



**EDUCATIONAL OBJECTIVE:** Readers will consider the results of randomized controlled trials when caring for women patients

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# Women's health 2016: An update for internists

## ABSTRACT

Internists are called upon on a daily basis to address a range of women's health issues. Staying up to date with the evidence in this wide field can be challenging. This article reviews important studies published in 2015 and early 2016 pertinent to urinary tract infection, osteoporosis, ovarian cancer screening, and contraception.

## KEY POINTS

Many women with mild uncomplicated urinary tract infections can avoid taking antibiotics and instead receive treatment for symptoms alone.

The American Society for Bone and Mineral Research now recommends reassessing the risk of osteoporotic fracture after 3 to 5 years of bisphosphonate therapy. Women at high risk may benefit from extending bisphosphonate therapy to 10 years.

Current evidence shows no clear benefit of ovarian cancer screening for women at average risk, and we should not recommend yearly ultrasonography or cancer antigen 125 level testing, either of which is likely to cause harm without providing benefit.

A large observational study found death rates were lower in parous than in nulliparous women, in women who had breastfed than in those who had never breastfed, and in nonsmokers who had used oral contraceptives.

Intrauterine contraception and subdermal implants are safe and are the most effective contraceptive options.

**W**OMEN'S HEALTH encompasses a variety of topics relevant to the daily practice of internists. Staying up to date with the evidence in this wide field is a challenge.

This article reviews important studies published in 2015 and early 2016 on treatment of urinary tract infections, the optimal duration of bisphosphonate use, ovarian cancer screening, the impact of oral contraceptives and lactation on mortality rates, and the risks and benefits of intrauterine contraception. We critically appraised the studies and judged that their methodology was strong and appropriate for inclusion in this review.

## ■ IBUPROFEN FOR URINARY TRACT INFECTIONS

*A 36-year-old woman reports 4 days of mild to moderate dysuria, frequency, and urgency. She denies fever, nausea, or back pain. Her last urinary tract infection was 2 years ago. Office urinalysis reveals leukocyte esterase and nitrites. She has read an article about antibiotic resistance and Clostridium difficile infection and asks you if antibiotics are truly necessary. What do you recommend?*

### Urinary tract infections are often self-limited

Uncomplicated urinary tract infections account for 25% of antibiotic prescriptions in primary care.<sup>1</sup>

Several small studies have suggested that many of these infections are self-limited, resolving within 3 to 14 days without antibiotics (Table 1).<sup>2-6</sup> A potential disadvantage of withholding treatment is slower bacterial clearance and resolution of symptoms, but reducing the number of antibiotic prescriptions may help slow antibiotic resistance.<sup>7,8</sup> Surveys and quali-

