# Women's Health

To see what's new in the women's health market, it might be necessary to take a look back. The return of the IUD is just one comeback shaping the future of a field that has never been a stranger to controversy. **Noah Pines** reports on the latest developments in this space

For those who want to get a hold on current trends in the treatment of women's health conditions, one place to look for guidance is, well, the past.

Take the birth control category as an example. Owing to improved safety and the endorsement of medical experts, the popularity of intrauterine devices (IUDs) has seen a dramatic spike over the last half-decade or so. While IUDs have historically been considered an effective mode of contraception, they had all but disappeared from the market in the wake of the Dalkon Shield tragedy of the 1970s and 1980s (see "Clinical Corner," pg. 48).

"What interests me is the rise of the IUD—and talk about trends shifting. If we were in a different decade, the term 'IUD' would strike fear into patients' hearts," says Martin Mannion, executive vice president and director of strategy and branding at ICC Lowe.

IUD brands such as Bayer's Mirena and Skyla, and Teva's ParaGard have jumped in popularity among both physicians and patients. Given the utility of such devices, nobody seems too surprised. To hear Dr. Nancy Gaba, chair of the Department of Obstetrics and Gynecology at the George Washington University School of Medicine and Health Sciences, tell it, today's IUDs are "more reliable and more woman-friendly."


This is a substantial change from even the recent past. "A few years ago, the American Congress of Obstetricians and Gynecologists endorsed long-acting reversible contraception (LARC) approaches including IUDs, due to dramatically better efficacy versus the pill, the patch or condoms. They also endorsed it for women who were not previously thought to be candidates," Gaba adds. "We would have never prescribed an IUD for a teenager. Now I do that all the time."

That same sentiment is echoed by Dr. Michael Zuckerman, principal and director of medical affairs for *in*Thought Research. A practicing OB/GYN, he considers the reappearance of the IUD one of the most significant recent trends in women's health. "The feeling towards IUDs has changed recently. We understand why women were getting these infections [with the Dalkon Shield], we solved the issue and now we can use IUDs for everyone," he says.

Besides their enhanced safety, Zuckerman says, IUDs offer guaranteed medication adherence—a clear advantage over taking a daily pill for some patient populations, like younger women. "A teenager is the least likely person to take a pill regularly, so she is a great candidate for a LARC method. She can't afford to be pregnant," he notes.

And for companies in the oral contraceptive space facing huge competition from generics, IUDs have become something of an antidote. "For the few branded oral contraceptives, the struggle they face is an enormously genericized marketplace where it's hard to find magic," Mannion explains.

## TOP 25 WOMEN'S HEALTH PRODUCTS, 2013

Category leaders, ranked by 2013 US sales and their media spend

| Rank | Product | Manufacturer | US sales $ (millions) | Vs. prior 12 months | TRx (000s) | Vs. prior 12 months | US DTC media $ (000s) | Vs. prior 12 months | US journal media $ (000s) | Vs. prior 12 months |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **Evista** | Eli Lilly | $830.3 | 8.0% | 2,941.0 | -12.0% | $0.0 | N/A | $1,291.0 | -14.6% |
| 2 | **Xgeva** | Amgen | $788.5 | 19.0% | 7.0 | 21.0% | $0.0 | N/A | $1,441.0 | -32.9% |
| 3 | **Mirena** | Bayer | $609.1 | -7.0% | 14.0 | -49.0% | $7,052.1 | -48.5% | $425.0 | 43.2% |
| 4 | **NuvaRing** | Merck | $579.5 | 12.0% | 5,018.0 | 1.0% | $20,253.0 | -18.9% | $0.0 | -100.0% |
| 5 | **Forteo** | Eli Lilly | $547.8 | 12.0% | 414.0 | 4.0% | $0.0 | N/A | $2,699.0 | 11.8% |
| 6 | **Prolia** | Amgen | $480.6 | 58.0% | 177.0 | 66.0% | $61,094.6 | 1.8% | $0.0 | -100.0% |
| 7 | **Ortho-Tri-Cy Lo 28** | Janssen | $476.0 | 10.0% | 3,198.0 | -7.0% | $0.0 | N/A | $0.0 | N/A |
| 8 | **Actonel** | Actavis | $329.8 | -21.0% | 1,623.0 | -34.0% | $0.0 | N/A | $0.0 | N/A |
| 9 | **Loestrin 24 FE** | Actavis | $299.3 | -45.0% | 3,058.0 | -48.0% | $0.0 | N/A | $0.0 | N/A |
| 10 | **Lo Loestrin FE** | Actavis | $276.4 | 70.0% | 2,915.0 | 49.0% | $0.0 | N/A | $0.0 | N/A |
| 11 | **Follistim AQ** | Merck | $257.0 | 5.0% | 122.0 | 8.0% | $0.0 | N/A | $0.0 | N/A |
| 12 | **Zoledronic acid** | Generic | $235.9 | N/A | 10.0 | N/A | $0.0 | N/A | $0.0 | N/A |
| 13 | **Progesterone** | Generic | $161.3 | 23.0% | 2,596.0 | 55.0% | $0.0 | N/A | $35.0 | -38.1% |
| 14 | **Medroxyprogesteron** | Generic | $154.9 | 6.0% | 4,564.0 | 6.0% | $0.0 | N/A | $0.0 | N/A |
| 15 | **Ortho Evra 3** | Janssen | $154.8 | 12.0% | 1,203.0 | -1.0% | $0.0 | N/A | $0.0 | N/A |
| 16 | **Zometa** | Novartis | $146.0 | -76.0% | 3.0 | -62.0% | $0.0 | N/A | $304.0 | -72.2% |
| 17 | **Menopur** | Ferring | $140.9 | 14.0% | 89.0 | 19.0% | $0.0 | N/A | $110.0 | -6.0% |
| 18 | **Ibandronate sodium** | Generic | $135.9 | -28.0% | 1,881.0 | 26.0% | $0.0 | N/A | $0.0 | N/A |
| 19 | **Reclast** | Novartis | $133.4 | -63.0% | 7.0 | -49.0% | $0.0 | -100.0% | $0.0 | N/A |
| 20 | **Gianvi** | Teva | $121.4 | -17.0% | 2,531.0 | -7.0% | $0.0 | N/A | $0.0 | N/A |
| 21 | **Minastrin 24 FE** | Actavis | $113.5 | N/A | 1,027.0 | N/A | $0.0 | N/A | $0.0 | N/A |
| 22 | **Beyaz-28** | Bayer | $112.8 | -12.0% | 1,097.0 | -25.0% | $0.0 | N/A | $0.0 | N/A |
| 23 | **Loryna** | Sandoz | $104.8 | -12.0% | 945.0 | -20.0% | $0.0 | N/A | $0.0 | N/A |
| 24 | **Next Choice 1 Dose** | Actavis | $99.0 | 173.0% | 218.0 | 211.0% | $0.0 | N/A | $0.0 | N/A |
| 25 | **Norgest-eth.estradiol** | Generic | $98.8 | 44.0% | 2,514.0 | 45.0% | $0.0 | N/A | $0.0 | N/A |

