Title

Contraceptive efficacy should primarily be measured using life table pregnancy rates

Authors

Mauck, Christine K
Dart, Clint
Thurman, Andrea
et al.

Publication Date

2023-08-01

DOI

10.1016/j.contraception.2023.110140

Peer reviewed

Contraception 127 (2023) 110140

Contents lists available at ScienceDirect

Contraception

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

Commentary

Contraceptive efficacy should primarily be measured using life table pregnancy rates☆,☆☆

Christine K. Mauck [a,*], Clint Dart [b], Andrea Thurman [a], Mitchell D. Creinin [c]

[a] Daré Bioscience, Inc., San Diego, CA, United States
[b] Premier Research, Morrisville, NC, United States
[c] Department of Obstetrics and Gynecology, University of California, Davis, Sacramento, CA, United States

ARTICLE INFO

Article history:
Received 13 June 2023
Received in revised form 2 August 2023
Accepted 4 August 2023

Keywords:
Contraceptive efficacy
Kaplan-Meier
Life table
Pearl Index

1. Introduction

Contraceptive users have always deserved accurate and easy-to-understand information about the pregnancy risk associated with different contraceptive methods. After the recent *Dobbs* vs. *Jackson* decision in which the Supreme Court held that the right to privacy stipulation in the United States Constitution does not include abortion, reproductive health access and choices have become severely more limited [1,2]. Sexually active couples are urgently reevaluating their contraceptive options and now, more than ever, deserve the most accurate and understandable information on how well methods work. This issue is especially crucial for those with significant medical contraindications to pregnancy who live in states with limited or no abortion access, for whom a contraceptive failure could be life-threatening.

2. Measurements of contraceptive efficacy

Historically, two methods have been used to measure contraceptive efficacy, the Pearl Index and survival analysis (performed by one of two methods: life table and Kaplan-Meier). Each of these methods has distinct pros and cons.

2.1. Pearl Index

Raymond Pearl, PhD, a biologist at Johns Hopkins University with a primary interest in biostatistics, first described this method in 1933 as a measure of human female fertility that corrected for the time when the woman was not at risk for pregnancy [3]. Although Dr. Pearl's primary goal was to make a distinction between fecundity (a person's maximum potential to reproduce) and fertility (a couple's actual reproductive success), he demonstrated how this calculation could take into account the use of contraception. The method's simplicity made it attractive for researchers and regulatory agencies to adopt for describing contraceptive efficacy.

$$\text{Pearl Index} = \frac{\text{number of pregnancies}}{\text{person} - \text{years of exposure to risk of becoming pregnant}} \times 100$$

Exposure refers to intercourse with the frequency and other requirements typically defined by the specific study or regulatory agency. Functionally, this calculation typically uses cycles or months of exposure. For cycles (28-day cycles), the number of pregnancies is

☆ Conflicts of interest: C.K.M. and A.T. are employees of Daré Bioscience, Inc., and C.D. is an employee of Premier Research. M.D.C. has received speaking honorarium from Gedeon Richter, Mayne, OLIC, and Organon, serves on an Advisory Board for Gedeon Richter, Mayne, and Organon, and is a consultant for Danco, Estetra SRL, Mayne, and Medicines360. The Department of Obstetrics and Gynecology, University of California, Davis, receives contraceptive research funding for M.D.C. from Chemo Research SL, Evofem, Medicines360, Merck, and Sebela.

☆☆ Funding: Drs. Mauck and Thurman are employees of, and compensated by, Daré Bioscience, Inc. Mr. Dart is employed and compensated by Premier Research, and Dr. Crenin is employed and compensated by the University of California, Davis.

* Corresponding author.
E-mail address: cmauck@darebioscience.com (C.K. Mauck).

https://doi.org/10.1016/j.contraception.2023.110140

divided by the number of cycles and multiplied by 1300 instead of 100. Thirteen hundred is simply the number of 28-day cycles in 1 year (13) times 100. For months, the denominator is the number of months, and the multiplier is 1200 instead of 100, reflecting 12 months in 1 year.

2.2. Survival analysis

Survival analyses can be performed in several ways, but the two most commonly used are the life table method (also called the actuarial method) and the Kaplan-Meier method (also called the product-limit method). The life table method is a grouped approach in which events are calculated for each period. For contraceptive efficacy, the events are pregnancies, and the periods are commonly 28-day intervals (cycles) or months. The Kaplan-Meier method does not group the data by cycle and only calculates survival when an event happens. However, the terms are often used interchangeably or as one being a descriptor of the other. For example, the US Food and Drug Administration (FDA)-approved label for the contraceptive gel Phexxi reads, "The primary efficacy endpoint was the 7-cycle typical use cumulative pregnancy rate as derived by Kaplan-Meier life-table analysis…" [4]. The Kaplan-Meier and life table methods have also been expressed as one being a means of calculating the other. For example, the 5-year Liletta intrauterine device publication states, "Secondary efficacy outcomes included cumulative Pearl Indices over five years and life-table pregnancy rates calculated using the Kaplan-Meier method" [5].

