Pediatr Pol 2020; 95 (1): 37–43
DOI: https://doi.org/10.5114/polp.2020.94927
Submitted: 11.12.2019; Accepted: 13.02.2020; Published: 31.03.2020

PEDIATRIA Polska
PISMO POLSKIEGO TOWARZYSTWA PEDIATRYCZNEGO
Polish Journal of PAEDIATRICS
OFFICIAL JOURNAL OF POLISH SOCIETY OF PAEDIATRICS

REVIEW PAPER

Epidemiology, pathophysiology, and pathogenesis of cryptorchidism. Evaluation and treatment of undescended testicle

Dorota Toliczenko-Bernatowicz, Ewa Matuszczak, Marta Komarowska, Adam Hermanowicz, Wojciech Dębek

Department of Paediatric Surgery and Urology, Medical University of Bialystok, Bialystok, Poland

ABSTRACT

Cryptorchidism – the absence of one or both testes in the normal scrotal position – is the most common birth defect of the male genitalia. In full-term newborn boys its incidence is estimated at 2–5%. During the first three months of life, in half of these boys the testicles will descend spontaneously into the scrotum, but at the end of the first year of life 1% of boys will have cryptorchidism. Among boys born prematurely, about 30% of them have undescended testicles at birth, but also in such cases approximately 80% of undescended testes descend by the third month of life. The authors discuss the epidemiology, pathophysiology, aetiology, and treatment of undescended testicle in boys.

KEY WORDS:

cryptorchidism, undescended testicle, boys, epidemiology, pathophysiology, aetiology.

INTRODUCTION

Cryptorchidism – the absence of one or both testicles in the normal scrotal position is the most common birth defect of the male genitalia. In full-term newborn boys its incidence is estimated at 2–5% [1]. During the first three months of life, in half of these boys the testicles will descend spontaneously into the scrotum, but at the end of the first year of life 1% of boys will have cryptorchidism [2]. Among boys born prematurely, about 30% have undescended testicles at birth, but also in such cases approximately 80% of undescended testes descend by the third month of life [3]. Most cases of cryptorchidism are isolated without other innate malformations; few are constituents of genetic or endocrine syndromes [1]. Over the years some testicles become retractile. This problem usually resolves spontaneously before or during puberty, but in rare cases the retractile testicle remains in the groin and is no longer movable. Recurrent cryptorchidism is defined as cryptorchid testes that were undescended at birth, descended spontaneously, and are subsequently defined as extrascrotal [4]. Secondary cryptorchidism and testicular retraction have been used to describe testes that are suprascrotal after inguinal hernia repair and as a complication of orchidopexy, respectively [4]. Testicular malposition after hernia repair could be caused by either postoperative scarring or primary maldescent [4].

There is conflicting evidence as to the changes of occurrence of cryptorchidism. Over the last decades some authors have reported an increasing incidence of this pathology, while [2, 5, 6] others report stable or decreasing numbers of boys with undescended testicles [7–9].

ADDRESS FOR CORRESPONDENCE:

Ewa Matuszczak, Department of Paediatric Surgery and Urology, Medical University of Bialystok, 17 Waszyngtona St., 15-274 Białystok, Poland, ORCID: 0000-0003-2425-9589, e-mail: ewamat@tlen.pl

TESTICULAR DESCENT

Testicular descent is a two-phase process that starts at eighth week of gestation and should be completed by the third trimester of pregnancy. During the first trans-abdominal phase, the testicle is guided to the lowest part of abdominal cavity by hypertrophy and growth of the gubernaculum. This phase is regulated by hormonal factors produced by the foetal testis, such as insulin-like 3 protein (*INSL3*) and androgens [4].

The second inguinoscrotal phase of the testicular descent depends on androgens that induce a cellular proliferation in the gubernaculum [4].

EVALUATION

The undescended testicle may be found along the "path of descent", such as: the retroperitoneal part of the abdomen, the internal inguinal ring, and inside the inguinal canal [10]. In rare cases an undescended testicle, takes a non-standard path and ends up in front of the thigh, femoral canal, skin of the penis, or behind the scrotum. These testis are referred to as ectopic [10].

Over 70% of undescended testicles are palpable during physical examination and do not need imaging evaluation [10]. In the remaining cases of non-palpable testes, the diagnostics should confirm the absence or presence of the testes and identify their location. The most commonly used imaging study evaluating undescended testicles is ultrasound, with the sensitivity and specificity to localise nonpalpable testes at 45% and 78%, respectively [11]. Computed tomography (CT) scanning should not be used routinely because of the radiation exposure and high costs [11]. Routine karyotype investigation of all patients with cryptorchidism does not seem necessary. In cases with ambiguous genitalia, a karyotype can confirm or exclude dysgenetic primary hypogonadism [1].

