## *Leading articles*

# How vulnerable is the developing testis to the external environment?

The onset of spermatogenesis occurs during puberty, before adult blood levels of testosterone are achieved. It can be detected early by the presence of spermaturia.[1] Sperm maturation is a temperature dependent process and most male mammals have externally sited gonads to maintain testicular hypothermy. In this issue of *ADC*, Partsch and colleagues (page 364) report the effect of reusable cotton versus plastic lined disposable nappies (diapers) on scrotal skin temperature during infancy and early childhood.[2] Studies in adult men showed a strong correlation between intratesticular and scrotal skin temperatures.[3] The use of plastic lined nappies resulted in significantly higher mean 24 hour scrotal skin temperatures in the 48 infants and children studied. The cooling effect of scrotal positioned testes can be quantified by measuring the rectoscrotal temperature difference. In one study of 36 normal adult men, examined in the supine position at room temperature, the mean temperature differential was 2.38°C (range 0.8–5.2°C).[4]

The intrascrotal cavity temperature in a study of boys treated surgically for cryptorchidism was as much as 4.8°C lower than body temperature.[5] The highest rectoscrotal temperature difference in Partsch and colleague's study (2.63°C) was observed in toddlers when clothed in cotton nappies. The temperature differential was blunted in all boys after wearing plastic lined nappies, and abolished altogether in just over a quarter of the boys studied.

How is the testis cooled and what are the functional consequences if this does not happen? Thermoregulatory control mechanisms involve modulation of radiant heat loss through thin scrotal skin, which is devoid of fat, and via a countercurrent heat exchange system in the blood vessels of the spermatic cord.[6–8] A higher environmental temperature leads to relaxation of the cremasteric and dartos muscles, increased blood flow to an enlarged scrotal skin surface area, and thus added heat loss. Outgoing venous blood is cooled so that heat exchange within the pampiniform vascular plexus in the spermatic cord ensures precooling of arterial blood supplying the testis. It has long been recognised that varicoele and venous dilatation of the spermatic cord is associated with male infertility.[9] Most studies indicate that scrotal temperature is increased in men with varicoeles, but whether this is the primary causative factor for associated infertility is not clear. Numerous studies in humans have shown reversible changes in sperm production when the scrotal temperature is increased by various manoeuvres[10–12]—for example, a single twenty minute sauna caused a fall in sperm count within one week, which returned to normal ten weeks after the heat exposure. Scrotal temperature can also be raised by other methods: intermittent immersion of the scrotal sac in hot water, use of athletic supports, and manipulation of the testes up to the inguinal canals all caused reduced sperm counts sufficient to consider heat as a possible form of reversible male contraception. In a recent study of healthy men who wore polyester lined athletic supports for most of the day over a one year period, there was a consistent increase in scrotal temperature but no quantitative or qualitative adverse effects on spermatogenesis.[13] A modest temperature increase of 0.8 to 1°C in this study may have been insufficient to alter sperm quality. There was a popular belief at one time that tight fitting underwear was detrimental to male reproductive health. A recent critical analysis of the role of underwear type on scrotal temperature showed no significant difference between the wearing of boxer shorts and briefs.[14] Younger men seem to prefer boxer shorts, a choice surely made on fashion grounds rather than because of concern over their future fecundity. Nevertheless, men subject to occupational heat exposures—such as, bakers, welders, taxi and lorry drivers, are reported to be at significant risk of adverse effects on sperm morphology.[8] The net effect is an increase in time to pregnancy, a sensitive and validated measure of fertility.[15]