3. Using Pearl Index and survival analysis methodologies

While simple to calculate, the primary issue with the Pearl Index is interpretation. The units used for Pearl Index are pregnancies per 100 woman-years. Although this may seem like a percentage, it is not. Accordingly, conveying what this means in a simple discourse between a clinician and patient can be challenging. The value is difficult for individuals to translate into their personal risk of becoming pregnant while using a method since most do not know how "100 woman-years of exposure" applies to their personal risk of contraceptive failure. Indeed, 100 woman-years of exposure could be achieved by 100 women using the method for 1 year, 50 women using it for 2 years, or even 25 women using it for 4 years.

Therefore, the Pearl Index cannot be used to compare studies of differing lengths. Early criticisms were noted more than 50 years ago [6]. More recently, Trussell and Portman noted in 2013 that "comparing results from different studies with different maximum durations of exposure is virtually meaningless, because failure is measured with a rubber yardstick" [7].

In addition, Pearl Index values tend to decline over time within a given observation period; there are more pregnancies in the beginning of the observation period because couples who are more fertile, have sex more frequently, or take longer to learn how to use the method consistently and correctly will likely get pregnant first [8]. The length of observation is often not even stated in study reports, making it difficult to tell whether one is comparing studies of differing lengths [9].

In a true life table analysis, a separate failure rate is typically calculated for each cycle or month (although other intervals can be used). Each individual cycle (13 cycles in a year) or month (12 months in a year) is then combined together to yield the cumulative pregnancy rate over 1 year. Importantly, these individual values can be combined for any period, including multiple years, without losing accuracy because the denominator for each unit (e.g., cycle or month) will reflect the number of users within the assessed duration. Accordingly, unlike the Pearl Index, life table analyses control for the artificial lowering of pregnancy rates that can occur with a longer duration of analysis. The results are expressed as the likelihood of becoming pregnant within a specific time frame. For example, someone using the Liletta intrauterine device[1] has a 1.37% chance of becoming pregnant over 8 years [10]. Thus, when a clinician or patient reads the life table analysis failure rate of a contraceptive, they know the overall failure rate for an individual during a specified duration of use.

Pregnancy rates calculated by both the Pearl Index and survival analyses have been increasing over the last few decades. Proposed reasons include more frequent pregnancy testing and inclusion of a broader range of study participants, which may impact adherence. In addition, requirements for cycles to be included in the study denominator may have become more restrictive. For example, in more recent studies, evaluable cycles may be defined as having at least one act of intercourse, using no back-up contraception (including emergency contraception), and having a certain cycle length. Having fewer cycles in the denominator will result in higher pregnancy rates [8]. Variations also exist in how regulatory agencies measure pregnancy; for example, the FDA includes any pregnancy diagnosed within 7 days of completing an investigational contraceptive to be "on-treatment," whereas the European Medicines Agency specifies only within 2 days. Changes in protocols and the definitions of pregnancy make it difficult to compare studies done at different points in time.

The Pearl Index and life table analyses have similar outcomes when studies last for 1 year or longer. For example, the year 1 Pearl Index for Liletta is 0.15 pregnancies per 100 women-years and the life table rate is 0.14% [10]. However, non-hormonal methods are commonly studied for regulatory approval in trials that are much shorter, commonly 6 months or seven cycles. In these scenarios, a Pearl Index can be calculated but does not reflect a true 1-year pregnancy outcome because the product was not evaluated for that length of time. The scientifically valid life table analysis will differ from the calculated Pearl Index with the Pearl Index usually being higher. For example, Phexxi's label includes an estimated Pearl Index based on data from the 7-cycle study of 27.5 pregnancies per 100 women-years, while the 7-cycle cumulative pregnancy rate by Kaplan-Meier analysis was 13.7% [4]. As we continue to evaluate more novel products, we need accurate statistics to truly understand efficacy and to be able to communicate that information well with patients in a format they can understand.

