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Environmental Estrogen-like Endocrine Disrupting Compounds and the Dangers they pose on Male Fertility: Review Case of Nairobi River Water

Mutembei Henry M'Ikiugu[1,2], Kipyegon Ambrose Ng'eno[2] and Mutiga Erastus Riungu[2]

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[1]Wangari Maathai Insitute for Peace and Environmental Studies, University of Nairobi, Kenya.
[2]Department of Clinical Studies, University of Nairobi, Kenya

ABSTRACT

Concerns were raised by pig farmers in Nairobi that suggested the presence of compounds within the water of Nairobi river capable of affecting male fertility through increased incidence of retained testis in piglets. Series of studies were conducted to verify the concerns of these farmers. Significant number (x^2=72, p≤0.05, n=80) of the farmers residing along the riparian were involved in urban agriculture and utilized the water from this river to rear pigs. The residents reported a 10% incidence (n=180) of retained testis in piglets born to sows accessing the river water. The levels of 17β-estradiol and alkylphenol in the sampled water of Nairobi river were in clinical significant levels (p≤0.05) (0.95µg/L for 17β-estradiol and 0.36µg/L for alkylphenol). The seminiferous tubules of the testis of the boars accessing the water revealed significant lesions likely to affect male fertility (P≤0.05); epithelial vacuolations, sloughed germ cells and patches of depleted tubules. The lesions were confirmed in the seminiferous tubules of naive experimental mice exposed to the same water for a period of 40 days in a laboratory. The results reviewed suggest presence significant levels of 17β-estradiol and alkylphenol compounds within the water of Nairobi river capable of affecting male fertility. It is recommended that a policy is needed to address the pollution of the water in Nairobi river in order to prevent the effects of such compounds on animals and/or humans.

Key words: Environmental pollutants, Endocrine disrupting compounds, Male fertility.

*Corresponding author. E-mail: hmutembei@uonbi.ac.ke

INTRODUCTION

Steroids play an important role as endocrine factors in the local control of male fertility through control of testicular function. They do this via specific target cells of the testis by stimulating their specific intranuclear receptors (Setchell et al., 1983; Hoffmann et al., 2010). Substantial studies are now available that relate the inherent relationship between production and function of steroids in the testis on one hand and overall male fertility on the other (Raeside et al., 2006; Mutembei et al., 2009; Hoffmann et al., 2010; Zdunczyk et al., 2012). Among males of mammalian species, the pig is exceptional in exhibiting extraordinarily high blood concentrations of numerous steroids including testosterone, dehydroepiandrosterone and estrone. The synthetic pathways, transport and the biological roles of these hormones are yet to be fully understood. However comparative measurements in the testicular artery and vein clearly showed that the steroids addressed so far do not primarily result from peripheral inactivation of free steroids but are mainly produced in the testicular-epididymal compartment (Setchell et al., 1983; Mutembei et al., 2009; Hoffmann et al., 2010; Zdunczyk et al., 2012). Environmental endocrine disrupting compounds (EDCs) that originate from household, industrial and agricultural wastes have the potential to affect fertility and are already being suspected in reproductive and developmental problems observed in animals and humans

Figure 1. Two sections of Nairobi River showing cases of water pollution and exposure of pigs to polluted water (sourced from Ambrose Kipyegon, Nairobi, 2016).

(Colborn et al., 1993; Brevini et al., 2004; Sharpe and Irvine, 2004). It is suggested that the EDCs achieve the observed effects by interfering with steroid endocrine signalling pathways at the receptor level during active reproduction and/or in embryological processes (Colborn et al., 1993). They are believed to alter and/ or reverse effects of androgens during these processes (Svechnikov et al., 2014). Presence of EDCs has been demonstrated in polluted river water draining busy urban cities (Kolpin et al., 2002; Stevens et al., 2003).

The EDCs present in that kind of polluted water have also been linked to disrupted male fertility by altering the function of testicular steroids (Hecker et al., 2002) and impairing gonadal development and spermatogenesis (Hemming et al., 2001; Sheahan et al., 2002). The EDC effects have specifically been shown to be as a result of estrogen-like actions at the steroid receptor level (Andersen et al., 2002). The pig served as a model to elucidate the effects of EDCs on male fertility because in most African urban farming setups the pig is reared using river water that in most cases drains through contaminated riparian catchment areas. There is striking resemblance between the genome of the pig and that of humans and understanding how the EDCs in such water would affect humans. The pig can be used to inform policy on humans accessing the same water through various carbon chains. Environmental water contamination with EDCs is an increasing phenomenon in developing countries due to human activities (Siyanda et al., 2015). The EDCs in such contamination emanates from released natural and synthetic substances containing phenols and phenolic containing compounds, which already have been proven to be estrogen-like endocrine disrupting compounds (Kavlock, 1996). Exposure to EDCs is likely to be through consumption of contaminated drinking water (Norstrom, 2002). Although it can be argued that such levels would be low in every bout of drinking, they can significantly build up in body of an animal or human after prolonged period of exposure (Meijer et al., 1999; Rhind et al., 2010). This is the likely case for pigs reared along the riparian of the polluted Nairobi River in Kenya (Figure 1). Some Nairobi residents are known to practice urban farming that includes rearing of pigs using polluted river water (Ndeda and Manohar, 2014). Concern has been raised on the effects of EDCs in the polluted water of Nairobi River. Farmers rearing the pigs along the riparian of the polluted Nairobi River reported an abnormally high incidence of infertility in mature male pigs (boars) and high incidence retained testis/es (mono-/ cryptochidism) in the piglets (Kipyegon et al., 2016a). These cases were suspected to be caused by EDCs in the water because, in the case of retained testis, the descent of the testis is highly dependent upon normal functioning of testicular testosterone through regulation of INSL-3 gene (Mutembei et al., 2005). Thus, the observed situation was suspected to be caused by estrogen-like endocrine disrupting compounds in the water of Nairobi River that tended to reverse normal functioning of testosterone at the receptor level (Sharpe and Irvine, 2004).

