Epidemiology and pathogenesis of cryptorchidism

H.E. Virtanen and J. Toppari

Departments of Physiology and Paediatrics, University of Turku, Kimanlyynkatu 10, FIN-20520 Turku, Finland

Correspondence address. Tel: +358-2-333-7579; Fax: +358-2-250-2610; E-mail: jorma.toppari@utu.fi

Prospective clinical studies have shown that the prevalence of cryptorchidism among boys with birth weight \( \geq 2500 \text{ g} \) has increased in UK from 2.7 to 4.1\% between the 1950s and the 1980s and in Denmark from 1.8 to 8.4\% between the 1950s and the 1990s. In similar studies performed in different countries during the last two decades the figures have varied from 2.1 to 8.4\%. Due to spontaneous descent of the testes lower figures, i.e. between 0.9 and 1.8\% have been described at 3 months. Acquired cryptorchidism contributes to the increase in the rate of cryptorchidism in school-aged children. Testicular descent occurs in two phases. During the first phase, before midgestation, testis remains anchored to the inguinal area by insulin like hormone 3 (INSL3)-driven development of the gubernaculum. The second inguinoscrotal phase is dependent on testicular androgens and it is usually completed by the time of birth. Mutations of specific genes have rarely been reported in cryptorchidism. However, several risk factors for cryptorchidism, such as preterm birth and low birth weight, have been described. Environmental factors may also have a role in the etiology of cryptorchidism. Future studies on the gene–environment interaction will give new insights to the pathogenesis of cryptorchidism.

Keywords: cryptorchidism; pathogenesis; testicular descent; incidence

Introduction

Cryptorchidism, i.e. undescended testis is one of the most common urogenital abnormalities in newborn boys. In addition, postnatal ascent of the testes can lead to acquired cryptorchidism. Very variable figures on the incidence of cryptorchidism have been described in different type of studies. Although the cause for testicular maldescent remains unknown in most cases, several pathogenetic mechanisms for cryptorchidism have been described, and these will be now reviewed together with the epidemiological aspects of cryptorchidism.

Epidemiology of cryptorchidism

Prevalence of cryptorchidism in different type of studies

Prospective studies on congenital cryptorchidism

In prospective studies using similar and clearly defined criteria of cryptorchidism the birth rate of cryptorchidism has varied between 1.6 and 9.0\% (Buemann \textit{et al.}, 1961; Scorer, 1964; Mital and Garg, 1972; Group JRHCS, 1992; Berkowitz \textit{et al.}, 1993; Thong \textit{et al.}, 1998; Ghirri \textit{et al.}, 2002; Boisen \textit{et al.}, 2004; Preiksa \textit{et al.}, 2005), and when including only boys with birth weight \( \geq 2500 \text{ g} \) the birth rate has varied between 1.8 and 8.4\% (Fig. 1). Comparison of the studies performed during the last two decades suggests that there are geographical differences in the birth rate of cryptorchidism (Thong \textit{et al.}, 1998; Boisen \textit{et al.}, 2004; Preiksa \textit{et al.}, 2005). Furthermore, results from countries where repeated studies have been performed suggest an increasing trend in the incidence of congenital cryptorchidism (Buemann \textit{et al.}, 1961; Scorer, 1964; Group JRHCS, 1992; Boisen \textit{et al.}, 2004).

Congenital cryptorchidism is often followed by spontaneous testicular descent and accordingly lower rates of cryptorchidism, i.e. between 0.9 and 1.8\%, have been described at the age of 3 months (Scorer, 1964; Group JRHCS, 1992; Berkowitz \textit{et al.}, 1993; Boisen \textit{et al.}, 2004) among boys with birth weight \( \geq 2500 \text{ g} \). This spontaneous descent occurs usually during the first few months of life (Scorer, 1964; Berkowitz \textit{et al.}, 1993; Boisen \textit{et al.}, 2004). Spontaneous descent has been proposed to be more likely in infants with low birth weight, preterm birth or bilateral cryptorchidism (Group JRHCS, 1992; Berkowitz \textit{et al.}, 1993; Thong \textit{et al.}, 1998).
Prevalence in malformation register-based reports