In 2014 the American Urologic Association (AUA) presented current guidelines for the evaluation and treatment of cryptorchidism [12].

PATHOPHYSIOLOGY

Descent of the testes into the lower temperature environment of the scrotum is crucial for future successful reproduction. Cryptorchidism is associated with decreased fertility, increased incidence of testicular germ cell tumours, and testicular torsion, and it can be a source of psychological problems [1–3].

Among men who develop testicular cancer, 5–9% have persistent cryptorchidism [2, 13–15]. Men with cryptorchidism operated on after puberty were 2–6-fold more likely to have had testicular cancer compared to men who received corrective treatment before the age of 12 years [16, 17]. Contrary to that observation, according to Khatwa *et al.*, the risk of cancer remains the same independently of the age of orchidopexy [18].

Men born with cryptorchidism are twice as likely to have reduced fertility when compared to those born with their testes in the scrotum, even after orchidopexy [2, 18, 19]. The reduction of fertility in men operated on because of bilateral cryptorchidism is estimated at 38% (infertility and azoospermia) [20]. According to latest research, fertility rates of patients operated for unilateral cryptorchidism are comparable to those seen in normal males [20]. Degeneration of spermatogenic tissue and reduced spermatogonia counts were observed after just the second year of life in patients born with cryptorchidism [20]. Also, the results of a survey by Matuszczak *et al.* suggest that the rise of the levels of MMP-1 and MMP-2 in the plasma of boys with cryptorchidism may reflect the level of apoptosis of the germ cells in undescended testicles, in response to heat stress [21, 22]. Those results prompt the recommendation for early surgery.

CLASSIFICATION

Cryptorchidism may be unilateral or bilateral, with a predominance of the right side (70–80%) [1–3, 5–7]. The undescended testis may be found anywhere on its path from the abdomen to the scrotum, starting from the high retroperitoneal position, through the inguinal canal, external ring, prescrotal to upper scrotal, or in an ectopic position (usually in the superficial inguinal pouch or perineal). There are also cases of hypoplastic, dysgenetic, or missing testicles. Around 80% of undescended testicles are reachable during physical examination within the inguinal canal or high scrotal area, whereas 20% of undescended testicles are not palpated [1–3, 5–7].

Nowadays, diagnostic laparoscopy is the gold standard that can confirm the absence of testis in patients with nonpalpable unilateral and many bilateral cryptorchidism [8–10].

The most commonly used radiological test evaluating undescended testicles is ultrasound, which has the sensitivity and specificity to localise nonpalpable testes at 45% and 78%, respectively [8–10]. CT scanning should not be used routinely because of the radiation exposure and high costs [8–10].

MRI stands out with great sensitivity and specificity, but its use is determined by high costs, low availability, and the need for anaesthesia [8–10].

TREATMENT

To reduce risks described above, undescended testes should be brought into the scrotum operatively by an orchidopexy, which is recommended between the ages of 6 and 18 months [2, 23, 24]. For boys born prematurely the timing of the operation should be determined using corrected age [20]. Ascending testes diagnosed in child-

hood should immediately be treated surgically [2, 25, 26]. The American Urological Association does not recommend hormonal therapy to induce testicular descent because evidence shows low response rates and lack of evidence for long-term efficacy [12]. In boys with undescended testes that are palpable, scrotal or inguinal orchidopexy should be performed. In boys with nonpalpable testes, examination under anaesthesia followed by surgical exploration and, if indicated, abdominal orchidopexy should be performed. During surgical exploration the testicular vessels should be identified. In the case of very short testicular vessels and vas deferens, dysmorphic or very hypoplastic testis, or postpubertal age and a normal contralateral testis, an orchiectomy should be performed. Parents should be counselled regarding potential long-term risks, infertility, and cancer [12].

AETIOLOGY

The aetiology of cryptorchidism is complex. Correct testicular descent depends on the hypothalamic-pituitary-gonadal axis. According to the literature, a combination of genetic, maternal, and environmental factors affect testicular development and descent.

Possible risk factors for cryptorchidism given in the literature include:

- prematurity,
- low birth weight,
- small for gestational age,
- maternal factors: age, obesity, diabetes, maternal alcohol consumption, maternal cigarette smoking,
- in vitro fertilisation,
- low parity,
- twinning,
- sex hormone imbalance,
- endocrine disrupting chemicals,
- family history, genetic alterations, and congenital genetic syndromes – Klinefelter syndrome, Down syndrome, Prader-Willi syndrome, Noonan syndrome.