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TABLE 1

**Randomized controlled trials of urinary tract infection treatment: Antibiotics vs placebo or delayed antibiotics**

Study <sup>a</sup>	Patients and treatment	Measures studied	Outcomes
<b>Christiaens et al<sup>2</sup></b>	88 women, ages 15–54 Nitrofurantoin 100 mg or placebo four times a day for 3 days	Symptoms and urinalysis over 14 days	Women who reported symptomatic cure (complete relief of symptoms) after 7 days: 24 (70%) of 40 with nitrofurantoin 14 (42%) of 38 with placebo  Women who reported symptomatic improvement (defined as “few symptoms”) after 7 days: 6 (18%) of 40 with nitrofurantoin 3 (9%) of 38 with placebo
<b>Bleidorn et al<sup>3</sup></b>	80 women, ages 18–85 Ibuprofen 400 mg three times a day vs ciprofloxacin 250 mg twice a day for 3 days	Symptoms and urinalysis over 28 days	Symptomatic improvement and cure after 4 days: 21 (58.3%) of 36 with ibuprofen 17 (51.5%) of 33 with ciprofloxacin  Receiving secondary antibiotic treatment due to ongoing or worsening symptoms by day 9: 12 (33%) of 36 with ibuprofen 6 (18%) of 33 with ciprofloxacin (not significant)
<b>Little et al<sup>4</sup></b>	309 women, ages 18–70 Immediate antibiotics vs 48-hour delay vs targeted antibiotics based on symptom severity, dipstick result, or positive midstream urine culture	Symptom severity at days 2–4  Rates of antibiotic use	Immediate antibiotic group had 3.5 days of moderately bad symptoms; most groups were similar; delayed antibiotic group reconsulted less (hazard ratio 0.57, 95% confidence interval 0.36–0.89, $P = .014$ ), but had symptoms for 37% longer than the immediate antibiotic group (incident rate ratio 1.37, 95% confidence interval 1.11–1.68, $P = .003$ )  Rates of antibiotic use: Immediate antibiotic group 97% Symptom severity group 90% Urine culture group 81% Urine dipstick group 80% Delayed antibiotic group 77% ( $P = .011$ )
<b>Ferry et al<sup>5</sup></b>	1,143 women, ages 18 and older  288 patients received placebo for 7 days	Symptoms, bacteriuria, and urine culture over 7 weeks	Associations between symptoms, bacteriuria, and urine culture results were unpredictable  Spontaneous cure rates in the placebo group: 28% symptom-free after the first week 37% symptom-free, and no bacteriuria after 5–7 weeks  Limitation: 39% dropout rate
<b>Gágyor et al<sup>6</sup></b>	779 women, ages 18–65 Ibuprofen 400 mg three times a day for 3 days vs a single 3-g dose of fosfomycin	Symptoms and urinalysis over 28 days  Safety data collected every 6 months over 2 years	See text for more details  Two-thirds of the women in the ibuprofen group recovered without antibiotic treatment  Within 28 days, 34% of the ibuprofen group received antibiotic treatment for persistent or worsening symptoms compared with 14% of the fosfomycin group (who received an additional course of antibiotics)  On days 0–4, patients in the ibuprofen group had more symptoms than those in the fosfomycin group

<sup>a</sup> Participants in these studies were not pregnant.

tative studies have suggested that women are concerned about the harms of antibiotic treatment and so may be willing to avoid or postpone antibiotic use.<sup>9–11</sup>

### Ibuprofen vs fosfomycin

Gágyor et al<sup>6</sup> conducted a double-blind, randomized multicenter trial in 42 general practices in Germany to assess whether treating the symptoms of uncomplicated urinary tract infection with ibuprofen would reduce antibiotic use without worsening outcomes.

Of the 779 eligible women with suspected urinary tract infection, 281 declined to participate in the study, 4 did not participate for reasons not specified, 246 received a single dose of fosfomycin 3 g, and 248 were treated with ibuprofen 400 mg three times a day for 3 days. Participants scored their daily symptoms and activity impairment, and safety data were collected for adverse events and relapses up to day 28 and within 6 and 12 months. In both groups, if symptoms worsened or persisted, antibiotic therapy was initiated at the discretion of the treating physician.

Exclusion criteria included fever, “loin” (back) tenderness, pregnancy, renal disease, a previous urinary tract infection within 2 weeks, urinary catheterization, and a contraindication to nonsteroidal anti-inflammatory medications.

**Results.** Within 28 days of symptom onset, women in the ibuprofen group had received 81 courses of antibiotics for symptoms of urinary tract infection (plus another 13 courses for other reasons), compared with 277 courses for urinary tract infection in the fosfomycin group (plus 6 courses for other reasons), for a relative rate reduction in antibiotic use of 66.5% (95% confidence interval [CI] 58.8%–74.4%,  $P < .001$ ). The women who received ibuprofen were more likely to need antibiotics after initial treatment because of refractory symptoms but were still less likely to receive antibiotics overall (**Table 1**).

The mean duration of symptoms was slightly shorter in the fosfomycin group (4.6 vs 5.6 days,  $P < .001$ ). However, the percentage of patients who had a recurrent urinary tract infection within 2 to 4 weeks was higher in the fosfomycin-treated patients (11% vs 6%  $P = .049$ ).

Although the study was not powered to show significant differences in pyelonephritis, five patients in the ibuprofen group developed pyelonephritis compared with one in the antibiotic-treated group ( $P = .12$ ).

An important limitation of the study was that nonparticipants had higher symptom scores, which may mean that the results are not generalizable to women who have recurrent urinary tract infections, longer duration of symptoms, or symptoms that are more severe. The strengths of the study were that more than half of all potentially eligible women were enrolled, and baseline data were collected from nonparticipants.

