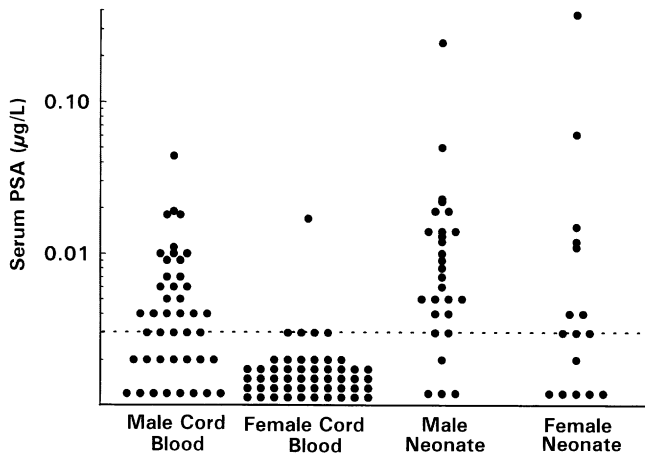


Fig. 1. Serum PSA concentrations in cord blood and in male and female neonates <48 h postpartum measured by IMMULITE Third Generation PSA assay. Dashed line shows the assay detection limit.

ages of the remaining 330 patients ranged from 3 days to 18 years. We also analyzed 94 cord-blood samples from 43 male and 51 female neonates. For calculation purposes, all samples with PSA values undetectable by the assay were assigned a value of 0.000 µg/L. All sera were stored at -20 °C until analysis.

STATISTICAL ANALYSIS

For statistical analyses, we used a spreadsheet program with statistical function capabilities (Microsoft Excel).

Results

Figure 1 shows the concentrations of PSA present in cord-blood serum and in serum from neonates <48 h after birth. Of the 43

male cord bloods, 28 (65%) had PSA concentrations at or above the analytical detection limit of the assay (0.003 µg/L), as did 5 of 51 females (10%). Serum PSA concentrations in cord blood from males were significantly (*P* <0.001) higher than those from females. PSA concentrations in both male and female neonates <48 h after birth were similar to each other and were similar to those of male cord blood. Of the 28 male neonates, 24 (86%) had PSA concentrations at or above the analytical detection limit, as did 10 of 16 female neonates (63%). The highest PSA concentrations found in neonates <48 h postnatally were 0.245 and 0.376 µg/L, measured in a male and a female neonate, respectively.

Median PSA values declined to below the assay detection limit in both sexes by age 12 months. Table 1 shows the PSA concentrations found in children up to age 18 years. Of 28 males between ages 3 days and 12 months, 12 (43%) had detectable concentrations of PSA. From age 13 months to 10 years, 10 of 95 males (11%) had detectable PSA. Of those children with detectable PSA in this age range, the highest value (0.029 µg/L) was seen in a 7-year-old boy who was prepubertal. Median PSA values remained below the detection limit even in the 11–14-year-old boys but became easily detectable (median value 0.206 µg/L) in 90% of the 15–18-year-old boys (20 of 22).

Girls had undetectable PSA more frequently than boys. PSA values were above the analytical detection limit in only 4 of 25 girls (16%) ages 3 days to 12 months; in 8 of 82 girls (10%) ages 13 months to 10 years; and in 9 of 55 (16%) girls ages 11 to 18 years. The highest PSA concentrations in 11–18-year-old girls were two values of 0.014 µg/L. We excluded the results for one 5-year-old girl with a PSA concentration of 0.008 µg/L because she was undergoing precocious puberty due to a 16-cm-diameter ovarian granulosa cell tumor (she had Tanner pubertal stage 2 breasts and her serum estradiol was 304 nmol/L).

Table 1. Serum PSA concentrations in children.

Age	No.	PSA conc, µg/L				% with undetectable PSA
		Mean	Median	Range	95th centile	
<i>Males</i>						
Cord blood	43	0.006	0.004	0–0.044	0.017	35
<48 h	28	0.019	0.008	0–0.245	0.041	14
3 days–12 months	28	0.007	<0.003	0–0.025	0.028	57
13–35 months	24	<0.003	<0.003	0–0.012	0.011	79
3–5 years	32	<0.003	<0.003	0–0.017	0.008	91
6–10 years	39	<0.003	<0.003	0–0.029	0.004	90
11–14 years	23	0.238	<0.003	0–3.01	0.904	52
15–18 years	22	0.254	0.206	0–1.02	0.632	9
<i>Females</i>						
Cord blood	51	<0.003	<0.003	0–0.016	0.003	90
<48 h	16	0.031	0.003	0–0.376	0.139	38
3 days–12 months	25	0.003	<0.003	0–0.042	0.009	84
13–35 months	20	<0.003	<0.003	0–0.007	0.007	75
3–5 years	29	<0.003	<0.003	0–0.052	0.006	90
6–10 years	33	<0.003	<0.003	0–0.003	<0.003	97
11–14 years	29	<0.003	<0.003	0–0.014	0.008	86
15–18 years	26	<0.003	<0.003	0–0.014	0.004	85

Discussion

To our knowledge, only one report has been published on serum PSA concentrations in boys and young adults, ages 8–25 years [10]. The authors used a sensitive ELISA with a detection limit of 0.005 $\mu\text{g/L}$. They showed that serum PSA increased with pubertal stage from median values of 0.005 $\mu\text{g/L}$ before puberty to 0.363 $\mu\text{g/L}$ in subjects at Tanner pubertal stage 5. The values correlated with increases in testosterone and luteinizing hormone.

