ORIGINAL ARTICLE: ANDROLOGY

Are proton-pump inhibitors harmful for the semen quality of men in couples who are planning pregnancy?

Nicole A. Huijgen, M.D.,[a] Maria A. J. de Ridder, Ph.D.,[b] Katia M. Verhamme, Ph.D.,[b] Gert R. Dohle, Ph.D.,[c] Ann M. Vanrolleghem, M.Sc.,[b] Miriam C. J. M. Sturkenboom, Ph.D.,[b,d] Joop S. E. Laven, Ph.D.,[e] and Régine P. M. Steegers-Theunissen, M.D., Ph.D.[a,f]

[a] Department of Obstetrics and Gynaecology, [b] Department of Medical Informatics, [c] Department of Urology, [d] Department of Epidemiology, [e] Department of Obstetrics and Gynaecology, Division of Reproductive Medicine, and [f] Department of Pediatrics, Division of Neonatology, Erasmus MC, University Medical Centre, Rotterdam, the Netherlands

Objective: To determine associations between proton-pump inhibitor (PPI) use and semen parameters in young men of couples who are planning pregnancy.
Design: Case-control study of a population-based registry.
Setting: Not applicable.
Patient(s): General practitioner patients comprising 2,473 men from couples planning pregnancy with a recorded semen analysis: 241 with a low total motile sperm count (TMSC ≤ 1) and 714 with TMSC >1 as matched controls.
Intervention(s): None.
Main Outcome Measure(s): Exposure to PPI; PPI dosage.
Result(s): The study of data from between 1996 and 2013 from the Integrated Primary Care Information database in the Netherlands, which incorporates the medical records of 1.5 million patients from 720 general practitioners, found that the use of PPIs in the period between 12 and 6 months before semen analysis was associated with a threefold higher risk of low TMSC (odds ratio 2.96; 95% confidence interval 1.26–6.97) adjusted for age and other medication. Use of PPIs during the 6 months immediately before the semen analysis was not statistically significantly associated with low TMSC.
Conclusion(s): The use of PPIs in the period 12 to 6 months preceding semen analysis is associated with a threefold higher risk of low TMSC, which suggests that a long-term increase in gastric pH results in a decline of sperm quality. This finding emphasizes the need for more preconceptional research and counseling on the potential effects of medication use on semen quality. (Fertil Steril® 2016;■: ■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Adverse drug reaction, fertility, proton-pump inhibitors, semen quality

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In 1 out of 10 couples, pregnancy is not achieved after 1 year of unprotected intercourse (1, 2). Subfertility is a major burden affecting 48.5 million people worldwide, and in a considerable number of cases a male factor is involved (3). A method for quantifying the severity of male factor subfertility is the assessment of sperm parameters, among which total motile sperm count (TMSC) is a reliable parameter for predicting the chance of a spontaneous ongoing pregnancy (4). The observed continuous decline in sperm quality over the last decades has been worrisome, as it seems to be related to increased exposure to endocrine disruptors, unhealthy lifestyles, obesity, and increased age (5–7). Health status declines accompany aging, which goes together

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Reprint requests: Régine P.M. Steegers-Theunissen, M.D., Ph.D., Professor of Periconceptional Epidemiology, Erasmus MC, University Medical Centre, Dr. Molewaterplein 50, 3000 DR, Rotterdam, the Netherlands (E-mail: r.steegers@erasmusmc.nl).

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with an increase in medication use. In the Netherlands the use of prescribed medication in men between 20 and 25 years of age is 18.7%, and rises to 52.9% by the ages of 55 to 65 years (8).

Proton-pump inhibitors (PPIs) are the most commonly used medication for gastroesophageal reflux disease and peptic ulcer disease. Its prevalence is 26.9% in men and women with gastrointestinal symptoms and 5% in those without gastrointestinal symptoms (9). In comparison with H_2-receptor antagonists (H2RAs) and antacids, PPIs are most effective in decreasing gastric acidity (10). A strong disulfide bond, binding irreversibly to the hydrogen-potassium ATPase pump, leads to a specific inactivation of the enzyme, which results in a long-lasting impairment of gastric acid secretion (11).

