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1 **Intrauterine exposure to drugs and reproduction – still reasons for concern!**

2

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13

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25 **Abstract**

26 The last decades have seen an increasing use of pharmaceutical drugs worldwide and the chemical
27 compounds have become ever more intertwined in lifestyles across the globe. Alone in the US,
28 statistics show that half of the population has taken at least one prescription drug within the last
29 month. The high use of pharmaceutical compounds is not without consequence and the last century
30 has shown that especially the combination of drugs and pregnancy can result in severe outcomes. In
31 this commentary, we will cover two of these examples, respectively thalidomide and
32 diethylstilbestrol, and couple this evidence with the emerging concern that intrauterine exposure to
33 widely used mild analgesics may also result in subtle by adverse effects. These include reproductive
34 congenital malformations that have been coupled with subsequent reproductive defects later in life.

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38 **Introduction**

39 In the last decades, xenobiotic compounds including pharmaceutical drugs have become ever more
40 intertwined in everyday life across the world. Simultaneously, evidence show that infertility affects
41 approximately 10-15% of the population in developed countries (Ombelet 2011; Rutstein and Shah
42 2004). This increase in infertility is suggested to have many causes including genetic differences,
43 fetal exposures, recreational drug or alcohol abuse, dietary issues, environmental or occupational
44 exposure to reprotoxicological agents, and pharmaceutical drugs (Skakkebaek et al. 2015). Due to
45 these multiple factors underlying infertility, it is hard to understand the etiology of the disorder and
46 whether it is due to a specific exposure from drugs. However, it remains that drug use is high across
47 the world. This is evident in the US, where in a period from 2011-2014, approximately half of the
48 U.S. population (48.9%) had taken a prescription drug in the last 30 days, with 23.1% of the
49 population having taken three or more prescription drugs during the last month (National Center of
50 Health Statistics 2017). This is likely an underestimation, as the data does not include non-
51 prescription drugs and over-the-counter drugs like mild analgesics consisting of non-steroid anti-
52 inflammatory drugs (NSAIDs) and N-acetyl-para-aminophenol (paracetamol/acetaminophen
53 (APAP)). The increase in exposure to drugs is exemplified by the increase in number of patients
54 placed on long-term medication regimens at a young age (including potential mothers) due to e.g.
55 diabetes, chronic migraine, epilepsy or clinical depression (Samplaski and Nangia 2015;
56 Westergaard et al. 2016; Lindsay and Loeken 2017). This results in a substantial number being at
57 risk of experiencing a decrease in fertility due to side effects of maternal drug treatment. The last 50
58 years have shown that this risk is not negligible, as drugs have been shown to disrupt reproduction
59 through prenatal and adult exposures by hormonal and non-hormonal mechanisms.

60

61

62 **Thalidomide**

63 The disastrous implications after maternal use of thalidomide during pregnancy is a solemn
64 reminder that the intrauterine period is a time of high vulnerability. Thalidomide (α -phthalimido-
65 glutarimide) is an immunomodulatory drug and the prototype of the thalidomide class of drugs
66 (Foster 2017; Nooka and Lonial 2019). Today, it is mainly used as a treatment of cancers (e.g.
67 multiple myeloma) due to its anti-angiogenesis effects. During 1957-1961, this anti-cancer drug
68 was sold in most European countries as a nonbarbiturate hypnotic sedative which was able to
69 produce deep sleep without hangover or risk of dependency or overdoses. In addition to this, the
70 secondary anti-emetic effect made it popular among pregnant women suffering from morning
71 sickness. This resulted in a tragedy as thalidomide was developed and introduced prior to formal
72 testing for harmful effects. The maternal use resulted in an increased rate of miscarriages in the
73 pregnant women and among the newborn, more than 10,000 were born with a range of severe and
74 debilitating malformations (Vargesson 2015; Smithells and Newman 1992). Some of these defects
75 included severe malformations of upper and lower limbs and abnormalities of the ear and eye
76 (Smithells and Newman 1992). Furthermore, genital defects were observed such as small or
77 complete absent testes, mal-descended testes (cryptorchidism), and midline fusion defect of the
78 male ventral urethra resulting in misplaced urethra opening (hypospadias) in the newborn males and
79 defects of reproductive tracts and malformations of the uterus in the females (Mani et al. 2017;
80 Vargesson 2015).