4. The FDA's position on reporting contraceptive efficacy outcomes

Guidance from the FDA itself and its advisory committees had long favored using the life table analysis rather than the Pearl Index until 2017 when the 1-year Pearl Index became the primary requirement for reporting contraceptive efficacy. In 1980, a proposed rule, based on the recommendations of the Advisory Panel on Over-the-Counter Contraceptives and Other Vaginal Drug Products, recommended: "The data from all effectiveness studies should be evaluated by the life-table method. The life-table has replaced the traditional Pearl formula because it makes possible valid comparisons among different studies extending over different time periods. Although previous data analyzed according to the Pearl formula may be salvaged by recalculation using the life-table method, new data will be required for a more precise evaluation. The data may be expressed as the percentage of women who become pregnant while using the method during the course of one year, i.e., the rate of accidental pregnancy" [11].

In the 1990s, the FDA released two updated guidelines. First, in 1997, the Guidance for Development of Vaginal Contraceptive Drugs

[1] Articles in *Contraception* generally use brand names only once. However, since this article refers to product labels, brand names are used throughout.

<table>
<tr><th>Product</th><th>Date approved</th><th>Excerpt from label, Section 14 “Clinical studies” (bolding added)</th></tr>
<tr><td>Liletta [10]</td><td>November 14, 2022</td><td>The pregnancy rate calculated as the Pearl Index (PI) in participants 16 to 35 years of age, inclusive, was the primary efficacy endpoint used to assess contraceptive reliability. The PI was calculated based on 28-day equivalent exposure cycles; evaluable cycles excluded those in which back-up contraception was used unless a pregnancy occurred in that cycle. The Year 1 PI was based on two pregnancies and the cumulative 8-year pregnancy rate was calculated by the life table method, based on a total of eleven pregnancies that occurred after the onset of treatment and within 7 days after LILETTA removal or expulsion. Table 8 shows the annual PI for each of the eight years and the calculated cumulative life table pregnancy rates through years 1, 2, 3, 4, 5, 6, 7, and 8. For Year 7 and Year 8, participants who were more than 39 years of age at the beginning of the respective study year were excluded from the efficacy analysis.

Table 8: Contraceptive Efficacy: Pregnancy Rates
<table>
<tr><th>LILETTA Clinical Trial</th><th>Number of 28-Day Cycles of Exposure By Year</th><th>Year-by-Year Pearl Index Pregnancy Rate (95% CI)</th><th>Cumulative 28Day Cycles of Exposure</th><th>Cumulative Year Life Table Pregnancy Rate (95% CI)</th></tr>
<tr><td>Year 1</td><td>17,175</td><td>0.15 (0.02, 0.55)</td><td>17,175</td><td>0.14 (0.04, 0.57)</td></tr>
<tr><td>Year 2</td><td>14,205</td><td>0.37 (0.10, 0.94)</td><td>31,380</td><td>0.50 (0.22, 1.10)</td></tr>
<tr><td>Year 3</td><td>11,760</td><td>0.11 (0.00, 0.62)</td><td>43,140</td><td>0.60 (0.29, 1.27)</td></tr>
<tr><td>Year 4</td><td>9,891</td><td>0.13 (0.00, 0.73)</td><td>53,031</td><td>0.73 (0.36, 1.48)</td></tr>
<tr><td>Year 5</td><td>8,337</td><td>0.16 (0.00, 0.87)</td><td>61,368</td><td>0.89 (0.45, 1.74)</td></tr>
<tr><td>Year 6</td><td>6,916</td><td>0.00 (0.00, 0.69)</td><td>68,284</td><td>0.89 (0.45, 1.74)</td></tr>
<tr><td>Year 7*</td><td>5,280</td><td>0.49 (0.06, 1.78)</td><td>73,564</td><td>1.37 (0.71, 2.62)</td></tr>
<tr><td>Year 8*</td><td>3,657</td><td>0.00 (0.00, 1.31)</td><td>77,221</td><td>1.37 (0.71, 2.62)</td></tr>
</table>
*Excludes participants >39 years of age at the beginning of the respective year. Conception rates after the removal of LILETTA were assessed and appeared consistent with conception rates in the general population of participants having regular unprotected sexual intercourse for 12 months. Of 244 participants who desired pregnancy after study discontinuation, 63.1% conceived within 6 months after removal of LILETTA and 83.2% conceived within 12 months after removal of LILETTA.</td></tr>
<tr><td>Mirena [21]</td><td>August 25, 2022</td><td>The safety and effectiveness of Mirena was studied in two clinical trials in Finland and Sweden. In these trials, 1,169 women 18 to 35 years of age at enrollment used Mirena for up to 5 years, for a total of 45,000 women-months of exposure. Of these, 5.6% (66) were nulliparous women. Subjects had previously been pregnant, had no history of ectopic pregnancy, had no history of pelvic inflammatory disease over the preceding 12 months, were predominantly White, and over 70% of the subjects had previously used IUDs (intrauterine devices). The reported 12-month pregnancy rates were less than or equal to 0.2 per 100 women (0.2%) and the cumulative 5-year pregnancy rate was approximately 0.7 per 100 women (0.7%).

