Inconstant ascending testis as a potential risk factor for spermatogenesis in infertile men with no history of cryptorchism

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The usual testicular location, either low or high in the scrotum, as well as testis ascent into suprascrotal position at least once a week from a usually scrotal position reported by the patient to occur spontaneously and regularly, were at least once a week from a usually scrotal position reported by the patient to occur spontaneously and regularly, were recorded in 85 fertile and 1014 infertile men, including 95 with a history of cryptorchism. The frequency of at least one testis being in a high scrotal location was similar in fertile (16.5%) and non-cryptorchid infertile (17%) men but higher in previously cryptorchid infertile men (27.2%), a difference probably due to cryptorchidism. Testicular ascent was more frequent when scrotal location was high rather than low. An ascending testis was encountered more frequently in previously cryptorchid (30.4%) than in non-cryptorchid infertile men without any history of cryptorchism (18.3%) or in fertile men (11.8%). Moreover, in infertile men, spermatogenesis was more depressed in cases of testicular ascent than when both testes were never ascending, independently of a varicocele. Testis ascent could be a risk factor for spermatogenesis in infertile men without any history of maldescended testicle.

Key words: cryptorchism/infertility/spermatogenesis/testis ascent/varicocele

Introduction

Cryptorchism or undescended testis is one of the several situations in medical–surgical management which repeatedly produces divergent opinions. Most disputes concern embryology (Backhouse, 1982; Hutson, 1994), definition (John Radcliffe Hospital Cryptorchism Study Group, 1988), epidemiology (Chilvers and Pike, 1989), aetiology (Swerdlov et al., 1983; Davies et al., 1986; Hutson et al., 1994), therapeutic management (Hazebroek et al., 1987), and results (Chilvers et al., 1986). The epidemiology of cryptorchism is still unclear, and many risk factors seem to be involved such as birthweight, gestational age or maternal exposure to hormones (Chilvers and Pike, 1989). Over the past 25–30 years, incidence of cryptorchism was reported to have increased from 1.7 to 3.2% when calculated from cumulative orchidopexy rates (Chilvers et al., 1984) and from 0.96 to 1.85% when evaluated from examination of infants 3 months old (John Radcliffe Hospital Cryptorchism Study Group, 1992).

Whatever the treatment, hormonal or surgical, cryptorchism is the only risk factor for testicular cancer that can be considered unequivocally established, with a mean relative risk of six (Chilvers et al., 1986; Strader et al., 1988; Giwercman et al., 1989). Infertility or subfertility is a less well defined risk, with discrepant data ranging from normal spermatogenesis (Puri and O’Donnell, 1988) or fertility (Cendron et al., 1989; Lee et al., 1993) to a depression in sperm concentration (Chilvers et al., 1986; Yavetz et al., 1992) or in subsequent fertility (Lipshultz, 1976). Finally, treatments of an undescended testis have an unusual feature in that although the initial anatomical result of orchidopexy or hormonal therapy is rapidly apparent, the functional result of treatment may not be known until ≥15 years later.

In the search for factors that can be further involved in the impairment of spermatogenesis and/or fertility, we have recently reported that a ‘retractile testis’ was more frequent in infertile men with a history of cryptorchism than in fertile men, and that testicular ‘retractility’ was associated with a decreased sperm output (Mieusset et al., 1995). As ‘retractility’ appeared to be a risk factor for fertility in formerly cryptorchid men, the aim of the present study was to determine whether ‘retractility’ was a phenomenon exclusively limited to history of cryptorchism or a common factor in infertile men. In this way, infertile men with or without a history of cryptorchism were compared to fertile men as to testicular location and ‘retractility’ (referred to as ‘ascending testis’ in the present study).

Materials and methods

Populations

From January 1989 to November 1993, 1014 new male patients presented for couple infertility, without evidence of main infertility factors in their partner (i.e. anovulation or tubal obstruction). During the same period, 85 successive fertile men, with fertility defined as the birth of at least one child, asked for a vasectomy (n = 20) or were candidate sperm donors (n = 65).

