ISSN: 3049-8074

Review Article

Journal of Clinical Medicine & Health Care

Potential Negative Effect of Diaper on the Fertility in Adulthood

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Received: July 15, 2026; **Accepted:** July 21, 2026; **Published:** July 29, 2026

ABSTRACT

This article rises a hypothesis and research question, not a proven conclusion. We propose that the use of disposable diapers for newborns and infants may lead reproductive harm in adulthood. Modern diapers feature the same original design as first baby diaper 70 years ago, which contains one unit of disposable material wrapped around the perineum to collect urine and feces. This design results in an increase in internal area temperatures by 2-4 °C, which can be detrimental to the function and development of reproductive cells. Moreover, the standard diaper template promotes the free passage of feces, including fecal bacteria contacting with the genitals, which can lead to urogenital infection and reproductive impairments in both sexes. The available clinical data suggest that diaper use during infancy may have a negative impact on fertility after puberty. There is a critical need for additional studies to better assess the impact of diapers on reproductive health.

Introduction

The global fertility rate is continuously declining [1-2]. There are multiple factors that can have adverse effects on the human reproductive system, some of which are general, e.g., environmental or lifestyle, while others are more specific, e.g., genetic or epigenetic [3-9]. Recently, it was proposed that the lack of natural selection among humans has been matched by a decline in reproductive functions [10].

Over 70 years ago, the first disposable synthetic, waterproof baby diaper was developed and marketed. The main impetus for this development was the mobilization of a female workforce during World War II, leaving women with little time or energy to manage the enormous task of washing cotton diapers at home. Today, baby diapers are in-widespread use across the world. The early disposable diaper comprised cellulose as the main absorbent material and a plastic outer sheet to prevent messy leakage. Apart from improvements in absorbency, textile and grip over time, there have been no conceptual changes in the product design/template. In fact, modern diapers share the same original, convenient and easy-to-use, simple template, which contains a single unit of a disposable material wrapped around the perineum to collect urine and feces. Recently, it was found that diapers increase the temperature of the genital area by 2-4°C [11]. Moreover, the standard diaper styling allows for free passage of feces, including fecal bacteria, which in contact with genitals can lead to acute or chronic urogenital infection. The present article proposes that use of disposable diapers for newborns and infants can potentially be detrimental to the child's health and reproduction functions in adulthood.

Maintaining Testicular Temperature

The optimal temperature range for normal spermatogenesis is 32-34°C, which is the average temperature range in the scrotum [12]. Yet, the average body temperature is 36.4°C, and can rise to 38°C or more in case of illness. High body temperature has been shown to negatively affect sperm quality, with the severity of testicular harm dependent on the duration and the amplitude of the fever [13-15]. The lower temperature of the scrotum is achieved mainly by the external position of the testicles. Testicular cooling and warming are both controlled by the tunica dartos and the cremasteric muscles, which lead to movement of the testes farther away from the body. The scrotal sac is also involved in testicular thermoregulation, by contributing to heat loss through evaporative cooling [16]. An additional mechanism involved in counter-current heat exchange, involves the pampiniform venous plexus which removes diverts heat from arriving warm arterial blood to the cooler venous blood

Citation: Eliezer Girsh. Potential Negative Effect of Diaper on the Fertility in Adulthood. J Clin Med Health Care. 2026. 3(3): 1-6.
DOI: doi.org/10.61440/JCMHC.2026.v3.60

leaving the testes [17-19]. When cooled, the scrotum muscles contract, which then draws the testicles closer to the body, preventing hypothermia. The negative impact of high body or scrotum temperature on male fertility is well established [20]. These data underscore the importance of scrotal ventilation and maintenance of the physiological scrotal temperature.

Heat Stress and Testicles

Failure to cool to the natural scrotal temperature has been associated with impaired spermatogenesis, low sperm count, poor sperm motility and abnormal morphology in ejaculate [21]. Lifestyle, occupational, environmental and pathophysiological factors contribute to increased scrotal temperatures range. A major outcome of heat stress on the testis is apoptotic destruction of germ cells, a bulk for further spermatogenesis. A 1°C increase in testicular temperature results in a more than 14% drop in spermatogenesis [22-24]. Hyperthermic exposure of spermatozoa impacts spermatozoa count, morphology, aneuploidy and DNA integrity, and triggers apoptosis, which results in poor fertilization capacity [25-27]. Chronically elevated scrotal temperature can lead to testicular germinal atrophy, spermatogenic arrest and aneuploidy of sperm cells [25]. Testicular heating mostly affects spermatocytes and round spermatids in adulthood [13, 28] and has therefore been proposed as a method of male contraception [29-31].