Earlier reports based on malformation registers proposed an increasing trend in the rate of cryptorchidism (Matlai and Beral, 1985; Paulozzi, 1999), for instance in the 1970s and 1980s the reported rates increased from below 20 per 10 000 total births to over 40 per 10 000 total births in USA and from below 15 per 10 000 total births to almost 30 per 10 000 total births in Canada (Paulozzi, 1999). However, results based on congenital malformation registers or newborn hospital records have shown lower cryptorchidism figures as compared to prospective studies (Choi et al., 1989; Toppari et al., 2001). Furthermore, comparison of data of the malformation registers in different countries is difficult due to possible variation in registration methods, diagnosis, and inclusion criteria (Paulozzi, 1999; Toppari et al., 2001).

Prevalence in studies based on orchidopexy figures

For instance in Denmark, the cumulative risk for being operated for cryptorchidism before the age of 20 years was 2 to 3% in the 1980s (Thorup and Cortes, 1990). In England and Wales, data based on orchidopexy rates indicated an increasing trend in the cumulative rate of cryptorchidism in boys below 15 years from 1.4 to 2.9% between the 1950s and the 1970s (Chilvers et al., 1984). However, a more recent study indicated a decreasing trend in the orchidopexy rates of 0–14-year old boys in England, Wales and Scotland (Toledano et al., 2003). Besides indicating changes in the rate of cryptorchidism, the figures based on orchidopexies may also reflect changes in surgical practice and diagnostics (Toledano et al., 2003; Hack et al., 2007a).

Prevalence in clinical studies on school-aged boys

In studies concerning school-aged children very variable figures on cryptorchidism rates have been described. For instance in a Nigerian study the rate was 0.82% among 5–13-year old boys (Okeke and Osegbe, 2001), whereas in Denmark a rate of 7.0% was reported in boys aged 6 to 16 years (Blom, 1984). In both studies cryptorchidism was defined as a testis that could not be manipulated into the bottom of the scrotum. In a Jordanian study 2.1% of 6–12-year old boys were described to have a testis that was either impalpable or could not be manipulated into the scrotum (al-Abbadi and Smadi, 2000). In general, retractility of normal testes is a common phenomenon among school-aged boys (Panayotou, 1965; Okeke and Osegbe, 2001), thus challenging the diagnostics of cryptorchidism at this age and thus possibly affecting the figures described in different studies (Cour-Palais, 1966).

Effect of age on the prevalence of cryptorchidism

As mentioned above, congenital cryptorchidism is often followed by spontaneous testicular descent and accordingly lower rates of cryptorchidism have been described at the age of 3 months (Scorer, 1964; Group JRHCS, 1992; Berkowitz et al., 1993; Boisen et al., 2004). Furthermore, although some studies have described high rates of cryptorchidism among school-aged boys, in a follow-up study ~75% of school-aged cases have been described to also show spontaneous testicular descent during puberty (Blom, 1984), and especially acquired undescended testes have been shown to have a high rate of spontaneous descent during puberty (Sijstermans et al., 2006). The spontaneous pubertal descent is likely to explain why older studies concerning army recruits have described cryptorchidism rates of only about 1% (see references in Villumsen and Zachau-Christiansen, 1966). Thus, the prevalence of cryptorchidism is also dependent on age, which should be taken into account when comparing results of different studies.

Cryptorchidism may also be acquired

Follow-up studies have shown that spontaneously resolved congenital cryptorchidism may re-ascend and require surgery later in
childhood (Group JRHCS, 1992). Also tests that were in scrotal position at birth may later ascend (Villumsen and Zachau-Christiansen, 1966; Group JRHCS, 1992). The description of existence of non-congenital cryptorchidism is in accordance with the observation that orchidopexies are performed to a significant number of older children, despite recommendations for treatment early in childhood (Kaul and Roberts, 1992; Donaldson et al., 1996). Thus, in addition to being congenital, cryptorchidism may also occur only at an older age, i.e. it may be acquired (Villumsen and Zachau-Christiansen, 1966; Robertson et al., 1988). The rate of acquired cryptorchidism was almost three times higher than that of congenital cryptorchidism in a study of boys referred for an undescended testis (Hack et al., 2003). Due to the high rate of spontaneous descent of acquired cryptorchidism, postponement of prepubertal orchidopexy in cases with acquired cryptorchidism has been shown to reduce the number of late orchidopexies (Hack et al., 2007a). However, the health consequences of postponing orchidopexy will be revealed only after follow-up studies (Hack et al., 2007a; Pettersson et al., 2007). In a recent study, the prevalence of acquired cryptorchidism was up to 2.2% among 6–13-year old boys (Hack et al., 2007b).