Sources: Sales/TRx, IMS Health; DTC media spend, Nielsen; journal spend, Kantar Media
Note: List includes contraceptives and products FDA indicates as approved for treating fertility, menopause and osteoporosis.

Bayer is a prime example. In recent years, IUDs have become a big part of the company's women's health commercial strategy, especially as it stares down the loss of patent protection on oral contraceptive brands Yaz and Yasmin. In 2013, the company acquired a permanent birth-control product (Essure, originally marketed by Conceptus) that is inserted into the fallopian tubes to stop conception. It's seen as an alternative to tubal ligation, another sterilization method. Bayer also has a transparent birth-control patch awaiting approval in Europe and another IUD in late-stage development.

A second area of major growth within women's health is the treatment of vasomotor symptoms (VMS) in menopausal women, where doctors are seeing an expanded array of both hormonal and non-hormonal options. While they still regard estrogen replacement therapy (ERT) as the gold standard, widespread patient concerns over its safety are driving the increased popularity of non-hormonal options such as Brisdelle, now jointly marketed in the US by Shionogi and Noven Therapeutics. Brisdelle was given the thumbs-up by the FDA in June 2013 and launched last November.

"I still think most OB/GYNs would say that the best treatment for vasomotor symptoms is hormone replacement therapy, but many women refuse to do that or they have contraindications. We've been prescribing SSRIs and SNRIs [in VMS] for a long time, so that is not new," Gaba explains. "Patients would push back when you'd tell them that Paxil is a medication for depression. But now you can tell them that Brisdelle is actually indicated for hot flashes, and that is much more favorably received."

Zuckerman, on the other hand, points to a recent article in the July issue of the *Journal of the American Medical Association*, which compared a commonly used ERT, low-dose Estradiol, to venlafaxine, an SNRI, in patients with vasomotor symptoms. The study referred to in the article, headed by Dr. Hadine Joffe from Boston's Brigham and Women's Hospital, buttresses the case for non-hormonal treatments (such as SSRIs/SNRIs), since the difference between them is seen as small and of uncertain clinical relevance.

"You marry that information with the recent approval of Brisdelle, and it seems there is more and more data moving towards non-hormonal methods of treating vasomotor symptoms," Zuckerman says.

Hormone and non-hormone therapy brands alike are also benefitting from a shift in focus. Dyspareunia, or painful intercourse, has been the primary indication for Shionogi's Osphena, an oral drug approved in February 2013 that acts like estrogen on vaginal tissues and restores vaginal flora and vasculature. The drug has been promoted through an extensive consumer-focused campaign aimed at destigmatizing the condition. The campaign, findingthewords.com, counts Academy Award-nominated actor Virginia Madsen as its spokesperson.

Pfizer is another of the major players that sees huge potential in the women's health space. It generated $1.1 billion in 2013 from sales of Premarin, with the vaginal cream formulation helping buoy the company's women's-health franchise in the face of HRT hysteria and competition from other prescription options. Premarin still remains among the company's top ten best-selling brands.