The contraceptive efficacy of Mirena during extended use beyond 5 years was studied in the Mirena Extension Trial (NCT02985541), a multi-center, open-label, uncontrolled study conducted in the United States. The trial enrolled women 18 to 35 years of age who had been using Mirena for not less than 4.5 years and not more than 5 years at enrollment. The population consisted of 362 women using Mirena. Of these 47.2% were nulliparous. The women were predominantly White (75.4%); 14.1% of the women were Black/African American, and 2.5% were Asian; 11.3 % were Hispanic. The weight range was 38.5–163.5 kg (mean weight: 75.6 kg) and mean BMI was 27.9 kg/m2 (range: 15.4–57.7 kg/m2).

The pregnancy rate calculated as the Pearl Index (PI) was the primary efficacy endpoint used to assess contraceptive efficacy. The PI was based on 28-day equivalent exposure cycles; evaluable cycles excluded those in which back-up contraception was used unless a pregnancy occurred in that cycle. The PI for the 6th year of use based on the 1 pregnancy that occurred during Year 6 and within 7 days after Mirena removal or expulsion and 3,870 evaluable cycles was 0.34 with a 95% upper confidence limit of 1.88 and the PI for the 7th year of use based on the 1 pregnancy that occurred during Year 7 and within 7 days after Mirena removal or expulsion and 3,232 evaluable cycles was 0.40 with a 95% upper confidence limit of 2.25. The PI for the 8th year of use based on no pregnancies occurring during Year 8 and within 7 days after Mirena removal or expulsion and 2,534 evaluable cycles was 0.00 with a 95% upper confidence limit of 1.90.

The cumulative 3-year pregnancy rate for Years 6, 7 and 8 was estimated by the Kaplan-Meier method. Based on 2 pregnancies (1 in Year 6 and 1 in Year 7) and 10,216 exposure cycles, the cumulative pregnancy rate at the end of the 3year period of extended use (Years 6, 7 and 8) was 0.68% with a 95% upper confidence limit of 2.71%.</td></tr>
<tr><td>Phexxi [4]</td><td>May 22, 2020</td><td>The primary efficacy endpoint was the 7-cycle typical use cumulative pregnancy rate as derived by Kaplan-Meier life-table analysis. A total of 101 on-treatment pregnancies occurred in 1183 subjects contributing 4769 evaluable natural cycles. The 7-cycle cumulative pregnancy rate was 13.7% (95% CI: 10.0%, 17.5%), excluding cycles with back-up contraception, cycles <21 days or >35 days in length and cycles in which no intercourse was reported. The estimated Pearl Index, calculated based on data from the 7-cycle study, was 27.5 (95% CI: 22.4%, 33.5%).</td></tr>
<tr><td>Twirla [19]</td><td>February 14, 2020</td><td>The efficacy of TWIRLA was evaluated in one open label, single arm, multicenter trial in the United States (Study 1) (NCT02158572) of one-year duration that enrolled 2,031 women, ranging in age between 18 and 60 years, who were healthy and sexually active with regular menstrual cycles…The primary efficacy endpoint was the Pearl Index (PI) defined as the pregnancy rate per 100 womanyears of use. The overall PI for the primary analysis population (TWIRLA-treated patients) was 5.8 (95% CI 4.5, 7.2).</td></tr>
<tr><td>Annovera [18]</td><td>August 10, 2018</td><td>The efficacy of ANNOVERA was evaluated in two 1-year multicenter trials enrolling 2,265 females, age 18–40 years, who were healthy and sexually active with regular menstrual cycles… The pooled pregnancy rate, evaluated by the Pearl Index (PI), was 2.98 (95% Confidence Interval [2.13, 4.06]) per 100 woman-years of ANNOVERA use.</td></tr>
</table>

Fig. 1. Pregnancy rates as expressed in labeling of recently approved non-oral contraceptives in the United States.

stated that “6-month life table pregnancy rates should be derived” [12]. In 1998, the Guidance for Industry - Uniform Contraceptive Labeling – Devices stated that “FDA considers the communication of information on pregnancy rates to users of contraceptive devices to be essential for their safe and effective use… The table recommended by FDA uses pregnancy rates based on data from Trussell, et al, from the 17th edition of *Contraceptive Technology* (1997)” [13]. Importantly, pregnancy rates in this table were calculated using Kaplan-Meier methodology.