Clinical investigations

A clinical examination was carried out for both fertile and infertile men. The location of the testes and the existence of a testicular ascent were recorded as follows: with the patient standing up and completely naked, the precise location of each testis was noted after a 5 min acclimatization (Mieusset et al., 1987) to room temperature (20–25°C). When a testis was lying in the low scrotum it was recorded as in a ‘normal location’. When it was located in the upper part of the scrotum, i.e. close to the root of the penis with part of the empty
Infertile patients with a history of cryptorchism, i.e. men who had been cryptorchid and then treated successfully to eliminate the condition, are referred to as ‘cryptorchid men’, while infertile men without any history of maledescended testes are referred to as ‘infertile men’ hereafter.

**Biological investigations**

Sperm characteristics of both fertile and infertile men were studied on semen samples collected by masturbation at the laboratory after a recommended period of 3–5 days without ejaculation. Volume of semen was measured using a graduated pipette. Sperm concentration was measured on a Malassez cell (Rogo et Cie, Arcueil, France) as previously described (Mieusset et al., 1989). Total sperm count was calculated as volume x sperm concentration. Semen samples were maintained at 37°C and assessment of motility was made within 1 h after ejaculation; spermatozoa crossing the microscope field with linear motility were recorded as motile (progressive motility) and (p < 0.05).

**Results**

**General characteristics of the populations**

A history of cryptorchism was found more frequently in infertile (9.4%) than in fertile (2.4%) men (95/1014 versus 2/ 85: OR = 4.29 (1.12–36.55)]. The mean age did not differ between fertile (33.4 years; range: 21–49), cryptorchid (31.8 years, 20–56), and infertile men (32.4 years; 20–59). The duration of infertility was not significantly different between the cryptorchid (38.3 ± 26.3 months) and the infertile men (43.5 ± 31.6 months). Secondary infertility, defined as a history of pregnancy resulting in spontaneous or voluntary abortion, or a child, did not differ between cryptorchid (16.8%) and infertile men (20.1%). An orchidectomy had been undertaken in three (one right and two left) of the cryptorchid men during the surgical treatment, and in five (all right) of the infertile men for either testicular torsion or orchitis.

There was no difference between fertile, cryptorchid and infertile men as regards the frequency of orchitis, either on the right or left side or bilaterally (5.9, 7.4 and 5.3% respectively) and the frequency of right varicocele (5.9, 3.2 and 7.6% respectively). However, there was a higher frequency of left varicocele in infertile (294/919) than in fertile (12/85) men (32.0 versus 14.1%; P < 0.0001) or cryptorchid (19/93) men (32.0 versus 20.4%; P = 0.022), while fertile and cryptorchid men did not significantly differ. In the 919 infertile men, 97 were azoospermic, of whom 51 (5.5%) had secretory azospermia, as defined by the lack of spermatozoa in the seminiferous tubules from testicular biopsies. In the 95
infertile one regarding the frequency of left varicocele, data were re-analysed taking into account this parameter. The distribution of left (8/42), right (9/33) or bilateral (2/17) varicocele was not different in the cryptorchid men with or without a left varicocele. As detailed in Table III, the frequency of left testis asent was not different in the presence or absence of a left varicocele in cryptorchid men. But asent was significantly more frequent in the infertile men without than with a left varicocele. Moreover, similar results were observed for asent of the right testis as a function of left varicocele (Table III). Independently of varicocele, testicular asent was associated with a more depressed spermatogenesis in the infertile population. Indeed, among men without a left varicocele (n = 622), those with a right and/or left asent testis (n = 130) had a more impaired spermatogenesis than those with no asent testes (n = 492), with a lower total sperm count (91.0 ± 122.2×10⁶/ejaculate versus 133.1 ± 177.9×10⁶/ejaculation); P = 0.045) and percentage of motile spermatozoa (26.2 ± 18.3% versus 31.0 ± 18.7%; P = 0.016). Among men with a left varicocele (n = 292), those with a right and/or left asent testis (n = 37) had a lower total sperm count than those (n = 255) with no asent testes (45.3 ± 88.3×10⁶/ejaculation versus 91.4 ± 128.2×10⁶/ejaculation; P = 0.004).

