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The impact of antenatal bisphenol a exposure on male reproductive function at 20–22 years of age

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KEY MESSAGE

Our findings suggested no adverse impact of antenatal BPA exposure on adult testicular function with a marginal positive correlation with sperm concentration and motility. However, as there was no association with testicular volume, testicular or pituitary hormones and total sperm output, these findings may be purely chance associations.

A B S T R A C T

Bisphenol A (BPA) is a ubiquitous chemical suspected to possess oestrogenic hormonal activities. Male population studies suggest a negative impact on testicular function. As Sertoli cell proliferation occurs during fetal or early postnatal life, it is speculated that oestrogenic environmental exposures may influence mature testicular function. Among 705 Western Australian Pregnancy Cohort (Raine) Study men aged 20–22 years, 404 underwent testicular ultrasound examination (149 had maternal serum available), and/or 365 provided semen (136 had maternal serum) and/or 609 serum samples for sex steroids, gonadotrophins and inhibin B analysis (244 had maternal serum). Maternal serum collected at 18 and 34 weeks' gestation was pooled and assayed for concentrations of total BPA (free plus conjugated) as an estimate of antenatal exposure. Testicular volume was calculated by ultrasonography, and semen analysis performed. Serum LH, FSH and inhibin B were measured by immunoassay; testosterone, oestradiol, oestrone and

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BPA were measured by liquid chromatography-mass spectrometry. BPA levels were detectable in most (89%) maternal serum samples. After adjustment for maternal smoking, abstinence and varicocele, sperm concentration and motility were significantly correlated to maternal serum BPA (r = 0.18; P = 0.04 for both). No other associations of maternal serum BPA with testicular function were observed.

Introduction

In recent times there has been an increasing awareness of the potential for the environment to affect reproductive health. The conflicting evidence regarding the hypothesis that sperm counts have been diminishing over the last 30 years has been fiercely debated (Cooper and Handelsman, 2013; Levine et al., 2017), but the incidence of undescended testis, hypospadias and testicular cancer is increasing in some countries (Handelsman, 2001; Skakkebaek et al., 2016; Toppari et al., 2010; Znaor et al., 2014). There has been speculation that environmental exposures to xenoestrogens may be implicated in this purported decline in sperm counts (Skakkebaek et al., 2016). The so-called 'testicular dysgenesis syndrome' (TDS) hypothesis proposes that, as a result of abnormal testicular development, a secondary abnormality in Leydig and/or Sertoli cells results during male sexual differentiation, leading to reproductive disorder in later life (Bay et al., 2006; Vidaeff and Sever, 2005), although this has been disputed (Akre and Richiardi, 2009). Animal studies have demonstrated that toxicological exposure to oestrogens (Sharpe et al., 2003), androgen receptor blockers (Atanassova et al., 2005) and environmental endocrine disrupters (van den Driesche et al., 2017) can elicit alterations in testicular function. Hence it is plausible, but unproven, that human fetal Sertoli cell proliferation may be altered by an excessive oestrogenic environment in early life.

Despite the increasing prevalence of oestrogenic endocrine disrupters in the environment, comprehensive animal studies show no decline in sperm production in farm animals over the last century (Setchell, 1997), although more recent data suggest a recent decline in semen quality, but not sperm output, of dogs used in breeding (Lea et al., 2016). Evidence collated by the World Health Organization (WHO) from human epidemiological studies links endocrine-disrupting chemicals with a wide variety of health effects including reproductive effects, neurobehavioral and neurodevelopmental changes, the metabolic syndrome, bone disorders, immune disorders and cancers (WHO, 2012), although whether these are causal effects or associations remains unclear from observational data.

Bisphenol A (BPA), first synthesised in 1891, has been widely used since the 1950s in the manufacture of polycarbonates, epoxy resins and plastics (vom Saal et al., 2007) with over 100 tonnes released into the atmosphere every year. Unconjugated BPA binds as a weak agonist to the oestrogen receptors α and β, although it is a potent activator of the non-classical oestrogen pathway, the G protein-coupled oestrogen receptor and the orphan nuclear receptor oestrogen-related receptor γ (summarized by Minguez-Alarcon et al., 2016). In the circulation, 95% of BPA is protein-bound (Teeguarden et al., 2013); peak serum BPA concentrations are reached 60–90 min after exposure and it is rapidly eliminated (Völkel et al., 2002). Free BPA is rapidly conjugated to form inactive glucuronides and sulphates by the liver of the mother and fetus, and also by the placenta prior to urinary excretion (Balakrishnan et al., 2010). However, the placenta can also deconjugate BPA via the actions of the placental sulphatase enzyme, potentially increasing fetal exposure, although the significance of placental metabolism is probably small (Balakrishnan et al., 2010). Serum levels of free BPA have been reported to be below the limits of detection (<0.2 μg/l) in several cohorts (EFSA Panel on Food Contact Materials, 2015; Teeguarden et al., 2013). Median levels have been calculated to be <2 pM, far below levels required to activate oestrogenic receptors (Teeguarden et al., 2013). This has led to doubts around the potential for environmental BPA exposure to exert endocrine-disrupting effects (Teeguarden et al., 2013). On the other hand, several studies have reported much higher circulating BPA values in pregnancy and in cord blood, although these studies have been criticized on the basis of potential problems with external contamination and assay methodology (Teeguarden et al., 2016).

BPA has oestrogenic effects in a wide range of reproductive toxicological and developmental studies, including on the developing breast of male and female rats, as well as leading to a reduction in the sperm production of mature male rats (Hass et al., 2016; Mandrup et al., 2016). Nevertheless, human studies of the reproductive effects of BPA exposure are inconclusive (Minguez-Alarcon et al., 2016), as would be predicted if most human environmental exposure to BPA is below the level required to activate receptors and exert effects (Teeguarden et al., 2013).

In this study we aimed to explore the potential influence of maternal BPA exposure on subsequent adult male reproductive function, by evaluating stored maternal antenatal serum from a birth cohort and relating total maternal BPA concentrations (as a surrogate of fetal exposure) to mature male reproductive function.

Methods

The raine study

The Western Australian (WA) Pregnancy Cohort (Raine) Study (www.rainestudy.org.au) was designed to measure the relationships between early life events and subsequent health and behaviour. The study recruited nearly 3000 women at 18 weeks' gestation in 1989–91 who delivered 2868 live-born children (Newnham et al., 1993). Mothers were enrolled over a total of 30 months, from May 1989 to November 1991. The last children were born in April 1992. The 2868 children (including 1454 boys) born to 2804 mothers were retained to form the Raine Study cohort. The study aimed to investigate the role of perinatal events on subsequent childhood and adult health. The cohort is unique because of the availability of multiple detailed antenatal, postnatal and childhood measurements. Subjects were randomized to an intensive investigation where maternal blood samples were collected at 18 and 34/36 weeks of gestation (and stored in aliquots without thawing at –80°C), and fetal ultrasound measurements were made. A maternal history of cigarette smoking was recorded prospectively at 18 and 34/36 weeks' gestation. Cohort follow-up was undertaken at ages 1, 2, 3, 5, 8, 10, 14, 17, 20 and 22 years, with the latest cohort including 1433 men still alive. This makes it one of the largest and most closely followed prospective cohorts of pregnancy, childhood and adolescence in the world (Straker et al.,

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