Many authors agree that the incidence of cryptorchidism correlates positively with prematurity, low birth weight, and small size for gestational age [2, 27–30].

MATERNAL FACTORS

A positive correlation between older (> 30 years) and younger (< 20 years) age of mothers and cryptorchidism in sons was observed, but contrary to this observation Jones *et al.* and McGlynn *et al.* found that young age of mothers may be protective against undescended testicles in sons [2, 29, 31, 32].

According to a study by Kjersgaard *et al.*, mothers with overweight and obesity in pregnancy were associated with higher occurrence of cryptorchidism in boys, but a meta-analysis performed by Zhang *et al.* did not prove this observation [33, 34]. Some studies found an association between cryptorchidism and maternal diabetes [35]. The same meta-analysis by Zhang mentioned before found moderate heterogeneity in studies of the effect of maternal diabetes and cryptorchidism [34].

Damgaard *et al.* observed that the sons of mothers who regularly consumed at least five drinks pre week during pregnancy had ten times greater odds of developing cryptorchidism compared to those not exposed [36]. However, a recent meta-analysis reported no such association [34].

Large meta-analyses reported higher incidence of cryptorchidism among sons of mothers who smoked tobacco during pregnancy. Some authors even observed correlation between the risk of cryptorchidism and the number of cigarettes smoked per day [34, 37, 38]. It is not debatable that the chemicals in tobacco smoke cause genetic mutation and vasoconstriction and disrupt the endocrine system. It is postulated that paternal smoking could also be associated with cryptorchidism, possibly because of passive inhalation of smoke by the mother and/or damage to the sperm cells [39].

A strong correlation between maternal use of pain killers and undescended testicles in their sons was observed by many authors [40, 41]. Up to 24% of cryptorchidism cases could be attributed to the use of pain killers by mother during pregnancy [40]. Still there are conflicting results with little or no influence of painkillers taken by mothers during pregnancy and undescended testicles in their sons [42, 43].

Studies that have investigated anti-nausea medications, anti-retrovirals, antibiotics, anti-depressives, laxatives, cough medications, anti-anaemics, hypnotics, and anti-epileptics have found little or no association with their use by mothers and cryptorchidism in sons [2, 44–48].

The recreational use of psychoactive drugs by mothers during pregnancy was also investigated, but the association with the risk of cryptorchidism was not found [2, 49].

Subfertility is a known risk factor for congenital malformation in offspring [2]. In the cohort of cryptorchid boys there is a higher representation of mothers who have had intrauterine insemination [1]. Berkowitz *et al.* found that clomiphene – an oral medication taken during intrauterine insemination – was associated with two-times higher risk of cryptorchidism, but statistical significance was not found [49]. Also diethylstilboestrol, a hormonal contraceptive, was found to be associated with increased risk of undescended testicles [1]. Mothers without problems with fertility had no higher risk of cryptorchidism in their sons [1].

PARITY

Surveys about parity and the risk or cryptorchidism give ambiguous results [2, 30, 50].

TWINNING

According to Schnack *et al.*, the risk of cryptorchidism in male twins was 2.6-fold higher than expected and may be related to the shared intrauterine environment [51].

HORMONES

Normal testicular development and descent is dependent on sex hormone balance [1].

OESTROGEN

According to Sharpe *et al.*, foetal exposure to high levels of endogenous oestrogen may be associated with maldescent of the testes. Contrary to that observation, some other authors connect cryptorchidism with lower oestrogen levels in mothers' serum [52, 53].

TESTOSTERONE

Testosterone is crucial to testicular descent. Still in the literature there is little or no evidence of the association of low maternal serum levels of testosterone and cryptorchidism [2, 53]. Also, lower testosterone levels in cord blood were not associated with undescended testicles [2, 54, 55].

HUMAN CHORIONIC GONADOTROPIN

Placentas of boys born with undescended testicles had lower total hCG levels than in control group, which could reflect lower testosterone production, probably leading to problems with testicular descent [56].

Also, mothers with vaginal bleeding during pregnancy had higher risk of cryptorchidism in their sons [1]. According to Damgaard *et al.*, vaginal bleeding may be an indicator of placenta malfunction, which in turn may affect hCG production [1].

INSULIN-LIKE FACTOR 3 (INSL3)

According to some authors, cord blood levels of INSL3 are lower in children born with cryptorchidism [54, 55]. It is postulated that exposure to exogenous endocrine-disrupting chemicals probably decrease concentrations of INSL3 [55].

