General discussion and perspectives
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The aim of this thesis was to obtain prevalence rates of testicular microlithiasis in symptomatic and asymptomatic boys in order to increase our understanding of the clinical relevance of testicular microlithiasis. In addition, this thesis aimed to assess the testicular volume of retractile testes and to assess testicular growth in boys with acquired undescended testis managed with a conservative attitude. The studies were performed at the Paediatric and Surgery departments of the Medical Centre Alkmaar, in close collaboration with the Youth Health Institution of the GGD Hollands Noorden, the Dutch Down Syndrome Association, the VU University Medical Centre and the Spaarne Hospital, whose databases were used for the recruitment of the participants.

For nearly two decades our department has studied and followed boys with non-scrotal testis. Earlier studies found that spontaneous descent occurred in three out of every four boys with acquired undescended testis. Furthermore, to assess testicular growth after spontaneous descent or pubertal orchidopexy, we analysed the testicular volume by Prader orchidometer and compared our findings with reference values. In the measurement of testicular volume, ultrasound offers the potential for greater accuracy than Prader orchidometer; however, reference data for ultrasonographically measured testicular volumes were unfortunately not available. Therefore, we analysed the testicular volumes of 936 healthy boys to obtain normative values. In addition, we obtained prevalence rates of testicular microlithiasis in different groups of boys, since testicular microlithiasis may be related to the development of testicular malignancies. The rates were obtained for asymptomatic boys and boys referred for scrotal pathologies. Furthermore, boys with undescended testis or Down syndrome, which gives a higher risk of testicular malignancies, were ultrasonographically scanned for testicular microlithiasis. By obtaining the prevalence rates in these different groups of boys, we wanted to clarify the association between testicular microlithiasis and testicular tumours. Furthermore, we reviewed the literature on testicular microlithiasis in boys and gave a suggestion for the management of boys with testicular microlithiasis.

The following questions regarding testicular microlithiasis and undescended testis were stated in this thesis:
1. What is the clinical relevance of testicular microlithiasis in boys, according to the literature?
2. What are the prevalence rates of testicular microlithiasis in healthy boys and in boys referred for scrotal pathologies?
3. Is the prevalence rate of testicular microlithiasis higher in boys with undescended testis and/or Down syndrome than in healthy boys?
4. What are the normative values for testicular volume in boys from birth to adolescence?
5. Are the volumes of retractile testes comparable to those of fully descended testes?
6. What are the consequences on the long-term testicular growth of acquired undescended testis after spontaneous descent or after pubertal orchidopexy?
7. Is the acquired undescended testis a separate condition or is it actually congenital?

1. Clinical relevance of testicular microlithiasis

We reviewed the paediatric literature on testicular microlithiasis and found that the prevalence rate of testicular microlithiasis is 4.2% in asymptomatic boys and between 1.1% and 2.8% in symptomatic referrals. A number of benign conditions are associated with testicular microlithiasis, but it is occasionally reported that the diagnosis of testicular microlithiasis is followed by the development of a testicular tumour. The management of boys with testicular microlithiasis varies widely. Most authors advise regular self-examination and some perform testicular ultrasound and/or screen for tumour markers.

For the follow-up of boys with testicular microlithiasis, we advise regular self-examination from the age of 15 years. However, if there is testicular pain or testicular enlargement, or the boy has Down syndrome, regular follow-up by ultrasound is additionally recommended (Chapter 1).

2. Prevalence of testicular microlithiasis in healthy boys and in boys referred for scrotal pathologies

We found a prevalence rate of testicular microlithiasis of 4.2% in asymptomatic boys and of 5.8% in boys referred for scrotal pathologies. In both groups, the prevalence of testicular microlithiasis increases with age. The rates in asymptomatic and symptomatic boys as found in both series compared to the much lower incidence of testicular cancer in a normal population may disprove an epidemiological association between testicular microlithiasis with testicular malignancies (Chapters 2.2 and 2.3).