In conclusion, several factors should be taken into account when evaluating results of different studies. These include the definition of cryptorchidism, type of the study (clinical study/register-based study), age of the patients, and possible inclusion of cases with acquired cryptorchidism.

**Pathogenesis of cryptorchidism**

**Genetic and hormonal factors affecting testicular descent**

The descent of the testis has been described to occur in two phases (Hutson and Hashtorpe, 2005a,b): In the first phase, which in humans occurs between 8 and 15 weeks of gestation, the testis is anchored in the internal inguinal ring by the enlargement of the caudal ligament called the gubernaculum. This anchoring prevents the testis from ascending like the ovaries do as the embryo enlarges (Shono et al., 1994). According to animal studies, the male-like development of the gubernaculum is dependent on the insulin-like hormone 3 (INSL3) and its receptor leucine-rich repeat-containing G protein-coupled receptor 8 (LGR8) (Nef and Parada, 1999; Zimmermann et al., 1999; Kubota et al., 2001; Overbeek et al., 2001; Gorlov et al., 2002; Tomiyama et al., 2003). However, although several hundreds of patients have been screened for mutations in INSL3 or LGR8 genes (Koskimies et al., 2000; Krausz et al., 2000; Tomboc et al., 2000; Lim et al., 2001; Marin et al., 2001a,b; Takahashi et al., 2001; Baker et al., 2002; Gorlov et al., 2002; Canto et al., 2003; Ferlin et al., 2003; Roh et al., 2003; Feng et al., 2004; Foresta and Ferlin, 2004; Bogatcheva et al., 2006; El Houate et al., 2007; Yamazawa et al., 2007), only some patients have been described to have mutations of these genes. The mutations found have appeared in heterozygous state (Tomboc et al., 2000; Lim et al., 2001; Marin et al., 2001b; Gorlov et al., 2002; Canto et al., 2003; Ferlin et al., 2003; Foresta and Ferlin, 2004; Bogatcheva et al., 2006; El Houate et al., 2007). Furthermore, only V18M, P49S and R102C mutations of the INSL3 gene and T222P mutation of the LGR8 gene have been shown to affect the function of the gene products in functional analyzes in vitro (Gorlov et al., 2002; Bogatcheva et al., 2003; El Houate et al., 2007). The P49S mutation was identified in a 46,XY individual with completely female external genitalia (Lim et al., 2001). In addition, R73X mutation of INSL3 gene has been described, and this leads to a truncated protein (Tomboc et al., 2000). The low frequency of mutations in INSL3 and LGR8 genes in cryptorchid patients may be linked to the fact that in humans the first phase of testicular descent is seldom disrupted, i.e. the inguinoscrotal phase is usually affected (Beltran-Brown and Villegas-Alvarez, 1988; Boisen et al., 2004; Preiksa et al., 2005). Furthermore, INSL3 may be important also in the second phase of testicular descent (Feng et al., 2006).

In addition to the development of the gubernaculum, the regression of the cranial suspensory ligament of the gonad also seems to contribute to the positioning of the gonad, at least in mice (Lee and Hutson, 1999). This regression is dependent on androgens and accordingly, female mice exposed prenatal to androgens show minor descent of the ovaries (Lee and Hutson, 1999) and male mice mutant for androgen receptor gene show retention of the cranial suspensory ligament (Zimmermann et al., 1999).