On the other hand, infertility of the boar is a reflection of disrupted process of spermatogenesis, which in normal cases, is mediated through the Hypothalamic-Pituitary-Leydig cell endocrine axis (Mutembei et al., 2005). Similarly there exist also an important local paracrine and autocrine regulation mechanism, mostly involving a delicate balance for steroid production within the testis to regulate spermatogenesis (Huleihel and Lunenfeld, 2004). The duration of spermatogenesis in the boar is 39 days with a daily production of at least 30-60 $x10^9$ of spermatozoa (Frankenhuis et al., 1982; Mutembei et al., 2005). Thus, this process could be very prone to dangers of endocrine disruption. Endocrine disruption of testicular function and spermatogenesis is manifested by failure of testis to descend during postnatal period trough

(Skakkebaek et al., 2001; Damgaard et al., 2002; Main et al., 2007; Bay et al., 2011) and vacuolation and germ cell sloughing within the seminiferous tubules in adulthood (Creasy, 2001). The effects in postnatal period is attributed to impaired INSL-3 gene expression that interferes with gubernaculum development (Emmen et al., 2000) while the effects in adulthood are due to anti-androgenic action. These observations in the pig led to a series of studies that sought to expound the potential danger of EDCs in polluted river water on male fertility based on the fact that such water is likely to contain varying levels of EDCs (Kolpin et al., 2002; Lintelmann et al., 2003). The pig was chosen as a model to inform policy on effects of EDCs on human beings. The results of the reviewed studies aim to inform advisory policy on protection of the water resource to avoid effects of such EDCs on humans and animals.

RESULTS AND DISCUSSION

A survey of the pig farmers along the riparian of Nairobi river in Nairobi city (*Kipyegon* et al., 2016a) indicated a high association between failure of the testis/es to descend (retained testis/es) and the consumption of polluted water by the affected pigs (X^2 = 22.93, P=0.01, n=80). Similarly, the retention of the testis/es was highly associated with the riparian zone where the pigs were reared (extent of water pollution, X^2 = 35.95, P= 0.01, n=80). There was no association between the level of education of the respondents and preference in the choice of water they used for pig rearing (X^2 = 2.08, P= 0.01, n=80). The use of polluted water for farming in Nairobi has been reported previously (Kagira and Kanyari, 2010). Thus, it was not surprising to find out that farmers from Kibera, Mathare and Dandora settlements of Nairobi utilized such water for pig rearing. Such water has been reported to contain effluents from household and industry waste due to lack of- or inadequate sewerage facilities (Norah et al., 2015). Additionally, the farmers have been reported to use such water because it is not associated with costs, easy to access and is convenient to them (Kagira and Kanyari, 2010; Ndunda and Mungatana, 2013; Kipyegon et al., 2016a). Cryptorchidism is the failure of testicles to descend into the scrotum (Svechnikov et al., 2014). The exact cause of testicular retention is not yet fully understood but exogenous estrogens and compounds with anti-androgenic effects have been linked to this condition (Damgaard et al., 2002). Estrogen-like EDCs have been shown also to pose anti-androgenic effects with a potential danger of causing cryptochidism (Main et al., 2007; Svechnikov et al., 2014). Consequently, it was correct to suspect that the polluted water of Nairobi river contained estrogen-like EDCs, just like such waters draining urban cities have been shown to contain similar EDCs (Rhind et al., 2010), which were also associated with the testicular retention (De Falco et al., 2015).

Examined sections of the seminiferous tubules of the affected testis (Kipyegon et al., 2016b, 2017) revealed significant seminiferous tubule lesions (Vacuolation, and germ cell sloughing and depletion) in animals exposed to drinking of polluted Nairobi river water.

