**Long-Acting Reversible Contraception (LARC) Extended Use**

KEY TALKING POINTS:

- Studies support off-label use of Mirena® (and, by extrapolation, Liletta®) for 7 years, ParaGard® for 12 years, and Nexplanon® for 5 years for pregnancy prevention, which is longer than the FDA-approved labeling of 6, 10, and 3 years, respectively, for these devices.
- There is insufficient data about the extended use of Nexplanon in people with obesity (BMI >30), although the data that is available does not show a decrease in contraceptive efficacy.
- There is currently no extended use data for Skyla® (FDA approved for 3 years) or Kyleena® (FDA approved for 5 years).
- Some patients may experience increased irregular bleeding with extended use of Mirena® and Nexplanon®.

SUMMARY OF DATA:

Recent studies have demonstrated that four LARC methods are effective for longer than their labels indicate. Currently, ParaGard® (T 380A Intrauterine copper contraceptive) is FDA labeled for 10 years of use, Nexplanon® (68 mg etonogestrel implant) for 3 years of use, Mirena® (52 mg levonorgestrel intrauterine device) for 6 years and Liletta® (52 mg levonorgestrel intrauterine device) for 6 years. All of these have been studied for extended contraceptive use past their FDA-approved duration. In addition, there are two other LARC devices available in the United States: Kyleena® (19.5 mg levonorgestrel intrauterine device) and Skyla® (13.5 mg levonorgestrel intrauterine device); neither of these devices has been studied for extended use.

In 1997, the World Health Organization (WHO) followed 1400 participants using the ParaGard® IUD for 12 years. The cumulative pregnancy rate was 2.2 per 100 person-years (compared to 0.8-1.9 person-years for all sterilization methods) and no pregnancies were reported between 8-12 years. [1]

In late 2016, WHO published their data comparing Implanon (68 mg etonogestrel implant) to the two-rod implant Jadelle® (75 mg levonorgestrel) that is labeled for 5 years of use (available in the U.K. but never released in the U.S). Both methods demonstrated comparable effectiveness over 5 years. No pregnancies occurred among 311 participants who extended use of their existing Nexplanon® to 4 years or in 204 participants who continued the method for 5 years of use. The 5-year cumulative pregnancy rate was 0.6. [2] There were few participants in the study over 70kg/BMI >30. In 2017, a study using participants from the Contraceptive CHOICE study indicated that the etonogestrel implant had a failure rate of 0 per 100 person-years in years 4 and 5 of use. This study indicated that all participants had decreases in serum etonogestrel levels in the extended use time period, but that the rate of decrease in relationship to BMI was not linear. This study included 127 participants with BMI > 30, with no pregnancies. This suggests that there is no loss of contraceptive efficacy for people with a BMI > 30 using Nexplanon up until 5 years, but more data is needed in this population. [3]

Also in late 2016, the UNDP/ UNFPA/WHO/World Bank Special Program of Research published their study showing that Mirena® is effective for 7 years. The investigators compared Mirena® to ParaGard® (T 380A Intrauterine copper contraceptive) in a randomized trial of almost 4,000 participants. By the end of year 7, only 0.53% of those with Mirena® had become pregnant versus 2.45% for the copper IUD. There were 717 Mirena® users who completed 6 years of follow-up and 398 participants who completed 7 years with no pregnancies in year 6 or 7. [4] Even longer durations of use continue to be examined for contraceptive efficacy,

including one already published study that demonstrated 0 pregnancies in a small number of participants who continued the Mirena® IUD for up to 15 years.[5] In August 2020, the FDA approved Mirena for the prevention of pregnancy for up to six years.

An ongoing trial aims to examine the contraceptive efficacy of Liletta® for up to 10 years; current data demonstrates that Liletta® is effective for at least 6 years.[6] In October 2019, the FDA approved extension of the duration of use of Liletta® for the prevention of pregnancy for up to six years. Studies examining extended use of Mirena® for contraception are likely able to be extrapolated to Liletta®, given that Liletta® contains an equal amount of levonorgestrel as Mirena® and releases it at a similar rate [7]

Bleeding patterns may change during extended use of LARC, including a decrease in amenorrhea rates and an increase in rates of return to regular menses.[2,5] This is thought to be due to the decline in serum hormone levels released from the implant over time. Some studies report minimal change in amenorrhea patterns over time, although it should be noted that some women are opting to remove the LARC device during the extended-use time period due to return of undesired bleeding. [5] Recent data suggests unchanged bleeding patterns between 60-72 months with Liletta®, with the majority of patients reporting amenorrhea, spotting, or light bleeding. [8]

TABLE: CONTRACEPTIVE FAILURE RATES

| | FDA approved (years) | Extended Use (years) | Failure Rate (per 100 person-years) for:<br>First year<br>FDA approved length of time<br>Extended length of time |
|---|---|---|---|
| Copper IUD (Paragard®) | 10 | 12 | 0.8 (first year)<br>1.9 (cumulative 10 years)<br>1.9 (cumulative 12 years) |
| LNG IUD 52 mg (Mirena®) | 6 | 7 | 0.2 (first year)<br>0.7 (cumulative 5 years)<br>0.03 (cumulative years 6-7) |
| LNG IUD 52 mg (Liletta®) | 6 | 7* | --<br>0.87 (cumulative 6 years)<br>-- |
| LNG IUD 19.5 mg (Kyleena®) | 5 | n/a | 0.16 (first year)<br>1.45 (cumulative 5 years)<br>-- |
| LNG IUD 13.5mg (Skyla®) | 3 | n/a | 0.41 (first year)<br>0.9 (cumulative 3 years) |
| Etonogestrel implant 68mg (Nexplanon®) | 3 | 5** | --<br>0.38 (cumulative 3 years)<br>0.6 (cumulative 5 years)** |
| Sterilization*** | n/a | n/a | 1.9 |

*Of note, Liletta and Skyla are not available in Canada. Mirena approval in Canada is for 5 years, although the SOGC (Society of OB/GYN of Canada) statement April 2020 did support extended use of Mirena for up to 7 years.*[9]

*Extrapolated from studies using Mirena IUD
**BMI < 30
***Sterilization is now more frequently being accomplished with bilateral complete salpingectomy, for which contraceptive failure is reported in case reports only.

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