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Hypothesis

Disposable Diapers in Infancy and Their Potential Detrimental Impact on Male Fertility in Adulthood

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Abstract

The overall human fertility rate has been continuously declining across the globe for a number of reasons. This review summarizes data, which proposes that the use of disposable diapers for newborns and infants may incur reproductive harm in adulthood. More than 70 years ago, a disposable synthetic waterproof baby diaper was developed, mainly to reduce the burden of working mothers. Modern diapers feature the same original design, 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, to the genitals, which can lead to urogenital infection and reproductive impairments. 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.

More Information

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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. Environmental risk factors include food and air pollution [3,6], and diurnal and seasonal periods [7]. Similarly, it was suggested that lifestyles, such as excessive/vigorous physical activity or sedentary behavior [8,9], occupation, and stress [10,13], could be harmful to fertility. Age, medical conditions, genetic diseases, and epigenetics can also negatively impact fertility [14,22]. Recently, it was proposed that the lack of natural selection among humans has been matched by a decline in reproductive functions [23].

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 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°C - 4 °C [24,25]. Moreover, the standard diaper styling allows for free passage of feces, including fecal bacteria, to the genitals, which can lead to acute or chronic urogenital infection. The present article proposes that the use of disposable diapers for newborns and infants can be detrimental to the child's health and reproduction functions in adulthood.

Maintaining testicular temperature

The optimal temperature range for normal spermatogenesis is 32°C - 34 °C [26], which is the average temperature range in the scrotum. 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 [27,28], with the severity of testicular harm dependent on the duration and amplitude of the fever [29]. 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. The tunica dartos muscle forms

the lining of the scrotum and relaxes when exposed to high temperatures, which leads to movement of the testes farther away from the body, resulting in its subsequent cooling. The cremasteric muscle is located in the spermatic cord and is also involved in moving the testes farther forward from the body. The scrotal sac is also involved in testicular thermoregulation, by contributing to heat loss through evaporative cooling [30]. An additional mechanism involved in counter-current heat exchange involves the pampiniform venous plexus which removes and diverts heat from arriving warm arterial blood to the cooler venous blood leaving the testes [31-34]. 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 [28,35]. High scrotal temperatures also increase the risk of testicular cancer [36]. These data underscore the importance of scrotal ventilation and maintenance of the physiological scrotal temperature.

Heat stress in adult 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 ejaculation [37]. Lifestyle, occupational, environmental, and pathophysiological factors contribute to increased scrotal temperature range. A major outcome of heat stress on the testis is apoptotic destruction of germ cells [38], a bulk for further spermatogenesis. A 1 °C increase in testicular temperature results in a more than 14% drop in spermatogenesis [39,40]. Hyperthermic exposure to spermatozoa impacts spermatozoa count, morphology, aneuploidy [41], and DNA integrity and triggers apoptosis [42,43], which results in poor fertilization capacity [44]. Chronically elevated scrotal temperature can lead to testicular germinal atrophy, spermatogenic arrest, and aneuploidy of sperm cells [41]. Testicular heating mostly affects spermatocytes and round spermatids in adulthood [27,45,46] and has therefore been proposed as a method of male contraception [47-50].

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 [51,52]. Indeed, significantly higher than average testicular temperature was measured in wheelchair-bound paraplegic men with spinal cord injuries [53]. In line with the above, the incidence of pathospermia among men with sit-down jobs, such as professional drivers, is significantly higher, as compared to other professionals, with increased prevalence in proportion to the number of years of driving [54] and delayed conception [55]. Similarly, scrotal temperature was 1.5°C - 2 °C higher in clothed as compared to naked men [56]. Further, sperm concentration gradually decreased after three months in men who regularly wore tight-fitting clothes and gradually increased after a change to loose-fitting clothing [57]. Also, the improvement of sperm motility and sperm morphology was statistically insignificant after three months by nocturnal scrotal cooling [58] with a positive trend of improved male fertility [59]. Taken together, these studies underscore the role of genital heat stress in impaired semen quality.