In January 2007, the Advisory Committee for Reproductive Health Drugs held a general meeting on contraceptives. The meeting minutes read, “The general feeling of the committee is that the Pearl

<table>
<tr><td>Kyleena [23]</td><td>September 19, 2016</td><td>The pregnancy rate calculated as the Pearl Index (PI) in women aged 18–35 years was the primary efficacy endpoint used to assess contraceptive reliability. The PI was calculated based on 28-day equivalent exposure cycles; evaluable cycles excluded those in which back-up contraception was used unless a pregnancy occurred in that cycle. The Year 1 PI was based on 2 pregnancies and the cumulative 5-year pregnancy rate was based on 13 pregnancies that occurred after the 24 onset of treatment and within 7 days after Kyleena removal or expulsion. Table 5 [should be 7] shows the calculated annual and cumulative pregnancy rates.
Table 7: Pearl Indices by Year and 5-Year Cumulative Pregnancy Rate
<table>
<tr><td>Kyleena Clinical Trial</td><td colspan="5">Pearl Index</td><td>Cumulative 5-Year Kaplan Meier Rate</td></tr>
<tr><td></td><td>Year 1</td><td>Year 2</td><td>Year 3</td><td>Year 4</td><td>Year 5</td><td></td></tr>
<tr><td>Number of Evaluable 28 day Cycles of Exposure</td><td>16,207</td><td>13,853</td><td>11,610</td><td>8,556</td><td>7,087</td><td>57,313</td></tr>
<tr><td>Pregnancy Rate (95% Confidence Interval)</td><td>0.16 (0.02, 0.58)</td><td>0.38 (0.10, 0.96)</td><td>0.45 (0.12, 1.15)</td><td>0.15 (0.00, 0.85)</td><td>0.37 (0.04, 1.33)</td><td>1.45 (0.82, 2.53)</td></tr>
</table></td></tr>
<tr><td>Caya diaphragm [17]</td><td>September 9, 2014</td><td>The Phase II/III contraceptive effectiveness study—conducted at six sites in the United States—recruited 450 couples to participate in the study. Couples were randomized to two groups: 300 to SILCS diaphragm used with BufferGel (BG—an investigational lactic-acid based contraceptive gel) and 150 to SILCS diaphragm with N-9 spermicide gel. Healthy, sexually active female volunteers 18–40 years old, at risk for pregnancy, and desiring contraception but at low risk for HIV/STIs, were considered for enrollment. Eligible volunteers were not pregnant, had normal menstrual cycles, were not actively desiring pregnancy and were willing to accept an unknown risk of pregnancy and engage in at least 4 acts of vaginal intercourse per cycle. Participants were followed for at least 190 days and 6 menstrual cycles, and were seen at enrollment and after menstrual cycles 1, 3, and 6. Study outcomes included pregnancy probability, safety, acceptability, diaphragm fit, and ease of use. Results on effectiveness and safety were compared to an historical control group who used the ORTHO® ALL-FLEX® Diaphragm with these gels. The historical control for the SILCS diaphragm pivotal study was a multi-center contraceptive study conducted by the National Institute for Child Health and Human Development (NICHD). That study demonstrated that BG used with an ORTHO® ALL-FLEX® Diaphragm worked about as well as N-9 with that diaphragm (6-month typical-use cumulative probability of pregnancy rates of 10.1 per 100 women (95% CI 7.1-13.1) and 12.3 (95% CI 7.7-16.9), respectively. 4 The design of the SILCS pivotal study was based on that previous study which was then used in the SILCS historical control analysis to compare the single-size SILCS diaphragm with the ORTHO® ALL-FLEX® Diaphragm on contraceptive effectiveness and safety. In the SILCS pivotal study, 35 study pregnancies were reported which yielded 6-month Kaplan Meier cumulative typical-use pregnancy probabilities per 100 women (with 95% confidence intervals) of 10.4 (6.9, 14.0), 9.6 (5.5, 13.6) and 12.5 (5.4, 19.5) for all SILCS users, SILCS with BG and SILCS with N-9, respectively. The rate for all SILCS users was non-inferior to the rate for all users of the ORTHO® ALLFLEX® Diaphragm, using data from the historical control groups. The observed 6-month cumulative typical-use pregnancy probability was 10.4 per 100 women (95% CI: 6.9, 14.0). The observed 6-cycle cumulative perfect-use probability was 7.9 per 100 women (95% CI: 1.7, 14.0). Extrapolated to 12 months these estimates are for typical use: 17.8 per 100 women (95% CI: 12, 23.6) and for perfect use: 14.0 per 100 women (95% CI: 3.0, 23.6)</td></tr>
<tr><td>Skyla [22]</td><td>January 9, 2013</td><td>The pregnancy rate calculated as the Pearl Index (PI) in women aged 18–35 years was the primary efficacy endpoint used to assess contraceptive reliability. The PI was calculated based on 28-day equivalent exposure cycles; evaluable cycles excluded those in which back-up contraception was used unless a pregnancy occurred in that cycle. Skyla-treated women provided 15,763 evaluable 28-day cycle equivalents in the first year and 39,368 evaluable cycles over the three year treatment period. The PI estimate for the first year of use based on the 5 pregnancies that occurred after the onset of treatment and within 7 days after Skyla removal or expulsion was 0.41 with a 95% upper confidence limit of 0.96. The cumulative 3-year pregnancy rate, based on 10 pregnancies, estimated by the Kaplan-Meier method was 0.9 per 100 women or 0.9%, with a 95% upper confidence limit of 1.7%.</td></tr>
<tr><td>Nexplanon [20]</td><td>November 9, 2011</td><td>In clinical trials of up to 3 years duration that involved 923 subjects, 18-40 years of age at entry, and 1756 women-years of use with the non-radiopaque etonogestrel implant (IMPLANON), the total exposures expressed as 28-day cycle equivalents by study year were: Year 1: 10,866 cycles Year 2: 8,581 cycles Year 3: 3,442 cycles The clinical trials excluded women who: • Weighed more than 130% of their ideal body weight • Were chronically taking medications that induce liver enzymes In the subgroup of women, 18-35 years of age at entry, 6 pregnancies during 20,648 cycles of use were reported. Two pregnancies occurred in each of Years 1, 2, and 3. Each conception was likely to have occurred shortly before or within 2 weeks after removal of the non-radiopaque etonogestrel implant. With these 6 pregnancies, the cumulative Pearl Index was 0.38 pregnancies per 100 women years of use.</td></tr>
</table>