In a sitting position, the scrotum comes into contact with the body, which can increase the scrotal temperature to body temperature in a short time [32-33]. Indeed, significantly higher than average testicular temperature was measured in wheelchair-bound paraplegic men with spinal cord injuries [34]. In line with the above, the incidence of pathozoospermia among men with sit-down jobs, such as professional drivers, is significantly higher, as compared to other professionals, with increased in prevalence in proportion to the number of years of driving and delayed conception [35, 36]. Also, the improvement of sperm motility and sperm morphology was statistically insignificant after three months by nocturnal scrotal cooling with positive trend of improved male fertility [37, 38]. Taken together, these studies underscore the role of genital heat stress in impaired semen quality.

Heat stress affects spermatogenesis also by indirect way via testicular somatic cells. Spermatogenesis is supported by somatic Sertoli cells in the seminiferous tubule and by somatic steroidogenic Leydig cells in the interstitial space of the testicle. Contacting Sertoli cells form the blood-testis barrier (BTB) by various types of cell junctions [39]. The BTB is responsible for the anchoring of spermatogonia to Sertoli cells, and differentiation of mature spermatogonia to primary spermatocytes [40]. As such, a functional BTB is obligatory for optimal spermatogenesis. The number of Sertoli cells in the human testis increases sharply during the first 3 months of life, stays stable until start of puberty with further increase during puberty and then gradually increases to adult values after 25 years of age [41]. Transient heating of the testis results in a broad range of changes in Sertoli cell function [42]. A reduction in the number of Sertoli cells in mice was noted one month following a single, 30-minute exposure to 42°C [43]. Increasing the temperature to 37°C inhibited androgen binding protein (ABP) production by Sertoli cells [44]. Microscopic examination of the rat testis after heat exposure showed mitochondrial degeneration, dilatation of the smooth endoplasmic reticulum, and wider spaces between Sertoli cells, all of which adversely impact normal spermatogenesis [45].

The somatic steroidogenic Leydig cells exhibit dynamic development and are responsible for testosterone production, Sertoli cell development and BTB function. The number of fetal-type Leydig cells reaches a maximum in the 15th week of pregnancy and is still appreciable at birth. These cells disappear at about 3-6 months of age. Thereafter, the number of Leydig cells begins to increase and reaches a plateau at approximately 1-8 years of age. These cells then disappear and are replaced by prepubertal-type followed by mature adult-type cells [46-47]. Serum and testicular testosterone concentrations are also appreciable up to about 6 months of age, after which, they drop to low levels until puberty [47]. Testicular testosterone concentrations declined in the 48 h after scrotal insulation in bulls, indicating a severe impact of heat stress on steroidogenesis in Leydig cells [48].

Heat-stressed Cell Apoptosis

Cell apoptosis can be induced by many triggers, with temperature being a strong inducer of the process [49]. Heat-stressed Sertoli and spermatogenic cells undergo apoptosis [50-51]. Generally, there are two major apoptotic pathways: the extrinsic/death receptor pathway (receptor Fas – cytosolic caspase 3 pathway) and the intrinsic/mitochondrial pathway (cytochrome-c – caspase 3 pathway) [52]. Molecules of one pathway can be influenced by molecules in the other [53]. Additional cell death pathways include the perforin/granzyme pathway and the tumor suppressor p53 pathway [54, 55].

The Fas and Fas ligand (FasL) system is also involved in germ cell apoptosis in humans. For example, hypospermatogenesis, such as in cases of maturation arrest and Sertoli cell-only syndrome, is a result of a Fas/FasL-mediated process. Patients with post-meiotic germ cell arrest show increased Fas expression in germ cells, suggesting that the Fas/FasL system is involved in gamete apoptosis [56].

Possible Adverse Effect of Diaper Usage on Fertility

As spermatocytes and round spermatids are not present in infancy, the topic of spermatogenesis in childhood has not received due attention, and the effect of high genital temperature during infancy on fertility in adulthood has not yet been studied [57].

Babies are often sedentary or asleep for long periods and diapers become a heat trap. Indeed, it was shown that cotton and synthetic diapers increase the scrotal temperature by 2° C-3° C and 3° C-4° C, respectively [11]. A significant increase in the scrotal/testicular temperature was observed in male neonates (0-4 weeks), infants (1-12 months) and toddlers (1-4.5 years) who wore plastic as opposed to cotton diapers [11]. However, there are no data regarding the effect of increased scrotal temperature in infancy on reproductive functions after puberty and in adulthood.