3. The prevalence rate of testicular microlithiasis in boys with undescended testis or Down syndrome

The hypothesis that the prevalence rate of testicular microlithiasis may be higher in boys with undescended testis or Down syndrome than in healthy boys seems realistic since both conditions give an increased risk of developing testicular malignancies. In boys with undescended testis, we found an overall prevalence of testicular microlithiasis of 2.8%; no difference was found between congenital (2.8%) and acquired undescended testis (2.8%). The overall rate is comparable with the prevalence of testicular microlithiasis in asymptomatic patients. Based on these data, we found no increased risk for the development of testicular cancer in patients with undescended testis and testicular microlithiasis. However, testicular microlithiasis may be related to the degeneration of testis parenchyma.
In another study, we found that the prevalence of testicular microlithiasis in boys with Down syndrome was 22.8%. Since testicular microlithiasis is considered to be an additional predisposing factor for testicular malignancy, the high prevalence of testicular microlithiasis in boys with Down syndrome may be related to the higher risk of developing testicular cancer. However, testicular microlithiasis has only been described once in an adult patient with Down syndrome and a testicular tumour. We also found that boys with Down syndrome have smaller testes than healthy boys. This also provides support for the association between testicular microlithiasis and the degeneration of the testis parenchyma because men with Down syndrome are infertile as a result of decreased spermatogenesis (Chapters 2.4 and 2.5).

4. Normative values for testicular volume in boys

We provided normative values for testicular volume measured by ultrasound in boys of 0.5 to 18 years old. Currently, a number of methods for testicular volume measurement are being used. Scrotal ultrasound is generally considered to potentially offer greater accuracy in testicular measurement than the Prader orchidometer. However, we found an accurate correlation between the volume measurements by ultrasound and by Prader orchidometer. Therefore, volume measurement with the Prader orchidometer, as generally used in practice by doctors, can still be used as a valid parameter to monitor testicular growth (Chapter 3.1).

5. Testicular volume of retractile testes

We investigated the volume of retractile testes by ultrasound and found that they are smaller than scrotal testes. This suggests that retractile testes may not be a variant of normal. However, we believe that hormonal or surgical treatment should not be recommended. On the other hand, we do recommend follow-up of boys with retractile testes to determine testicular growth, also because they are at risk of developing acquired undescended testis. Furthermore, the volumes of retractile testes measured in inguinal position were smaller than the volumes of retractile testes measured in scrotal position. This may result from the fact that measurement in the inguinal region is less accurate than measurement in scrotal position. Future research is necessary on the testicular volume of men with a history of retractile testes (Chapter 3.2).

6. The consequences on long-term testicular growth of acquired undescended testis after spontaneous descent or pubertal orchidopexy

There is controversy about the management of acquired cryptorchidism. Prompt surgical correction at the time of diagnosis is usually routinely recommended, but the effect of prepubertal orchidopexy on long-term testicular growth of acquired cryptorchidism remains unknown. We found that after spontaneous descent or after pubertal orchidopexy
in case of non-descent, long-term testicular growth is within the normal range. These data do not seem to indicate a negative effect of the inguinal environment on testicular growth. Another conclusion of our study was that there is a higher tendency of spontaneous descent in high scrotal acquired undescended testis than in the inguinal or impalpable variant. We strongly recommend that a randomized controlled trial of prepubertal orchidopexy versus 'watchful waiting' is initiated. Until then, the results of this series do not indicate a need to change our wait-and-see policy towards acquired undescended testis (Chapter 4.1).

7. Is the acquired undescended testis a separate condition or is it actually congenital?

We believe that there is emerging evidence that acquired undescended testis is in fact a previously unrecognized congenital undescended testis. Around birth, the testis descends to a low position at the bottom of the scrotum with the funiculus being just long enough to allow a low-scrotal position. As the boy grows, inadequate lengthening of the funiculus will at first result in a high-scrotal position and at a later age in an inguinal position. At puberty, most testes will re-descend as a result of gonadal stimulation and testis growth. The concept of the undescended testis is therefore not static, but dynamic. It behaves like a yo-yo to reach its final position at early puberty. Retractibility may contribute to this effect. We believe that our view of congenital undescended testis should not be limited to the first 3 to 6 months after birth, but should be longer lasting (Chapter 4.2).

Perspectives

During the last decade the view on undescended testis has dramatically changed. The phenomenon of a non-congenital undescended testis was recognised by Scorer as early as 1955, but has only been studied in large series in recent years. As a result of these studies, acquired undescended testis is now a well-recognised condition. Moreover, the late-orchidopexy enigma can now be explained on the basis of this acquired condition.