Fig. 1. (*continued*)

Index, although providing simplicity, is a less desirable analysis method in almost all circumstances. Life-table analysis should be the standard" [14].

Within the last 10 years, however, the FDA has provided two more updates, now favoring the Pearl Index. In 2017, the FDA issued a draft guidance for labeling of combined hormonal contraceptives, stating that "contraceptive efficacy should be reported in terms of the 1-year Pearl Index and 95% confidence interval around the point estimate" [15]. In 2019, the FDA issued another draft guidance entitled "Establishing Effectiveness and Safety for Hormonal Drug Products Intended to Prevent Pregnancy" [16]. This guidance indicated that "The primary efficacy endpoint should be the pregnancy rate described by the Pearl Index (PI) during the first year of use of the product." It further specified that "Life table analysis should also be used as a supportive analysis to provide monthly and cumulative failure rates for any specific length of exposure and will be included in labeling for long-acting contraceptive products that are evaluated in trials of more than 1 year's duration."

5. Labeling of recently approved contraceptive products

Figure 1 shows excerpts of the labeling for non-oral contraceptive products approved by the FDA since 2001. The Caya diaphragm shows only Kaplan-Meier rates [17]. The hormonal products Annovera, Twirla, and Nexplanon show only Pearl indices [18–20]. Annovera and Twirla were studied for 1 year and provided 1-year Pearl indices. Nexplanon was studied for 3 years and provides a cumulative 3-year Pearl Index of 0.38 pregnancies per 100 woman-years. A cumulative Pearl Index over multiple years will typically significantly underestimate pregnancy rates because it does not account in the denominator for participant discontinuations during the entire study duration. The denominator in life table analyses, however, decreases in all evaluations over time, providing an accurate cumulative pregnancy rate calculation.

Hormonal intrauterine devices (Liletta, Mirena, Skyla, and Kyleena) report both a Pearl Index and a life table pregnancy rate, consistent with FDA guidance that Pearl indices should be primary,

Table 1
Hypothetical data representing calculation of life table and Pearl Indices over 26- to 28-day cycles