Heat stress affects spermatogenesis also in an 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 [60]. The BTB is responsible for the anchoring of spermatogonia to Sertoli cells, and the differentiation of mature spermatogonia to primary spermatocytes [61,62]. 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 the start of puberty with a further increase during puberty, and then gradually increases to adult values after 25 years of age [63]. Transient heating of the testis results in a broad range of changes in Sertoli cell function [64,65]. A reduction in the number of Sertoli cells in mice was noted one month following a single, 30-minute exposure to 42 °C [66]. Increasing the temperature to 37 °C inhibited Androgen Binding Protein (ABP) production by Sertoli cells [67]. Microscopic examination of the rat testis after heat exposure showed mitochondrial degeneration, dilatation of the smooth endoplasmic reticulum, and wider spaces between Sertoli cells [68], all of which adversely impact normal spermatogenesis.

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 [69-71]. Serum and testicular testosterone concentrations are also appreciable up to about 6 months of age, after which, they drop to low levels until puberty [70,71]. Steroidogenic Acute Regulatory Protein (StAR) gene expression and testicular testosterone concentrations declined in the 48 h after scrotal insulation in bulls [72], indicating a severe impact of heat stress on steroidogenesis in Leydig cells.

Heat-stressed cell apoptosis

Cell apoptosis can be induced by many triggers, with temperature being a strong inducer of the process [73]. Heat-stressed Sertoli and spermatogenic cells undergo apoptosis [74,75]. 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) [76] (Figure 1). Molecules of one pathway can be influenced by molecules in the other [77]. Additional cell death pathways include the perforin/granzyme pathway [78] and the tumor suppressor p53 pathway [79]. 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 [80].

Possible adverse effects of diaper usage on fertility

As spermatocytes and round spermatids are not present in infancy [81], 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.

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 and 3 °C, respectively [24,25]. 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 [24]. However, there is 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 (Figure 2). 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 forms a self-mitotic-replicating pool (warehouse) of spermatogonial stem cells that will contribute to future spermatogenesis [82-84]. During these periods, mitotic gonocytes and spermatogonia are vulnerable to heat stress [85-87].

As proliferation and transformation of spermatogonia occurs in the first period of life, associated with high levels of testosterone, differentiation of spermatogonia into primary spermatocytes begins later, at the age of 3-5 years [88], when the level of testosterone is low. 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 [89]. The endocrine activity at different ages affects testicular development. The testis of boys <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 and 18 years, the testes rapidly increase in size to about 12 g each and later to an adult size of 20-25 g [90]. This testicular development is driven by the proliferation of all types of testicular cells, including gonocytes and somatic cells, and is

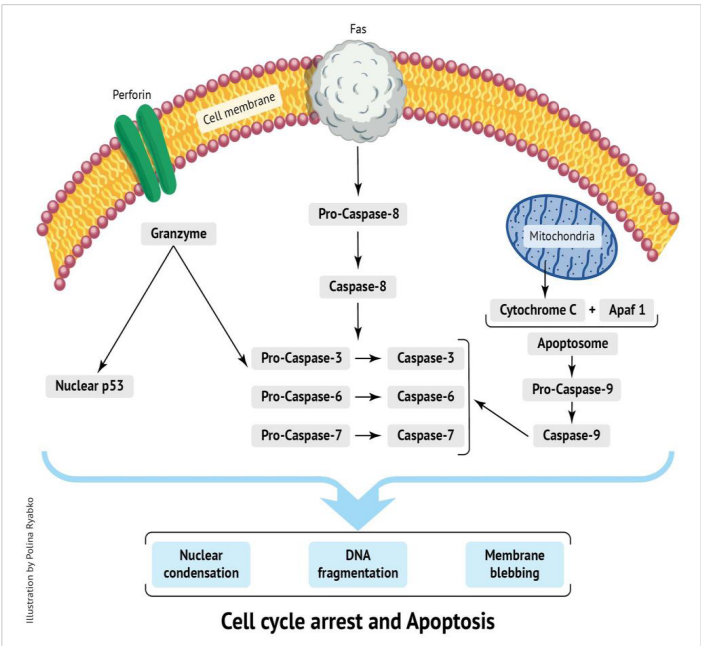

Figure 1: Effect of stress on testicular functions.

