Reproductive Toxicology 45 (2014) 14–19

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

Congenital bladder exstrophy associated with Duogynon hormonal pregnancy tests—Signal for teratogenicity or consumer report bias?

Gregor Tümmler[a], Anke Rißmann[b], Reinhard Meister[c], Christof Schaefer[a,*]

[a] Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy, Charité – University Clinic Berlin, Berlin, Germany
[b] Malformation Monitoring Centre Saxony-Anhalt, Medical Faculty Otto-von-Guericke-University Magdeburg, Magdeburg, Germany
[c] Department of Mathematics, Beuth Hochschule für Technik Berlin (University of Applied Sciences), Berlin, Germany

ARTICLE INFO

Article history:
Received 12 July 2013
Received in revised form
21 November 2013
Accepted 18 December 2013
Available online 2 January 2014

Keywords:
Pregnancy
Duogynon
Primodos
Norethisterone
Hormonal pregnancy test
Bladder exstrophy
Teratogen

ABSTRACT

A combination of ethinylestradiol and 10 mg norethisterone under the brand names of Duogynon (Germany) or Primodos (UK) was used as a pregnancy test until the 1970s. Until very recently there was continuing public concern about the safety of these drugs and legal proceedings were instituted against the medicinal authorization holder. Given the lack of epidemiological studies focusing on Duogynon/Primodos, the present study evaluates 296 consumer reports of the German Duogynon database and compares the reported birth defects with data from a population based birth registry. The most striking result is an increase of bladder exstrophy (OR = 37.27; 95%-CI 14.56–95.28). Neural tube defects (OR = 2.99; 95%-CI 1.85–4.84) and renal agenesis (OR = 2.53; 95%-CI 1.17–5.45) were also significantly increased. Bladder exstrophy may be a yet undetected teratogenic effect of Duogynon, but may also represent a reporting bias. The present study highlights the difficulties of evaluating consumer reports which may be influenced by public media.

1. Introduction

In 1950 a compound named Duogynon was licensed in former West Germany by Schering AG, Berlin as a pregnancy test and to treat secondary amenorrhea. Duogynon contained 10 mg norethisterone acetate and 0.02 mg ethinylestradiol (oral application) or 50 mg progesterone and 3 mg estradiol benzoate (intramuscular application). The drug was marketed as Primodos in the United Kingdom.

Gal and associates [1] were the first to report an association between the incidence of neural tube defects and maternal exposure to sex hormones used in pregnancy tests. In the following years many studies of the potential teratogenic hazards of hormonal pregnancy tests or oral contraceptives have been done, with contradictory results. Some authors reported malformations such as heart defects [2], limb reduction defects [3] or hypospadias [4]. In contrast to these findings, larger case-control studies found no increased risk of congenital anomalies associated with the use of hormonal pregnancy tests (e.g. [5,6]) or oral contraceptives during early pregnancy (e.g. [7]).

Duogynon was finally withdrawn from the market in 1981. The indication hormonal pregnancy test had already been withdrawn in 1973.

Given the persistent mass media discussion of Duogynon's safety in pregnancy as well as legal proceedings instituted by patients claiming to be affected by prenatal Duogynon exposure, there was a need to reevaluate the teratogenic risk. In 2011, the Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy at the Charité University Clinic Berlin was commissioned by the German Federal Institute for Drugs and Medical Devices (BfArM) to analyze the cumulative database of potentially Duogynon affected individuals. The aim was to evaluate the contribution of this dataset to the question of teratogenicity of Duogynon.

2. Materials and methods

2.1. Ascertainment and classification of study cases

Our analysis is based on retrospective case reports made to the BfArM either directly by affected patients (primary source) or

* Corresponding author at: Pharmakovigilanz- und Beratungszentrum für Embryonaltoxikologie, Charité-Universitätsmedizin Berlin, Spandauer Damm 130, Haus 10, 14050 Berlin, Germany. Tel.: +49 3030308119; fax: +49 3030308122.
E-mail address: christof.schaefer@charite.de (C. Schaefer).
URL: http://www.embryotox.de (C. Schaefer).

0890-6238/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.reprotox.2013.12.007

forwarded by a self-nominated patient advocate who, being himself affected by bladder exstrophy, had collected data of other patients (secondary source). Primary and secondary sources are comprised in the cumulative dataset (August 2011) of patients claiming to be affected by their mother's exposure to Duogynon.

The primary source consists of 78 case reports documented by the BfArM using a standardized questionnaire for adverse drug effects that covers details such as total dosage, indication, time and type of application, maternal age, medical history, family history, exposure to other drugs, complications during pregnancy, details in case of pregnancy loss, gestational age at birth, sex, birth weight, length, head circumference, and developmental disorders.

No standardized protocol was applied for the documentation of the 333 case reports of the secondary source. These case data lack information on most co-variables and provide only gross descriptions of the observed congenital anomalies. The obvious difference in data quality makes a distinction between primary and secondary sources advisable. Neither the primary source nor the secondary source cases were clinically verified by a health care professional.

