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Differences in Reporting Pearl Indices in the United States and Europe: Focus on a 91-Day Extended-Regimen Combined Oral Contraceptive with Low-Dose Ethinyl Estradiol Supplementation

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Abstract

Background—Regulatory agencies in the United States (US) and Europe differ in requirements for defining pregnancies after the last dose of oral contraceptive, sometimes resulting in discrepant Pearl Indices (PIs) for the same product despite identical clinical data. This brief report highlights one such example, a 91-day extended-regimen combined oral contraceptive (COC).

Methods—The US- and European-based PI methodologies were compared for a 91-day extended-regimen COC consisting of 84 days of active levonorgestrel/EE 150 μg/30 μg tablets, followed by 7 days of EE 10 μg tablets in place of placebo.

Conclusions—At the times of approval of the 91-day extended-regimen COC in the US and Europe, the requirements for defining 'on-treatment' pregnancies differed (14-day vs. 2-day rule, respectively). This difference resulted in a higher PI in the US- vs. European-based calculation (1.34 and 0.76, respectively). The differences in the PI should not be interpreted as the extended-regimen COC being less effective in preventing pregnancy in the US compared with Europe.

Keywords

Pearl Index; combined oral contraceptive; extended-regimen

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DECLARATION OF INTEREST

Dr. Giljanovic is an employee of Teva Pharmaceutical Europe.
Dr. Howard and Dr. Weiss are employees of Teva Global Medical Affairs.
Prof. Trussell is on advisory committees for Teva and Merck and is a consultant to Bayer.
Dr. Lobo Abascal has received lecture fees and is a member of advisory boards and/or a consultant for Bayer, Effik, HRA Pharma, Merck Sharp & Dohme, and TEVA.
Prof. Luzar-Stiffler is Director of Statistical Methods at CAIR Center – The House of Statistics.

INTRODUCTION

Historically, regulatory agencies in the United States (US) and Europe have had different requirements for defining pregnancies after the last dose of oral contraceptive, and these requirements have changed over time. Although to our knowledge these requirements are not officially published by the US or European agencies, the prescribing information or public assessment reports of individual oral contraceptives often contain information describing some of the methodologies for Pearl Index (PI) calculation, including definitions of 'on-treatment' pregnancies. For example, based on the prescribing information for 2 different oral contraceptives with extended regimens approved in 2006 and 2013 (one with 84 days of levonorgestrel [LNG]/ethinyl estradiol [EE] 150 μg/30 μg, and 7 days of EE 10 μg and one with ascending dose EE with 42 days of LNG/EE 150 μg/20 μg, 21 days of LNG/EE 150 μg/25 μg, 21 days of LNG/EE 150 μg/30 μg, and 7 days of EE 10 μg, respectively; both manufactured by Teva Branded Pharmaceutical Products R&D, Inc., Frazer, PA, USA), the US Food and Drug Administration (FDA) has, at various times, required the PI to be calculated according to a 14-day or a 7-day rule for on-treatment pregnancies. The 14-day rule defines on-treatment pregnancies as those diagnosed on or after the date of the first combined oral contraceptive (COC) dose but within 14 days after the last combination dose; whereas the 7-day rule defines on-treatment pregnancies as those diagnosed within 7 days after the last dose of any pill (active combination, EE only, or placebo)[1,2]. In contrast, the European Medicines Agency (EMA) has used a 2-day rule, counting pregnancies diagnosed within 2 days after the day of last intake of trial medication (active combination, EE only, or placebo)[3]. Such geographic differences in PI calculation may not be evident to consumers or healthcare professionals and could cause confusion or doubt about COC efficacy. As an aside, it should be noted that there are many differing opinions on how to define on-treatment pregnancies. In 2007, a meeting of the Advisory Committee for Reproductive Health Drugs recommended to the FDA that on-treatment pregnancies be limited to those in which conception occurred during the established treatment cycle[4].

METHODS

This brief report examines different methodologies for calculating the PI in the US vs. Europe for a 91-day extended-regimen COC with low-dose EE supplementation consisting of 84 days of active LNG/EE 150 μg/30 μg tablets, followed by 7 days of EE 10 μg tablets (Seasonique®; Teva Branded Pharmaceutical Products R&D, Inc., Frazer, PA, USA) in place of placebo.