### Can our patient avoid antibiotics?

Given the mild nature of her symptoms, the clinician should discuss with her the risks vs benefits of delaying antibiotics, once it has been determined that she has no risk factors for severe urinary tract infection. Her symptoms are likely to resolve within 1 week even if she declines antibiotic treatment, though they may last a day longer with ibuprofen alone than if she had received antibiotics. She should watch for symptoms of pyelonephritis (eg, flank pain, fever, chills, vomiting) and should seek prompt medical care if such symptoms occur.

### ■ DISCONTINUING BISPHOSPHONATES

*A 64-year-old woman has taken alendronate for her osteoporosis for 5 years. She has no history of fractures. Her original bone density scans showed a T-score of  $-2.6$  at the spine and  $-1.5$  at the hip. Since she started to take alendronate, there has been no further loss in bone mineral density. She is tolerating the drug well and does not take any other medications. Should she continue the bisphosphonate?*

### Optimal duration of therapy unknown

The risks and benefits of long-term bisphosphonate use are debated.

In the Fracture Intervention Trial (FIT),<sup>12</sup> women with low bone mineral density of the femoral neck were randomized to receive alendronate or placebo and were followed for 36 months. The alendronate group had significantly fewer vertebral fractures and clinical fractures overall. Then, in the FIT Long-term Extension (FLEX) study,<sup>13</sup> 1,009 alendronate-

**Uncomplicated urinary tract infections account for 25% of antibiotic prescriptions in primary care**

treated women in the FIT study were rerandomized to receive 5 years of additional treatment or to stop treatment. Bone density in the untreated women decreased, although not to the level it was before treatment. At the end of the study, there was no difference in hip fracture rate between the two groups (3% of each group had had a hip fracture), although women in the treated group had a lower rate of clinical vertebral fracture (2% vs 5%, relative risk 0.5, 95% CI 0.2–0.8).

In addition, rare but serious risks have been associated with bisphosphonate use, specifically atypical femoral fracture and osteonecrosis of the jaw. A US Food and Drug Administration (FDA) evaluation of long-term bisphosphonate use concluded that there was evidence of an increased risk of osteonecrosis of the jaw with longer duration of use, but causality was not established. The evaluation also noted conflicting results about the association with atypical femoral fracture.<sup>14</sup>

Based on this report and focusing on the absence of nonspine benefit after 5 years, the FDA suggested that bisphosphonates may be safely discontinued in some patients without compromising therapeutic gains, but no adequate clinical trial has yet delineated how long the benefits of treatment are maintained after cessation. A periodic reevaluation of continued need was recommended.<sup>14</sup>

### **New recommendations from the American Society for Bone and Mineral Research**

Age is the greatest risk factor for fracture.<sup>15</sup> Therefore, deciding whether to discontinue a bisphosphonate when a woman is older, and hence at higher risk, is a challenge.

A task force of the American Society for Bone and Mineral Research (ASBMR) has developed an evidence-based guideline on managing osteoporosis in patients on long-term bisphosphonate treatment.<sup>16</sup> The goal was to provide guidance on the duration of bisphosphonate therapy from the perspective of risk vs benefit. The authors conducted a systematic review focusing on two randomized controlled trials (FLEX<sup>13</sup> and the Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly Pivotal Fracture Trial<sup>17</sup>) that provided data on long-term bisphosphonate use.

The task force recommended<sup>16</sup> that after 5 years of oral bisphosphonates or 3 years of intravenous bisphosphonates, risk should be reassessed. In women at high fracture risk, they recommended continuing the oral bisphosphonate for 10 years or the intravenous bisphosphonate for 6 years. Factors that favored continuation of bisphosphonate therapy were as follows:

- An osteoporotic fracture before or during therapy
- A hip bone mineral density T-score  $\leq -2.5$
- High risk of fracture, defined as age older than 70 or 75, other strong risk factors for fracture, or a FRAX fracture risk score<sup>18</sup> above a country-specific threshold.

