Prostate Specific Antigen in Cord Blood

Renu Nagar · K. K. Sharma

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Abstract Recent studies have demonstrated the presence of prostate specific antigen (PSA) in cord blood of male as well as female babies. The placental progesterone and estradiol up-regulate the synthesis and secretion of PSA in Placenta. This PSA is presumed to play a role in intra-uterine growth of fetus by virtue of its proteolytic action on several substrates including insulin-like-growth-factor-binding-protein-3, insulin chains and Interleukin-2. This study was planned with the objective of correlating the levels of PSA in cord blood to gestation at delivery, the type of delivery and gender of the fetus. Fifty-seven cord blood samples were collected from the umbilical cord during delivery or mid-trimester abortion and analyzed for PSA using 'Active PSA DSL-9700 ultra sensitive' kit employing two-site immuno-radiometric assay principle and having a detection limit of 0.001 ng/ml. Mean PSA levels in cord blood were found to be 0.112 ± 0.027 ng/ml. The concentration of PSA in cord blood was found to be higher in case of higher gestational age, male baby and operative delivery. 50 % of cord bloods for female babies had PSA below detection limit (range <0.001–0.460 ng/ml), while all the male samples had detectable PSA (range 0.11–0.973 ng/ml). Higher Progesterone levels found in prenatal maternal blood in case of male babies may be responsible for the higher cord blood PSA. Mean cord blood PSA was 0.150 ± 0.150 ng/ml in forceps delivery and 0.078 ± 0.012 ng/ml in normal vaginal delivery. Forceps delivery causes much more stress and strain as compared to a normal vaginal delivery, resulting in

increased levels of adrenal glucocorticoids, and therefore, higher cord blood PSA.

Keywords Prostate specific antigen · Cord blood · Gestation · Mode of delivery · Gender of baby

Introduction

Although prostate specific antigen (PSA) was earlier thought to be exclusively synthesized and secreted by prostate gland, its presence has now been recorded in several non-prostatic tissues and body fluids of males as well as females. Recent studies have reported the presence of PSA in cord blood [1–4].

Endometrium and syncytio-trophoblast synthesize PSA and contribute to the PSA in cord blood and amniotic fluid. The PSA gene is present and functionally active in placenta. PSA is synthesized in the rough endoplasmic reticulum cisternae, transported and then secreted mainly in the apical region and in a much lower amount in the basal region, as free or complexed molecules. PSA synthesis is up-regulated by steroid hormones including placental estradiol and progesterone [3–5].

Yu and Diamandis [2] reported the presence of PSA in the cord blood collected during delivery and found PSA less than 0.05 µg/L in most of them. Only 2 samples out of 33 had higher values. The PSA in cord blood was much lower than the PSA in the amniotic fluid (0.059–1.04 µg/L) at term.

Randell et al. [1] found higher PSA concentrations in male cord blood than in female cord blood. 65 % of male cord bloods had PSA >0.003 µg/L whereas, only 10 % female cord bloods had values >0.003 µg/L [1].

Some authors have proposed that the higher PSA concentrations in male cord bloods may represent the

R. Nagar (✉) · K. K. Sharma
Department of Biochemistry, Dr. RP Government Medical
College, Kangra, Himachal Pradesh, India
e-mail: dr.renunagar@yahoo.com

production of PSA by the infant prostate due to high concentrations of androgens around the time of birth, which stimulates the synthesis of this PSA [1, 6].

During pregnancy, the presence of increased levels of PSA in cord blood, amniotic fluid, placenta and endometrium suggests that PSA plays an important role in fetal growth [3, 7, 8] and development [2]. Its role has also been suggested in translational or post translational protein regulation of mammalian tissues.

PSA gene (hklk-3), situated on chromosome 19, shows 70–80 % homology to the human glandular kallikrein and tissue kallikrein [9].