Sperm analysis based on concentration counts and qualitative markers—that is, morphology of the spermatozoon head and motility, is an objective method to measure adverse effects from alterations in the thermoregulation of the testes. Of what relevance is this to prepubertal boys subject to such changes in environmental temperature as described in Partsch and colleagues' study? The infant testis is an active endocrine organ producing concentrations of steroids and peptides within the adult range, as a result of stimulation by pituitary gonadotrophins.[16] Male germ cells undergo extensive mitosis during fetal and postnatal life but the first meiotic division does not occur until puberty. Consequently, the immature testis contains spermatogonia and Sertoli cells within the seminiferous tubules, as maturation through spermatocytic and spermatid stages to the secreted spermatozoon does not happen until puberty. The mitotic activity of the Sertoli cells in infancy is indicated by a marked increase in Sertoli cell number during the first year, under the influence of follicle stimulating hormone (FSH) secretion.[17] A further FSH induced stimulation of Sertoli cell growth occurs at puberty and is principally responsible for the increase in testis volume. The Sertoli cell "supports" the development of the germ cells so that the capacity for spermatogenesis by the adult testis is a function of Sertoli cell number; an association which is influenced by activity of the testes in the fetal and infantile periods.[18] That spermatogenesis in adulthood may be directly influenced by events in infancy is illustrated by lower sperm counts in monkeys subjected to reversible blockade of the pituitary–gonadal axis during early postnatal life.[19]

Assessment of the endocrine activity of the infantile testis has focused mainly on Leydig cells with measurements on basal and HCG stimulated testosterone concentrations.[20] A number of peptide hormones are produced by the Sertoli cell, including anti-mullerian hormone (AMH) and inhibin. Measurement of serum AMH concentrations have been proposed as a marker of testicular function in infancy as well as indicating whether testes are present in bilateral cryptorchidism and intersex disorders.[21] Inhibin is a glycoprotein, which is produced predominantly in men by

the Sertoli cells. The peptide circulates as a heterodimer, and the inhibin B form is regarded as a marker of Sertoli cell function and spermatogenesis in the adult.[22 23] Gonadal hormone levels measured longitudinally during the first two years of life showed raised levels of FSH, luteinising hormone (LH), testosterone and inhibin B at three months.[24]

Median peak levels of inhibin B were twofold higher than values in adult men, and remained raised into the second year of life. This may reflect the increasing Sertoli cell numbers observed in infancy and indicate the importance of a developmental period in the reproductive tract for later spermatogenesis. Furthermore, recent studies report a strong correlation between basal inhibin and HCG induced increments in testosterone levels in prepubertal boys.[25] Thus, there are measurable indices of Sertoli cell (and indirectly germ cell) function in male infants, but whether these are altered by changes in the thermal environment is unknown. In a remarkable study of dogs who were clothed in cotton or polyester underpants continuously for two years, there was a significant decrease in sperm count, and motile forms, as well as degenerative changes, were seen on testicular biopsy only when the polyester variant had been worn.[26] The underpants had been fitted loosely to avoid any temperature effect accounting for the difference. Significant electrostatic potentials were generated by the polyester underpants, suggesting that an electrostatic field traversing the scrotal contents may adversely affect the testis and epididymis.

Partsch and colleagues are sufficiently bold to hypothesise that increased scrotal temperature in boys as a result of disposable napkin use could be an important contributor towards a decline in male reproductive health observed in recent years.[27] The circumstantial evidence of the effects of testicular hyperthermia indicates that the hypothesis is plausible, but currently untestable. There is now considerable evidence from worldwide studies to substantiate the data from a meta-analysis reported in 1992, which shows that the mean sperm count in the general population has decreased by 50% during the past 50 years.[28] Allied to this change is a marked increase in testicular cancer, a disorder affecting mainly young men.[29] Hypospadias and cryptorchidism are also increasing in incidence; it has been proposed that the quartet of disorders leading to the recent decline in male reproductive health is the result of environmental chemicals acting to disrupt endocrine events, either in xenoestrogenic or antiandrogenic fashion.[30] It is possible that postnatal events—such as, a marked change in the thermal environment, are an additional factor which increase the risk from damaging environmental effects during the crucial phase of fetal testis development.

Should parents be concerned about the findings of this study of scrotal temperature and disposable nappy use? Retailers report almost universal sales of disposable nappies, and some do not even stock the reusable cotton variety. That practice is unlikely to change although environmental friendly initiatives may have some effect. Further prospective studies are warranted now that indices of testicular function in infancy are available to measure. For practical purposes, consideration should at least be given to how nursing infants and young toddlers should be clothed (naked or in cotton-based nappies) during a febrile illness.

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