AMH

AMH is secreted by immature Sertoli cells during the eighth week of gestation and is responsible for the regression of Müllerian ducts in the male foetus. Mutations in the AMH receptor cause persistent Müllerian duct syndrome in males and disrupt the descent of the testis [57].

Matuszczak *et al.* found that "AMH was lower in boys with unilateral cryptorchidism (also found to have smaller testis) when compared with the control group" [57]. In another study, which investigated serum levels of AMH one year after orchidopexy, the authors observed an upward trend in AMH concentration, but it was statistically insignificant [58].

Contrary to the previous findings, Komarowska *et al.* showed that the levels of AMH, INSL3, and inhibin B were not different in the group of boys with undescended testicles and those in the control group [59].

ENVIRONMENTAL EXPOSURE

Many studies have shown that exposure to endocrine-disrupting chemicals, such as bisphenol A, dibutyltin, dioxin, heptachlor epoxide, hexachlorobenzene, polychlorinated biphenyls, and polybrominated diphenyl ethers, interrupt the testicular descent [2, 60–63]. Some other authors did not find such associations [55, 64]. It is postulated that not individual chemicals but the mixture has an effect on testicular descent [65].

Jorgensen *et al.* (C138) observed that "sons of mothers who farmed during pregnancy were nearly a third more likely to develop cryptorchidism" [66]. Morales-Surez-Varela *et al.* observed the same effect of paternal exposure to heavy metals [67]. Bornman *et al.* observed that "sons born to women who lived in areas sprayed with dichlorodiphenyltrichloroethane (DDT) were more than twice as likely to be born with undescended testicles" [68].

Czeizel *et al.* found that the proximity of an acrylonitrile factory increased the risk of cryptorchidism [69]. Kim *et al.* found the same association between cryptorchidism and living near a petrochemical plant [70].

As for diet, consumption of smoked food during pregnancy seemed to have influence on testicular descent in sons [71]. The evidence for the influence of the caffeine use are conflicting, some authors observed no association, others found positive correlation with cryptorchidism [2, 49, 72].

GENETIC CAUSES

A higher than average number of boys with undescended testes have a positive family history of cryptorchidism when compared to healthy controls. Some authors report that 7% of siblings of boys with undescended testes have cryptorchidism [3]. In Denmark "the concordance rates of cryptorchidism were 3.2% in boys with no familial relationship, 3.4% in paternal half-brothers, 6.0% in maternal half-brothers, 8.8% in full brothers, and around 25% dizygotic and monozygotic twins" [73]. These findings stress the importance of the shared intrauterine environment of the twins [73]. There is also evidence of varying risk of undescended testicles depending on the ethnicity, e.g. In the United

States White males have higher incidence of cryptorchidism than Black males [29].

The frequency of genetic alterations in boys with cryptorchidism is reported to be low [74]. The most common genetic findings in boys with undescended testicles were cases of Klinefelter syndrome and mutations in the *INSL3* receptor gene [74]. An analysis of the literature shows a 2% prevalence of mutation in the *INSL3* gene in cryptorchid boys and mutation in the *RXFP2* gene in 4%; these mutations may be more frequent in bilateral cryptorchidism [4, 75–77]. Some authors conclude that the disruption of *INSL3*, *Rxfp2*, or *AR* genes or the gubernaculum mesenchyme alters the testicular descent [4, 75–77]. Also, all genetic disorders responsible for insufficient androgen production can alter descent of the testis.

The *AR* gene provides instructions for making a protein called an androgen receptor. In an animal model of *AR* knockout in the gubernaculum, "the males exhibited a suprascrotal cryptorchidism despite normal plasma levels of testosterone" [78]. However, mutations of the *AR* gene are rarely associated with isolated cryptorchidism [79]. Ferlin *et al.* reported that "the prevalence of *AR* mutations was 1.63% in adult men with a history of undescended testis" [74].

According to animal studies The *HOXA10* transcriptional factor is implicated in the early embryonic development of the reproductive system, and male knockout mice present bilateral cryptorchidism [4].

In animal studies inactivation of *Wilms Tumour 1* (*WT1*) – a transcription factor expressed in the early embryonic development and differentiation of the renal and gonadal system *WT1* in the gubernaculum – caused abnormal differentiation of the gubernaculum, and unilateral cryptorchidism in 40% of animals [80].

The *AXIN1* gene encodes a cytoplasmic protein that contains a regulation of G-protein signalling (*RGS*) domain and a dishevelled and Axin (*DIX*) domain. The *AXIN1* gene is thought to have an impact on migration of the testis because of different repartition of *AXIN1* SNPs between cryptorchid and normal boys [81].