PSA hydrolyzes insulin chains and Interleukin-2, enzymatically digests insulin like growth factor binding proteins (IGFBPs), activates latent transforming growth factor-P, inactivates protein C-inhibitors and regulates the hormonal bioactivity of parathormone-related protein. The proteolytic activity of PSA on these different biological substrates, detected in term placenta, could in part explain the potential role of placental PSA as an initiator of protease cascade, which is an important biological mechanism for tissue remodeling in the uterus [3, 4].

PSA, by virtue of its IGFBP-3 protease activity plays a significant role in fetal maturity by removing the regulatory influence of IGFBP-3 on the mitogenic activity of insulin like growth factors I and II (IGF-I and II) [10]. Levels of IGFBP-3 are negatively correlated with fetal maturity where as, the IGF levels are high in latter half of pregnancy [11].

Thus it may be inferred that PSA plays the role of growth factor or growth factor regulator.

This study was planned with the aim of correlating PSA in cord blood to type of delivery and gestation at delivery.

Materials and Methods

Healthy Indian women aged 18–45 years delivering or aborting in the hospital were included in this study. Women with history of antenatal complications or women taking hormonal preparations were excluded from the study. None of the subjects had any malignancy. Antenatal history, significant past obstetrical history and medical history were noted. History of non-hormonal drug intake was also recorded.

The gender and birth weight of the baby, the type of delivery and gestation at delivery were noted.

Cord blood samples were collected from the umbilical cord just after delivery or mid-trimester abortion. The samples were transferred to clean plain glass vials and transported to the biochemistry laboratory immediately. There the samples were allowed to clot at 37 °C and then centrifuged at 3,000 rpm for 5 min to separate the serum.

The cord blood sera were transferred to well labeled, clean plain vials and frozen till analyzed for PSA.

All the samples collected for this study were analyzed for PSA using 'Active PSA DSL-9700 ultra sensitive' kit. The procedure employs a two-site immunoradiometric assay principle [12].

Results

Fifty-seven cord blood samples were collected in this study. The difference in values was considered significant if *P* value was less than 0.05 and *P* value of 0.01 was considered highly significant. Standard error of mean (SEM) was calculated. Levels of PSA below the detection limit (0.001 ng/ml) were reported as 0.000 ng/ml for the purpose of statistics.

PSA concentration in these 57 cord blood samples ranged between 0.000 and 0.100 ng/ml with the mean PSA concentration of 0.112 ± 0.027 ng/ml.

Discussion

A total of 57 cord blood samples were analyzed for PSA in this study. PSA concentration in these cord blood samples ranged between 0.000 and 0.100 ng/ml. The mean PSA concentration was 0.112 ± 0.027 ng/ml.

The Relationship of Cord Blood PSA to the Gestation at Delivery

PSA levels in cord blood correlated positively with gestation at delivery. The PSA levels at gestation lesser than 28 weeks was 0.080 ± 0.038 ng/ml, whereas at 28–32 weeks it was 0.150 ± 0.150 ng/ml. After 36 weeks PSA levels decreased slightly and were 0.107 ± 0.029 ng/ml.

Yu and Diamandis analyzed cord blood PSA only in women delivering at term, and reported PSA less than 0.05 ng/ml in 31 of the 33 samples analyzed by them; only 2 samples had PSA more than 0.05 ng/ml [2] (Fig. 1).

No previous study correlating PSA levels to gestation was found in the literature.

Relationship of Cord Blood PSA to the Birth Weight of the Baby

Values of PSA were found in cord bloods of babies weighing lesser than 2,000 gm as compared to babies weighing more than 2,000 gm. The correlation of PSA and birth weight was not significant statistically.

No studies analyzing PSA levels in cord blood on basis of birth weight of baby have been found in the literature.

Fig. 1 PSA in cord blood vis. gestation at delivery

PSA is now regarded as a growth factor and an anabolic and mitogenic molecule [7]. Higher values of PSA in cord bloods of bigger babies found in this study corroborate these views (Table 1).

