The effects of partial thyroidectomy on the development of the equine fetus

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Keywords: horse; fetus; hypothyroid; development; ossification

Summary

A syndrome of congenital hypothyroidism and dymaturity has been an important cause of reproductive loss and foal mortality in western Canada. The cause and pathogenesis of this syndrome is under investigation. One issue to be addressed is whether all the anomalies present in affected foals are produced concurrently by the same agent, or if affected foals are primarily hypothyroid in utero which induces the associated lesions. This study was designed to document the effects of fetal thyroidectomy, at about 215 days of gestation, on the growth and development of the equine fetus and to compare the anomalies present to those reported in the spontaneously occurring syndrome of foals in western Canada.

Two sham-operated controls and 4 partially thyroidectomised foals were carried to term following surgery. Sham-operated control foals were normally developed. Partially thyroidectomised foals were hypothyroid; had hyperplastic thyroid gland remnants; abnormal behaviour and locomotor skills; and numerous, marked deficiencies in their skeletal development. The anomalies present in partially thyroidectomised foals were comparable to those reported in congenitally hypothyroid neonates of other species, including human infants, and were similar to those described in congenitally hypothyroid and dysmature foals reported in western Canada.

Introduction

A syndrome of newborn foals characterised by thyroid gland hyperplasia and musculoskeletal lesions was described by McLaughlin and Doige (1981), and continues to be an important cause of reproductive loss and foal mortality in western Canada. These foals typically have long gestations; are born weak and unable to stand; and have musculoskeletal lesions of mandibular prognathia, flexural deformities of the legs, ruptured common and lateral digital extensor tendons, and inappropriately ossified bones. Despite the prolonged gestation, foals exhibit signs of immaturity, including: a short, fine or 'silky' coat; soft, pliable ears; lax joints; and poorly ossified bones (Allen et al. 1993, 1994; Allen 1995, 1996). Full term foals with signs of immaturity are referred to as dysmature (Koterba 1990). Affected foals are believed to be congenitally hypothyroid based on low serum thyroid hormone levels (McLaughlin et al. 1986) and a poor response to thyroid-stimulating hormone (TSH) (Allen 1996) and have been referred to as congenitally hypothyroid and dysmature (CHD). The cause of this syndrome is unknown, but is under investigation (Allen 1996; Allen et al. 1996). What remains unclear is whether all the anomalies present in affected foals are caused concurrently by the same agent, or if affected foals are primarily hypothyroid in utero which induces the associated lesions.

The objectives of the current study were to document the effects of thyroidectomy on the growth and development of the equine fetus and to compare the anomalies present in thyroidectomised foals with those reported in congenitally hypothyroid foals seen in western Canada.

Materials and methods

All procedures received approval from the University Committee on Animal Care and Supply at the University of Saskatchewan, and were conducted in accordance with the guidelines established by the Canadian Council on Animal Care.

Animals and animal management

Six light breed mares were kept on pasture during the months of May to October and bred naturally by an Arabian stallion. Dates of conception were estimated by observing the mares for behavioural evidence of oestrus combined with manual and ultrasonographic examination of the reproductive tract. From November until foaling, the mares were kept in a pen at the Western College of Veterinary Medicine.

Mares received ivermectin in May, July, October and March; were vaccinated against equine influenza, herpesvirus (1 and 4), encephalitis, rabies, and with tetanus toxoid in May; and vaccinated against equine herpesvirus (1p and 1b) at about the fifth, seventh, and ninth months of gestation.

Surgery

The 6 pregnant mares underwent surgery between 202 and 238 days gestation. In 4, as much fetal thyroid gland as possible was removed and 2 served as sham-operated controls. The mares (identified as Nos. 10, 13, 14, 17, 18, and 19) had similar management around the time of surgery. They received a combination of trimethoprim, sulphamamide, penicillin, and flunixin meglamine prophylactically. Mares Nos. 13, 14, and 19...
Effects of partial thyroidectomy

Fig 1: The plantar (a and c) and medial (b and d) surfaces of the distal right hind leg of foal F18 (a and b) and foal F10 (c and d). There is normally developed, coarse, long hair completely covering the pastern area and coronary band of sham-operated control foal F18. The hair on the pastern area of partially thyroidectomised foal F10 is not fully developed, is fine, incompletely covers the plantar surface, and is too short to cover the coronary band.