According to Hadziselimovic *et al.*, "most cases of isolated cryptorchidism have either a disruption of FGFs, FGFr1, and FGFR3 and/or a disturbance of the genes involved in the regulation of the hypothalamo-pituitary-gonadal axis" [82].

Cryptorchidism is also associated with several syndromes including abnormal muscle development, e.g. prune-belly, which consists of: cryptorchidism, abdominal wall defects, and genitourinary defects [4]. Also, children with Down syndrome have an increased risk of cryptorchidism [4]. In Noonan syndrome, the occurrence of primary hypogonadism depends on the existence of cryptorchidism, and Prader-Willi syndrome may present with either primary or combined forms of hypogonadism [4].

CONCLUSIONS

Undescended testicle is the most common congenital genital malformation in boys. The aetiology of cryptorchidism is complex with a high probability of genetic predispositions and environmental exposures at the same time playing a role in increasing its risk. Large cohort studies are needed to verify this.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Damgaard IN, Jensen TK; Nordic Cryptorchidism Study Group, et al. Risk factors for congenital cryptorchidism in a prospective birth cohort study. PLoS One 2008; 3: e3051.
2. Gurney JK, McGlynn KA, Stanley J, et al. Risk factors for cryptorchidism. Nat Rev Urol 2017; 14: 534-548.
3. Braga LH, Lorenzo AJ, Romao RLP. Canadian Urological Association-Pediatric Urologists of Canada (CUA-PUC) guideline for the diagnosis, management, and follow up of cryptorchidism. Can Urol Assoc J 2017; 11: 251-260.
4. Kalfa N, Gaspari L, Ollivier M, et al. Molecular genetics of hypospadias and cryptorchidism recent developments. Clin Genet 2019; 95: 122-131.
5. Boisen KA, Kaleva M, Main KM, et al. Difference in prevalence of congenital cryptorchidism in infants between two Nordic countries. Lancet 2004; 363: 1264-1269.
6. Toppari J, Kaleva M, Virtanen HE. Trends in the incidence of cryptorchidism and hypospadias, and methodological limitations of registry-based data. Hum Reprod Update 2001; 7: 282-286.
7. Abdullah NA, Pearce MS, Parker L, et al. Birth prevalence of cryptorchidism and hypospadias in northern England, 1993–2000. Arch Dis Child 2007; 92: 576-579.
8. Bonney T, Southwell B, Donnath S, et al. Orchidopexy trends in the paediatric population of Victoria, 1999–2006. J Pediatr Surg 2009; 44: 427-431.
9. Richiardi L, Vizzini L, Nordenskjold A, et al. Rates of orchiopexies in Sweden: 1977–1991. Int J Androl 2009; 32: 473-478.
10. Berger C, Haid B, Becker T, et al. Nonpalpable testes: Ultrasound and contralateral testicular hypertrophy predict the surgical access, avoiding unnecessary laparoscopy. J Pediatr Urol 2018; 14: 1631-1637.
11. Cheng L, Albers P, Berney DM, et al. Testicular cancer. Nat Rev Dis Primers 2018; 4: 29.
12. Smith SC, Nguyen HT. Barriers to implementation of guidelines for the diagnosis and management of undescended testis. Version 1. F1000Res. 2019; 8: F1000 Faculty Rev-326. Published online 2019 Mar 25. doi: 10.12688/f1000research.15532.1
13. Lip SZL, Murchison LED, Cullis PS, et al. A meta-analysis of the risk of boys with isolated cryptorchidism developing testicular cancer in later life. Arch Dis Child 2013; 98: 20-26.
14. Kanto S, Hiramatsu M, Suzuki K, et al. Risk factors in past histories and familial episodes related to development of testicular germ cell tumor. Int J Urol 2004; 11: 640-646.
15. Prener A, Engholm G, Jensen OM. Genital anomalies and risk for testicular cancer in Danish men. Epidemiol 1996; 7: 14-19.
16. Pettersson A, Richiardi L, Nordenskjold A, et al. Age at Surgery for Undescended Testis and Risk of Testicular Cancer. N Engl J Med 2007; 356: 1835-1841.