Cycle	Number of persons entering cycle	Cumulative cycles	Pregnancies	Cumulative pregnancies	Conception rate, per cycle (%)	Survival rate, per cycle (%)	Proportion still protected (%)	Cumulative life table failure rate (%)	Pearl Index per cycle (pregnancies/ 1300 woman-cycles)	Overall Pearl Index (pregnancies/ 1300 woman-cycles)
1	500	500	15	15	3.0	97.0	97.0	3.0	39.0	39.0
2	485	985	13	28	2.7	97.3	94.4	5.6	17.4	37.0
3	472	1457	10	38	2.1	97.9	92.4	7.6	9.2	33.9
4	462	1919	9	47	1.9	98.1	90.6	9.4	6.3	31.8
5	453	2372	10	57	2.2	97.8	88.6	11.4	5.7	31.2
6	443	2815	3	60	0.7	99.3	88.0	12.0	1.5	27.7
7	440	3255	4	64	0.9	99.1	87.2	12.8	1.7	25.6
8	436	3691	7	71	1.6	98.4	85.8	14.2	2.6	25.0
9	429	4120	3	74	0.7	99.3	85.2	14.8	1.0	23.3
10	426	4546	4	78	0.9	99.1	84.4	15.6	1.2	22.3
11	422	4968	3	81	0.7	9.93	83.8	16.2	0.8	21.2
12	419	5387	5	86	1.2	98.8	82.8	17.2	1.3	20.8
13	414	5801	3	89	0.7	99.3	82.2	17.8	0.7	19.9
14	411	6212	5	94	1.2	98.8	81.2	18.8	1.1	19.7
15	406	6618	4	98	1.0	99.0	80.4	19.6	0.9	19.3
16	402	7020	3	101	0.7	99.3	79.8	20.2	0.6	18.7
17	399	7419	5	106	1.3	98.7	78.8	21.2	1.0	18.6
18	394	7813	3	109	0.8	99.2	78.2	21.8	0.5	18.1
19	391	8204	3	112	0.8	99.2	77.6	22.4	0.5	17.7
20	388	8592	5	117	1.3	98.7	76.6	23.4	0.8	17.7
21	383	8975	4	121	1.0	99.0	75.8	24.2	0.6	17.5
22	379	9354	2	123	0.5	99.5	75.4	24.6	0.3	17.1
23	377	9731	3	126	0.8	99.2	74.8	25.2	0.4	16.8
24	374	10,105	3	129	0.8	99.2	74.2	25.8	0.4	16.6
25	371	10,476	2	131	0.5	99.5	73.8	26.2	0.3	16.3
26	369	10,845	1	132	0.3	99.7	73.6	26.4	0.1	15.8

with life table results supportive for these products evaluated for more than 1 year [10,21–23]. However, these labels further illustrate the difficulty in understanding Pearl indices. For example, the Liletta approval for 8 years of use shows year-by-year Pearl Indices, ranging from 0.00 to 0.49 [10]. These are to be interpreted as, for example, in year 5 of use, there were 0.16 pregnancies per 100 woman-years. Unlike Nexplanon, an overall cumulative Pearl Index is not provided; rather and more appropriately, the cumulative life table pregnancy rate is provided, which is more easily understandable as the likelihood of pregnancy for a woman using this product for 5 years being 0.89%; for 8 years, the likelihood is 1.37%. Similarly, the Mirena label reports year-by-year Pearl Indices for years 6, 7, and 8 and also Kaplan-Meier rates for that 3-year period [21].

Table 1 presents a calculation of cumulative life table and Pearl Indices using hypothetical data over 26 cycles (it assumes subjects complete 26 cycles if they do not become pregnant). We note that interpretation of the cumulative life table rates makes sense. For example, the likelihood of pregnancy for a person using this product for 26 cycles is 26.4%. As a corollary, interpretation of the cumulative Pearl Index is less easy to understand. For example, over 26 cycles, 15.8 pregnancies per 100 woman-years occurred. As described in Section 3 earlier, cumulative life table pregnancy probabilities increase over time, as one would expect, while cumulative Pearl Indices tend to go down over time [8]. This decrease is a function of naturally decreasing pregnancy probability with time for the reasons described above; if the chance of pregnancy were the same for each cycle, Pearl Indices would also go up over time.

6. Recommendations for the future

Life table analysis should be the primary method for reporting contraceptive efficacy in clinical studies and product labels. This methodology is the most accurate and understandable way to convey contraceptive efficacy for the individual since it describes the pregnancy rate for a study of any duration, without the duration itself affecting the pregnancy rate. In the post-*Dobbs* era of new product development, this issue can no longer be ignored. It is unrealistic to suggest that previously completed studies reporting only Pearl rates should be repeated or even reanalyzed by the FDA. The Pearl Index could be required as supportive data for comparison with older studies but truly works best, today, as a historical footnote in contraceptive development. Going forward, the results of life table analyses should be the primary end point for contraceptive efficacy to provide accurate information about new products.