Also received altrenogest and mare No. 14 received clenbuterol hydrochloride following surgery.

All 6 mares were premedicated with xylazine followed by 5% glyceryl guaiacolate. General anaesthesia was induced with ketamine hydrochloride and maintained on halothane vaporised in oxygen. The mares received dobutamine hydrochloride and all but mare No. 13 received butorphanol intraoperatively.

Mares were placed in dorsal recumbency and their abdomens prepared for a midline laparotomy. Incisions were made into the uterus, chorioallantois, amnion and fetal skin. Blunt dissection of the neck was used to expose the fetal thyroid gland. The fetuses of mares Nos. 10, 13, 17, and 19 had as much thyroid gland removed as possible. All fetuses received trimethoprim and sulphonamide intraoperatively and the fetus of mare Nos. 13, 14 and 19 also received ampicillin. The incisions were closed with polydioxanone suture except the chorioallantois which was not closed, and the mare’s skin which was closed with stainless steel staples.

**Data collection**

Serum was collected from the 6 foals as soon as possible after parturition. A physical examination was performed and TSH

<table>
<thead>
<tr>
<th>Feature</th>
<th>Foal</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>F18</td>
<td>F14</td>
<td>Median</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>female</td>
<td>female</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Crown-to-rump length (cm)</td>
<td>95</td>
<td>100</td>
<td>97.5</td>
<td></td>
</tr>
<tr>
<td>Length of gestation (days)</td>
<td>336</td>
<td>331</td>
<td>333.5</td>
<td></td>
</tr>
<tr>
<td>Gestational age at surgery (days)</td>
<td>204</td>
<td>216</td>
<td>210</td>
<td></td>
</tr>
<tr>
<td>Days from surgery to birth (days)</td>
<td>132</td>
<td>115</td>
<td>123.5</td>
<td></td>
</tr>
<tr>
<td>Proportion of gestation after surgery (%)</td>
<td>39.3</td>
<td>34.7</td>
<td>37.0</td>
<td></td>
</tr>
</tbody>
</table>
administered to the 5 foals born alive. Live foals were subjected to euthanasia within 12 h of birth and a post mortem examination, including radiographs of the legs, was conducted immediately. Skeletal development was assessed using published criteria (Getty and Hillmann 1975; Adams and Poulos 1988). Thyroid glands or thyroid gland remnants were fixed, weighed, and histological sections were prepared routinely.

Serum samples were analysed for triiodothyronine (T3) and thyroxine (T4) levels using a fluorescence polarisation immunoassay. The sensitivity of the T3 assay was 0.5 nmol/l and

TABLE 1b: Selected features of the history and signalment of partially thyroidectomised foals

<table>
<thead>
<tr>
<th>Feature</th>
<th>F10</th>
<th>F17</th>
<th>F19</th>
<th>F13</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>female</td>
<td>male</td>
<td>male</td>
<td>female</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>29.1</td>
<td>36.0</td>
<td>36.8</td>
<td>25.1</td>
<td>32.6</td>
</tr>
<tr>
<td>Crown-to-rump length (cm)</td>
<td>94</td>
<td>96</td>
<td>100</td>
<td>95</td>
<td>95.5</td>
</tr>
<tr>
<td>Length of gestation (days)</td>
<td>337&lt;sup&gt;a&lt;/sup&gt;</td>
<td>338&lt;sup&gt;b&lt;/sup&gt;</td>
<td>344</td>
<td>345</td>
<td>344.5</td>
</tr>
<tr>
<td>Gestational age at surgery (days)</td>
<td>202</td>
<td>209</td>
<td>208</td>
<td>238</td>
<td>208.5</td>
</tr>
<tr>
<td>Days from surgery to birth</td>
<td>135</td>
<td>149</td>
<td>136</td>
<td>107</td>
<td>135.5</td>
</tr>
<tr>
<td>Proportion of gestation after surgery (%)</td>
<td>40.1</td>
<td>41.6</td>
<td>39.5</td>
<td>31.0</td>
<td>39.8</td>
</tr>
</tbody>
</table>