17. Wood HM, Elder JS. Cryptorchidism and Testicular Cancer: Separating Fact From Fiction. J Urol 2009; 181: 452-461.
18. Khatwa UA, Menon PS. Management of undescended testis. Indian J Pediatr 2000; 67: 449-454.
19. Wei Y, Wang Y, Tang X, et al. Efficacy and safety of human chorionic gonadotropin for treatment of cryptorchidism: A meta-analysis of randomised controlled trials. J Paediatr Child Health 2018; 54: 900-906.
20. Fawzy F, Hussein A, Eid MM, et al. Cryptorchidism and Fertility. Clin Med Insights Reprod Health 2015; 9: 39-43.
21. Matuszczak E, Komarowska MD, Sankiewicz A, et al. Plasma concentration of MMP-1 and MMP-2 in boys with cryptorchidism and its lack of correlation with INSL3 and inhibin B. Scand J Clin Lab Invest 2019; 11: 1-7.
22. Tokarzewicz A, Romanowicz L, Sveklo I, et al. SPRI biosensors for quantitative determination of matrix metalloproteinase-2. Anal Methods 2017; 9: 2407-2414.
23. Kollin C, Karpe B, Hesser U, et al. Surgical Treatment of Unilaterally Undescended Testes: Testicular Growth After Randomization to Orchiopexy at Age 9 Months or 3 Years. J Urol 2007; 178: 1589-1593.
24. Kolon TF, Herndon CD, Baker LA, et al. Evaluation and treatment of Cryptorchidism: AUA guideline. J Urol 2014; 192: 337-345.
25. Jensen MS, Olsen LH, Thulstrup AM, et al. Age at cryptorchidism diagnosis and orchiopexy in Denmark: a population based study of 508,964 boys born from 1995–2009. J Urol 2011; 186: 1595-1600.
26. Ritzén EM. Undescended testes: a consensus on management. Eur J Endocrinol 2008; 159: S87-S90.
27. Jensen MS, Wilcox AJ, Olsen J, et al. Cryptorchidism and hypospadias in a cohort of 934,538 Danish boys: The role of birth weight, gestational age, body dimensions, and fetal growth. Am J Epidemiol 2012; 175: 917-925.
28. Zakaria M, Azab S, El Baz M, et al. Cryptorchidism in Egyptian neonates. J Pediatr Urol 2013; 9: 815-819.
29. McGlynn KA, Graubard BI, Klebanoff MA, Longnecker MP. Risk factors for cryptorchism among populations at differing risks of testicular cancer. Int J Epidemiol 2006; 35: 787-795.
30. Biggs ML, Baer A, Critchlow CW. Maternal, delivery, and perinatal characteristics associated with cryptorchidism: A population-based case-control study among births in Washington State. Epidemiol 2002; 13: 197-204.
31. Jones ME, Swerdlow AJ, Griffith M, Goldacre MJ. Prenatal risk factors for cryptorchidism: A record linkage study. Paediatr Perinatal Epidemiol 1998; 12: 383-396.
32. Mavrogenis S, Urbán R, Czeizel AE. Characteristics of boys with the so-called true undescended testis diagnosed at the third postnatal month - A population-based case-control study. J Mat Fetal Neonatal Med 2015; 28: 1152-1157.
33. Kjersgaard C, Arendt LH, Ernst A, et al. Lifestyle in pregnancy and cryptorchidism in sons: a study within two large Danish birth cohorts. Clin Epidemiol 2018; 10: 311-322.
34. Zhang L, Wang XH, Zheng XM, et al. Maternal gestational smoking, diabetes, alcohol drinking, pre-pregnancy obesity and the risk of cryptorchidism: a systematic review and meta-analysis of observational studies. PLoS One 2015; 10: e0119006.
35. Virtanen HE, Tapanainen AE, Kaleva MM, et al. Mild gestational diabetes as a risk factor for congenital cryptorchidism. J Clin Endocrinol Metab 2006; 91: 4862-4865.
36. Damgaard IN, Jensen TK, the Nordic Cryptorchidism Study Group, et al. Cryptorchidism and maternal alcohol consumption during pregnancy. Env Health Perspectives 2007; 115: 272-277.