Following the classical policy, every undescended testis requires surgical correction to preserve normal fertility and to diminish the risk of developing a testicular malignancy. However, this perspective can no longer be used so stringently. Although orchidopexy is still recommended between 6and12 months after birth for congenital undescended testis, for acquired undescended testis surgical intervention is often not necessary. Many physicians are still performing orchidopexies for acquired undescended testis in the belief that they are dealing with a congenital undescended testis. Furthermore, many people believe that surgery is the only or the best treatment for an acquired undescended testis.
However, it has been known for some years now that the wait-and-see policy in the evaluation of acquired undescended testis results in spontaneous descent in three out of four cases. Follow-up data of acquired undescended testis are now available; these show that both testes operated on during mid-puberty as a result of non-descent and spontaneously descended testes have testicular volumes which are within normal range. However, there are no such follow-up data available for acquired undescended testis after prepubertal orchidopexy. It is known that in adults who have undergone prepubertal orchidopexy for undescended testis, without differentiation between congenital and acquired forms, the operated testis is often significantly smaller than its counterpart. It is likely that prepubertal orchidopexy for only acquired undescended testis will also result in smaller testis volume, as there is no doubt that many acquired forms have been included in these series in adults. In view of the follow-up data associated with a conservative attitude, the question is not only whether orchidopexy is superior to the wait-and-see policy, but also whether surgery is inferior to a conservative policy. Testicular volume measurement of boys who have undergone prepubertal orchidopexy will give a first indication to the answer of this crucial question. Possible complications like iatrogenic vascular complications and damage of spermatic cord structures due to surgical intervention may result in impairment of testicular growth. Although testicular volume is directly related to fertility, long-term follow-up is needed to show what the results of orchidopexy and the wait-and-see policy are on the spermatogenesis and paternity of boys with acquired undescended testis.

Prognostic factors for spontaneous descent need to be identified. Moreover, it is not entirely clear either what the best moment is for surgical intervention for non-descent in mid-puberty. The follow-up data on testicular volume lead to the conclusion that Tanner’s puberty stage G3 may at least not be too late. However, it is unknown whether orchidopexy in pubertal stages later than G3 gives similar results. If the decision to operate in later pubertal stages also results in testicular volumes within the normal range, it may lead to higher rates of spontaneous descent. The question whether orchidopexy versus wait-and-see and the moment to decide for orchidopexy influence the risk of developing a testicular tumour needs to be investigated further. It seems likely that the malignancy risk for acquired undescended testis is not higher than in the general population since in acquired forms the testes were descended at birth and in the first two years of life. During this period the germ cells were able to develop normally, which indicates that there may not be a higher risk of tumour development.

In the clinical setting, there should be more awareness and education regarding the two different types of undescended testis. Previous testicular position is the cornerstone in the diagnosis of acquired undescended testis; therefore, testis position should be consistently recorded by general practitioners and youth health doctors. This may result in more
patients in whom the diagnosis of acquired undescended testis is certain. This may also help to initiate a multicentre randomised control trial in the Netherlands on prepubertal orchidopexy versus wait-and-see to determine which treatment of acquired undescended testis should be favoured. Such a trial may lead to consensus on the treatment of acquired undescended testis in the near future.

It is clear that testicular volume measurement in the evaluation of boys with a variety of disorders affecting testicular growth, such as acquired undescended testis, is clinically relevant. In addition, there is also no doubt that ultrasound has been proven to be more accurate in the measurement of testicular volume than the Prader orchidometer. Therefore, in the next few years scrotal ultrasound will be increasingly performed and testicular microlithiasis will be diagnosed more often by coincidence. In adults, testicular microlithiasis is associated not only with several benign afflictions and syndromes but also with testicular malignancy and infertility. However, in the past, only a few studies reported on testicular microlithiasis in boys, and most of these were case reports. Now, there are prevalence rates for testicular microlithiasis in healthy boys as well as in boys with undescended testis and Down syndrome, who have a higher risk of developing a testicular tumour. The prevalence rates in these patients vary between 3% and 22%. This disproves an epidemiological association between testicular microlithiasis and testicular malignancies because the prevalence of testicular cancer is many times lower in these patients. However, there may be a genetic susceptibility to testicular microlithiasis that also predisposes to testicular tumours. Testicular microlithiasis may itself be an expression of a degenerative process of the testes. Therefore, the testicular volume of boys with testicular microlithiasis needs to be measured. Analysis of these data may shed light on the question whether a possible degenerative process results in impairment of testicular growth. Annual ultrasound or screening for tumour markers is not recommended in the follow-up of boys with testicular microlithiasis because so far no direct relation to testicular cancer has been determined. Nevertheless, regular self-examination of the testes is advised, except in boys with an additional risk factor for developing a testicular malignancy. In these boys, annual ultrasound is recommended in addition to regular self-examination. Whether testicular microlithiasis persists or resolves, and whether boys with testicular microlithiasis develop testicular malignancies or become infertile in adulthood needs to be investigated during long-term follow-up.