<sup>a</sup>foal was stillborn; <sup>b</sup>parturition was induced.
the upper limit of the curve was 9.2 nmol/l; the cross reactivity with T₄ was 0.23%. The sensitivity of the T₄ assay was 5 nmol/l and the upper limit of the curve was 232 nmol/l; the cross reactivity with T₃ was 8%. The interassay coefficient of variation for reference sera with mean T₄ concentrations between 0.84 and 21.5-95 nmol/l was 2.6-7.5% for samples ranging in concentrations 21.5-95 nmol/l. An intraassay coefficient of variation for T₃ was not calculated (Allen et al. 1995; Allen 1996).

Results

Two sham-operated control foals (F14 and F18) and 4 partially thyroidectomised foals (F10, F13, F17 and F19) were carried to term. Foal F10 was stillborn; parturition of foal F17 was induced, and foals F13, F14, F18, F19 were delivered spontaneously and without assistance.

Details regarding the sex, weight, size, and features of TABLE 2a: Selected features of the physical and post mortem examination of sham-operated control foals

<table>
<thead>
<tr>
<th>Feature</th>
<th>F18</th>
<th>F14</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mentation</td>
<td>normal</td>
<td>normal</td>
<td>-</td>
</tr>
<tr>
<td>Locomotor skills</td>
<td>St, F, N</td>
<td>St, F, N</td>
<td>-</td>
</tr>
<tr>
<td>Short, fine ('silky') hair coat</td>
<td>no</td>
<td>no</td>
<td>-</td>
</tr>
<tr>
<td>Soft, pliable ears</td>
<td>no</td>
<td>no</td>
<td>-</td>
</tr>
<tr>
<td>Joint and tendon laxity</td>
<td>no</td>
<td>no</td>
<td>-</td>
</tr>
<tr>
<td>Degree of mandibular prognathism (mm)</td>
<td>1 to 2</td>
<td>1 to 2</td>
<td>1.5</td>
</tr>
<tr>
<td>Size of defect around umbilicus (cm)</td>
<td>4</td>
<td>3.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Flexural deformity of the legs</td>
<td>mild</td>
<td>no</td>
<td>-</td>
</tr>
<tr>
<td>Lesions of the CDETs</td>
<td>no</td>
<td>no</td>
<td>-</td>
</tr>
<tr>
<td>Skeletal maturity</td>
<td>normal</td>
<td>normal</td>
<td>-</td>
</tr>
<tr>
<td>Dysmaturity</td>
<td>no</td>
<td>no</td>
<td>-</td>
</tr>
<tr>
<td>Weight (g) of thyroid gland⁵</td>
<td>11.4</td>
<td>8.2</td>
<td>9.8</td>
</tr>
</tbody>
</table>

CDETs = common digital extensor tendons; St = stand without assistance; F = able to follow mare; N = attempt to nurse from mare; ⁵carpal area of right front leg only; ⁶after fixation in 10% neutral buffered formalin.

gestation are presented in Tables 1a and 1b. The 2 groups of foals did not appear to differ in terms of their weight or crown-to-rump length. However, each of the partially thyroidectomised foals had a longer gestation than either of the sham-operated control foals.

Physical and post mortem examination findings are presented in Tables 2a and 2b. Sham-operated controls were normally developed. In contrast, the partially thyroidectomised foals had abnormal mentation and locomotor skills, as well as signs of immaturity. Examples of differences in the development of the hair coat are presented in Figure 1 and of differences in the ossification of the carpal and tarsal bones in Figure 2.

The fixed thyroid glands of sham-operated controls were 2.5 to 14.3 times heavier than the thyroid gland remnants of the partially thyroidectomised foals (Tables 2a and 2b). Histologically, the thyroid glands of sham-operated controls were normal. The thyroid gland remnants of partially thyroidectomised foals were hyperplastic. Follicles were markedly variable in size, irregularly shaped, and composed of short to tall columnar epithelium. The epithelium was sometimes multiple layers thick. Normal colloid was scant and the majority of follicles contained a poorly staining, granular to vesicular material. The results of TSH administration are presented in Figures 3 and 4. The resting T₃ levels of the 2 sham-operated control foals were 1.0 to 8.8 times higher than the 4 partially thyroidectomised foals. The 2 sham-operated control foals were able to elevate their T₃ levels by 122 and 181% following TSH administration, while none of the partially thyroidectomised foals could double their T₃ levels and 2 foals could not increase their T₃ levels more than 17%. The resting T₄ levels of the 2 sham-operated control foals were 1.1-14.0 times higher than that of the 4 partially thyroidectomised foals. None of the foals had elevated T₄ levels by an appreciable amount following TSH administration.