(The FRAX score is based on age, sex, weight, height, previous fracture, hip fracture in a parent, current smoking, use of glucocorticoids, rheumatoid arthritis, secondary osteoporosis, alcohol use, and bone mineral density in the femoral neck. It gives an estimate of the 10-year risk of major osteoporotic fracture and hip fracture. High risk would be a 10-year risk of major osteoporotic fracture greater than 20% or a 10-year risk of hip fracture greater than 3%.)

For women at high risk, the risks of atypical femoral fracture and osteonecrosis of the jaw are outweighed by the benefit of a reduction in vertebral fracture risk. For women not at high risk of fracture, a drug holiday of 2 to 3 years can be considered after 3 to 5 years of treatment.

Although the task force recommended reassessment after 2 to 3 years of drug holiday, how best to do this is not clear. The task force did not recommend a specific approach to reassessment, so decisions about when to restart therapy after a drug holiday could potentially be informed by subsequent bone mineral density testing if it were to show persistent bone loss. Another option could be to restart bisphosphonates after a defined amount of time (eg, 3–5 years) for women who have previously experienced benefit.

The task force recommendations are in line with those of other societies, the FDA, and expert opinion.<sup>19–23</sup>

The American Association of Clinical Endocrinologists recommends considering a drug holiday in low-risk patients after 4 to 5 years of

**Age is the greatest risk factor for fracture**



treatment. For high-risk patients, they recommend 1 to 2 years of drug holiday after 10 years of treatment. They encourage restarting treatment if bone mineral density decreases, bone turnover markers rise, or fracture occurs.<sup>19</sup> This is a grade C recommendation, meaning the advice is based on descriptive studies and expert opinion.

Although some clinicians restart bisphosphonates when markers of bone turnover such as NTX (N-telopeptide of type 1 collagen) rise to premenopausal levels, there is no evidence to support this strategy.<sup>24</sup>

The task force recommendations are based on limited evidence that primarily comes from white postmenopausal women. Another important limitation is that the outcomes are primarily vertebral fractures. However, until additional evidence is available, these guidelines can be useful in guiding decision-making.

### Should our patient continue therapy?

Our patient is relatively young and does not have any of the high-risk features noted within the task force recommendations. She has responded well to bisphosphonate treatment and so can consider a drug holiday at this time.

## OVARIAN CANCER SCREENING

*A 50-year-old woman requests screening for ovarian cancer. She is postmenopausal and has no personal or family history of cancer. She is concerned because a friend forwarded an e-mail stating, "Please tell all your female friends and relatives to insist on a cancer antigen (CA) 125 blood test every year as part of their annual exam. This is an inexpensive and simple blood test. Don't take no for an answer. If I had known then what I know now, we would have caught my cancer much earlier, before it was stage III!" What should you tell the patient?*

Ovarian cancer is the most deadly of female reproductive cancers, largely because in most patients the cancer has already spread beyond the ovary by the time of clinical detection. Death rates from ovarian cancer have decreased only slightly in the past 30 years.

### Little benefit and considerable harm of screening

In 2011, the Prostate Lung Colorectal Ovarian (PLCO) Cancer Screening trial<sup>25</sup> random-

ized more than 68,000 women ages 55 to 74 from the general US population to annual screening with CA 125 testing and transvaginal ultrasonography compared with usual care. They were followed for a median of 12.4 years.

Screening did not affect stage at diagnosis (77%–78% were in stage III or IV in both the screening and usual care groups), nor did it reduce the rate of death from ovarian cancer. In addition, false-positive findings led to some harm: nearly one in three women who had a positive screening test underwent surgery. Of 3,285 women with false-positive results, 1,080 underwent surgery, and 15% of these had at least one serious complication. The trial was stopped early due to evidence of futility.

### A new UK study also found no benefit from screening

In the PLCO study, a CA 125 result of 35 U/mL or greater was classified as abnormal. However, researchers in the United Kingdom postulated that instead of using a single cutoff for a normal or abnormal CA 125 level, it would be better to interpret the CA 125 result according to a somewhat complicated (and proprietary) algorithm called the Risk of Ovarian Cancer Algorithm (ROCA).<sup>26,27</sup> The ROCA takes into account a woman's age, menopausal status, known genetic mutations (BRCA 1 or 2 or Lynch syndrome), Ashkenazi Jewish descent, and family history of ovarian or breast cancer, as well as any change in CA 125 level over time.