81 As thalidomide has multiple effects on body homeostasis, the specific mechanisms
82 remain debated. It has been suggested that thalidomide disrupts the early mesodermal
83 differentiation by damaging undifferentiated cells (Tachikawa et al. 2018) as well as resulting in
84 anti-angiogenesis, evasion of apoptosis and inhibition of pro-inflammatory innate responses
85 (Paravar and Lee 2008; Hideshima et al. 2000; Du et al. 2005). Furthermore, thalidomide can bind

86 as an antagonist to the androgen receptor (AR) (Capitosti et al. 2004) and hence inhibit different
87 androgens like testosterone which have a pivotal impact during development of male secondary sex
88 characteristics and reproductive tissues. The antagonistic mechanisms on AR may account for some
89 of the milder malformations like cryptorchidism and hypospadias, while the complete absent of
90 testis are more likely associated with the anti-angiogenesis effects. Hence, the defects observed
91 after prenatal thalidomide exposure are likely results of both reduced or blocked hormonal actions
92 and non-hormonal effects.

93

94 **Diethylstilbestrol**

95 A decade after the initial reports showing effects of thalidomide and prenatal exposure to a
96 hormonal active compound, the synthetic nonsteroidal estrogen diethylstilbestrol (DES), was shown
97 to be associated with reproductive developmental disruption and subsequent congenital
98 malformations (Swan 2001; Palmer et al. 2009). During a period of close to 40 years from the
99 1940s and into the 1970s, DES was prescribed for pregnant women in the belief that it was
100 preventing spontaneous abortion and premature births (Swan 2001; Johansson et al. 2017). DES
101 was finally banned from use during pregnancy in 1971 after numerous adverse effects being
102 described including different pregnancy-related problems like spontaneous abortion, preterm
103 delivery and ectopic pregnancy together with abnormalities of the reproductive tract (Jishi and
104 Sergi 2017; Adam et al. 2011; Gill et al. 1979). Among abnormalities which remain controversial
105 to this day, it was suggested that DES was associated with in increased risk of vaginal/cervical clear
106 cell adenocarcinoma (CCA) among exposed girls and testicular cancer, cryptorchidism, and
107 hypospadias in boys (Swan 2001; Johansson et al. 2017; Jishi and Sergi 2017; Adam et al. 2011;
108 Newbold et al. 1998). Recent data have suggested that some of these increased risks may be passed
109 on to the third generation (grandchildren) that never been directly exposed to the synthetic estrogen

110 (Jishi and Sergi 2017; Newbold et al. 1998; Newbold et al. 2006; Newbold 2008). Still
111 controversial, this would suggest that DES may disrupt endocrinology through transgenerational
112 epigenetic changes established during the intrauterine exposure of their parents (Walker and Haven
113 1997; Ho et al. 2017).

114

115 **Still need for concern!**

116 Although the effects of DES remain disputed, the studies conducted in order to understand the
117 effects of this estrogen have proven long lasting as they contributed to laying the foundation for the
118 development of the field of endocrine disruption. The estrogenic effects of DES made it clear that
119 hormonal active compounds can disturb the delicate reproductive development. This realization in
120 turn was instrumental for the development of the estrogen hypothesis in the early 1990s, proposing
121 that prenatal exposure to multiple hormonal active xenobiotics may disrupt reproductive
122 development (Sharpe and Skakkebaek 1993).

123 In recent years, several drugs types have been associated with prenatal problems. Of
124 these, especially the mild analgesics (from now on analgesics) used to relieve pain, fever and
125 malaise during pregnancy have received increasing attention (Kristensen et al. 2016). Rodent
126 studies have showed analgesic-induced endocrine disruptions of fetal gonadal development (both
127 testis and ovaries) resulting in infertility and premature ovarian insufficiency (Leverrier-Penna et al.
128 2018). Like thalidomide and DES, several of the analgesic drugs were developed prior to formal
129 testing and have been on the market for many decades. Acetylsalicylic acid (ASA, aspirin) was
130 developed in the 19th century and has been marketed >100 years, while APAP and
131 isobutylphenylpropionic acid (IBP, ibuprofen) have been marketed for ~60 and ~50 years,
132 respectively. Moreover, sales of analgesics have been steadily increasing over the past 20 years and
133 are now the most commonly used over-the-counter drugs worldwide. Of concern is the generally