Discussion

Features of congenital hypothyroidism in human infants include prolonged gestation (in 20–50% of cases), umbilical hernia (25–60%), lethargy (30–40%), hypotonic muscles (35%), and retarded skeletal development (40–75%) (LaFranchi 1979; Letarte and Garagorri 1989; Newland et al. 1991; Behrman 1992; Grant et al. 1992; Styne 1994). It has been suggested that the delay in skeletal maturation at birth is proportional to the
severity and duration of the fetal hypothyroidism, and hence the amount of functioning thyroid tissue (Ilicki et al. 1990; Newland et al. 1991; Grant et al. 1992). In untreated hypothyroidism, bone maturation is reported nearly to stop, the physical growth plates may remain open indefinitely, and the radiographic appearance of the bones is so distinctive it is considered by some to be virtually diagnostic (DeLellis 1989; Chew 1991). These congenitally hypothyroid neonates not only exhibit delayed ossification of epiphyses, but irregular and fragmented epiphyseal ossification referred to as epiphyseal dysgenesis (Wilkins 1941; LaFranchi 1979; DeLellis 1989; Chew 1991; Newland et al. 1991). Further, the medullary cavities in the tubular and flat bones are characteristically small and narrow, with corresponding thickening of the overlying cortex (Silverman 1993).

Congenital hypothyroidism has been described in altricial mammals e.g. the rat (Goldberg and Chaikoff 1949; Weiss and Noback 1949; Becks et al. 1950), cat (Arnold et al. 1984; Sjolllema et al. 1991; Jones et al. 1992), dog (Robinson et al. 1988; Greco et al. 1991; Saunders and Jezyk 1991), and rhesus monkey (Lusted et al. 1953; Kerr et al. 1972; Olson et al. 1985). In these species, newborn congenitally hypothyroid individuals appear normal at birth, but develop signs of hypothyroidism during their first several days to several weeks of life. Typically, affected individuals are weak; lethargic and depressed; constipated with a thickened stool; and usually die within a few days after birth. Congenitally hypothyroid lambs also have short bones which, radiographically, have retarded maturation in the form of delay in the appearance of ossification centres. When ossification is present within epiphyses and other small bones it is irregular and fragmented, i.e. dysgenic (Lascelles and Setchell 1959; Hopkins and Thorburn 1972; Thorburn and Hopkins 1973). Hopkins and Thorburn (1972; Thorburn and Hopkins 1973) have suggested that the lack of osseous maturity present at birth in congenitally hypothyroid lambs is related to the duration of in utero hypothyroidism. These lambs also had abnormally shaped bones with a poorly hallowed medullary cavity (Lascelles and Setchell 1959) which is believed to be the result of a failure to remodel primary bone (Hopkins and Thorburn 1972).

To the best of our knowledge, this is the first report of fetal thyroidectomy being used to create in utero hypothyroidism leading to congenital hypothyroidism in foals. Congenitally hypothyroid foals in this study had prolonged gestations, were depressed, were weak and unable to stand, had umbilical hernias, and had an incomplete coat that tended to be short and immature in texture. Most striking was the delay in skeletal maturation characterised by retarded ossification of epiphyses, cuboidal bones of the carpi and tarsi, patellae, proximal sesamoid bones, and distal sesamoid (or navicular) bones; and by delayed closure of the physeal growth plates. When ossification did occur within the epiphyses it was irregular and fragmented. These foals also had short bones, and radiographically had retarded maturation of the growth plates in the bones of the limbs of these foals.

The congenitally hypothyroid foals in this study also had mandibular prognathism. The pathogenesis of this lesion is not known, but it may represent a failure of the maxilla to lengthen and advance rostrally due to retarded growth at the sphenoccipital and intersphenoid synchondroses.

