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Title

Oral contraceptive generations - Time to stop using a marketing myth to define nomenclature.

Permalink

<https://escholarship.org/uc/item/6fc3157c>

Journal

Contraception, 102(3)

ISSN

0010-7824

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Publication Date

2020-09-01

DOI

10.1016/j.contraception.2020.05.017

Peer reviewed

1 Commentary

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3 **Oral Contraceptive Generations - Time to stop using a marketing**
4 **myth to define nomenclature**

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20 Word Count: 997

21 The use of the term “generation” to describe different formulations of
22 combined oral contraceptives (COCs) has no basis in pharmacology and
23 creates confusion when used to classify products in epidemiologic studies.
24 Beginning in the 1990s, pharmaceutical company marketing teams
25 introduced this nomenclature in an effort to boost sales of newer progestins.
26 The idea of a “next generation” suggests improvement; that the newer
27 ligands are safer or “better.”

28

29 Prior to this time, clinicians had come to understand the concept of “high-
30 dose” and “low-dose” oral contraceptive formulations based on the estrogen
31 content. Unlike the term “generation,” this demarcation was based on
32 clinical outcomes and clear medical guidance; low-dose contraceptives,
33 which contained ethinyl estradiol (EE) doses less than 50 mcg, had lower
34 venous thromboembolism (VTE) rates than high-dose products.[1]

35

36 In the early 1990s, the introduction of COC formulations containing newly
37 patented progestins led to a marketing push that attempted to differentiate
38 products using a generation concept.

- 39 • First generation: EE doses of 50 mcg or more, regardless of progestin;
- 40 • Second generation: EE doses less than 50 mcg combined with
41 levonorgestrel (norgestrel) or norethindrone;
- 42 • Third generation: EE doses less than 50 mcg combined with
43 desogestrel, gestodene, or norgestimate.

44 Pharmacologically, the available progestins in COCs at the time were derived
45 from testosterone (19-nortestosterone products), built on a fused
46 phenanthrene/cyclopentene 4-ring backbone common to all steroids.

47 Although the term “gonane” in chemical nomenclature broadly refers to all
48 compounds with this ring structure, in the contraception literature this term
49 refers specifically to the 13-ethylgonanes, while the 13-methyl variants are

commonly known as estranes. The gonanes include levonorgestrel (norgestrel), desogestrel, gestodene, and norgestimate.

The World Health Organization (WHO) recommends use of a drug classification system to provide a common language for describing the drug assortments in a country or region. This helps to identify problems in drug use, to initiate educational or other interventions and to monitor the outcomes of these interventions and compare data between countries.[2] The WHO recommends the Anatomical Therapeutic Chemical (ATC) classification system developed by Norwegian researchers. Logical systems classify drugs according to their mode of action, indications, or chemical structure. The generation nomenclature for COCs does not represent a logical pharmacologic classification system.

Consider that estrogen dose differentiates first and second generation products but not subsequent generations despite the introduction of pills with even lower EE doses and natural estrogens (estradiol and estetrol). While evidence does support a dose-dependent reduction in thrombosis risk associated with estrogen, [3] the nomenclature implies, without evidence, a lowering of VTE risk with advancing generation.[4]

Rather than continuing with a classification system based on estrogenicity, the generation scheme defines advancement beyond the second generation by progestin type only. The second generation combines an estrane (norethindrone) and a gonane (levonorgestrel) while the other gonanes are third generation. However, important differences exist between progestins based on numerous cellular, biological and clinical effects, confirming the lack of a class effect.[5] Accordingly, grouping these products together is false, inferring to providers, for example, that adverse effects within each grouping are the same.

Real life has demonstrated that differentiating progestins by generations is not the correct way to understand COCs. The marketing of norgestimate as a “third generation” progestin, provides a great example. Norgestimate is a pro-drug with the primary metabolites being a levonorgestrel derivative (levonorgestrel-3-oxime, renamed by the original company as norelgestromin) and levonorgestrel. Pharmacologically, it makes sense to classify norgestimate with levonorgestrel (as a second-generation product) but pharmaceutical companies found a marketing benefit using the next, or “third generation” nomenclature.