REFERENCES

[1] Supreme Court of the United States, syllabus, October term 2021. ⟨https://www.supremecourt.gov/opinions/21pdf/19–1392_6j37.pdf⟩ (accessed June 4, 2023).
[2] Kaufman R, Brown R, Martínez Coral C, Jacob J, Onyango M, Thomasen K. Global impacts of Dobbs v. Jackson Women's Health Organization and abortion regression in the United States. Sex Reprod Health Matters 2022;30(1):2135574. https://doi.org/10.1080/26410397.2022.2135574
[3] Pearl R. Factors in human fertility and their statistical evaluation. Lancet 1933:607–11.
[4] Evofem, Inc. Phexxi prescribing information. ⟨https://22077562.fs1.hubspotusercontent-na1.net/hubfs/22077562/Phexxi:July2022/PDFs/PhexxiUSPI.pdf⟩ (accessed June 4, 2023).
[5] Teal SB, Turok DK, Chen BA, Kimble T, Olariu AI, Creinin MD. Five-year contraceptive efficacy and safety of a levonorgestrel 52-mg intrauterine system. Obstet Gynecol 2019;133(1):63–70. https://doi.org/10.1097/AOG.0000000000003034
[6] Potter RG. Application of life table techniques to measurement of contraceptive effectiveness. Demography 1996;3(2):297–304. https://doi.org/10.2307/2060159
[7] Trussell J. Methodological pitfalls in the analysis of contraceptive failure. Stat Med 1991;10(2):201–20. https://doi.org/10.1002/sim.4780100206
[8] Trussell J, Portman D. The creeping Pearl: why has the rate of contraceptive failure increased in clinical trials of combined hormonal contraceptive pills? Contraception 2013;88(5):604–10. https://doi.org/10.1016/j.contraception.2013.04.001
[9] Trussell J. Understanding contraceptive failure. Best Pract Res Clin Obstet Gynaecol 2009;23(2):199–209. https://doi.org/10.1016/j.bpobgyn.2008.11.008
[10] Allergan and Medicines360. Liletta prescribing information. ⟨https://www.rxabbvie.com/pdf/liletta_pi.pdf⟩ (accessed July 31, 2023).
[11] U.S. Food and Drug Administration. Department of Health and Human Services. 21 CFR Part 351 [Docket No. 80N-0280] Vaginal contraceptive drug products for over-the-counter human use; establishment of a monograph; proposed

rulemaking. In Federal Register, Vol. 45, No. 241 / Friday, December 12, 1980 / Proposed Rules. Page 82046.
[12] U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Guidance for development of vaginal contraceptive drugs. ⟨https://www.fda.gov/media/71584/download⟩ (accessed June 4, 2023).
[13] U.S. Food and Drug Administration. Center for Devices and Radiological Health. Uniform contraceptive labeling - Guidance for industry. ⟨https://www.fda.gov/media/72591/download⟩ (accessed June 4, 2023).
[14] U.S. Food and Drug Administration. Advisory Committee for Reproductive Health Drugs meeting. Final summary minutes. January 23 and 24, 2007. ⟨chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://wayback.archive-it.org/7993/20170404050830/https://www.fda.gov/ohrms/dockets/ac/07/minutes/2007–4274m1.pdf⟩ (accessed June 4, 2023).
[15] U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Labeling for combined hormonal contraceptives guidance for industry, draft guidance. ⟨https://www.fda.gov/media/110050/download⟩ (accessed June 4, 2023).
[16] U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Establishing effectiveness and safety for hormonal drug products intended to prevent pregnancy. Guidance for industry. ⟨https://www.fda.gov/media/128792/download⟩ (accessed June 4, 2023).
[17] FDA marketing approval letter for Caya. ⟨https://www.accessdata.fda.gov/cdrh_docs/pdf14/K140305.pdf⟩ (accessed June 4, 2023).
[18] TherapeuticsMD, Inc. Annovera prescribing information. ⟨https://www.annovera.com/pi.pdf⟩, (accessed June 4, 2023).
[19] Agile Therapeutics, Inc. Twirla prescribing information. ⟨https://www.twirla.com/pdf/Twirla%20FINAL%20USPI%20PPI%20IFU.pdf⟩ (accessed June 4, 2023).
[20] Organon USA LLC. Nexplanon prescribing information. ⟨https://www.organon.com/product/usa/pi_circulars/n/nexplanon/nexplanon_pi.pdf⟩ (accessed June 4, 2023).
[21] Bayer HealthCare Pharmaceuticals. Mirena prescribing information. ⟨https://labeling.bayerhealthcare.com/html/products/pi/Mirena_PI.pdf⟩ (accessed June 4, 2023).
[22] Bayer HealthCare Pharmaceuticals. Skyla prescribing information. ⟨https://labeling.bayerhealthcare.com/html/products/pi/Skyla_PI.pdf⟩ (accessed June 4, 2023).
[23] Bayer HealthCare Pharmaceuticals. Kyleena prescribing information. ⟨https://labeling.bayerhealthcare.com/html/products/pi/Kyleena_PI.pdf⟩ (accessed June 4, 2023).