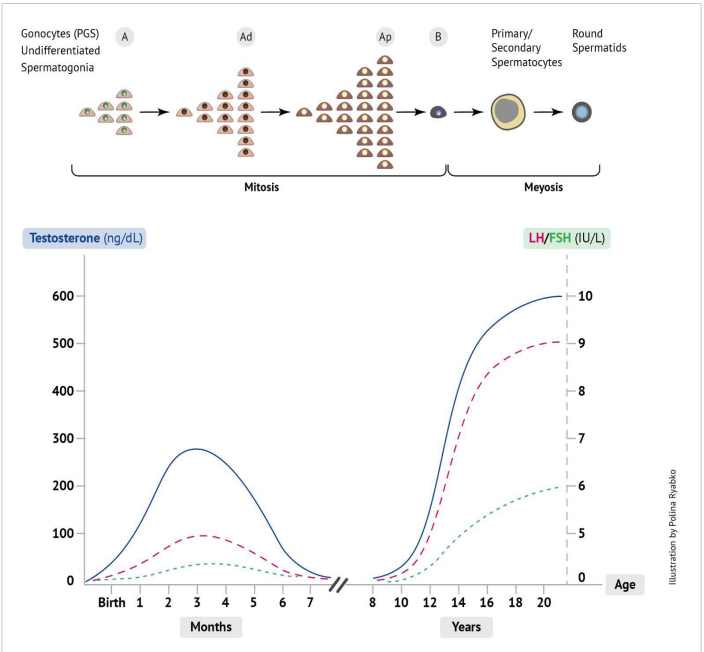

Figure 2: Endocrine axis and spermatogenesis at neonate, infancy, and puberty.

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 [63]. Lower testicular volume and sperm count were observed in monkeys subjected to reversible blockade of the pituitary-gonadal axis during early postnatal life [92]. 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 [92]. This can be explained by the impaired transition of gonocytes into type Ad spermatogonia in cryptorchid testes [93], which has been associated with spermatogenic arrest [94]. Indeed, undescended testicles contain a significantly lower number of Ad spermatogonia, which is a high risk for subsequent infertility, as compared to descended testes [95-97]. In line with the above, infants with low Ad stem cell counts later showed 25 times lower spermatozoa count as compared to men with normal numbers of Ad stem cells in infancy [98]. One of the explanations for infertility in cryptorchidism is the negative effect of body temperature stress on the proliferation and differentiation of spermatogonia in the neonate and infant testicles [99,100].

Currently, there is growing evidence that the scrotum requires a low physiological temperature in the neonatal period as well. Taken together, diaper use during infancy may have a negative impact on fertility after puberty.

Possible 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*) [101], which maintain a local pH, rendering it difficult for other, external microorganisms to develop and grow. When contaminated, for example by fecal microorganisms, the balance of the microbiome is disrupted. This can lead to an acute inflammatory process of the genital and urinary tracts, followed by chronic inflammation.

Bacterial families of fecal origin are divided into six major groups: Prevotellaceae, Ruminococcaceae, Lachnospiraceae, Enterobacteriaceae, Moraxellaceae, and Aeromonadaceae, which include well-known genera and species, such as *Ruminicoccus*, *Clostridium*, *Bifidobacterium*, *Helicobacter*, *Streptococcus*, *Mycobacterium*, *Actinomycetes*, *Campylobacter*, *Escherichia coli*, *Enterococcus fecalis*, and others. Some of these genera (*Enterococcus*, *Enterobacter*, *Helicobacter*, *Campylobacter*) are resistant to antibiotics.