134 high use of analgesics during pregnancy, especially for APAP, with women using well above 50%
135 across the world, as it is used without the need to consult a physician or pharmacist (Kristensen et
136 al. 2016). This concern has increased after intrauterine exposure to analgesics was suggested to
137 increase the risk of congenital cryptorchidism in two studies in 2010 (Kristensen et al. 2016). An
138 epidemiological study, using hospital registry data for cryptorchidism, reported that exposure to
139 APAP for 4 weeks was associated with an increased risk (Jensen et al. 2010), while a second study
140 using a standardized assessment of cryptorchidism combined with experimental rodent approaches
141 showed that use of analgesics during especially the second trimester increased the risk of
142 cryptorchidism through anti-androgenic mechanisms. The latter study also showed that this risk
143 remained significant when IBP and ASA were examined separately, and a tendency was seen for
144 APAP. The risk was amplified if the exposure was >2 weeks with similar results found in separate
145 analyses for APAP and ASA. The risk was highest among the few mothers who used more than one
146 compound simultaneously for >2 weeks, suggesting an additive cocktail effect (Kristensen et al.
147 2011). Subsequent studies have found similar associations to both cryptorchidism and hypospadias
148 together with reductions in anogenital distance among infants supporting the potential anti-
149 androgenic effects of analgesics (Fisher et al. 2016; Lind et al. 2017).

150 Although a subsequent meta-analysis of analgesic use during pregnancy and risk of
151 cryptorchidism was inconclusive (Gurney et al. 2017), studies using human abortion material have
152 subsequently strongly supported a direct effect of analgesics on the fetal testis (Maamar et al. 2017;
153 Driesche et al. 2015). Concern about the effects on the female reproductive development has
154 similarly been increasing after three rodent studies showed disrupted ovary development and
155 subfertility in female offspring after analgesic exposure (Holm et al. 2016; Dean et al. 2016;
156 Johansson et al. 2016). These data may suggest that APAP in the animals reduced the migration of
157 primordial germ cells or proliferation of the oogonia. This in turn lead to a decreased germ pools

158 (reduced by approximately 50%), resulting in reduced fertility in the adult rodent dams and
159 premature ovarian insufficiency (Arendrup et al. 2018).

160 The rodent data has subsequently been supported from studies using human fetal
161 gonadal explants that have been exposed to IBP and APAP (Leverrier-Penna et al. 2018; Arendrup
162 et al. 2018). These data show e.g. that exposure during the first trimester to IBP diminished ovarian
163 germ cells though a cytotoxic effect induced already after two days of exposure (Leverrier-Penna et
164 al. 2018). In male rats there has been observed a postnatal compensation of fetal germ cell reduction
165 because germ cell proliferation resumes after birth (Dean et al. 2016), a mechanism that likely could
166 also happen in human males. However, in human females, proliferation of germ cells in the ovaries
167 is restricted by the meiosis happening from week 11 of gestation, so any fetal germ cell loss is
168 irreversible and could therefore potentially have long-term consequences for oocyte reserves and
169 fertility (Arendrup et al. 2018). As mentioned above, the latter has been shown in both mice and
170 rats where in utero exposure to APAP resulted in a reduction in germ cells in both sexes but only
171 persisted into adulthood in the female and not male offspring (Arendrup et al. 2018).

172 It is still too early to be giving a precise explanation of the actions of analgesics,
173 resulting in congenital malformations. However, it is obvious that the effects of prenatal analgesic
174 exposure are much less severe and more subtle than the effects of thalidomide and DES. It is
175 therefore likely that analgesics, unlike thalidomide and DES, will continue to play a vital role in the
176 clinic for pregnant women in many years to come. It is also clear that thalidomide, DES, and
177 analgesics all share the fact that they are drugs developed in the 19th and the first of half of the 20th
178 century prior to the thorough testing seen today. Other compounds belonging to this category of
179 drugs, valproate and metformin, have recently been associated with reproductive problems after
180 prenatal exposure as well (Bertoldo et al. 2014; Veroniki et al. 2017). Especially valproate used for
181 neurological diseases such as epilepsy and migraine has caused increased concern after several

182 studies have showed increased risk of numerous congenital malformations including cryptorchidism
183 and hypospadias together with fetal loss (Rodríguez-Pinilla et al. 2008; Raghavan et al. 2018;
184 Veroniki et al. 2017). It is therefore likely that the next years will see data supporting the disruptive
185 effects of this early generation of drugs on reproduction after prenatal exposure, emphasizing the
186 need to further caution the use among the pregnant.