In human males, there are three endocrine stages of "puberty maturation" that are dependent on testosterone secretion from

the developing testes prior to real puberty. The first wave of testosterone is observed during embryonic development (10-24 weeks of gestation) and affects the development of the male reproductive system. The second wave of testosterone normally occurs at the age of 2-3 months and is associated with the active mitotic proliferation and transformation of gonocytes (fetal reproductive stem cells) into the A dark (Ad) spermatogonia. This period is characterized by densely stained chromatin of Ad spermatogonia, which later shifts to the pale A (Ap) spermatogonia with granular chromatin, and later to mature type B spermatogonia, which form a self-mitotic-replicating pool (warehouse) of spermatogonial stem cells that will contribute to future spermatogenesis [58-60]. During these periods, mitotic gonocytes and spermatogonia are vulnerable to heat stress [61-62]. While male germ cells undergo extensive mitosis during fetal and postnatal life, meiotic division begins at puberty. The third wave of testosterone occurs between the ages of 9 and 14 years and persists until approximately age 50, after which testosterone levels slowly decline [63]. The endocrine activity at the different ages affects testicular development. The testis of boys less than 1 year of age weighs about 0.5 g, and there is a slow increase in weight until the age of 10-14 years, when each testis weighs about 1.5 g. Between ages 14-18 years, the testes rapidly increase in size to about 12 g each and later to an adult size of 20-25 g [64]. This testicular development is driven by proliferation of all types of testicular cell, including gonocytes and somatic cells, and is driven by endocrine activity. It also was noted that endocrine activity during infancy is associated with proliferation but not maturation of the Sertoli and germ cells, whereas during puberty both proliferation and maturation occur [41]. Lower testicular volume and sperm count were observed in monkeys subjected to reversible blockade of the pituitary-gonadal axis during early postnatal life [65]. Considering the above, it can be postulated that spermatogenesis in adulthood is directly influenced by events in infancy. This phenomenon is well described in cryptorchid patients.

Cryptorchidism is a well-known infant pathology, in which one or both testicles do not descend into the scrotum after birth, and remain at different levels of the inguinal canal. Failed testicular descent into the scrotum before the age of 6 months has been associated with infertility [66]. This can be explained by the impaired transition of gonocytes into type Ad spermatogonia in cryptorchid testes, which has been associated with spermatogenic arrest [67]. Indeed, undescended testicles contain a significantly lower number of Ad spermatogonia, which is a high risk for subsequent infertility, as compared to descended testes [68-70]. In line with the above, infants with low Ad stem cell counts later showed 25-times lower spermatozoa counts as compared to men with normal numbers of Ad stem cells in infancy [71]. One of explanations for infertility in cryptorchidism is the negative effect of body temperature stress on proliferation and differentiation of spermatogonia in the neonate and infant testicles [72-73]. Currently, there is growing evidence that the scrotum requires a low physiological temperature in the neonatal period as well.

Probable Effect of Fecal Infections on Fertility

The genital tract is not sterile, and features a unique microbiome that exists in symbiosis with the body. The most common bacteria in the vaginal microbial community are lactobacilli (L. iners, L. jensenii, L. helveticus), which maintain a local pH, rendering it difficult for other, external microorganisms to develop and grow [74]. In diapers, feces easily spread to the front compartment of the diaper, providing access of fecal flora to the genitals and urethral tract. Typically, half of infected infants are asymptomatic [75]. At neonatal age and early infancy, babies cannot yet verbalize the feeling of pain or discomfort. The only way to express discomfort is by crying, the cause of which is not always clear to adults. This discomfort can be triggered by bacterial infection and inflammation, mostly of fecal origin, e.g., E. coli and E. faecalis. Urinary tract infections (UTI) are one of the most common bacterial infections in infants under 1 year of age [76-79]. E. coli is the most frequent bacterial pathogen responsible for UTI, accounting for 85-90% of case, followed by Enterococcus faecalis [78, 80]. A study conducted in 7 day-care-centers found that 19% of diapered children were colonized with resistant E. coli [81]. It was suggested that decreased frequency of diaper changes allows more time for urinary and fecal bacteria to colonize the peri-urethral area, leading to infection [82]. In line with this, there are no data regarding the effect of fecal contamination of the genital tract in infancy and childhood, and inflammation on both male and female reproductive functions in adulthood.

Conclusion

Testicular thermoregulation is of great importance to ensure the production of viable spermatozoa and to maintain fertility. Failure to regulate scrotal temperatures or exposure to high temperatures results in testicular heat stress, apoptosis and testicular hypofunction. Understanding the mechanisms of testicular heat stress can help guide preventive actions and the development of targeted male infertility therapies. Future studies on the effect of bacterial fecal contamination of the genital tract in infancy and childhood on reproductive health in adulthood will be of great importance. The accumulated evidence suggests that the standard diaper template may have a negative effect on reproductive health both in childhood and after puberty. Therefore, further investigation of the health implications of the current diaper template is warranted.

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