## CLINICAL CORNER

There are many reasons that women and physicians have warmed once again to the use of intrauterine devices (IUDs), among them educational efforts by the American College of Obstetricians and Gynecologists and the pervasive view that IUDs "are truly the most effective and economical type of birth control," according to Dr. Lisa Dietrich, executive vice president and director of medical affairs at ICC Lowe. But one factor that can't be dismissed is the age of the patients who are using them—they are too young to remember the notorious and tragic case of the Dalkon Shield.

Lisa Dietrich

Developed by Dr. Hugh Davis of Johns Hopkins University, the Dalkon Shield was an intrauterine contraceptive device sold by the A.H. Robins Company in the 1970s. Owing to its unique shape—it had a crab-like design, with five prongs—the device was difficult to remove, which necessitated a multifilament tail string to aid with removal (by comparison, modern IUDs use monofilament strings). It was thought that the multifilament string allowed bacteria to climb into the vagina, causing pelvic infections that resulted in infertility or even death.

As reports of these pelvic infections started to surge, the Food and Drug Administration advised A.H. Robins to withdraw the product from the market. In 1983, the FDA recommended that women using the Dalkon Shield should have it removed. Ultimately, the Dalkon Shield was found to have been responsible for 18 deaths and more than 200,000 infections and miscarriages. Bending beneath the weight of litigation, A.H. Robins abandoned the Dalkon Shield in the mid-1980s. The company was ultimately sold in bankruptcy to American Home Products (now Wyeth).

It's no surprise, then, that the Dalkon Shield almost single-handedly ended IUD usage in the US. "In another age, the term 'IUD' struck fear in people," Dietrich recalls. It was not until 1988 that IUDs began to reemerge as an option for many women, thanks to GynoPharma's release of a new copper IUD, ParaGard.

Years later, the Dalkon Shield legacy extends beyond the damage it inflicted on the lives of women and their families, according to Wayne Pines, president of regulatory services and healthcare at APCO Worldwide and a former associate commissioner of the FDA. "The Dalkon Shield episode was a seminal example of where litigation became the predominant factor in driving medical decision-making," he says. "At the same time, the litigation caused IUDs to gain such a bad reputation that it became unfeasible for companies to develop and market the technology. It changed the dynamic of birth control for that generation."

According to the Guttmacher Institute, a nonprofit group that works on reproductive health issues, 2.14 million US women used IUDs in 2010—5.6% of all US women who practice contraception.

Additionally, earlier this year Pfizer launched Duavee, a drug which combines estrogen conjugates with the antagonist bazedoxifene to treat moderate-to-severe hot flashes in menopausal women who haven't had a hysterectomy. Dr. Daniel Ferrante, a practicing OB/GYN within Lifeline Medical Associates, predicts that Duavee will be "a safety-based sell… The idea behind Duavee is good. The Women's Health Initiative showed that the increased cancer risk was associated with estrogen combined with progesterone. So Pfizer took the 'bad player' out and is protecting the lining of the endometrium with a SERM [selective estrogen receptor modulators]."

And then there's a semi-new player on the scene. After emerging from bankruptcy, K-V Pharmaceutical, makers of Makena for preterm birth and other brands for women's health, relaunched in May as Lumara Health. In the wake of concerns about compounded medications—raised after the New England Compounding Center meningitis outbreak in 2012—the company is seeing increased demand for Makena, a hormone injection that reduces the risk of preterm birth in at-risk patients. While the initial launch was controversial, Makena seems to be back on track, winning the endorsement (and business) of its key audiences.

"Makena is positioned nicely now. I think the major battles are over," says Ferrante. "It has been recognized as the safest, most effective treatment. [Lumara Health] did a great job regaining their position after the emotional response after launch. I am not getting any pushback from using it." One interested party, Gregg Raybuck, president of Lumara's maternal health division, agrees: "In such a highly specialized environment, our partnerships with patient advocacy and healthcare professional communities are a critical area of focus."

Still, despite all the energy within the reproductive health and menopause categories, the most exciting pipeline area in women's health might be osteoporosis, which has two major next-generation products in late-stage development from Merck and Amgen.

In May, Merck announced that it will seek approval for odanacatib after the drug's debut was delayed for a reassessment of its clinical trial data. While it offers a new mechanism of action, the company informed analysts about certain safety signals, including a higher incidence of stroke, atrial fibrillation and skin thickening. At the same time, it was noted that odanacatib was not associated with osteonecrosis of the jaw, a reaction that has long been associated with bisphosphonates, the mainstay of osteoporosis therapy.

Last January, Amgen announced promising Phase-II results for monoclonal antibody romosozumab. The results showed that it increases bone mineral density and bone formation and reduces bone resorption in postmenopausal women with low bone mineral density. Romosozumab, which is administered subcutaneously, increases bone formation by binding to sclerostin. Current osteoporosis medicines do not restore bone architecture and/or are limited by dosing challenges. However, romosozumab's biomarker benefits have yet to translate into reduction in fractures, and long-term safety has not yet been established.

The biggest challenge that both Merck and Amgen will face is the increased genericization of the osteoporosis treatment category. Add to that a comparatively apathetic audience that is preoccupied with other long-term health concerns, and the two pharma giants have their marketing work cut out for them. ■

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