In the second phase of testicular descent the testis migrates from the internal inguinal area to the scrotum (Hutson and Hashtorpe, 2005a,b). This phase is usually completed in humans by the time of birth, whereas in rodents it occurs only postnatal (Klonisch et al., 2004). The gubernaculum enlarges and possibly causes the widening of the inguinal canal (Heyns, 1987; Barteczko and Jacob, 2000). Subsequent shrinkage of the gubernaculum and intra-abdominal pressure may force the testis through the inguinal canal. This has been described to occur by the seventh month of gestation in most boys (Heyns, 1987; Barteczko and Jacob, 2000).

The inguinoscrotal phase of testicular descent is dependent on androgens both in the human and mouse, and consequently, this phase is generally abnormal in androgen insensitivity (Hutson, 1986). The effect of intra-abdominal pressure or partial androgen effect may explain the fact that a few patients with androgen insensitivity have testes in their labia (Hutson, 1986). History of cryptorchidism has been associated with an increased GGN repeat length of the androgen receptor gene, which in turn may be linked to a decreased function of the receptor (Aschim et al., 2004). Bilateral cryptorchidism has also been proposed to be associated with an increased CAG repeat lengths (Silva-Ramos et al., 2006). However, previous studies concerning cryptorchidism found no such association (Sasagawa et al., 2000; Aschim et al., 2004). Furthermore, although a tendency of familial aggregation of cryptorchidism has been described (Elert et al., 2003), mutations in the genes of androgen receptor and 5-alpha-reductase seem also to be rare in isolated cryptorchidism (Wiener et al., 1998; Suzuki et al., 2001, 2002).

Cryptorchidism may also be associated with genital undermasculinization caused by other factors than deficient action of the androgen receptor. Undervirilization of 46,XY male may be caused by factors such as impaired gonadotropin action or function, inborn error of cholesterol biosynthesis, or impaired androgen biosynthesis and metabolism (Forest, 2006). Hypogonadalotrophic hypogonadism is often associated with cryptorchidism (Quinton et al., 2001).

During pregnancy hCG may replace the missing function of luteinizing hormone (LH) and this may explain why not all boys with hypogonadotrophic hypogonadism are born as cryptorchid. Pituitary gonadotropins may also have a role in keeping the testes in scrotal
position, since hypogonadotropic hypogonadism may be associated with ascent of the testes in infancy (Main et al., 2000).

The persistent Müllerian duct syndrome is due to abnormality of the anti-Müllerian hormone or its receptor. In this syndrome the location of the testes may be intra-abdominal, or inside an inguinal hernia together with female internal accessory reproductive organs and the contralateral testis (Clarnette et al., 1997b). It seems that the transabdominal phase of testicular descent is disturbed, since the gubernaculum has been reported to be feminized in this syndrome (Clarnette et al., 1997b). Cryptorchidism may occur also in several other syndromes, such as Down, prune belly, and Prader-Willi syndromes (reviewed in Virtanen et al., 2007).

In mice targeted disruption of the Hoxa10 gene, which is involved in the development of the posterior part of the body, caused uni- or bilateral cryptorchidism (Rijli et al., 1995; Satokata et al., 1995). Also in humans, developmental defects of the caudal field are associated with cryptorchidism (Cortes et al., 1998). However, mutations in the HOXA10 gene appear to be rare in human cryptorchidism (Kolon et al., 1999; Bertini et al., 2004).

In rodents, androgens have been suggested to affect the migration and growth of the gubernaculum in the inguinoscrotal phase of testicular descent via the genitofemoral nerve (GFN) and its neurotransmitter CGRP (calcitonin gene related peptide) (Beasley and Hutson, 1987; Park and Hutson, 1991; Hutson and Hasthorpe, 2005a,b; Ng et al., 2005; Shenker et al., 2006). The observation that boys with spina bifida have an increased frequency of cryptorchidism suggests that GFN may have a role in controlling testicular descent also in humans (Hutson et al., 1988). Although no pathogenic sequence changes were found in the CGRP pathway in patients having idiopathic cryptorchidism (Zuccarello et al., 2004), CGRP has been proposed to have a role in the obliteration of the processus vaginalis after the testis has descended, since it has been shown to cause fusion of processus vaginalis in vitro (Hutson et al., 2000; Hutson and Hasthorpe, 2005b). Accordingly, cryptorchid patients have been shown to have an increased frequency of patent processus vaginalis and epididymal anomalies as compared to fetuses (Favorito et al., 2006), which may also demonstrate deficient fetal androgen action in cryptorchid boys. Table 1 describes examples of factors that have been proposed to affect the two phases of testicular descent.