37. Hackshaw A, Rodeck C, Boniface S. Maternal smoking in pregnancy and birth defects: A systematic review based on 173 687 malformed cases and 11.7 million controls. Hum Reprod Update 2011; 17: 589-604.
38. Jensen MS, Toft G, Thulstrup AM, et al. Cryptorchidism according to maternal gestational smoking. Epidemiology 2007; 18: 220-225.
39. Kurahashi N, Kasai S, Shibata T, et al. Parental and neonatal risk factors for cryptorchidism. Med Sci Monitor 2005; 11: 274-283.
40. Snijder CA, Kortenkamp A, Steegers EA, et al. Intrauterine exposure to mild analgesics during pregnancy and the occurrence of cryptorchidism and hypospadia in the offspring: The Generation R Study. Hum Reprod 2012; 27: 1191-1201.
41. Jensen MS, Rebordosa C, Thulstrup AM, et al. Maternal use of acetaminophen, ibuprofen, and acetylsalicylic acid during pregnancy and risk of cryptorchidism. Epidemiol 2010; 21: 779-785.
42. Philippat C, Giorgis-Allemand L, Chevrier C, et al. Analgesics During Pregnancy and Undescended Testis. Epidemiology 2011; 22: 747-749.
43. Rebordosa C, Kogevinas M, Horváth-Puhó E, et al. Acetaminophen use during pregnancy: effects on risk for congenital abnormalities. Am J Obstetr Gynecol 2008; 198: 171-178.
44. Townsend CL, Willey BA, Cortina-Borja M, et al. Antiretroviral therapy and congenital abnormalities in infants born to HIV-infected women in the UK and Ireland, 1990–2007. AIDS 2009; 23: 519-524.
45. Ács N, Bánhidy F, Puhó EH, Czeizel AE. No association between vulvovaginitis-bacterial vaginosis, related drug treatments of pregnant women, and congenital abnormalities in their offspring – a population-based case-control study. Central Eur J Med 2008; 3: 332-340.
46. Louik C, Lin AE, Werler MM, et al. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. New Engl J Med 2007; 356: 2675-2683.
47. Ács N, Bánhidy F, Puhó EH, Czeizel AE. Senna treatment in pregnant women and congenital abnormalities in their offspring – a population-based case-control study. Reprod Toxicol 2009; 28: 100-104.
48. Kjær D, Horvath-Puhó E, Christensen J, et al. Use of phenytoin, phenobarbital, or diazepam during pregnancy and risk of congenital abnormalities: A case-time-control study. Pharmacoepidemiol Drug Saf 2007; 16: 181-188.
49. Berkowitz GS, Lapinski RH. Risk factors for cryptorchidism: A nested case-control study. Paediatr Perinatal Epidemiol 1996; 10: 39-51.
50. Weidner IS, Møller H, Jensen TK, SkakkebÆk NE. Risk factors for cryptorchidism and hypospadias. J Urol 1999; 161: 1606-1609.
51. Schnack TH, Zdravkovic S, Myrup C, et al. Familial aggregation of cryptorchidism--a nationwide cohort study. Am J Epidemiol 2008; 167: 1453-1457.
52. Sharpe RM, Skakkebaek NE. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? Lancet 1993; 341: 1392-1396.
53. McGlynn KA, Graubard BI, Nam JM, et al. Maternal hormone levels and risk of cryptorchism among populations at high and low risk of testicular germ cell tumors. Cancer Epidemiol Biomarkers Prev 2005; 14: 1732-1737.
54. Fénichel P, Lahlou N, Coquillard P, et al. Cord blood Insulin-like peptide 3 (INSL3) but not testosterone is reduced in idiopathic cryptorchidism. Clin Endocrinol 2015; 82: 242-247.
55. Chevalier N, Brucker-Davis F, Lahlou N, et al. A negative correlation between insulin-like peptide 3 and bisphenol A in human cord blood suggests an effect of endocrine disruptors on testicular descent during fetal development. Hum Reprod 2015; 30: 447-453.
56. Chedane C, Puissant H, Weil D, et al. Association between altered placental human chorionic gonadotrophin (hCG) production and the occurrence of cryptorchidism: A retrospective study. BMC Pediatr 2014; 14: 191.