All exposed pregnancies occurred between 1957 and 1981 with the exception of 2 infants from the secondary source born between 1982 and 1983, i.e. after withdrawal of Duogynon from the market.

After correcting for inappropriate case descriptions and duplication between primary and secondary sources as well as within each source a total of 296 reports could be included in the study (Fig. 1). The resulting sample consisted of live-born infants with congenital malformations claiming to have been exposed to Duogynon during pregnancy as well as fetal deaths and pregnancy terminations with documented fetopathology after prenatal Duogynon exposure.

Birth defects were grouped according to Rasmussen and associates [8] and the EUROCAT (European Surveillance of Congenital Anomalies) working group [9]. Due to the lack of detailed information in many cases only major birth defects were coded. We classified cases as having isolated or multiple birth defects, the latter covering two or more unrelated defects in different organ systems [8].

2.2. Study design and comparison group

At the time when Duogynon was on the market there were neither reliable birth defect registers established in West Germany nor databases on drug exposures of pregnant women. Therefore, neither a classical cohort study with a comparison group nor a case control study was feasible. Thus the data from the Malformation Monitoring Centre Saxony-Anhalt (formerly East German birth registry) were used as a control group to screen for disproportions of the reported congenital anomalies. This birth defect registry is population-based using multiple sources of information including hospital records, birth and death certificates, and post-mortem examinations and includes information on live births, fetal deaths with gestational age $\geq$16 weeks and terminations of pregnancy after prenatal diagnosis of fetal anomaly. All structural malformations, syndromes and chromosomal anomalies are included in the database except for minor and poorly specified anomalies according the EUROCAT guide (see detailed information under www.eurocat-network.eu/content/EUROCAT-Old-List-Minor-Anomalies.pdf). Only cases with diagnosis confirmed after birth are included in the database. The Saxony-Anhalt birth defect registry started in 1980 [10]. All cases ascertained between 1980 and 1989, i.e. 3 676 malformed infants out of a total of 171 660 births, served as a control group for our study. Duogynon was not marketed and no comparable products were licensed in East Germany at that time. Due to the political situation at that time, it is safe to assume that the control cohort was not exposed to Duogynon or similar hormonal pregnancy tests.

2.3. Statistical analysis

Crude rates were calculated by dividing the number of a specific malformation group by the number of all malformed subjects. We performed a proportional reporting ratio (PRR) to compare relative frequencies of malformations between exposed and non-exposed controls. Statistical analysis was done by using 2×2 tables (χ^2-test) of case–control infants for each group of congenital anomalies. Due to missing information on potentially confounding co-variables only crude odds ratios (OR) are presented.

3. Results

3.1. Maternal characteristics

The primary source includes 75 patients born to 73 mothers (1 pair of siblings and 1 pair of twins). Most of the mothers took Duogynon as a pregnancy test (n = 58/79.4%) and used it during the first trimester (n = 51/69.9%). Only 2 mothers took Duogynon for secondary amenorrhea. In some cases the primary source information on time of exposure and indication was not available. Only a small proportion of these mothers received Duogynon intramuscularly during the first trimester (n = 9/12.3%). Details are given in Tables 1 and 2. For this source information on maternal age, medical history, family history, complications during pregnancy, exposure to other drugs and details of delivery is missing in most of the cases.

The secondary source describes 4 fetal losses and 217 patients born to 213 mothers (1 pair of siblings and 3 pairs of twins). Data on time and type of application, indication and maternal characteristics are missing or incomplete in most of these reports. In only 24 cases is it definitely stated that Duogynon was used as a pregnancy test.

3.2. Congenital anomalies

All the cases in the primary source were live births. The secondary source includes 2 spontaneous abortions and 2 stillbirths with information on fetopathology.

43 infants (57.3%) in the primary source were born with an isolated birth defect and 31 (41.3%) with multiple birth defects. In the secondary source 154 infants (69.7%) were affected with an isolated birth defect and 45 (20.4%) with multiple birth defects. A classification was not possible in 1 case in the primary source and 22 in the secondary source. A detailed overview of the birth defects in the exposed groups is given in Table 3.

Defects of the skeletal system represent the largest group (primary source: n = 32, 42.6%; secondary source: n = 86, 38.9%), followed by malformations of the urinary tract and/or the kidney (primary source: n = 18, 24%; secondary source: n = 36, 17.1%), and the heart (primary source: n = 17, 22.7%; secondary source: n = 26, 11.8%). For details see Table 4 and Fig. 2.

Based on the route of Duogynon administration – orally or intramuscularly – we could not identify significant differences in the distribution patterns of affected organ systems in the primary source (data not shown).

When comparing the case cohorts and the control group bladder exstrophies were most strikingly overrepresented among exposed (OR = 37.27, 95%-CI 14.56–95.28). In addition, we observed statistically significant differences for neural tube defects (OR = 2.99, 95%-CI 1.85–4.48), cleft lip/palate (OR = 1.59, 95%-CI 1.05–2.40),