### Minipuberty and testicular descent

The spontaneous postnatal descent after congenital cryptorchidism may be due to the postnatal increase in the levels of the sex hormones, called the minipuberty (Andersson et al., 1998), although results on minipubertal hormone levels in cryptorchidism have been somewhat contradictory. Some studies have suggested that LH and testosterone levels are decreased in boys with cryptorchidism as compared to controls or to boys with spontaneous testicular descent (Gendrel et al., 1978; Gendrel et al., 1980; Job et al., 1987; Baker et al., 1988), whereas some studies found no difference in the hormone levels (de Munck Keizer-Schrama et al., 1988; Barthold et al., 2004). However, in some studies where special attention was paid to the time point of sampling, cryptorchidism was associated with increased minipubertal gonadotropin levels and reduced inhibin B levels as compared to controls (Kaleva et al., 2005b; Suomi et al., 2006). Furthermore, suprascrotal or more severe cryptorchidism has also been associated with immesurable serum androgen bioactivity at the age of 3 months (Raivio et al., 2003).

### Risk factors of cryptorchidism in epidemiological studies

Several risk factors for cryptorchidism have been described in epidemiological studies. Several studies have described low birth weight, being born as small for gestational age (SGA), and preterm delivery as such risk factors (Table 2). Low birth weight has been identified as a risk factor also in studies where gestational age was taken into account (Berkowitz et al., 1995; Akre et al., 1999; Weidner et al., 1999), which is in accordance with the description of SGA as a risk factor for cryptorchidism. In addition, the risk of cryptorchidism has been described to increase with decreasing gestational age (Preiksa et al., 2005), which in line with the above described timing of testicular descent. Furthermore, prematurity has been associated with a two-fold risk of being cryptorchid at the age of 1 year, even after adjustment for confounding factors including birth weight (Berkowitz et al., 1995), although register-based studies found no significant association between cryptorchidism and gestational age after adjustment for birth weight (Hjertkvist et al., 1989; Jones et al., 1998; Akre et al., 1999; Weidner et al., 1999).

Cryptorchidism has also been associated with an increased incidence of other genital abnormalities, e.g. hypospadias, in several studies (Table 2). This observation supports the theory of placental malfunction and subsequently disturbed fetal androgen production as etiological factors in cryptorchidism, which has been proposed in the epidemiological studies (Hjertkvist et al., 1989; Jones et al., 1998; Akre et al., 1999; Möller and Weidner, 1999). Androgens have been suggested to explain the gender difference in birth weight (de Zegher et al., 1998). Thus, also the description of low birth weight as a risk factor for cryptorchidism is in accordance with the theory of disturbed androgen action having a role in the development of cryptorchidism. Impaired placental function and possibly altered hCG secretion has also been proposed to explain the seasonal variation of cryptorchidism that has been described in some studies (Table 2) (Hjertkvist et al., 1989).

### Table 1: Examples of factors that have been proposed to influence testicular descent

<table>
<thead>
<tr>
<th>Factors affecting transabdominal testicular descent</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSL3</td>
</tr>
<tr>
<td>LGR8</td>
</tr>
<tr>
<td>Estrogens</td>
</tr>
</tbody>
</table>

Factors affecting inguinoscrotal testicular descent:

- Androgens
- Androgen receptor genes
- Gonadotropins
- GFN
- CGRP

Other factors affecting testicular descent:

- HoxA10
- AMH
- AMH receptor gene

INSL3, insulin-like hormone 3; LGR8, leucine-rich repeat-containing G protein-coupled receptor 8 (also known as GREAT or RSFB2); AMH, anti-Müllerian hormone; GFN, genitor femoral nerve; CGRP, calcitonin gene related peptide.
Table 2: Factors associated with cryptorchidism in several studies (some representative studies included)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Cohort studies</th>
<th>Study results</th>
<th>Register-based studies</th>
<th>Study results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low birth weight</td>
<td>Group JRHCS (1992)</td>
<td>Rate of cryptorchidism by birth weight, test for trend $P &lt; 0.0001$ (case at birth) and $P = 0.002$ (case at 3 months)</td>
<td>Hjertkvist et al. (1989)</td>
<td>Operated for cryptorchidism or case at $\geq 1$ year vs. all boys: birth weight 1.5–2.5 kg; adjusted IR 1.5 (95% CI 1.3–1.8), $P &lt; 0.001$</td>
</tr>
<tr>
<td>Berkowitz et al. (1993)</td>
<td>Rate of cryptorchidism: birth weight $&lt;2500$ g vs. $\geq 2500$ g: 19.8 vs. 2.2%, $P &lt; 0.001$</td>
<td>Jones et al. (1998)</td>
<td>Operated cases: $\leq 2.4$ kg vs. 3.0–3.4 kg: adjusted RR 1.87 (95% CI 1.45–2.42) 2.5–2.9 kg vs. 3.0–3.4 kg: adjusted RR 1.23 (95% CI 1.04–1.14)</td>
<td></td>
</tr>
<tr>
<td>Berkowitz et al. (1995)</td>
<td>Cryptorchidism at 1 year: $&lt;2500$ g vs. $\geq 2500$ g, adjusted OR 2.29 (95% CI 1.12–4.70)</td>
<td>Akre et al. (1999)</td>
<td>Operated cases: $&lt;1500$ g vs. 2500–3999 g: adjusted OR 3.53 (95% CI 1.85–6.73) 1500–2499 g vs. 2500–3999 g: adjusted OR 1.76 (95% CI 1.29–2.34)</td>
<td></td>
</tr>
<tr>
<td>Thong et al. (1998)</td>
<td>Cryptorchidism by birth weight, test for trend $P &lt; 0.001$</td>
<td>Weidner et al. (1999)</td>
<td>Operated cases or diagnosis of cryptorchidism in register: $&lt;2500$ g vs. 3500–3999 g: OR 2.22 (95% CI 1.98–2.49) 2500–2999 g vs. 3500–3999 g: OR 1.52 (95% CI 1.39–1.67) 3000–3499 g vs. 3500–3999 g: OR 1.16 (95% CI 1.08–1.25)</td>
<td></td>
</tr>
<tr>
<td>Boisen et al. (2004)</td>
<td>RR for cryptorchidism: $&lt;2500$ g vs. $\geq 2500$ g Denmark: at the expected date of delivery: 2.7 (95% CI 1.4–4.9), $P = 0.007$ Finland: at the expected date of delivery: 8.2 (95% CI 3.4–19.6), $P = 0.00047$ 2.9 (95% CI 1.8–4.8), $P &lt; 0.0001$ (total hospital cohort) Finland: at 3 months: 6.9 (95% CI 1.6–29.8), $P = 0.041$ 2.6 (95% CI 1.2–5.4), $P = 0.018$ (total hospital cohort)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preiksa et al. (2005)</td>
<td>Bilateral cryptorchidism $&lt;2500$ g vs. $\geq 2500$ g: OR 3.8 (95% CI 1.04–15.80), $P = 0.03$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preiksa et al. (2005)</td>
<td>Any type of cryptorchidism, $\chi^2$ test for weight groups, $P &lt; 0.0001$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGA</td>
<td>Berkowitz et al. (1993)</td>
<td>Rate of cryptorchidism: 7.5% in SGA, 3.7% in AGA, 1.7% in LGA boys. Test for trend $P &lt; 0.001$</td>
<td>Akre et al. (1999)</td>
<td>Operated cases of cryptorchidism: $&lt;33$ weeks SGA vs. 37–41 weeks non-SGA: adjusted OR 7.19 (95% CI 2.60–19.87) 33–36 weeks SGA vs. 37–41 weeks non-SGA: adjusted OR 2.18 (95% CI 1.23–3.88) 37–41 weeks SGA vs. 37–41 weeks non-SGA: adjusted OR 2.32 (95% CI 1.75–3.09)</td>
</tr>
<tr>
<td>Ghirri et al. (2002)</td>
<td>Rate of cryptorchidism: 17.1% in IUGR vs. 6.3% in AGA boys, $P &lt; 0.01$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boisen et al. (2004)</td>
<td>Rate of cryptorchidism SGA vs. non-SGA Finland: at birth 3.0 (95% CI 1.7–5.5), $P = 0.002$ (total hospital cohort) Finland: at 3 months: 2.7 (95% CI 1.1–6.8), $P = 0.042$ (total hospital cohort)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk factor</td>
<td>Cohort studies</td>
<td>Study results</td>
<td>Register-based studies</td>
<td>Study results</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------------------</td>
<td>---------------------------------------------------</td>
<td>-------------------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Prematurity</td>
<td>Berkowitz et al. (1993)</td>
<td>Rate of cryptorchidism:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>17.2% of preterm vs. 2.1% of full-term boys, <em>P</em> &lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Berkowitz et al. (1995)</td>
