

Case Report

How safe is soy in infancy? Case report of thelarche in an infant

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ABSTRACT

Soy protein based formulas are commonly used in infant nutrition for various indications like lactose intolerance and cow's milk protein allergy. There are concerns regarding phytoestrogen related and other side effects of these formulas. We are describing a case of possible soy formula induced thelarche in a 7 months infant. There was normalization of estradiol levels with some clinical improvement after stopping soy formula over a follow-up of 12 months duration. We suggest further studies to evaluate hormone levels in infants on soy formulas and to consider it only for appropriate clinical indication and age group.

Keywords: Cow's milk protein allergy, Infant, Phytoestrogen, Soy formula, Thelarche

INTRODUCTION

Soy protein based milk formulas are commonly used in infants for indications like lactose intolerance and cow's milk protein allergy (CMPA).¹ Because of the multiple possible side effects of soy protein, now soy based formulas are not recommended below 6 months of age except for limited indications like galactosemia.² But despite all the concerns, soy based formulas are widely used in early infancy. We are reporting a commonly discussed but uncommonly reported possible complication of soy formula in an infant suffering from CMPA.

CASE REPORT

A 7 months girl presented with progressively increasing bilateral breast size for last 2 months. There was no redness, pain, tenderness or discharge from the breasts. She had history of diarrhea at 2 months of age for more than 2 weeks, which was large volume and watery. Child was on breast milk along with cow's milk based formula at that time. Patient was managed elsewhere with possibility of CMPA and started on amino acid formula

along with breast feeding after stopping milk and milk products in mother's diet. After 1 month, elemental formula was stopped and breast feed was continued with normal maternal diet (including milk and milk products) but patient had recurrence of diarrhea. Then patient was started on soy formula which was continued till the time of presentation to us. Complementary diet devoid of milk and milk products were started at 6 months but patient remained predominantly on soy formula (around 1 litre/day with proper dilution). There was no recurrence of diarrhea after 3 months of age with weight gain of 2.7 kg. Parents observed increasing breast size since 5 months of age. Vaginal discharge, acne or oily skin was not present. On physical examination growth was normal, breast development was tanner stage 3 for both breasts and pubic hair tanner stage 1 with no axillary hairs. Other systemic examinations were normal and there was no clitoromegaly. Laboratory evaluations suggested high serum estradiol levels (Table 1). Bone age was 2 years on the Greulich Pyle atlas which was advanced for age.

Soy feeds were replaced with extensively hydrolyzed formula at 7 months age and milk-free complementary

feeds were continued. At 14 month of age, breast size decreased bilaterally. Repeat hormonal evaluation suggested normalization of estradiol levels. Cow's milk challenge was performed at this visit following standard protocol.² Patient tolerated the bovine milk and continued on normal milk diet.

At last follow up of 19 months age, growth remained normal, breast size decreased further. Hormonal evaluation suggested normal values. Bone age was 2 years 6 months on Greulich Pyle atlas. Ultrasound pelvis was done which was normal.

Table 1: Clinical and biochemical changes at presentation and follow-up.

| Parameters | 7 month age (at presentation) | 14 month age | 19 months age |
|----------------------------------|-------------------------------|--------------|---------------|
| Breast size | | | |
| Left | | | |
| Tanner stage | 3 | 3 | 2 |
| Horizontal diameter (cm) | 3 | 1.5 | 1 |
| Vertical diameter (cm) | 3 | 1 | 1 |
| Right | | | |
| Tanner stage | 3 | 3 | 3 |
| Horizontal diameter (cm) | 3 | 1.5 | 1.5 |
| Vertical diameter (cm) | 3 | 1.5 | 1 |
| Pubic hair (tanner stage) | 1 | 1 | 1 |
| Axillary hair | No | No | No |
| Bone age (years) | 2 | - | 2.5 |
| Basal LH (mIU/ml) | 0.37 | 0.3 | 0.01 |
| FSH (mIU/ml) | 8.95, | 8.17 | 5.77 |
| Estradiol (pg/ml) | 26.0 | <5 | <5 |
| Prolactin (ng/ml) | 22.8 | - | - |
| TSH (mIU/l) | 2.16 | - | - |

LH: luteinizing hormone; FSH: follicle stimulating hormone; TSH: thyroid stimulating hormone

DISCUSSION

Thelarche in infancy is common which is usually physiological. In our case, temporal correlation with introduction of soy formula with simultaneously high estradiol levels without increased levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH) is suggestive of the effect of external estrogen. Normalization of estradiol levels after stopping soy formula further supports possibility of phytoestrogen induced thelarche in the child. The advanced bone age could be linked to phytoestrogen exposure in soy formula, but could also be constitutional advancement in bone age which is considered a physiological variant in normal children. Central precocious puberty has rarely been reported in infancy but in our case normal LH and FSH levels are not suggestive of the same.³

High intake of phytoestrogen has been previously reported in association with premature thelarche.⁴ It has also been implicated to cause early menarche in adolescence.⁵ Infants exposed to soy formula have different organ development trajectory as compared to infants on breast milk or cow's milk due to exogenous estrogen exposure.⁶ In our case, there was a high intake of soy formula followed by development of premature thelarche which gradually reduced in size after stopping soy.

There is no clear consensus on significant effect of soy formulas on sexual maturation in humans.^{7,8} Animal

studies have shown altered alveolar maturation, ovarian function and estrous cycle on early exposure to soy.^{9,10}

Soy formulas are frequently used in infant nutrition despite very limited indications. Galactosemia and hereditary lactase deficiency are indications for soy formula in infants while other formulas like extensive hydrolyzed and amino acid formulas are preferable in CMPA. Studies have shown that soy formulas constitute 12-25% of all infants on formula feeding.¹¹ There is no such data from India. Soy formula is frequently prescribed in infants for persistent diarrhea, lactose intolerance and CMPA due to easy availability, low cost and palatability.

We suggest that infants with thelarche should be evaluated with nutritional history to rule out possibility of external phytoestrogen intake and appropriate hormone evaluation for precocious puberty when necessary. Further studies are required regarding hormonal evaluation of infant on soy formulas in Indian scenario.

CONCLUSION

Prolonged use of soy formula early in infancy can cause hormonal imbalance leading to thelarche. We suggest that use of soy formulas should be limited to appropriate and recommended indications and age group.

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