In a 2016 UK study,<sup>26</sup> 202,638 postmenopausal women ages 50 to 74 were randomized to no screening, annual screening with transvaginal ultrasonography, or multimodal screening with an annual CA 125 blood test interpreted with the ROCA algorithm, adding transvaginal ultrasonography as a second-line test when needed if the CA 125 level was abnormal based on the ROCA. Women with abnormal findings on multimodal screening or ultrasonography had repeat tests, and women with persistent abnormalities underwent clinical evaluation and, when appropriate, surgery.

Participants were at average risk of ovarian cancer; those with suspected familial ovarian cancer syndrome were excluded, as were those with a personal history of ovarian cancer or other active cancer.

**High-risk women may benefit from 10 years of bisphosphonate therapy**

**Results.** At a median follow-up of 11.1 years, the percentage of women who were diagnosed with ovarian cancer was 0.7% in the multimodal screening group, 0.6% in the screening ultrasonography group, and 0.6% in the no-screening group. Comparing either multimodal or screening ultrasonography with no screening, there was no statistically significant reduction in mortality rate over 14 years of follow-up.

Screening had significant costs and potential harms. For every ovarian or peritoneal cancer detected by screening, an additional 2 women in the multimodal screening group and 10 women in the ultrasonography group underwent needless surgery.

Strengths of this trial included its large size, allowing adequate power to detect differences in outcomes, its multicenter setting, its high compliance rate, and the low crossover rate in the no-screening group. However, the design of the study makes it difficult to anticipate the late effects of screening. Also, the patient must purchase ROCA testing online and must also pay a consultation fee. Insurance providers do not cover this test.

### Should our patient proceed with ovarian cancer screening?

No. Current evidence shows no clear benefit to ovarian cancer screening for average-risk women, and we should not recommend yearly ultrasonography and CA 125 level testing, as they are likely to cause harm without providing benefit. The US Preventive Services Task Force recommends against screening for ovarian cancer.<sup>28</sup> For premenopausal women, pregnancy, hormonal contraception, and breastfeeding all significantly decrease ovarian cancer risk by suppressing ovulation.<sup>29–31</sup>

### REPRODUCTIVE FACTORS AND THE RISK OF DEATH

*A 26-year-old woman comes in to discuss her contraceptive options. She has been breastfeeding since the birth of her first baby 6 months ago, and wonders how lactation and contraception may affect her long-term health.*

Questions about the safety of contraceptive options are common, especially in breastfeeding mothers.

In 2010, the long-term Royal College of

General Practitioners' Oral Contraceptive Study reported that the all-cause mortality rate was actually lower in women who used oral contraceptives.<sup>32</sup> Similarly, in 2013, an Oxford study that followed 17,032 women for over 30 years reported no association between oral contraceptives and breast cancer.<sup>33</sup>

However, in 2014, results from the Nurses' Health Study indicated that breast cancer rates were higher in oral contraceptive users, although reassuringly, the study found no difference in all-cause mortality rates in women who had used oral contraception.<sup>34</sup>

### The European Prospective Investigation Into Cancer and Nutrition

To further characterize relationships between reproductive characteristics and mortality rates, investigators analyzed data from the European Prospective Investigation Into Cancer and Nutrition,<sup>35</sup> which recruited 322,972 women from 10 countries between 1992 and 2000. Analyses were stratified by study center and participant age and were adjusted for body mass index, physical activity, education level, smoking, and menopausal status; alcohol intake was examined as a potential confounder but was excluded from final models.

**Findings.** Over an average 13 years of follow-up, the rate of all-cause mortality was 20% lower in parous than in nulliparous women. In parous women, the all-cause mortality rate was additionally 18% lower in those who had breastfed vs those who had never breastfed, although breastfeeding duration was not associated with mortality. Use of oral contraceptives lowered all-cause mortality by 10% among nonsmokers; in smokers, no association with all-cause mortality was seen for oral contraceptive use, as smoking is such a powerful risk factor for mortality. The primary contributor to all-cause mortality appeared to be ischemic heart disease, the incidence of which was significantly lower in parous women (by 14%) and those who breastfed (by 20%) and was not related to oral contraceptive use.<sup>35</sup>

Strengths of this study included the large sample size recruited from countries across Europe, with varying rates of breastfeeding and contraceptive use. However, as with all observational studies, it remains subject to the possibility of residual confounding.