### High location of the testis

The percentage of patients with a right and/or left testis in a high location did not differ between fertile and infertile populations, nor between fertile and cryptorchid groups, but was significantly higher in the cryptorchid than in the infertile populations (Table I). In infertile and in cryptorchid populations, there was no difference in total sperm count between men with a right and/or left testis in a high location and those with both testes in a permanent low scrotal position (data not shown). As detailed in Table IV, the frequency of a left testis high location was not different in the presence or absence of a left varicocele in cryptorchid men. However, the frequency of a left testis high location was significantly higher in the infertile men without than with a left varicocele. Similar results

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### Table I. Distribution of men with right and/or left ascending and high located testes in fertile, cryptorchid, and non-cryptorchid men

<table>
<thead>
<tr>
<th>Populations</th>
<th>Cryptorchid</th>
<th>Non-cryptorchid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertile men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of men</td>
<td>85</td>
<td>94b</td>
</tr>
<tr>
<td>Right and/or left ascending testes (%)</td>
<td>10a</td>
<td>28d</td>
</tr>
<tr>
<td>No. of patients</td>
<td>64</td>
<td>28</td>
</tr>
<tr>
<td>Total sperm count (×10⁶/ejaculate)</td>
<td>(798)</td>
<td>(836)</td>
</tr>
<tr>
<td>Motility</td>
<td>27.5</td>
<td>23.4</td>
</tr>
<tr>
<td>(1 h; %)</td>
<td>(105.5)</td>
<td>(20.3)</td>
</tr>
<tr>
<td>Right testis</td>
<td>23.1</td>
<td>19.1</td>
</tr>
<tr>
<td>volume (ml)</td>
<td>(11.2)</td>
<td>(11.3)</td>
</tr>
<tr>
<td>Left testis</td>
<td>20.7</td>
<td>16.8</td>
</tr>
<tr>
<td>volume (ml)</td>
<td>(10.9)</td>
<td>(9.8)</td>
</tr>
</tbody>
</table>

Comparisons between means (± SD) carried out using the Mann–Whitney U-test.
Cryptorchid: *P = 0.044. Yes versus No.
Non-cryptorchid: 2P = 0.006; 3P = 0.009. Yes versus No.

cryptorchid men, 13 cases of secretory azoospermia (13.7%) were found, which was a significantly higher rate than in infertile men [OR = 2.70 (1.29–5.29)].

### Ascending testis

The percentage of men with right and/or left ascending testes did not differ between fertile and infertile men [OR = 1.68 (0.84–3.72)]. However, this percentage was significantly higher in cryptorchid than in fertile men, or in infertile men (Table I). Asent of one or both testes was associated with a more depressed spermatogenesis than when both testes were never ascending, with a lower total sperm count in cryptorchid men and a lower total sperm count and percentage of motile spermatozoa in infertile men. Testicular volumes were not significantly reduced (Table II).

As the fertile and cryptorchid populations differed from the
were observed for the right testis high location as a function of left varicocele (Table IV).

### Relationships between testis location and ascent

Whether on the left or right side, testis ascent and high location of the testis were parameters independent of each other in fertile men; but these two parameters were related both in cryptorchid and in infertile men, with a testis more frequently ascending when in a high than in a low scrotal location (Table V). When both testes were simultaneously taken into account similar results were observed, with the number of testes ascending from a high location significantly higher in cryptorchid (18/39; OR = 9.43; 95% CI = 1.83–90.74) and in infertile (79/267; OR = 4.62; 95% CI = 1.09–41.34) men than in fertile men (2/24). In both cryptorchid and infertile men, such a relation between high location and ascent of the testes did remain in the absence of left varicocele, but disappeared when a left varicocele was present (Table VI).

### Multivariate analyses

Total sperm count and sperm motility were significantly reduced when testes were inconstantly ascending. However, because many of the variables being compared may be inter-related, multiple linear regression analyses were conducted, including, apart from testes ascent, the following variables: age, right and left testicular volumes and the presence or absence of right and/or left varicocele.

Age did not contribute significantly to total sperm count. The relationships between total sperm count and the other variables are given in the following equation: total sperm count = 3.0 × right testis volume + 2.4 × left testis volume – 31.4 × varicocele – 34.2 × testes ascent + 21.1 (multiple r = 0.38; r² = 0.14; P < 0.001). As regards sperm motility, only total sperm count and testes ascent significantly contributed to it, with the following equation: sperm motility = 0.03 × total sperm count – 3.23 × testes ascent + 30.04 (multiple r = 0.25; r² = 0.06; P < 0.0001).