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336 **Figures/Tables**

337 Table 1:
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| Prenatal Exposure | Timing Window | Reported Reproductive Effects | Mechanisms |
|--------------------------|---|--|---|
| Thalidomide | Throughout gestation but increased sensitivity in the first trimester | <p>Absent or malformed testes (infertility) (Vargesson 2015; Mani et al. 2017)</p> <p>Cryptorchidism (Vargesson 2015; Mani et al. 2017)</p> <p>Hypospadias (Vargesson 2015; Mani et al. 2017)</p> <p>Miscarriages (Vargesson 2015; Smithells and Newman 1992)</p> <p>Defects of the female reproductive tracts (Vargesson 2015; Mani et al. 2017)</p> <p>Malformations of the uterus (Vargesson 2015; Mani, Danasekaran, and Annadurai 2017)</p> | Multiple mechanisms incl. anti-angiogenesis, antagonism of the androgen receptor and disruption of early mesodermal differentiation (Tachikawa et al. 2018; Paravar and Lee 2008; Hideshima et al. 2000; Du et al. 2005; Capitosti et al. 2004) |
| Diethylstilbestrol (DES) | First trimester | <p>Cryptorchidism (Swan 2001; Jishi and Sergi 2017; Johansson et al. 2017)</p> <p>Hypospadias (Swan 2001; Jishi and Sergi 2017; Johansson et al. 2017)</p> <p>Increased risk of clear cell adenocarcinoma in females and testicular cancer in males (Swan 2001; Johansson et al. 2017; Jishi and Sergi 2017; Adam et al. 2011; Troisi et al. 2007; Newbold et al. 1998)</p> <p>Abnormalities in female</p> | Estrogenic |

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|-----------------|----------------------------|---|---|
| | | <p>reproductive tract (Jishi and Sergi 2017; Adam et al. 2011; Gill et al. 1979)</p> <p>Spontaneous abortion (Jishi and Sergi 2017; Adam et al. 2011; Gill et al. 1979)</p> <p>Preterm delivery (Jishi and Sergi 2017; Adam et al. 2011; Gill et al. 1979)</p> <p>Ectopic pregnancy (Jishi and Sergi 2017; Adam et al. 2011; Gill et al. 1979)</p> <p>Transgenerational effects (Jishi and Sergi 2017; Newbold et al. 1998; Newbold et al. 2006; Newbold 2008; Ho et al. 2017; Walker and Haven 1997)</p> | |
| Mild analgesics | First and second trimester | <p>Cryptorchidism (Kristensen et al. 2016; Jensen et al. 2010; Kristensen et al. 2011; Maamar et al. 2017; Driesche et al. 2015; Fisher et al. 2016; Lind et al. 2017)</p> <p>Hypospadias (Kristensen et al. 2016; Jensen et al. 2010; Kristensen et al. 2011; Maamar et al. 2017; Driesche et al. 2015; Fisher et al. 2016; Lind et al. 2017)</p> <p>Reduction in anogenital distance (Fisher et al. 2016; Lind et al. 2017)</p> <p>Disruption of fetal testis steroids secretion (Maamar et al. 2017; Driesche et al. 2015)</p> | <p>Anti-androgenic (Kristensen et al. 2016; Kristensen et al. 2011), resulting in decreased hormone levels in a time-, dose-, and age-dependent manner (Maamar et al. 2017; Driesche et al. 2015)</p> <p>Inhibited expression of genes encoding steroidogenic enzymes resulting in disrupted androgen synthesis (Kristensen et al. 2016)</p> <p>Reduction in germ migration and proliferation (Driesche et al. 2015)</p> <p>Cytotoxic effects (Leverrier-Penna et al. 2018)</p> |

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|-----------|-----------------|--|---------|
| | | <p>Disruption of fetal gonadal development (testis and ovaries) (Leverrier-Penna et al. 2018)</p> <p>Disrupted ovary development and subfertility in females (Dean et al. 2016; Holm et al. 2016; Johansson et al. 2016; Arendrup et al. 2018)</p> | |
| Valproate | First trimester | Hypospadias and undescended testis (Raghavan et al. 2018; Rodríguez-Pinilla et al. 2008) | Unknown |

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