**Current evidence shows no clear benefit of ovarian cancer screening for women at average risk**

### What should we tell this patient?

After congratulating her for breastfeeding, we can reassure her about the safety of all available contraceptives. According to the US Centers for Disease Control and Prevention (CDC),<sup>36</sup> after 42 days postpartum most women can use combined hormonal contraception. All other methods can be used immediately postpartum, including progestin-only pills.

As lactational amenorrhea is only effective while mothers are exclusively breastfeeding, and short interpregnancy intervals have been associated with higher rates of adverse pregnancy outcomes,<sup>37</sup> this patient will likely benefit from promptly starting a prescription contraceptive.

### ■ HIGHLY EFFECTIVE REVERSIBLE CONTRACEPTION

*This same 26-year-old patient is concerned that she will not remember to take an oral contraceptive every day, and expresses interest in a more convenient method of contraception. However, she is concerned about the potential risks.*

Although intrauterine contraceptives (IUCs) are typically 20 times more effective than oral contraceptives<sup>38</sup> and have been used by millions of women worldwide, rates of use in the United States have been lower than in many other countries.<sup>39</sup>

#### A study of intrauterine contraception

To clarify the safety of IUCs, researchers followed 61,448 women who underwent IUC placement in six European countries between 2006 and 2013.<sup>40</sup> Most participants received an IUC containing levonorgestrel, while 30% received a copper IUC.

**Findings.** Overall, rates of uterine perforation were low (approximately 1 per 1,000 insertions). The most significant risk factors for perforation were breastfeeding at the time of insertion and insertion less than 36 weeks after the last delivery. None of the perforations in the study led to serious illness or injury of intra-abdominal or pelvic structures. Interestingly, women using a levonorgestrel IUC were considerably less likely to experience a contraceptive failure than those using a copper IUC.<sup>41</sup>

Strengths of this study included the pro-

spective data collection and power to examine rare clinical outcomes. However, it was industry-funded.

The risk of pelvic infection with an IUC is so low that the CDC does not recommend prophylactic antibiotics with the insertion procedure. If women have other indications for testing for sexually transmitted disease, an IUC can be placed the same day as testing, and before results are available.<sup>42</sup> If a woman is found to have a sexually transmitted disease while she has an IUC in place, she should be treated with antibiotics, and there is no need to remove the IUC.<sup>43</sup>

#### Subdermal implants

Another highly effective contraceptive option for this patient is the progestin-only subdermal contraceptive implant (marketed in the United States as Nexplanon). Implants have been well-studied and found to have no adverse effect on lactation.<sup>44</sup>

Learning to place a subdermal contraceptive is far easier than learning to place an IUC, but it requires a few hours of FDA-mandated in-person training. Unfortunately, relatively few clinicians have obtained this training.<sup>45</sup> As placing a subdermal contraceptive is like placing an intravenous line without needing to hit the vein, this procedure can easily be incorporated into a primary care practice. Training from the manufacturer is available to providers who request it.

### What should we tell this patient?

An IUC is a great option for many women. When pregnancy is desired, the device is easily removed. Of the three IUCs now available in the United States, those containing 52 mg of levonorgestrel (marketed in the United States as Mirena and Liletta) are the most effective.

The only option more effective than these IUCs is subdermal contraception.<sup>46</sup> These reversible contraceptives are typically more effective than permanent contraceptives (ie, tubal ligation)<sup>47</sup> and can be removed at any time if a patient wishes to switch to another method or to become pregnant.

Pregnancy rates following attempts at “sterilization” are higher than many realize. There are a variety of approaches to “tying tubes,” some of which may not result in complete tubal oc-

**IUCs and subdermal contraceptives are typically more effective than tubal ligation**

clusion. The failure rate of the laparoscopic approach, according to the US Collaborative Review of Sterilization, ranges from 7.5 per 1,000 procedures for unipolar coagulation to a high of

36.5 per 1,000 for the spring clip.<sup>48</sup> The relatively commonly used Filshie clip was not included in this study, but its failure rate is reported to be between 1% and 2%.

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