The increase in pH that accompanies PPI use reduces the uptake of B vitamins, which are essential for biologic processes involved in DNA synthesis and cellular growth and development such as spermatogenesis (12–14). Thus, patients on long-term PPI treatment should be periodically screened for nutrient deficiencies (14, 15). The other suggested adverse effects of PPIs are direct gonadotoxic effects and interactions with the hypothalamic-pituitary-gonadal axis. To explore these effects further, we examined whether the use of PPIs is associated with impaired semen quality in a population-based study of men in couples who are planning pregnancy and have been visiting a general practitioner.

MATERIALS AND METHODS

Design

Our case-control study was conducted using the Dutch Integrated Primary Care Information (IPCI) database. The IPCI database, which consists of medical records of 1.5 million patients from 720 general practitioners (GPs) spread across the Netherlands, is validated to be used for pharmacoepidemiologic research (16). It complies with the European Union guidelines on the use of data for medical research. More details concerning the IPCI database have been provided elsewhere (17).

Patients who visited a GP between 1996 and 2013 are registered in the IPCI database with anonymous longitudinal information (coded and in free text) on age, symptoms, test results, disease outcome, referrals, and prescription data. The database comprises all men with at least 12 months of data registered before the study period (1996 and 2013). We extracted additional information on obesity, weight, smoking, and the use of alcohol in the period of 15 months preceding the visit until the day of the semen analysis by using search codes and text strings. From the prescription files we extracted data on dosage, frequency, and duration of medication use in the same time window based on the Anatomical Therapeutic Chemical (ATC) classification system. The Scientific Advisory Board of the IPCI Project approved the study protocol and use of IPCI data (Project number: 01/13).

Study Population

A study cohort was selected of men aged ≥ 18 years during the study period and found via one of the following search codes: A97.02 (wish to become parents), Y10 (male sub/infertility), W15 (female sub/infertility), or the additional text strings "sperm," "semen," "ferti," "androl," and "YS" (the text code for semen analysis). Records including the text "vasectomy," "sterilisation," "spermatocele," "hematospermia," or "epididymitis" in the same notation were automatically excluded. Every medical record was manually validated, and the semen analysis data were extracted. The manual review excluded the false hits such as patients without semen analysis data or without the wish to become parents.

In the study population we only included men in couples who were planning a pregnancy and with a recorded semen analysis at the first visit (Table 1). We excluded men with a history of testicular surgery, chemotherapy or radiotherapy, congenital absence of the vas deferens, varicocele, or who had an incomplete or unreliable semen analysis (for example, due to fever). Subsequently, we excluded men without any recorded prescription data or with an incomplete medication history (Fig. 1).

Cases and Controls

Cases were defined as men with a low TMSC ≤ 1, which is the clinical diagnosis of severe oligoasthenoteratozoospermia (18). All men with a TMSC >1 were selected as controls and were matched with cases managed by the same GP.

Proton-pump Inhibitor Exposure

Proton-pump inhibitor exposure (ATC code A02BC) was assessed for the period 12 to 6 months preceding the semen analysis (period 1) and in the period 6 months immediately before the semen analysis (period 2). Men without PPI exposure in the corresponding period were defined as nonusers. Exposure to other ATC-coded drugs in the period 12 to 0 months before the semen analysis was defined as "Medication use other."

We expressed PPI dosage as the defined daily dosage (DDD)—the assumed average maintenance dose per day for a drug used for its main indication in adults—to account for differences in the standard dosing regimen between the types of PPIs. The cumulative PPI dose was calculated by multiplying the DDD and the duration of use. If the duration of use was missing, we imputed a value calculated by dividing the prescribed number of units by the dosing regimen.

Semen Sample Data

The following semen sample data were extracted: ejaculate volume (mL), sperm concentration (10^6/mL), sperm motility parameters type A (rapid progressive motility, %) and type B (slow or sluggish progressive motility, %), total sperm count (10^6/ejaculate), and total motile sperm count (TMSC, 10^6/ejaculate) calculated as the product of ejaculate volume, sperm concentration, and grade A + B motility. Additional information was collected on the abstinence period, time between semen collection and analysis, pH, and completeness of the sample. Semen analyses were performed in hospital-affiliated laboratories participating in the external quality control scheme of the Dutch foundation for quality