Two of the partially thyroidectomised foals in this study had hemorrhage, tearing, and rupture of the common digital extensor tendons. It is interesting to note that the 2 foals that developed these lesions were the 2 congenitally hypothyroid foals that were strong enough to attempt to stand. It appears that the tendons of congenitally hypothyroid foals are not as strong as normally developed foals, but that sufficient stress is required to bring about injury.

### Table 2b: Selected features of the physical and post mortem examination of partially thyroidectomised foals

<table>
<thead>
<tr>
<th>Feature</th>
<th>Foal F10</th>
<th>Foal F17</th>
<th>Foal F19</th>
<th>Foal F13</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mentation</td>
<td>NA</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td>Locomotor skills</td>
<td>NA</td>
<td>Lr</td>
<td>Sr</td>
<td>Sr, SrA</td>
<td>-</td>
</tr>
<tr>
<td>Short, fine ('silky') hair coat</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>-</td>
</tr>
<tr>
<td>Soft, pliable ears</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>-</td>
</tr>
<tr>
<td>Joint and tendon laxity</td>
<td>marked</td>
<td>marked</td>
<td>marked</td>
<td>no</td>
<td>-</td>
</tr>
<tr>
<td>Degree of mandibular prognathism (mm)</td>
<td>6</td>
<td>12</td>
<td>7</td>
<td>0</td>
<td>6.5</td>
</tr>
<tr>
<td>Size of defect around umbilicus (cm)</td>
<td>8</td>
<td>4.5</td>
<td>8</td>
<td>1</td>
<td>6.3</td>
</tr>
<tr>
<td>Flexural deformity of the legs</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lesions of the CDETs</td>
<td>no</td>
<td>no</td>
<td>H, T, R</td>
<td>H, T</td>
<td>-</td>
</tr>
<tr>
<td>Skeletal maturity</td>
<td>immature</td>
<td>immature</td>
<td>immature</td>
<td>immature</td>
<td>-</td>
</tr>
<tr>
<td>Dysmaturity</td>
<td>no</td>
<td>no</td>
<td>H, T</td>
<td>H, T</td>
<td>-</td>
</tr>
<tr>
<td>Weight (g) thyroid gland remnant</td>
<td>0.8</td>
<td>1.0</td>
<td>2.6</td>
<td>3.3</td>
<td>1.8</td>
</tr>
</tbody>
</table>

CDETs = common digital extensor tendons; H = haemorrhage; T = partial tearing; R = complete rupture; NA = not applicable; Lr = lateral recumbency; Sr = sternal recumbency; SrA = stand with assistance; D = depressed and lethargic; *a after fixation in 10% neutral buffered formalin.
The anomalies and lesions present in the partially thyroidectomised foals of this study are comparable to those of congenitally hypothyroid neonates of other species including human infants. The histories, clinical appearances, and lesions are also strikingly similar to those reported in the CHD foals described previously in western Canada. One exception is the absence of flexural deformities of the legs. The reason for this is not known, but may relate to the duration of fetal hypothyroidism. The congenitally hypothyroid foals in this study were partially thyroidectomised for 107 to 149 days. Abattoir studies have suggested that the equine fetal thyroid gland becomes active by the fourth or fifth month of gestation (Allen et al. 1995; Allen 1996), which is on average, about 190 to 220 days before the birth of normal foals, and 210 to 240 days before the birth of most CHD foals. It may be that fetuses which are hypothyroid throughout their gestations are more likely to develop flexural deformities at birth.

Various reports (Lowe and Kallfelz 1970; Rooney 1972; Shaver et al. 1979; Lokai and Ford 1981; McLaughlin and Doige 1981, 1982; Vivrette et al. 1984; McLaughlin et al. 1986) have implicated hypothyroidism as having a role in producing certain types of skeletal disease collectively referred to as developmental orthopedic disease (Pool 1993) in growing horses. Since the lesions of congenital hypothyroidism in foals have been described here, it should now be easier to recognise affected foals in the future and allow for a prospective study to determine if they develop lesions of developmental orthopedic disease more often than other foals. If congenital hypothyroidism is found to have a role in developmental orthopedic disease it will then be important to identify the causes of congenital hypothyroidism in horses.

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