57. Matuszczak E, Hermanowicz A, Debek W, et al. Serum AMH concentration as a marker evaluating gonadal function in boys operated on for unilateral cryptorchidism between 1st and 4th year of life. Endocrine 2012; 41: 334-337.
58. Komarowska MD, Hermanowicz A, Matuszczak E, et al. Anti-Müllerian hormone levels in serum 1 year after unilateral orchiopexy. J Pediatr Endocrinol Metab 2012; 25: 1073-1076.
59. Komarowska MD, Milewski R, Charkiewicz R, et al. Are anti-Müllerian hormone and its receptor polymorphism associated with the hormonal condition of undescended testes? Adv Med Sci 2016; 61: 288-292.
60. Komarowska MD, Hermanowicz A, Czyzewska U, et al. Serum Bisphenol A Level in Boys with Cryptorchidism: A Step to Male Infertility? Int J Endocrinol 2015; 2015: 973154.
61. Shono T, Shima Y, Kondo T, Suita S. In utero exposure to mono-N-butyl phthalate impairs insulin-like factor 3 gene expression and the transabdominal phase of testicular descent in fetal rats. J Pediatr Surg 2005; 40: 1861-1864.
62. Gray LE, Ostby J, Furr J, et al. Effects of environmental antiandrogens on reproductive development in experimental animals. Hum Reprod Update 2001; 7: 248-264.
63. Krysiak-Baltyn K, Toppari J, Skakkebaek NE, et al. Association between chemical pattern in breast milk and congenital cryptorchidism: Modelling of complex human exposures. Int J Androl 2012; 35: 294-302.
64. Toft G, Jönsson BAG, Bonde JP, et al.: Perfluorooctane sulfonate concentrations in amniotic fluid, biomarkers of fetal leydig cell function, and cryptorchidism and hypospadias in Danish boys (1980–1996). Environ Health Perspect 2016; 124: 151-156.
65. Damgaard IN, Skakkebæk NE, Toppari J, et al. Persistent pesticides in human breast milk and cryptorchidism. Environ Health Perspect 2006; 114: 1133-1138.
66. Jørgensen KT, Jensen MS, Toft GV, et al. Risk of cryptorchidism among sons of horticultural workers and farmers in Denmark. Scand J Work Environ Health 2014; 40: 323-330.
67. Morales-Surez-Varela MM, Toft GV, Jensen MS, et al. Parental occupational exposure to endocrine disrupting chemicals and male genital malformations: A study in the Danish national birth cohort study. Environ Health 2011; 10: 3.
68. Bornman R, de Jager C, Worku Z, et al. DDT and urogenital malformations in newborn boys in a malarial area. BJU Int 2010; 106: 405-411.
69. Czeizel AE, Hegedüs S, Tímár L. Congenital abnormalities and indicators of germinal mutations in the vicinity of an acrylonitrile producing factory. Mutat Res 1999; 427: 105-123.
70. Kim SC, Kwon SK, Hong YP. Trends in the incidence of cryptorchidism and hypospadias of registry-based data in Korea: A comparison between industrialized areas of petrochemical estates and a non-industrialized area. Asian J Androl 2011; 13: 715-718.
71. Giordano F, Carbone P, Nori F, et al. Maternal diet and the risk of hypospadias and cryptorchidism in the offspring. Paediatr Perinatal Epidemiol 2008; 22: 249-260.
72. Mongraw-Chaffin ML, Cohn BA, Cohen RD, Christianson RE. Maternal smoking, alcohol consumption, and caffeine consumption during pregnancy in relation to a son's risk of persistent cryptorchidism: A prospective study in the child health and development studies cohort, 1959–1967. Am J Epidemiol 2008; 167: 257-261.
73. Jensen MS, Toft G, Thulstrup AM, et al. Cryptorchidism concordance in monozygotic and dizygotic twin brothers, full brothers, and half-brothers. Fertil Steril 2010; 93: 124-129.
74. Ferlin A, Zuccarello D, Zuccarello B, et al. Genetic alterations associated with cryptorchidism. JAMA 2008; 300: 2271-2276.
75. El Houate B, Rouba H, Sibai H, et al. Novel mutations involving the INSL3 gene associated with cryptorchidism. J Urol 2007; 177: 1947-1951.
76. Mamoulakis C, Georgiou I, Dimitriadis F, et al. Genetic analysis of the human insulin-like 3 gene: absence of mutations in a Greek paediatric cohort with testicular maldescent. Andrologia 2014; 46: 986-996.
77. Ferlin A, Zuccarello D, Garolla A, et al. Mutations in INSL3 and RXFP2 genes in cryptorchid boys. Ann N Y Acad Sci 2009; 1160: 213-214.
78. Kaftanovskaya EM, Huang Z, Barbara AM, et al. Cryptorchidism in mice with an androgen receptor ablation in gubernaculum testis. Mol Endocrinol 2012; 26: 598-607.
79. Wiener JS, Marcelli M, Gonzales ET, et al. Androgen receptor gene alterations are not associated with isolated cryptorchidism. J Urol 1998; 160: 863-865.
80. Kaftanovskaya EM, Neukirchner G, Huff V, Agoulnik AI. Left-sided cryptorchidism in mice with Wilms' tumour 1 gene deletion in gubernaculum testis. J Pathol 2013; 230: 39-47.
81. Zhou B, Tang T, Chen P, et al. The variations in the AXIN1 gene and susceptibility to cryptorchidism. J Pediatr Urol 2015; 11: 1321-1325.
82. Hadziselimovic F. Involvement of fibroblast growth factors and their receptors in epididymo-testicular descent and maldescent. Mol Syndromol 2016; 6: 261-267.