Our study showed that PSA is present in cord-blood serum at higher concentrations in boys than in girls. Values rise transiently and then become very low in both sexes by age 13 months until puberty. During puberty, girls continue to have low PSA, but concentrations rise in boys. The median value of 0.206 $\mu\text{g/L}$ in the 15–18-year-old boys we studied is lower than that given for “healthy males” in the package insert from the kit manufacturer (0.9 $\mu\text{g/L}$). Also the 95th centile in this group (0.632 $\mu\text{g/L}$) and range upper limit (1.02 $\mu\text{g/L}$) are lower than the 2.6 $\mu\text{g/L}$ given as the upper limit of the 95% reference range in the kit insert. The males studied by the kit manufacturer were probably much older than 18 years, but the age range was not given. Oesterling [11], reviewing several studies of the age dependence of PSA in older men, reported that the median value increased with age from 0.7 $\mu\text{g/L}$ for 40–49-year-old men to 2.0 $\mu\text{g/L}$ in 70–79-year-olds, and the corresponding upper limit of the reference range increased from 2.5 to 6.5 $\mu\text{g/L}$.

Recent studies with highly sensitive assays have discounted the claimed specificity of PSA for prostatic tissue. In females, detectable PSA concentrations are found under a variety of physiological and pathological conditions—not only in adult female serum [5] but also in endometrium [12] and breast cytosols [13] and in various biological fluids such as amniotic fluid [14] and breast milk [15]. Diamandis et al. showed that PSA was present in $\sim 30\%$ of breast tumor cytosols and that its presence was associated with the steroid hormone receptor positivity, early disease stage, and younger patient age [16]. In vitro stimulation of certain breast cancer cell lines with steroid hormones (including progestins, androgens, and glucocorticoids) induced PSA production [17, 18]. PSA has also been detected in cell cytosols from a variety of other tumors including those of ovary, colon, lung, and parotid gland but at concentrations much lower than those found in breast tumors [19]. The finding of PSA in certain salivary gland neoplasms [20] has led to the recent suggestion that PSA may have some role as a growth factor regulator or growth factor during normal development and in malignancy [6].

Steroid hormones are present in serum at higher concentrations during fetal life and around the time of birth than in older prepubertal children [7]. It is likely that, at birth and in early infancy, serum PSA is derived from steroid hormone-responsive tissues under the influence of these hormones. We speculate that higher PSA concentrations in male than in female cord-blood serum may represent the production of PSA by the infant prostate under the influence of relatively high concentrations of androgens around the time of birth [7, 21, 22]. This would be supported by a previous report on PSA in prostatic tissues taken at autopsy from 42 children, newborns to age 18 years [23]. In

that study, PSA immunoreactivity in the tissue (assessed as the percentage of cells showing positive immunostaining) was high in boys < 6 months old and in adolescent boys, but was undetectable in prostates from boys of ages 6 months to 10 years. Perhaps the presence of detectable serum PSA in a substantial number of female neonates shortly after birth may be related to the stimulation of the estrogen-primed breast by the prolactin surge that occurs within the first hour after birth [24]. Alternatively, progesterone might be responsible, the concentration of progesterone in cord blood being ~ 500 – 1000 times that in serum from children older than 6 days [25]. In view of the stimulatory action of progestins on cell lines from breast cancers [17–18], perhaps the transiently high concentration of progesterone stimulates breast or other tissue in the neonate to produce PSA. The subsequent decrease in PSA concentrations observed after the first few months, which is sustained for most of childhood, may reflect the decreased production of sex steroid hormones during childhood in both sexes. The reappearance of detectable PSA during male puberty may result from increased hormone-mediated stimulation of the prostate, leading to increased PSA content as well as increased mass of this gland [10, 23]. Although most children at ages 1–10 years had undetectable PSA, it was detectable in a few. The lack of any apparent sex-related difference again suggests that nonprostatic sources may contribute to serum PSA.

Given previous suggestions that PSA measurements might be useful in the hormonal evaluation of puberty in males [10], we had speculated that PSA was produced exclusively by the prostate after birth, when near-pubertal concentrations of androgens are present, and that PSA might serve as a useful marker of male sex in cases of ambiguous genitalia. However, although PSA was higher in male cord-blood serum than that from females, there was much overlap in values between the two groups. The overlap in values was even more pronounced in blood taken during the first 48 h after birth. Because of this, PSA cannot be regarded as a reliable marker of male sex. Whether detectable PSA has any value in other stages of childhood is not clear. Although we found detectable PSA (0.008 $\mu\text{g/L}$) in one girl with precocious puberty caused by an ovarian neoplasm, higher concentrations were found in other girls of similar ages.

In summary, we have measured serum PSA concentrations in children of various ages. These children were not normal and healthy, because they needed blood cross-matching, but their conditions were not urogenital; we would guess that their conditions would not influence serum PSA. Our results for these patients show that PSA concentrations reach detectable concentrations in a substantial proportion of male cord-blood samples and in neonates of both sexes. We speculate that the presence of PSA in these cases may be related to dynamic changes in sex hormones or progestins in early neonatal life. In most prepubertal children PSA remains undetectable (by currently available assays). It becomes detectable during teenage years in boys, presumably reflecting prostate development in response to increased testosterone production during this period.

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