Relationship of Cord Blood PSA to the Gender of the Baby

The mean PSA levels in cord blood of male babies (0.179 ± 0.050 ng/ml) were six times higher than the values found in cord bloods of female babies (0.043 ± 0.029 ng/ml). This difference was statistically significant. The PSA in cord blood of females ranged from 0.000 to 0.460 ng/ml whereas in cord blood of male babies, it ranged from 0.11 to 0.973 ng/ml (Fig. 2).

Randell et al. also reported significantly higher mean PSA levels in cord blood of male babies as compared to cord bloods of female babies. 35 % of male cord bloods and 90 % of the female cord bloods in their study had PSA levels <0.003 ng/ml (detection limit). The authors proposed that the higher concentration of PSA in male cord bloods may represent the production of PSA by infant prostate under the influence of relatively high concentrations of androgens at the time of birth [1].

Table 1 PSA in cord blood versus birth weight of the baby

Birth weights (gm)	Observation (n)	Mean PSA $\pm$ SEM (ng/ml)
500–1000	3	0.133 ± 0.033
1000–1500	3	0.067 ± 0.033
1500–2000	5	0.080 ± 0.058
2000–2500	9	0.167 ± 0.109
2500–3000	23	0.113 ± 0.042
3000–3500	9	0.144 ± 0.073
>3500	4	0.000 ± 0.000

p Value = 0.92

No specific correlation could be found between PSA and birth weight of babies

Fig. 2 PSA in the cord blood vis. gender of the baby

In this study, the detection limit being lower (0.001 ng/ml), 50 % of cord bloods of female babies had PSA below detection limit, while all the male samples had detectable concentrations of PSA (>0.001 ng/ml).

Yu and Diamandis proposed that massive amounts of steroid hormone produced by the placenta up-regulate PSA synthesis [2]. In vitro studies performed on T-47 breast cancer cell line have shown that Glucocorticoids, Androgens and Progestins (but not Estrogens) are capable of up-regulating PSA synthesis [13].

Maternal Progesterone Levels Prepartum and Postpartum

In this study, Pre-natal and Post-natal maternal blood showed higher progesterone levels in case of male babies. It is, therefore, proposed that these higher progesterone levels may also be responsible for higher PSA levels in male cord blood (Figs. 3, 4).

Relationship of Cord Blood PSA to the Type of Delivery

A total of 30 samples were collected during normal vaginal deliveries (NVD) (with or without episiotomies), 25 samples were collected during caesarian sections (LSCS) and 2

Fig. 3 Mean progesterone in prepartum maternal serum vis. gender of the baby

Fig. 4 Mean progesterone in postpartum maternal serum vis. gender of the baby

Table 2 PSA in cord blood versus type of delivery

Type of delivery	Observation (n)	Mean PSA $\pm$ SEM (ng/ml)
Normal vaginal delivery (NVD)	30	0.078 ± 0.012
Caesarian section (LSCS)	25	0.144 ± 0.042
Forceps delivery	2	0.150 ± 0.150

p Value = 0.59

during Forceps deliveries (both of them were Outlet forceps deliveries).

PSA was found be least in case of NVD (0.078 ± 0.012 ng/ml) higher (nearly double) in Caesarian sections (0.144 ± 0.042 ng/ml) and highest in case of Forceps delivery (0.150 ± 0.150 ng/ml) (Table 2).

No study comparing cord blood PSA levels in different types of delivery has been found in the literature.

It is suggested that the stress and strain of a forceps delivery is probably responsible for increased secretion of adrenal glucocorticoids, and thereby, higher PSA levels in cord blood. caesarian Section, being a more controlled process, possibly does not put as much strain on the mother and the baby as a forceps delivery.

A study done on 301 healthy males found PSA levels increasing three times after 15 min of exercise [14]. No such study has been done on female subjects.

Authors opine that further research should be done in this respect using the recently developed more sensitive assay techniques such as the assay using europium(III) chelate-dyed polystyrene nanoparticles as labels with detection limits as low as 0.00021 ng/ml [15].

Conclusions

The concentrations of PSA in cord blood were found to be higher when the gestational age was more, baby was a male

and mode of delivery was operative. Mean PSA levels in cord blood were (0.112 ± 0.027 ng/ml).

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