The idea that new products represented a third (newer) generation implied everything would be “better,” including safety. However, by the mid-1990s, epidemiologic evidence began to accumulate suggesting that the “third-generation” pills incurred slightly higher risk of VTE than “second-generation” pills.[6,7] While observational bias (healthy user effect, preferential prescribing) likely explains the increased VTE risk, these findings contradict the concept of increased safety with advancing generations. The same companies that spent a lot of money pushing “next generation” pills as “better” found themselves in the position of convincing clinicians they were really the same, resulting in confusion. We know now that progestin type has little impact on VTE risk induced by the potent synthetic estrogen EE used in most combined products.[8-10]

The subsequent introduction of contraceptives containing drospirenone (a spiro lactone) led to a new classification as “fourth-generation” products by marketers and epidemiologists. However, even newer pills containing estradiol and not EE combined with dienogest (a novel non-ethinylated estrane) and norgestrol acetate (a 19-norprogesterone) have not been referred to as “fifth generation.” The inclusion of the natural estrogen pills with EE products as “fourth generation” provides further confirmation of the limitations of this nomenclature. Current evidence suggest equal or lower

rates of VTE with estradiol pills compared to second and third-generation EE-containing products.[11] With the future holding the potential for a new COC with estetrol and drospirenone, [12] categorization of combined hormonal products by generations will make even less sense.

The use of generations to define COCs was a marketing idea that has confused clinicians and the scientific community for years. This system does not provide valid differentiation of product safety or efficacy and was never intended to do so. Moreover, this non-evidence-based approach to describing COCs can result in a misunderstanding of the safety of progestin-only products. For example, one U.S. insurance company restricts coverage of a new progestin-only oral contraceptive containing drospirenone, with approval dependent on multiple criteria, one of which is: "Prescriber attests the benefits of drospirenone-containing, progestin-only contraceptives outweigh the potential risk of venous thromboembolism." [13]

As we move into the next decade, we recommend abandoning use of generations in publications and educational materials. Instead, use clear descriptive classifications that make biological and pharmacologic sense. We can better understand differences and potential benefits if we simply know what hormones are in the products we prescribe. We further advise that clinicians understand and refer to the various progestins according to established scientific nomenclature (e.g. estranes, gonanes, spiro lactones, etc.) and evaluate individual products according to the results of clinical trials.

Acknowledgements: This commentary is adapted, with permission, from Creinin MD, Jensen JT. Reproduction and hormonal contraception (Ch. 2). In: Jensen JT, Creinin MD, editors. Speroff and Darney's Clinical Guide to Contraception, 6th ed., Wolters Kluwer, 2019, p. 59-63.

143 Funding: This research did not receive any specific grant from funding
144 agencies in the public, commercial, or not-for-profit sectors.

145

146 Disclosures: Dr. Creinin serves on an Advisory Board for Lupin, Merck & Co.,
147 and TherapeuticsMD and is a consultant for Danco, Estetra, Mayne, and
148 Medicines360. The Department of Obstetrics and Gynecology, University of
149 California, Davis, receives research funding for contraceptive research from
150 Daré, HRA Pharma, Medicines360, Merck & Co. and Sebela. Dr. Jensen has
151 received payments for consulting from Abbvie, Cooper Surgical, Bayer
152 Healthcare, Merck, Sebela, and TherapeuticsMD. OHSU has received
153 research support from Abbvie, Bayer Healthcare, Daré, Estetra SPRL,
154 Medicines360, Merck, and Sebela. These companies and organizations may
155 have a commercial or financial interest in the results of this research and
156 technology. These potential conflicts of interest have been reviewed and
157 managed by OHSU.

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208 Accessed May 20, 2020.