### Discussion

It is now largely accepted that a normally descended testis is a testis located in the scrotum (John Radcliffe Hospital Cryptorchism Study Group, 1988). If such a definition is a basic part of the clinical examination of newborn boys and children in the search for a maldescended testis, the location of the testis has drawn little attention in adult men. In the present work, a systematic and standardized clinical examination revealed that the frequency of one or both testes in a high scrotal location was similar in fertile (16.5%) and infertile men (17%) but higher in cryptorchid men (27.2%). It seems obvious that this difference is due to cryptorchism, as recently

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**Table IV. High location of right or left testis as a function of left varicocele in cryptorchid and in non-cryptorchid men**

<table>
<thead>
<tr>
<th>Populations</th>
<th>Cryptorchid (n = 92)</th>
<th>Non-cryptorchid (n = 914)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left varicocele</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>High location</td>
<td>15/74</td>
<td>104/625ab</td>
</tr>
<tr>
<td>left testis</td>
<td>(20.3)</td>
<td>(16.6)</td>
</tr>
<tr>
<td>High location</td>
<td>16/73</td>
<td>107/622bc</td>
</tr>
<tr>
<td>right testis</td>
<td>(21.9)</td>
<td>(17.2)</td>
</tr>
</tbody>
</table>

*Non-cryptorchid men: varicocele absent versus present: Corrected \( \chi^2 \); \( P < 0.004; \) OR = 1.97 (95% CI = 1.24–3.22). Cryptorchid men varicocele absent versus non-cryptorchid men left varicocele present: Corrected \( \chi^2 \); \( P < 0.014; \) OR = 2.51 (95% CI = 1.16–5.24). Right testis

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**Table V. Relationships between testis location and ascent in fertile and cryptorchid and non-cryptorchid infertile men**

<table>
<thead>
<tr>
<th></th>
<th>Fertile men (n = 85)</th>
<th>Infertile men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scrotal position of testis</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Right testis No</td>
<td>65</td>
<td>10</td>
</tr>
<tr>
<td>Yes</td>
<td>9</td>
<td>1b</td>
</tr>
<tr>
<td>(112)</td>
<td>(9.1)</td>
<td></td>
</tr>
<tr>
<td>Left testis No</td>
<td>65</td>
<td>12</td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>1b</td>
</tr>
<tr>
<td>(9.7)</td>
<td>(7.7)</td>
<td></td>
</tr>
</tbody>
</table>

*Values in parentheses are percentages.

**Fertile men**

*Right testis: Fisher’s exact test: \( P = 0.618; \) not significant.

*Left testis: Fisher’s exact test: \( P = 0.646; \) not significant.

**Non-cryptorchid men**

*Right testis: Corrected \( \chi^2 \); \( P < 0.0001; \) OR = 2.71 (95% CI = 1.73–4.18).

*Left testis: Corrected \( \chi^2 \); \( P < 0.0001; \) OR = 2.98 (95% CI = 1.87–4.68).

**Cryptorchid infertile men**

*Right testis: Fisher’s exact test: \( P = 0.013; \) OR = 5.73 (95% CI = 1.67–19.33).

*Left testis: Fisher’s exact test: \( P = 0.014; \) OR = 4.20 (95% CI = 1.16–14.60).
in cases of testicular ascent than when both testes were never
mean diameter of the seminiferous tubules, a decreased number

Left varicocele cryptorchid men: Furthermore, recent reports have suggested rather an active
Comparisons 'low and ascending' versus 'high and ascending': cell morphology (Ito

Infertile populations

Right and left testes

Non-varicocele
cryptorchid
Left varicocele
cryptorchid
Non-varicocele
Non-cryptorchid
Left varicocele
Non-cryptorchid

15/116
12/9
6/30
20
154/1036
14/9
48/530
(9.1)

16/31*
(51.6)
2/8*
(25)
72/211*
(34.1)
7/56*
(12.5)

Table VI. Relationship between testis location and ascent in cryptorchid and in non-cryptorchid men as a function of a left clinical varicocele

Values in parentheses are percentages. Comparisons 'low and ascending' versus 'high and ascending':

*Non-varicocele cryptorchid men:
Corrected $\chi^2$: $P < 0.00001; OR = 7.18 (95\% CI = 2.68–19.13)$.