<td>Cryptorchid at 1 year:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 37 weeks vs. ≥ 37 weeks: adjusted OR 2.25 (95% CI 1.16–4.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thong et al. (1998)</td>
<td>Incidence of cryptorchidism:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>17.3% in preterm vs. 3.3% in full-term boys, <em>P</em> &lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ghirri et al. (2002)</td>
<td>Rate of cryptorchidism at birth:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>30.1% in preterm vs. 3.4% in full-term boys, <em>P</em> &lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ghirri et al. (2002)</td>
<td>Rate of cryptorchidism at 1 year:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.3% of preterm vs. 1.5% of full-term boys (first study decade)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.1% of preterm vs. 1.2% of full-term boys (second study decade)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Boisen et al. (2004)</td>
<td>RR for cryptorchidism:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 37 weeks vs. ≥ 37 weeks:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Denmark: at the expected date of delivery:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.6 (95% CI 1.6–4.5), <em>P</em> = 0.00040</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Finland: at the expected date of delivery:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.9 (95% CI 1.1–8.1), <em>P</em> = 0.055</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Finland: at 3 months:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.6 (95% CI 1.6–19.7), <em>P</em> = 0.024</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Preiksa et al. (2005)</td>
<td>Any type of cryptorchidism:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>χ²-test for gestational age groups, <em>P</em> &lt; 0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Having other</td>
<td>Group JRHCS (1992)</td>
<td>Rate of hypospadias:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>genital abnormality</td>
<td></td>
<td>5.2% of cases at 3 months vs. 1.6% of normal boys, <em>P</em> &lt; 0.05. Small scrotum: 43.1% of cases at 0 months only and 55.7% of cases at 3 months vs. 3.6% of controls, <em>P</em> &lt; 0.05 in both comparisons. Poor scrotal rugation: 5.7% of cases at 0 months only and 8.7% of cases at 3 months vs. 0.14% of controls, <em>P</em> &lt; 0.05 in both comparisons</td>
<td>Hjertkvist et al. (1989)</td>
<td>IR for hypospadias 2.7 (95% CI 1.4–4.7), <em>P</em> &lt; 0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thong et al. (1998)</td>
<td>16.7% of cryptorchid boys vs. 4.9% of other boys, <em>P</em> = 0.0016</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Preiksa et al. (2005)</td>
<td>21.7% of cases vs. 6.7% of controls, <em>P</em> &lt; 0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Season of birth</td>
<td>Berkowitz et al. (1995)</td>
<td>Peak of cryptorchidism (case at 1 year) in September–November and a smaller peak in March–May. Test for seasonal variation, <em>P</em> = 0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kaleva et al. (2005a)</td>
<td>February–April vs. May–July: OR for cryptorchidism 1.79 (95% CI 1.23–2.63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IR, intensity ratio; RR, relative risk; OR, odds ratio; SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; IUGR, intrauterine growth retardation; CI, confidence interval.
Complications during pregnancy, e.g. pre-eclampsia and maternal diabetes, have been associated with cryptorchidism in some studies (Hjertkvist et al., 1989; Preiksa et al., 2005; Virtanen et al., 2006). The mechanism of the association between cryptorchidism and gestational diabetes is unknown. However, in theory, gestational diabetes may be associated with an imbalance of fetal androgen and estrogen action (Sharpe, 2003; Virtanen et al., 2006), since it has been associated with reduced levels of maternal sex hormone binding globulin (SHBG) (Bartha et al., 2000; Kopp et al., 2001; Thadhani et al., 2003), and fetal hyperinsulinemia (Magee et al., 1993), which in turn might reduce fetal SHBG levels.