In both disposable and reusable diapers, feces, especially in a soft state or liquefied by urine, easily spread to the front compartment of the diaper, providing access to fecal flora to the genitals and urethral tract. Typically, half of infected infants are asymptomatic [102]. 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 [103-106]. *E. coli* is the most frequent bacterial pathogen responsible for UTI, accounting for 85% - 90% of cases [107], followed by *Enterococcus faecalis* [105]. However, asymptomatic colonization of the urinary tract can occur and may be missed in as many as 50% of infants who need to get to primary care [108]. Among infants presenting with fever, the overall prevalence of UTI was 7% [103]. Before the age of 1 year, the incidence of UTI in boys is higher than in girls. Shaikh et al. found a 7.5% and 20.1% incidence of febrile UTI in female and male infants less than three months of age, respectively [103]. However, after 1 year, girls are much more likely to develop a UTI than boys [109].

The number of infants treated for UTI is steadily increasing [110,111]. For example, in 2013, aggregate hospital charges for inpatient UTI management exceeded 630 million dollars [112]. UTI in children is of concern because it can be associated with acute mortality (i.e., urosepsis) and/or chronic medical complications, such as renal scarring, hypertension, chronic renal insufficiency, and pre-eclampsia [111,113,114]. Approximately 10% of young infants with UTI have concomitant bacteremia. A study conducted in 7 Houston (TX, USA) day-care centers found that 19% of diapered children were colonized with resistant *E. coli* [115]. 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 [116].

Endometriosis is a common benign gynecological condition affecting 15% of women at reproductive ages and is associated with chronic pain and reduced quality of life [117]. The etiology and clinical course of endometriosis are not yet clear [118]. Recently, it was suggested that genital, intestinal, and oral microbiota influence the development of endometriosis [119]. It was shown that microorganisms of fecal origin, such as *E. coli* and *Enterococcus* could be involved in endometriosis and uterine infection by shifting the intravaginal pH to higher than 4.5 [120,121]. Increased presence of *Enterobacteriaceae*, *Streptococcaceae,* and *Staphylococaceae* bacteria, alongside a decrease in the normal flora of *Lactobacillaceae*, were detected in endometrial swab and cervical mucus samples from women with endometriosis [122,123]. A difference in the distribution of the microbiota from the lower to the upper reproductive

tract has been shown in patients with endometriosis, with a gradual microbiota increase and spreading up the reproductive tract [124].

Microbiological analysis detected asymptomatic genital tract infection in more than 40% of in vitro fertilization (IVF) couples [125]. Analysis of genital swabs from females failing IVF showed the presence of *Enterococcus faecalis*, *Escherichia coli,* and *Streptococcus agalactiae*. In sharp contrast, 86% of couples with successful IVF outcomes showed microbiologically negative results [125]. In line with this, there are no data regarding the effect of fecal contamination of the genital tract in infancy and childhood, and inflammation of the endometrium on female reproductive functions in adulthood. In male IVF patients, increases in sperm cell DNA fragmentation, and decreases in sperm cell concentration, motility, progressive motility, and protamine composition have been associated with bacteriospermia, partly of intestinal origin [126]. The same work showed that the fertilization rate of oocytes by sperm cells from patients with bacteriospermia (*Staphylococcus*, *Escherichia coli*, *Enterococcus faecalis*, *Streptococcus agalactiae*) was significantly reduced compared to patients without bacteriospermia. *Enterococcus faecalis* was the most prevalent species in bacteriospermia-positive semen samples and was found to negatively affect both sperm cell morphology and motility [125]. Both *E. coli* and *E. faecalis* are the most frequent pathogens in chronic prostatic infections [127]. The relationship between this pathology in adulthood and fecal contamination of the genitals and urinary tract during infancy and childhood remains to be verified.

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 male and female health and reproductive functions both in childhood and adulthood. Therefore, further investigation of the health implications of the current diaper template is warranted. Recommendations on the measures to be taken on the use of disposable diapers may include reducing as much as possible the utilization of diapers both in daily use and age and leaving neonates, infants, and toddlers without diapers as much as possible at every opportunity. The development of a new diaper design could potentially help treat newborns more naturally and possibly partially prevent infertility in adulthood.

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