In the contrast, within the experimental study, the histology of the tubules obtained from control group of mice exposed to clean water were devoid of testicular lesions ($p \leq 0.05$), clearly indicating that the pathological lesions observed were associated with drinking of polluted water. Similar findings have been reported in rats exposed to known estrogen-like EDCs (Adamkovicova et al., 2014), which then suggest that the water the boars and mice consumed from Nairobi river contained such EDCs. Vacuolation within seminiferous epithelium of the testis and sloughing of germ cells with partial depletion of the seminiferous epithelium have been previously demonstrated to be indicative of environmental endocrine disrupting toxicity, pointing towards effects of estrogen-like EDCs on the testicular tissue (Knez, 2013).

The EDCs of this nature are toxicants expected with increasing human population and industrialization that lead to an increase in the factory, farm land and domestic waste discharges into the environment (Bustos-Obregón and Hartley, 2008; Knez, 2013).

The estrogen-like EDCs in water affect animals through ingestion of polluted water or feed (Norstrom, 2002). Although it may be argued that the exposure rates of such contaminants are low and the reproduction of the animals may remain unaltered by such low levels of exposure (Rhind et al., 2010), certain production systems like urban farming in Nairobi continuously expose animals to an extent that lead to a build-up of high concentrations of environmental EDC contaminants to cause reproductive side effects (Norstrom, 2002). It is therefore correct to postulate from these study results that the observed effects are likely due to prolonged exposure of estrogen-like EDCs in polluted water of Nairobi River. Analysis of the polluted water of Nairobi River (Kipyegon et al., 2016c) revealed significant detrimental levels of two estrogen-like EDCs ($P \leq 0.05$); 17β-estradiol and alkyphenol.

The levels of the two estrogen-like EDCs reported in this case study were comparable to those reported by Sole et al. (2000) for similarly polluted water and to some extent higher than those reported by Jafari et al. (2009).

The difference might be due to different extents of pollution in different situations as pointed out by others (Johnson and Sumpter, 2001; Zhang et al., 2014). What is similar to all of these studies and that of our case is the fact that urban river waters are likely to contain detrimental levels of estrogen-like EDCs capable of affecting male fertility (Bello et al., 2014). What was surprising is the fact that the levels detected for the two EDCs in three riparian zones of the Nairobi river (upper, middle and lower zones at 10 km spacing) were all significantly higher ($p \leq 0.05$) than the documented detrimental levels capable of causing cryptochidism in postnatal period and lesions in seminiferous tubules of the testis in adulthood (Aerni et

al., 2004). It is therefore correct to confirm that presence of the two estrogen-like EDCs within the water of Nairobi river pose a danger of causing lesions in the test is capable of affecting male fertility.

From the review of the series of studies conducted in Nairobi, it is in order to point out that alkyl phenol and 17β-estradiol compounds are estrogen-like EDCs found within the polluted water of Nairobi river that have the potential to disrupt male fertility by causing cryptochidism and lesions within seminiferous tubules of the testis. Contamination of river water by estrogens or estrogen-like compounds has been suspected to be a concern for male infertility (Sim et al., 2010; Zhang et al., 2014) due to their ability to cause endocrine disruption due to reversal of the functions of androgens like testosterone (Baronti et al., 2000). There are reports of detected 17β estradiol in polluted river water (Peng et al., 2008; Jafari et al., 2009; Knez, 2013), and in stagnant waste water within urban areas (Ma et al., 2007; Ying et al., 2012).

In the currently review results, there are indications that prolonged exposure of farmed animals to polluted water with environmental estrogen-like EDCs can lead to male infertilities. Cryptochidism and male infertility have been demonstrated in other animals chronically exposed to estrogen-like EDCs in polluted water (Skakkebaek et al., 2001; Damgaard et al., 2002; Main et al., 2007; Paul et al., 2005; Bay et al., 2011; Bellinghan et al., 2012; Svechnikov et al., 2014). Thus, as supported by similarly concluded consistent observations on effects of estrogen-like endocrine disrupting compounds on male fertility by other authors (Hecker et al., 2002; Jobling et al., 2002; Sheahan et al., 2002; Paul et al., 2005; Rhind et al., 2010), one can deduce that Nairobi river water contains sufficient levels of estrogen-like environmental pollutants capable of affecting male fertility.

In consistence with other authors (Wandiga, 2001; Falconer et al., 2006; Ndeda and Manohar, 2014; Siyanda et al., 2015; Sole et al., 2000; Jafari et al., 2009; Zhang et al., 2014), the water draining through Nairobi urban settlement would tend to be contaminated with such pollutants mainly from farm land, industry and household waste.

CONCLUSION

Based on the reviewed study results in Nairobi, it is concluded that the polluted water of Nairobi River contains significant levels of 17β-estradiol and alkyl phenol compounds that are estrogen-like EDCs capable of affecting male fertility due to retained testis and lesions within seminiferous epithelium of the testis. Using this as an example it is also concluded that water of rivers draining urban cities in developing countries pose a danger to male fertility due to contamination with estrogen-like environmental pollutants.

RECOMMENDATION

It is prudent to have policy in place that can lead to public awareness on the risks associated with the utilization of the polluted water of Nairobi river water for urban farming. In addition, further studies are also required to determine if similar effects would be observed in other males, especially in men, consuming farm produce like kales farmed using the polluted water of this river.

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