BRIEF OVERVIEW OF THE 91-DAY EXTENDED-REGIMEN COC WITH LOW-DOSE EE SUPPLEMENTATION

The 91-day extended-regimen COC with low-dose EE supplementation allows for just 4 bleeding episodes per year, as preferred by some women[5]. In addition, supplementation of the standard 7-day hormone-free interval with 10 μg EE may continue to suppress follicular development and minimise hormone withdrawal symptoms[6]. The extended-regimen COC has been approved since 2006 in the US then in Canada, Israel, Chile, and Brazil (March

2010, March 2012, November 2013, and April 2014, respectively) and most recently in Europe (January 2015).

PI CALCULATION IN US VS. EUROPE FOR THE EXTENDED-REGIMEN COC WITH LOW-DOSE EE SUPPLEMENTATION

At the time of approval of the 91-day extended-regimen COC, the US FDA required the PI to be calculated according to the 14-day rule for on-treatment pregnancies. As such, the FDA labelling for the extended-regimen COC states that in women aged 18 to 35, the PI was 1.34 pregnancies per 100 women-years of use (95% confidence interval [CI] 0.54–2.75; Exact method), based on 7 pregnancies that were diagnosed after treatment onset and within 14 days after the last combination LNG/EE pill and excluding cycles in which another contraceptive method was used[1]. By comparison, the European-based PI, as reported in the final Summary of Product Characteristics, is 0.76 (95% CI 0.0–1.76; Bootstrap method) based on 3 pregnancies that occurred after COC initiation and within 2 days after intake of the last tablet (combination or EE only) in women aged 18 to 35, excluding cycles in which another contraceptive method was used (internal document). These US- and European-based PI calculations are both based on efficacy data from the pivotal, US-based, phase 3 trial of the extended-regimen COC[7]; however, because of differing definitions of ‘on-treatment’ pregnancies, 4 additional pregnancies are counted in the US-based PI calculation, resulting in a higher PI than the European-based PI (1.34 and 0.76, respectively). As an aside, it is important to note that the CIs in the US labelling and the European labelling for the extended-regimen COC were calculated using different methodologies (Exact method and Bootstrap method, respectively) and are therefore not directly comparable. A detailed analysis of the CI methodologies is beyond the scope of this brief report; the focus here is on PI point estimates only. However, it should be noted that although EMA guidance requires the calculation of a CI for the PI, it does not insist on a specific CI methodology[8].

DISCUSSION/CONCLUSION

Previous reports have suggested various factors that may impact estimates of contraceptive efficacy, including geographic study location, procedures for detecting pregnancy, and definitions of ‘on-treatment’ pregnancy post-study[9]. As demonstrated with the extended-regimen COC with low-dose EE supplementation, even when using the same clinical data, different calculation methodologies regarding classifying pregnancies as ‘on-treatment’ can impact PIs and result in inconsistencies between regulatory agencies’ labelling.

In the current report, the relatively higher PI in the US labelling vs. the European labelling (1.34 vs. 0.76) is the result of differences in the definition of ‘on-treatment’ pregnancies (14-day vs. 2-day rule).

The occurrence of 4 pregnancies within 2 to 14 days after the end of COC treatment is consistent with previous findings showing a rapid return to fertility within 32 days following the last dose of extended-regimen COC in the majority of women.[10] Women should be made aware of the potential for pregnancy immediately after completion of COC in order to avoid unintended pregnancy.

Life-table estimates are well known to be superior to the PI as a measure of contraceptive failure. However, life-table estimates would not avoid the inconsistencies noted here so long as the late pregnancies—those occurring after the established treatment cycle—were included in the last cycle of use. It is the inclusion of a different number of late pregnancies that creates the inconsistency in the US vs. European PI calculations.

In conclusion, the discrepant PIs for the extended-regimen COC in the US vs. Europe are the result of differing regional definitions of 'on-treatment' pregnancies. They should not be interpreted as the extended-regimen COC being less effective in preventing pregnancy in the US compared with Europe. We hope this information preempts any concerns related to efficacy of the extended-regimen COC that merely result from regional differences in regulatory/labelling preferences.

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