Extremely low incidence of hypospadias in the highly POP exposed population in Greenland: Possible protective effect of androgen receptor genotype

Yvonne Lundberg Giwercman1, Knud Erik Kleist2, Aleksander Giwercman3, Gunnar Toft4, Jens-Peter Bonde4, Henning Sloth Pedersen5 (1. Dept. of Clinical Sciences, Lund University, Malmö, Sweden; 2. Centre for Arctic Environmental Medicine, Nuuk, Greenland; 3. Reproductive Medical Centre, Malmö University Hospital, Lund University, Malmö, Sweden; 4. Dept. of Occupational Medicine, Aarhus University Hospital, Aarhus, Denmark.; 5. Dept. of Surgery, Queen Ingrid’s Hospital, Nuuk, Greenland)

Exposure to endocrine disrupters, including persistent organohalogen pollutants (POPs) were suggested to increase the risk of hypospadias, a common congenital anomaly in males, affecting 0.2-0.7%. Normal male sexual differentiation is dependent on the androgen receptor (AR). AR function is regulated by polymorphic repeats of CAG and GGN trinucleotide bases. We have previously reported that GGN=23 was less frequent in patients with hypospadias than in the general population and we, therefore, suggested that this genotype contributes to the protection against the risk of hypospadias.

Greenlanders, are one of the most POP exposed populations on earth. Interestingly, among the 11,076 boys born in Greenland 1982-2002, only 2 cases of hypospadias were noted (incidence 0.02%; 95% CI: 0.002-0.06), which is 10 times lower than in Sweden. In Greenland 85% were carriers of GGN=23 (Sweden 52%). The activity of the AR carrying GGN=23 was in vitro compared with GGN=10, 24 and 27, respectively, in the presence of 0.1-100 nM testosterone or DHT. At 100 nM DHT, GGN=24 showed 35% lower transactivating activity (95% [CI]: 20-50%) than GGN=23. GGN=10 and GGN=27 also showed significantly less AR activity than GGN=23. The same trend was also observed at lower DHT concentrations. In response to testosterone, GGN=23 activity was significantly higher than for other lengths.

In conclusion, GGN=23 is superior in function in response to both testosterone and DHT than shorter or longer repeats. The adverse effect of endocrine disruptors on male reproductive function can be modified by polymorphisms in the AR and other strategic genes.