*Non-varicocele cryptorchid men:
Fisher’s exact test: not significant; OR = 1.33 (95\% CI = 0.11–10.36).

*Non-varicocele non-cryptorchid men:
Corrected $\chi^2$: $P < 0.00001; OR = 2.97 (95\% CI = 2.09–4.18)$.

*Left varicocele non-cryptorchid men:
Corrected $\chi^2$: not significant; OR = 1.43 (95\% CI = 0.52–3.42).

reported (Sack et al., 1993). In infertile men, high location of
the testes was without any effect on the sperm output, as in
cryptorchid infertile men (Mieusset et al., 1995), which seems to
indicate that a scrotal location of the testis, either low or
high, is a physiological one. However, high scrotal location
of the testis could not be a variant of the physiological
situation, as the length of the spermatic cord as well as the
anatomical structures that constitute the spermatic cord could
differ. Indeed, testis ascent was more frequent in cases of high
than low scrotal location, and both ascent and high location
were more frequent when a left varicocele was absent; also,
the relation between ascent and high location, i.e. more frequent
ascent when a testis was in a high location, that existed in
the absence of a varicocele disappeared when varicocele was
present. In connection with varicocele, there is a close relation
between a clinical varicocele and both the scrotal position and
inconstant ascent of the testis in the infertile population. While
this inverse relationship seems to indicate that some of the
anatomical structures of the spermatic cord are involved, we
have no documented explanation for this phenomenon.

To our knowledge, there have been no reports on the
modifications in the position of a scrotal testicle in adult men
while an acquired permanent ascent of the testis was reported
in children (Villumsen and Zachau-Christiansen, 1966; Atwell,
1985; Schiffer et al., 1987; Fenton et al., 1990; Eardley et al.,
1994). An ascending testis, i.e. a testis normally located in the
scrotum but that ascends spontaneously and regularly (at least
once a week) to a supra-scrotal position, was more frequently
encountered in cryptorchid (30.4%) than in infertile (18.3%)
or in fertile men (11.8%). As regards cryptorchid men, and as
stated previously (Mieusset et al., 1995), the high frequency of
ascending testes may reflect a failure of either medical or
surgical treatment permanently to secure the testis in a scrotal
position, which is not surprising. There was, however, no
history of maldescended testis, i.e. cryptorchism, retractile or
late descending testis (Bremholm Rasmussen et al., 1988) in
infertile men. But in this infertile population, sperm output
and sperm motility, i.e. spermatogenesis, were more depressed
in cases of testicular ascent than when both testes were never
ascending. This association between ascending testis and
impaired spermatogenesis could result from two factors.

Firstly, in adult men, the ascending testis, which is a scrotal
testis that becomes spontaneously and regularly a supra-scrotal
one, could be a crude pattern of the retractile testis which is
defined in children as a non-scrotal (i.e. a supra-scrotal) testis
that becomes a scrotal one only when manipulated (Schoorl,
1982; Palmer, 1991). Retractility was reported to be associated
with histological anomalies during childhood such as a reduced
mean diameter of the seminiferous tubules, a decreased number
of spermagonia per tubule and various alterations in Sertoli
cell morphology (Ito et al., 1986; Saito and Kumamoto, 1989;
Nistal et al., 1991; Rune et al., 1992; Cinti et al., 1993).
Furthermore, recent reports have suggested rather an active

Secondly, when ascending from a scrotal to a supra-scrotal
location, the testis is submitted to thermic modifications in its
environment, as the temperature of the supra-scrotal location
is about 2°C higher than the scrotal cavity (Kitayama, 1965).
When testes of fertile men were located and maintained
in such a supra-scrotal location, testicular temperature was
increased about 2°C (Shafik, 1991). And such an increase in
testis temperature repeated daily for 16h is known to result in
a severe depression of spermatogenesis within 3 months
(Mieusset et al., 1987; Mieusset and Bujan, 1994). However,

References