Environmental factors
It has been proposed that cryptorchidism, hypospadias, testicular cancer, and decreased semen quality may often represent testicular dysgenesis syndrome (TDS) of fetal origin (Skakkebaek et al., 2001). In animal studies exposure to chemicals with estrogenic or anti-androgenic effects have been shown to cause these TDS-linked disorders, except for germ cell cancer (Skakkebaek et al., 2001; Damgaard et al., 2002; Fisher, 2004). Similarly, in humans, for instance maternal exposure to diethylstilbestrol (DES) has been associated with cryptorchidism (Gill et al., 1979). Environmental factors having estrogenic or anti-androgenic effects have therefore been proposed to have a role in the increasing frequency of disorders of male reproductive health (Sharpe and Skakkebaek, 1993; Toppari et al., 1996). Some studies have provided support to the hypothesis of environmental factors being linked to cryptorchidism by suggesting an association between human cryptorchidism and exposure to environmental chemicals (Kristensen et al., 1997; Weidner et al., 1998; Hosie et al., 2000; Damgaard et al., 2006; Main et al., 2007). Furthermore, cryptorchidism has been associated with a specific haplotype of estrogen receptor alpha gene (Yoshida et al., 2005). It has been proposed that homozygosity for this haplotype would increase susceptibility to the effects of estrogenic environmental endocrine disrupters (Yoshida et al., 2005), like some of the pesticides. However, the final role of environmental factors in the etiology of cryptorchidism remains to be elucidated in further studies.

Pathogenesis of testicular ascent
As mentioned above, cryptorchidism may also appear as acquired abnormality after spontaneous testicular descent in infancy. Some of operated ascending testes have previously been described as retractor (Lamah et al., 2001) or they may be caused by entrapment of the testis into inguinal scar after previous operation (Eardley et al., 1994). Furthermore, ascensus testis has also been proposed to be caused by improper elongation of the spermatic cord during childhood due to a fibrous remnant of the processus vaginalis (Clarnette et al., 1997a) or by spasticity of the cremaster muscle, e.g. in the cerebral palsy patients (Smith et al., 1989).

Conclusions
Variable figures for the rate of cryptorchidism have been described. However, the diagnosis is highly dependent on the used criteria and the experience of the examiner. Therefore, prospective studies using similar criteria are needed to get comparable results on the rates of both congenital and acquired cryptorchidism. Such studies have suggested an increasing trend and geographical differences in the incidence of congenital cryptorchidism.

Several etiologies for cryptorchidism have been described. However, despite the tendency of familial aggregation of cryptorchidism, genetic abnormalities have been found only in a few patients. Environmental factors may have a role in the etiology of some cryptorchid cases. Further studies on gene-environment interactions may reveal common pathogenetic mechanisms of cryptorchidism.

Acknowledgements
This work was supported by the Academy of Finland, the European Commission (contract QLK4-CT-2002-00603), the Pediatric Research Foundation, the Sigrid Juselius Foundation, and the Turku University Hospital.

Funding
Funding to pay the Open Access publication charges for this article was provided by the Sigrid Juselius Foundation.

References

Epidemiology and pathogenesis of cryptorchidism
Virtanen and Toppari


Bogatcheva NV, Truong A, Feng S, Engel W, Adham IM, Agoulnik AI. GREAT/LGFR is the only receptor for insulin-like 3 peptide. **Mol Endocrinol** 2003;**17**:2639–2646.


Virtanen and Toppari


Submitted on January 31, 2007; resubmitted on June 13, 2007; accepted on August 6, 2007.